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A. I'm being represented by Mr. Chris Hall from Saul Ewing and Lisa Dykstra from Morgan Lewis.
Q. Have you ever been deposed before?
A. Yes, I have.
Q. In what kind of case?
A. One was a -- many, many years ago, a Securities and Exchange Commission case that -- typical Securities and Exchange Commission case. It was, in general, in terms of who said what to whom in various circumstances. And then there was a subsequent case that was very similar to that basically.
Q. Also involving securities?
A. Generally involving securities.
Q. Were you ever deposed in a case involving any medical or pharmaceutical issues?
A. No, not at all. The ones involving securities was simply because I was aware of transactions that were ongoing.
Q. Was Merck a party to those cases?

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A. The first one, yes.
Q. About what year was that case?
A. That was 1980s, early 1990s.
Q. Have you met with your -- with your counsel prior to --
A. Just to correct, Merck was not a party to it, the parties that were involved was the Security and Exchange Commission and a private citizen, but it related to a transaction that Merck was a party to just while I was there.
Q. And have you met with your attorneys prior to the deposition?
A. At this deposition, yes. Yes, I have.
Q. When?
A. We've had several meetings, the most recent one being yesterday; and then two prior to that, which were several months ago, I believe.
Q. Which lawyers did you meet with?
A. Lisa Dykstra was there and Chris Hall were present.
Q. Anyone else?
A. There were -- I believe you were

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in the room, weren't you? Yes. Yes, you were. Sorry if I don't remember entirely.
Q. You being?
A. I'm sorry.
Q. Lindsey?
A. Lindsey. Lindsey Mills. I'm sorry.
Q. Okay.
MR. HALL: Lindsey Mills.
THE WITNESS: Lindsey Mills was definitely present, yesterday. I just couldn't remember previously. I'm sorry.
BY MR. BEGLEITER:
Q. Have you ever testified at a trial?
A. No, I have not.
Q. Did you review documents prior to this deposition?
A. Yes.
Q. And did any of these documents refresh your recollection?
A. The documents generally refreshed my recollection of things that were happening. They did not necessarily reflect my -- refresh

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my recollection of actual events that occurred.
Q. I'm trying to understand --
A. I saw -- well, the refreshing of the recollection -- that's a fair question. The refreshing of the recollection was that when I saw the documents, I certainly recollected the events that occurred. But if the question was do I actually remember the occurrence of the events? With the exception of a couple of occasions, the answer is no, because it was, after all, close to 20 years ago.
Q. Can you tell me which documents refreshed your recollection?
A. I told you --
MS. DYKSTRA: Objection. The documents we prepared for Mr. -- Dr. Emini are protected by privilege. I don't know if there is a specific one that he recalls, but if there is a specific document that he recalls that refreshes his recollection, I'll let him identify it for you.
MR. BEGLEITER: Okay. Great.

BY MR. BEGLEITER:
Q. Is there any specific document that you recall?
A. It was the entire ream of documents we were looking at.
Q. What's your position with the Bill & Melinda Gates Foundation?
A. I am the Director of the Global HIV Program with the foundation.
MS. DYKSTRA: Dr. Emini, I think the court reporter is going to ask you to slow down just a little bit.
THE WITNESS: Oh, I shall. I shall.
BY MR. BEGLEITER:
Q. How long have you been at the Bill & Melinda Gates Foundation?
A. This July will be two years.
Q. And would it be correct to say that you're focusing on AIDS research?
A. Yes, it is.
Q. Anything more than just research?
A. Well, it is research, the Bill & Melinda Gates Foundation funds research efforts. It also funds what we call delivery



efforts which is how to get the fruits of those research to individuals at risk of HIV or suffering from HIV infection in specific parts of the world that are of focus for the foundation. In the case of HIV, that would be Southern and Eastern Africa.
Q. Can you tell me -- you did work for Merck?
A. Yes, I did.
Q. Can you tell me approximately when you started and when you ended?
A. I started in August of 1983 and left at the end of January 2004.
Q. And what were the circumstances of your leaving?
A. It had been 22 years that I was at the company, and I decided that 22 years was long enough. At the time the company had a program in place to permit early retirement with full benefits associated with early retirement, and I raised my hand. And since it had been that period of time, I took the opportunity.
Q. So your departure was amicable?
A. Totally amicable.



Q. Did your departure have anything to do with, we haven't defined yet, but I think you'll know, Protocol 007?
A. No, not at all.
Q. Did it have anything to do with the MMR II vaccine?
A. Not at all.
Q. I want you to take a look at Emini-1.
- - -
(Exhibit Emini-1, Curriculum vitae, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. I'd like to show you -- I'd like to hand the court reporter and you and your counsel a document. I don't know how it was marked, but it's marked 00001 EMINI. We'll call this Emini-1 for this deposition. Just what is this, sir?
A. This is my curriculum vitae as of January 2016.
Q. Did you prepare this curriculum vitae?
A. Yes, I did.



Q. As far as you know, is it accurate?
A. As far as I'm aware, yes.
Q. Up to January 2016?
A. Yeah, it is.
Q. Is it?
A. Yes. It does appear to be the one that I prepared up until that time, yes.
Q. And tell me, sir, have there been any changes since January 2016 that you would ordinarily put in your curriculum vitae?
A. There may very well have been. There are probably one or two additional publications that were published since then that would have wound up on the publication list. And I was recently elected a Fellow of the College of Physicians of Philadelphia, and that would have been included.
Q. Congratulations on that.
If we can go back, if you can go to the "PROFESSIONAL HISTORY" section, which begins towards -- about two-thirds of the way down the first page and ends about a third of the way down the second.
A. Yes.

Q. And just a few questions about your professional history.
A. Yes, please.
Q. Looking at Item 10, Director of HIV Biology and Immunology at Merck Research Laboratories, do you see that?
A. Yes, sir.
Q. Did you have any responsibility for clinical trials as a Director of HIV Biology and Immunology?
A. My direct responsibility was in supportive research.
Q. I see.
A. In supportive research. But the clinical, the medical group did not report to me at Merck. It was the research group.
Q. When did -- and the research group would not have included clinical research?
A. The research group would not normally have included clinical research, no.
Q. Can you tell me which one of these numbers was the first time that you began to have any involvement with clinical research?



A. Involvement with clinical research was, I guess the word I would use is ancillary in the sense that the nature of how we operated within the organization was an open operational collaboration between regulatory and medical research and the research laboratories, where I was in research group which -- that I was responsible for. So there would be occasions where in the preparation of regulatory documents or in the conduct of research, they would be in support -- in the conduct of activities that would be in support of clinical activities that would have occurred.
Q. Did you -- was there a time in which you had a supervisory role with regard to clinical research?
A. Not in the context of a clinical -- not in the context of the execution of the clinical research, per se. In other words, the execution of the clinical protocol. That would have been the responsibility of the medical research group.
Q. And did you have any supervisory responsibility with regard to the medical



research group?
A. No. It was an independent group.
Q. You were -- let's go to number 8. Executive Director of Department of Antiviral Research. What were your duties as the Executive Director of Department of Antiviral Research?
A. The same thing. I was responsible for the research efforts that led to the development of antiviral drugs.
Q. Did that include mumps research?
A. No, these were antiviral drugs. These are chemotherapeutics. These are not vaccines.
Q. Did the Department of Antiviral Research exist before you became the executive director?
A. No, I was actually the founding executive director of the Department of Antiviral Research.
Q. Let's go to number -- you were the executive director -- number 7 is you're Vice President of Vaccine and Biologics Research?
A. Yes, that's right.



Q. Was 8 to 7 a promotion?
A. From 7 to 8. So when I --
Q. 7 to 8. 8 would be -- just to be clear, 8 is further back in time, 7 is more recent.
A. Yes, I'm sorry, reading backwards. Yes. So, yes, it was. I mean, vice president is a higher level than an executive director.
So after I completed what was approximately five years as the head of the Department of Antiviral Research, the efforts we were originally formed to do had, in fact, largely been completed and then the position became available at the head of vaccines research. I was offered the position. And I took it.
Q. And as number 8 did you have any responsibility, supervisory responsibility for any clinical research?
A. It was the same setup. The medical research group, there's always a separate operation, a separate reporting relationship than the research group.
Q. I just need a clarification.

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You know a Dr. David Krah?
A. Yes.
Q. Were you his -- was there a time in which you were a supervisor of Dr. Krah?
A. I was -- he was in my department, so I was the supervisor of his supervisor.
Q. And as a -- and what did you supervise him doing?
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. What was he doing that you supervised him for?
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. Go ahead.
MS. DYKSTRA: Form.
BY MR. BEGLEITER:
Q. Okay. What was his job when you were supervising him? Ask it that way.
A. His job was to run a research laboratory. That was his -- that was his predominant job, just like everybody else in the group.
Q. And was this -- was he -- he was

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doing research into the blood of children who either had mumps or had received mumps MMR II?
A. You're referring to a different set of circumstances. So as I said earlier, even though the medical research group was separate from us, we were a large collaborative operation. So there would be occasions, and this was true for regulatory and medical and research, where there would be activities that would be conducted by one group, okay, but would essentially be in support of another group.
Q. What group was Dr. Krah in?
A. So Dr. Krah was formally in this group, which is my group, which is the research group.
Q. And what was his job?
A. His job, his job was to conduct whatever research needed to be conducted plus whatever other activities needed to be done in support of the goals of the research group and in support of collaborative work that we did with the other groups such as medical and regulatory. But that was all of our jobs.
Q. The -- when it came to staffing,

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did you have any responsibility in staffing decisions in Mr -- in Dr. Krah's laboratory?
MS. DYKSTRA: Objection to form. I'm not sure what time frame you're talking about.
MR. BEGLEITER: I'm talking about the time frame of number 8. I should have said that.
THE WITNESS: I did not --
MS. DYKSTRA: I'm sorry, number 8 is antiviral research.
BY MR. BEGLEITER:
Q. Number 9 -- number 7, excuse me. Number 7.
MS. DYKSTRA: Thank you.
THE WITNESS: I delegated staffing responsibilities to the senior staff in the department.
BY MR. BEGLEITER:
Q. Who is that? Was there a particular person who had that responsibility for Dr. Krah?
A. That would have been his direct supervisor which would have been Dr. Alan Shaw, who would have worked in collaboration

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with Dr. Krah at the laboratory.
Q. All right. Was this relationship the same from April '97 to January '02 as number 7 indicates you held that position?
A. That would have generally been true, yes. Though I can't attest to the exact timing, but Dr. Shaw did report to me up until such time as I left the company.
Q. Now, Dr. Krah's group was doing clinical trial. Is that right?
A. No, he was not performing a clinical trial.
Q. Was he working in support of a clinical trial?
A. He did work in support of a specific clinical trial, yes.
Q. Tell me what specific clinical trial.
A. The one trial that we just mentioned which was the 007 mumps trial.
Q. What's the purpose of clinical trials?
A. The purpose of clinical trials is to generate data in a clinical setting and,

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therefore, in humans to answer a specific question.
Q. Is the purpose to determine -- is the purpose to develop a vaccine? Is the purpose when it comes to the kind of thing that Dr. Krah was doing to test the vaccine? What was the purpose specifically?
A. It could have been, it could have been, it could have been anything. The specific purpose of the clinical study is defined in the specific goals of the clinical trial as defined by the protocol of the study.
Q. Was one of the purposes of the clinical trial that Dr. Krah was involved with to assess efficacy of the MMR II vaccine?
A. I do not recall the exact wording of the specific trial goals as defined in the protocols, but it was not to -- it was not to assess efficacy because the vaccine's effectiveness and efficacy had been defined many years previously in a former trial for efficacy.
Q. Was it to study the immunogenicity of the vaccine?
A. It was designed to, best of my

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recollection, to study the immunogenicity of the vaccine using a specific set of assays as a measure of that immunogenicity, yes.
Q. And the assays, if you recall, were what?
A. There were two specific assays. One was an assay referred to as a plaque reduction neutralization assay. And the other one was an assay that was referred to as an ELISA assay, both developed to measure antibody responses elicited by the vaccine.
Q. Was it designed to study safety?
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. Was it designed to study safety? You can answer.
A. It was -- again, it depends on what was written and I don't -- I did not review the protocol so I don't know what was written as a specific objective of the study.
MS. DYKSTRA: Just to be clear, when we're saying it and the study, you're talking about 007?
MR. BEGLEITER: Yes, 007. I'm actually going to switch gears in a

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second, but that question certainly involved 007.
THE WITNESS: 007, yes.
BY MR. BEGLEITER:
Q. It was important that the MMR II be safe and effective. Right?
MS. DYKSTRA: Objection.
THE WITNESS: Well, it was important that the MMR II, as is true for any vaccine, be safe and effective, yes, of course. Or for that matter, any pharmaceutical product.
BY MR. BEGLEITER:
Q. Now, before a clinical trial began at -- withdrawn.
Was Protocol 007, had it begun by the time you arrived -- you became number 7?
A. I do not recollect.
Q. Have you heard of Protocol 006?
A. I have no recollection of 006.
Q. Do you recall that there was a head-to-head trial of Priorix and MMR II?
A. I do recall that there was such a trial, yes.

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Q. Was that trial, to your recollection, in progress when you became number 7, Vice President of Vaccine and Biologics Research?
A. I do not know. I don't recollect.
Q. Now, in 006, did you make any scientific -- excuse me, withdrawn. You don't know what 006 is.
In the study that's done the head-to-head comparison of Priorix and MMR II, did you make any scientific decisions?
A. Not to my recollection.
Q. Did you make any clinical decisions with regard to that?
A. Not to my recollection.
Q. How about research decisions?
A. Not to my recollection.
Q. Were you on any committees while you were at Merck?
A. I was on several committees, yes.
Q. Can you tell me what committees you were on, let's say, from 1997 on?
A. I can't give you the specific details because I don't even remember what

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they were called, to be honest with you, because this is well over 20 years ago. Well, close to 20 years ago. So but I do recall certainly being on a research management committee, I believe it's still referred to that way, which was a -- literally what it entails is a research management committee.

I may have served as not necessarily a committee member but as an observer to other committees such as committees related to clinical study design and things of that nature. Chances are I would have been an observer and an expert, if you will, present, but not making any decisions. As a matter of fact, now that I recall back, I was not a formal member of that committee. I remember making presentations to the committee, but I was never a formal member of the committee.

Q. Were you involved in any committees -- committee, I'll give you the name and tell me if you -- it jogs your recollection, the Critical Assay Subcommittee, CAS?

A. I remember the committee, but I

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do not believe I was a member.

Q. Were you involved in something called the Vaccine Assay Committee?

A. I do not recollect, but I don't believe I was a member.

Q. Did you -- were you a member of the Vaccine Marketing Committee?

A. I don't even recall that committee, but I doubt I would have been a member because normally someone from research would not have been part of the marketing committee.

Q. How about the Vaccine Product Approval Committee, were you a member of that?

A. Again, that is probably a marketing and regulatory committee. I don't recall the committee directly, but, again, I doubt I would have been a formal part of it.

Q. Did you ever attend any meetings of committees regarding competition?

A. I do not recollect any specifically.

Q. Let me go back now to Protocol 007. I asked you questions about Protocol 006.

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Were you involved -- did you make scientific decisions regarding the conduct of Protocol 007?

A. I don't recollect directly, but I don't believe I did.

Q. How about any clinical decisions regarding the conduct of 007?

A. No, I did not because I would not have been permitted to do that.

Q. Can you explain why you weren't permitted?

A. Again, clinical decisions were the responsibility of the medical clinical group. That was not my group and I was not responsible for that group.

Q. Do you recall the years '97 to 2002 which is number 7 on your list, who was in charge of that group?

A. I do not recall.

Q. Did you make any research decisions regarding Protocol 007?

A. I made -- I don't recall any specific decisions related to the protocol. There were activities that went on related to the protocol in which I was involved and

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participated.

Q. Did you -- were you consulted by others in the conduct of 007?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I was consulted with regards to the assays that were developed and run in support of the study.

BY MR. BEGLEITER:

Q. What assets of the assays were you consulted on?

A. Well, the assays were being conducted in the laboratory of Dr. David Krah, and there were some questions that arose with regard to the assays. And because it was in my employment relationship, I was obviously consulted.

Q. Do you recall any of what those questions were?

A. The questions that arose, the ones that I recollect very clearly are the questions that arose subsequent to an FDA inspection that occurred of the laboratory in which the FDA inspector noted, if I recall, four very specific observations that were part

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of a formal report from the agency and from the inspector known as a Form 483. I recall that correctly because that Form 483 was because of my level, handed directly to me by the inspector.

Q. Was it appropriate for the inspector to hand it to you considering your responsibilities or should it have been handed to somebody else?

A. No, because the inspection was related specifically to Dr. David Krah's laboratory and what was going on in there; and because I was, as noted, the most senior level person in that reporting relationship, I was the person.

Q. So when you said no -- you began your answer with no, and people do that all the time, so does that really mean yes, you were the right person?

A. Yes, I was the right person. The answer to your question, no, I was not the wrong person.

Q. So tell me, so there was this reporting relationship between you and Dr. Krah?

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A. Well, Dr. Krah, again, was in my department, his direct reporting relationship was with Dr. Shaw who was my direct report.

Q. And who did you report to in those years, number 7?

A. I believe, and, again, this is because I reported to a fairly large number of individuals over time because of the 22 years I spent in the company, but upon review of the documents, it appeared that at that time my direct supervisor was Dr. Anthony Ford-Hutchinson.

Q. Can you repeat the last name, please?

A. Ford-Hutchinson.

Q. Who did Dr. Anthony Ford-Hutchinson report to?

A. He reported to at the time, if I recall correctly, was directly to Dr. Edward Scolnick who was the head of the research laboratories. Though by that time, Dr. Peter Kim had joined the company. I don't recall exactly the time when that happened. So there was some reporting relationship changes that occurred as a result of that at the time.

Q. And what was Dr. Anthony

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Ford-Hutchinson's title, if you recollect?

A. I honestly don't recollect. I mean, it was obviously a more senior title than mine, but I can't tell you.

Q. How did his responsibilities differ from yours?

A. He had broader responsibilities over an entire range of departments within the research laboratories, all research departments. Again, clinical was a separate sphere of activities. So was regulatory.

Q. And the vaccine and biologics research in '97 to 2002 was just involved with clinical research, is that right, clinical studies?

A. No. Again, that was my department. That was the one that was involved with research.

Q. I see. But that was your responsibility?

A. Research.

Q. Research. Okay.

A. Just as it says. Vaccine and Biologics Research.

Q. Clinical research?

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MS. DYKSTRA: Objection.

THE WITNESS: No, clinical research was a function of the clinical research group. There were collaborative events between my department, vaccine and biologics research, and the vaccine clinical research group. But the responsibility was the clinical research group for the conduct of clinical studies.

BY MR. BEGLEITER:

Q. Were you ever asked to consult on compliance defense for MMR II?

MS. DYKSTRA: Objection.

BY MR. BEGLEITER:

Q. I'm talking, again, in this period from '97 to 2000.

MS. DYKSTRA: Did you say compliance defense?

MR. BEGLEITER: That's what I said, compliance defense.

THE WITNESS: It depends on your definition of the word "compliance" and it depends on the definition of the word "consult." Because I can define

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those in a number of different ways.
BY MR. BEGLEITER:
Q. Well, did -- was the regulatory group involved with -- at Merck involved with compliance in those years from '97 to '02?
A. By definition the regulatory group is involved with compliance, right.
Q. And specifically with regard to 007?
A. Yes.
Q. Did you ever -- did they ever come to you and ask you any questions, for any guidance, things like that?
MS. DYKSTRA: Object to the form.
THE WITNESS: I do not recollect. In terms of specific regulatory guidance, I've given -- but again, you know, that's a very general term, guidance. So if it were general regulatory guidance, no, because they were the experts in regulatory, so why would they come to me for guidance.
BY MR. BEGLEITER:
Q. Well, would they come to you,

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for example, if there was a regulatory question regarding research?
MS. DYKSTRA: Objection.
THE WITNESS: If there was a regulatory question regarding the activities of events that were going on in laboratories that are responsible to me, yes, they would come to me, of course.
BY MR. BEGLEITER:
Q. Let me understand how it worked at Merck in those five years. People were collaborative. Is that correct?
A. There were independent departments that were responsible for various activities. So if we look within the entire vaccine research effort, the entire vaccine research and development effort included within the overall responsibilities of the research laboratories, included the regulatory group which reported independently into head of regulatory; the clinical research group which reported independently into the head of medical and medical research; and then the research group, the fundamental research group

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which was mine that reported independently into the head of research.
Q. When you began in '07 -- excuse me, in '97 with that position in biologics and vaccine, did you -- had MMR II been licensed, as far as you knew?
A. MMR II had been licensed for many years prior to that. Decades.
Q. Did you know Dr. Hilleman?
A. Yes, I had the pleasure of knowing Dr. Hilleman. As a matter of fact, the reason I joined the research laboratories in 1983 is because Dr. Hilleman was the head, had done all the work that he did. My interest was in vaccines.
Q. Do you know if in '97 to '02, while you were with the vaccine and biologics research, whether or not Merck had the exclusive license for mumps vaccine in the United States?
MS. DYKSTRA: Objection. Form.
THE WITNESS: Well, yes. And it still does, I believe, yes.
BY MR. BEGLEITER:
Q. Eliminate that question.

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A. Yeah.
Q. Do you know if, again, in '97 to '02, whether it perceived a potential competitor for that meaning, if Merck perceived a potential competitor for its exclusive license for MMR II?
A. Merck is an institution. Perception is a human endeavor. So I can't answer that question the way you posed it.
Q. You can't answer the question what you perceived?
A. What I personally perceived?
Q. Yes, you're right. I asked if Merck perceived. I'll ask it as you, did you perceive that Merck had a potential competitor?
A. I did not perceive that.
Q. We discussed Priorix just for a moment or two in relation to another clinical trial. Do you -- what was your understanding in the '97 to '02 time period as to what Priorix was?
MS. DYKSTRA: Object to the form.
THE WITNESS: Priorix was the GSK version of the vaccine, of Merck's

MMR vaccine.
BY MR. BEGLEITER:
Q. You understood that Priorix was GSK, GlaxoSmithKline's version, that there was -- did you understand that there was potential competition between the two vaccines?
MS. DYKSTRA: Objection.
THE WITNESS: Well, there's certainly competition worldwide between the two vaccines, but in the United States I did not perceive that as being a competitive issue.
BY MR. BEGLEITER:
Q. Were you involved with any kind of research outside the United States?
A. Not that I recollect.
Q. Let's talk about Dr. Shaw. When did you first meet Dr. Shaw? Approximately, I don't need the exact date.
A. I don't recall. Dr. Shaw had been at the company when I joined, when I joined the company. Met him probably very early.
Q. And when you became --



A. Or a little bit thereafter. I don't recall exactly.
Q. When you became the VP of vaccines and biologics research in '97, was he with that division?
A. With the vaccine, yes. With the vaccine research division, yes, he was with that division.
Q. Okay. He was with the division when you left that division in January of 2002?
A. You know, Dr. Shaw also left the company and honestly, I don't recall who went first. I really don't.
Q. Would you say, though, that for a good period between April '97 and January 2002 you were supervising Dr. Shaw?
A. During that period I was, yes.
Q. It may not be to the actual end but for a good period?
A. As I said, I don't recall when we got to 2004 who had left first.
Q. Let's go to Dr. Krah. Was Dr. Krah -- when did you first meet Dr. Krah?
A. I don't recollect when I first



met Dr. Krah.
Q. Do you recollect that he was -- you supervised him during the period of time April '97 --
A. Yes, I do.
Q. -- to January 2002?
A. Yes, I do.
Q. For that entire period?
A. As to the best of my recollection.
Q. Everything is to the best of your recollection.
A. That's true.
Q. All right. Now, with regard to Dr. Shaw, going back to Dr. Shaw for a second, did you see him outside of work? Did you socialize?
A. Not routinely in those days, no. Subsequent to that, after I had left the company.
Q. And how about with Dr. Krah, did you socialize with him?
A. Never did.
Q. When was the last time you saw Dr. Krah?
A. I have not seen Dr. Krah since I



left the company, so I can't tell you exactly when, but certainly not since I left the company.
Q. Did you ever work on any papers with Dr. Krah?
A. There were, I believe, some publications, but I can't -- they would be listed in my CV. I don't remember exactly. It was quite a while.
Q. If a paper -- in these years of April '97 to January of '02, were there papers written regarding any clinical trials that you were involved with?
A. Within that exact period, again, I don't recollect. We would have to look through my CV, and you will see it.
Q. Was there any paper written regarding the trial where the head-to-head competition between Priorix and MMR II?
A. I don't recollect.
Q. Was there any paper written between -- written regarding Protocol 007's results?
A. There may very well have been, but I don't recall -- but I really don't

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recall.
Q. Now, when you and Dr. Shaw were working together sometime during the period of April to -- '97 to January of '02, how would you characterize your working relationship with him?
A. With Dr. Krah, it was a very formal --
Q. Dr. Shaw.
A. Dr. Shaw, yeah, the same way. Very formal working relationship. He was one of my direct reports, and all my direct reports were very formal relationships.
Q. Did you and Dr. Shaw have offices in the same building?
A. Yes, next door to each other. At least during this period, if I remember.
Q. And if he wanted to see you -- withdrawn.
Did you have an open door policy with regard to him? Could he just come to see you when he wished?
A. I had a general open door policy.
Q. In fact, did Dr. Shaw see you

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frequently during the time that he worked there close to the four years?
A. It depends how you define the word "frequently." Besides I can't -- I don't know. I mean, obviously there were multiple interactions between me and Dr. Shaw and all my direct reports and even other people. You know, I was there all the time. Most of the time.
Q. So when you say multiple interactions, you mean it wasn't a rare event for you to be seeing Dr. Shaw?
A. It was not a rare event for me to see anybody who wanted to see me. Certainly with my direct reports that was true.
Q. Who other than Dr. Shaw was your direct report in those four years?
A. The ones that I recollect directly were Dr. John Shiver and Kathrin Jansen. Those would be two -- among those three, they ran the three major areas.
Q. How about Peter Kniskern?
A. Peter Kniskern, yes. Actually, now that you mention his name, I believe I -- I don't formally recollect if he reported

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directly to me, but he had -- he did have an independent operation. He may have, I don't know.
Q. I'll ask the questions about Dr. Krah now, the same kind of questions. Was his office and your office in the same building?
A. Yes, we were all in the same building.
Q. How far was his office from your office?
A. I would have been on a different floor, because I was on the floor that had the office areas. So he was laboratory 1, so he would have been on one of the lab floors.
Q. Your open door policy pertained to him also. Is that correct?
A. Pertained to anybody.
Q. So if he wanted to speak to you, did he have to go through a secretary or any intermediary, any assistant?
A. No. Only insofar if he could find me or he needed to find me if I wasn't immediately available.
Q. Would you say that with Dr. Shaw

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you had a close working relationship?
A. I had the standard working relationship that one would have with one's direct reports.
Q. Did you trust Dr. Shaw?
A. Did I trust Dr. Shaw?
Q. Yes, if he told you something, did you take it as gospel?
A. It depends. We're scientists, right, so if he told me a conclusion to something or statement about something, I would usually ask for the supporting data.
Q. But if he told you a fact, like a fact regarding personnel, for example, would you trust his statement?
A. No, particularly when it comes to -- again, everything. It's such a science, it's everything, right. You always need supporting data, right. So if someone comes, and it doesn't matter who it is, and tells me a fact, I always ask for the supporting information. Or if it's not immediately available and if it's an important fact to determine -- that I would like to really determine if it is a fact, I will ask -- I

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will go find the supporting data.
Q. And did you ever find -- do you recall anything he ever told you that turned out to be unreliable?
MS. DYKSTRA: Objection.
THE WITNESS: No. I don't recollect anything like that.
BY MR. BEGLEITER:
Q. Let's go to Dr. Krah now for a second. I take it -- I'll ask the question. Did you respect Dr. Shaw?
A. Yes, I respected Dr. Shaw. I respected everyone.
Q. Let's go to Dr. Krah. Did he ever tell you anything that you found to be unreliable?
A. No, not to my recollection.
Q. And did you respect him?
A. As I said, I respected everyone who worked for me.
Q. Is there anybody that ever worked for you that did something that you lost respect for them?
A. No, because that would have probably -- losing respect for me means

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essentially doing something which is overtly wrong. And that I did not, to my recollection, see anything like that in those years, or for that matter any subsequent years or any previous years.
Q. Did you trust Dr. Krah's ability to keep you informed of essential goings on in the lab?
A. He would have kept Dr. Shaw informed who, in turn, would have kept me informed.
Q. So if Dr. Krah told Dr. Shaw something important, you would expect at least Dr. Shaw to tell you?
MS. DYKSTRA: Objection.
THE WITNESS: If Dr. Shaw perceived it to be at the same level of importance and supportable.
BY MR. BEGLEITER:
Q. Let me ask you a question. Do you recall the official title of Protocol 007?
A. No, I don't. I did not review the protocol.
Q. What about, do you recognize the following words, a study of MMR at mumps

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expiry potency in healthy children 12 to 18 months of age? Do you recognize those words?
A. Yes, I do.
Q. What do you recognize them as?
A. I recognize them as what would likely have been the title of Protocol 007.
Q. Sitting here today, do you understand what the purpose of Protocol 007 was?
A. Sitting here today and subsequent to the review of the documents over the last period of time, yes.
Q. And what was that purpose or purposes?
A. The original purpose, to my recollection, of the study was to determine whether or not the vaccine, if administered to children at various what were, used to be so-called potencies of the vaccine which would have reflected the amount of actual vaccine virus that is in the vaccine, raised potencies, were capable of eliciting immune responses that were reflective of the immune response, that were reflective of the immune

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response that would be elicited by the vaccine, and to determine whether or not those immune responses were equivalent at -- I believe there were several levels of potencies that were tested in the study.
Q. And it was the expiry potencies that were being looked at. Is that correct?
A. Well, the study was designed to evaluate three different potencies. Now, would they -- how they related to the potential of their being declared as expiry potencies was part of the entire larger question that was being addressed.
Q. Was one of the potencies that was being looked at the current potency at the time of MMR II?
A. The current expiry potency?
Q. Well, the current potency, let's say release potency?
A. Well, no. To my recollection, the three potency levels that were being assessed were being assessed as potential -- at expiry potency levels. So one of them would have been one that would have been reflective of the vaccine in circulation at

the time.
Q. And that -- do you recall what the potency level was of that, of the vaccine as --
A. I don't know.
Q. You mentioned now a few times there are three potencies.
A. There were three potencies, 4.3, 4.1 and 3.7.
Q. 4. --
A. 4.3, 4.1 and 3.7. Again, that was from my review of the documents.
Q. Knowing what you know, was one of those potencies the potency on the label?
A. The label at the time indicated, and what raised the question to begin with, the label that had been present since the virus -- since the vaccine, rather, had been originally licensed was a potency level of, I believe it was 4 -- it was the 4.3 potency level. But what the label said -- again, upon my review of that original label, it said that the vaccine contains, you know, 4.3 logs of mumps virus.
Q. When you became involved with



Protocol 007, was -- did anyone communicate to you from Merck that there was a desire to lower the labeled potency?
A. Not that there was a direct desire to lower the label potency but rather to determine if the -- what were likely to be the end of shelf life potencies, which would be, of course, the expiry potency, were potencies that were capable of eliciting immune responses that would be -- again, remember the assays that one uses are indirect measures of immune responses -- rather indirect measure of what the effect of an immune response might be, it's not the direct measure. But to determine whether or not there were equivalent abilities to elicit immune responses to the vaccine.
Q. Okay. But was -- I understand that, but I'm asking whether or not anybody told you that they wanted to change the label potency?
MS. DYKSTRA: Objection to form.
BY MR. BEGLEITER:
Q. This is, again, the period '97 to '01.



A. Not to change the question, The question is too broad. So it's difficult for me to answer which is why I'm hesitating here. The label potency, so are you referring to expiry potency or the release potency? It depends. They're two different things.
Q. Did the label, when you were at Merck, have an expiry potency on it?
A. The label had a potency on it. What had -- potency. The question as to whether or not it should be the expiry -- formally established as the expiry potency, that number was a question that had been raised by the FDA in previous discussions.
Q. So did Merck, as far as you know, take the position that that 4.3 was good enough, was a good number for the potency of the vaccine at expiry?
A. Its position was that that number was good enough at expiry and probably also good enough at original release. Because the way the original label was written suggested, this goes back decades, suggested that that number was reflective of the amount of vaccine virus that was used to actually



produce the vaccine.
Q. Do you know how much virus was used to produce the vaccine?
MS. DYKSTRA: Objection to form.
THE WITNESS: No, I don't other than what it says. So if I were to read the label at face value, what goes in is -- when it was originally developed was approximately 4.3 logs of mumps virus.
BY MR. BEGLEITER:
Q. What is -- well, let me ask, do you know what 4.3 logs comes to in terms of units?
A. 4.3 logs, four logs would be 10,000, so that would be roughly 20,000.
Q. One less document to look at. So approximately 20. Is the scientific way of referring to it, would that be -- of the 4.3, would that be 4.3 log10 TCID50?
A. So that would be 4.3 log to the base ten, because there are multiple logs that are not base ten, but that's log to the base 10, tissue culture, 50 percent tissue culture

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effective doses.
Q. Let's return to the 006 -- excuse me, to the head to head, the Priorix versus MMR II. Do you know why that study was conducted?
A. I don't recollect.
Q. Do you know what the results were?
A. I do not recollect directly.
Q. Do you know if they were published?
A. I don't recollect.
Q. Do you recall who won in that head to head?
MS. DYKSTRA: Objection.
THE WITNESS: I don't recollect the results.
BY MR. BEGLEITER:
Q. I'm not asking specific results, I'm asking just a general question. Did either one of them turn out to be a better one than the other?
A. I don't recollect. I really don't.
Q. Were you involved with budgets

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at all?
A. Only with regard to the budgets in my own department.
Q. Did you -- was there a budget for Protocol 007?
A. That would not have been in my responsibility. My responsibility were the budgets of the overall department. I would not have been responsible for the budgets of a specific study.
Q. Who would have been?
A. The medical research group.
Q. And who was in charge of that then, do you know?
A. I honestly don't recall.
Q. Did you ever review the budget?
MS. DYKSTRA: Objection.
THE WITNESS: No, I would not -- not just -- normally, I would not review the budget of a clinical study.
BY MR. BEGLEITER:
Q. While you were at Merck, would outside labs ever do work for Merck?
A. That was routine practice. Outside laboratories would do various studies

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in collaboration of this, yes.
Q. Were there contracts with these outside laboratories?
A. It depended on the nature of the study. It could have been research collaborations, it could have been contracts to do specific work.
Q. Do you know whether there was a contract, whether an outside lab did work on that head-to-head study of Priorix and MMR II?
A. I don't recollect.
Q. When Merck retains an outside lab -- withdrawn.
Were you involved ever with determining whether an outside lab should be used in a Merck study?
A. I don't recollect in the context of MMR II or within this time, but other points of my responsibility there I was involved, yes.
Q. What criteria, if you know, were used by Merck to determine whether or not -- let me finish -- whether or not an outside laboratory was competent?
A. It depended on the work that

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needed to be done.
Q. How would Merck go about doing the analysis?
A. It would depend on the work that needed to be done and an assessment would probably be performed of the laboratory and -- to make sure that it would maintain the appropriate standards, generated reproducible data. Typical.
Q. Merck wouldn't contract with an outside laboratory, as far as you know, that was incompetent?
MS. DYKSTRA: Objection.
THE WITNESS: Of course not.
BY MR. BEGLEITER:
Q. Or lacked integrity?
A. Of course not.
Q. Was not professional?
A. Of course not.
Q. Now, you mentioned a few moments ago that there was this difference of opinion between Merck and the FDA regarding the end expiry potency that was on the label?
MS. DYKSTRA: Objection.
THE WITNESS: To the best of my

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recollection, it was not a difference of opinion. What it was was that the label indicated that the potency of the vaccine was 4.3 logs of mumps. The vaccine like every pharmaceutical product has a shelf life. The agency's position in the late 1990s was, and this was at a time that they were reviewing their internal rules and regulations, took the position that what was listed on the label as the potency needed to reflect the potency at the end of shelf life, hence the expiry potency.

BY MR. BEGLEITER:

Q. Do you know what the shelf life of MMR II was?

A. I believe it was approximately 24 months at the time. I believe. I don't recall directly, to be honest.

Q. When you say "approximately," you mean because you're not 100 percent sure or because --

A. No, it's because I'm not 100 percent certain. Normally the shelf life

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would be -- it wouldn't be 23 months, it would be 24 months or 36 months, something of that nature.

Q. The people at the FDA that you -- that would be -- withdrawn.

There was a question, if I used the word before, there was a question about whether the 4.3 met the FDA's requirement of end expiry potency?

MS. DYKSTRA: Objection to the form.

THE WITNESS: Whether it met FDA's new perception of what that number should mean. Because prior to that time, there was no question at all with regard to what 4.3 logs refer to. It was only when we got to the point of there being an indication that the agency said, you know, this number should really reflect end expiry potency. That was the change that happened.

BY MR. BEGLEITER:

Q. That's what they said, but I want to know if you're aware that anyone at

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Merck challenged that mandate, that conclusion of the FDA?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I don't think anyone necessarily challenged it. I think that what it was was a question that came up which said simply that if now this number of 4.3 is to be considered the end expiry potency and, of course, given that, just like any pharmaceutical product, the product does decay over time, it's second law of thermodynamics, does decay over time on storage, then the question is, you know, is the end expiry potentially somewhat less than 4.3. We don't know. And, therefore, should the number be, in fact, lower to really represent end expiry potency.

BY MR. BEGLEITER:

Q. First of all, when you were dealing with the FDA, was there a specific division of the FDA that you would deal with?

A. The division at the FDA was the old division that was referred to as the

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Bureau of Biologics, then became known as the Center for Biologics, Evaluation and Research. It's the same division that is responsible today for vaccines.

Q. And that Center for Biologics was known colloquially as CBER?

A. Center For Biologics, Evaluations and Research, CBER. That's right.

Q. Okay. So just to be clear, I think you've touched it, but let's make it clear, the question was, at end expiry, whether or not the vaccine had 20,000 base ten TCID50? Isn't that really the question?

A. No. Just to take a step back, the label of the vaccine from the day it was first licensed many decades ago indicated that the amount of virus in the vaccine was 20 -- for mumps was 20,000 TCID50. There was no indication in the label as to whether that was the end expiry number or the release number. So, in fact, one could argue it either way, that the vaccine had to have at least 20,000 on the day it left the factory or had to have 20,000 on the day it could no longer be used because it achieved the end of shelf life.

Q. And then --
MS. DYKSTRA: Can he finish?
BY MR. BEGLEITER:
Q. I'm sorry, I thought you were finished.
A. No. So the agency, taking a conservative position at that time in the late 1990s, said that number should reflect the end expiry potency. It was a declaration by the agency. There was no data at that time to support whether or not vaccine that contained, actually contained less than 20,000 at end expiry would not be effective. There was no data to support that. It was simply a declaration.
Q. Now, the declaration of 20,000 TCID50 --
A. At end expiry.
Q. -- at end expiry, CBER wanted to know if that was true. Isn't that right?
MS. DYKSTRA: Objection.
THE WITNESS: What do you mean by "true"?
BY MR. BEGLEITER:
Q. In other words, that was what --



if one tested the vaccine, one would find 20,000 TCID50?
MS. DYKSTRA: Objection.
THE WITNESS: No, that's not to my recollection as to whether or not that question came up. The question that came up was whether or not the vaccine would retain potency at what -- that the potency that was present at 20,000 was also retained at levels below 20,000, on the assumption that if 20,000 was considered to be the release potency, that there was a likelihood that at the end of the shelf life, this effective vaccine would contain less than 20,000 so, therefore, what is that number, so that one could actually put an end expiry number in the label that was reflective of the actual potency of an effective vaccine.
BY MR. BEGLEITER:
Q. During your time at Merck in the biologic and -- vaccine biologics research, had there been any other end expiry trials?
A. Not -- had there been? Not to



my recollection, but -- no, not to my recollection. But it depends, again, what you defined as end expiry trials. In the development of any pharmaceutical substance, there are studies that are conducted, you know, certainly in current last period of time. Let's go back to, let's call it the last 20 years. There are studies that are typically conducted to determine what should be the end expiry potency, however you define potency, in the label. But that was not the standard going back certainly to the 1960s and early 1970s.
Q. Well, are you aware -- there's no doubt that Protocol 007 was an end expiry study. Right?
A. That was to answer a very specific question, which was, what would the potency of the -- what would the immunological potency of the vaccine be. That's what that study was designed to measure. What was the immunological potency of the vaccine at levels that were below 4.3.
The vaccine was -- there was never a question by the agency or by Merck as



to whether or not the vaccine that was being used was effective or not. It was effective. The question was, okay, what level is still -- what level should be present, what level, what potency level, use that terminology, should still be present in the vaccine at the end of shelf life that reflects the effectiveness of the vaccine. Because remember, 4.3 was simply a declaration, not based on data.
It was known that the vaccine at 4.3 was effective because it was originally designed to have 4.3 in it at release and, therefore, that was what probably was present at the time that the efficacy studies were ongoing, but there was no evidence of any loss of efficacy over time.
Q. Let's maybe have some definitions. What is immunological potency?
A. Immunological potency is -- so when immunological potency, the question -- so let's do it -- it's a broad question. So we'll do it in the context of the 007 trial.
The 007 trial was designed to determine whether or not different levels of the vaccine or the vaccine produced that

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contained different levels of the mumps virus, right, 4.3, 4.1, 3.7 logs, were capable, were each capable of equivalently eliciting immune responses as measured, that's a key point, as measured, that were reflective of the immune response that would be elicited by the vaccine.

Q. Can you give me a definition of what you mean by "efficacy"?

A. Efficacy has a very specific definition. It is whether or not -- well, again, it depends the context of the product. But in the context of a vaccine is whether or not the vaccine, okay, is effective in a clinical setting to prevent disease caused by the pathogen against which the vaccine is designed to be effective.

Q. Now, let me just see if I understand what you said about the direction from the FDA, from CBER. Are you saying that CBER had no scientific basis, at the time that 007 was begun, to direct that Merck have this -- have 4.3 TCID whatever at expiry? TCID50, I'm sorry. Because you said a couple of times --

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A. Please be more specific in your question.

Q. Well, I believe you said that the FDA was acting conservatively --

A. Right.

Q. -- when they required this end expiry study. And I'm asking you whether or not there was any scientific reason, health reason, medical reason to do it?

MS. DYKSTRA: Objection to form.

THE WITNESS: To my knowledge, to my knowledge, and based upon the way in which the questions were asked, the study was conducted and subsequent discussions, you know, between the agency and the company, the agency did not have a reason to declare 4.3 as a requirement because of fear that there would be loss of efficacy or that the vaccine was not efficacious at levels less than 4.3. There's no evidence for that.

The reason why the agency declared end expiry should be 4.3 was because the agency was concerned, this

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was something -- this was a general concern that had arisen within the agency around this time, not just related to mumps but to every other product that they were responsible for regulating over the issue of control. How do you know that the product that you make is the same all the time and how do you know that the product that you use, that includes the product all the way up to the end of expiry, is the same all the time with regards primarily to its efficacy.

BY MR. BEGLEITER:

Q. How do you know the -- how do you know that the FDA was requiring this in more than MMR II?

A. This was across the industry. These questions came up across the industry with regards to how does one tighten the language in the label, how does one tighten manufacturing control processes, you know, because there were many issues, and which were, again, across the industry in general, roughly around this time, late 1990s, early

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2000s. And as a result, language needed to be tightened in the labels. This is an example of that. Additional control processes needed to be put into place during manufacturing for a whole number of other vaccines. This was, again, and it wasn't -- I just want to make the point, it wasn't Merck specific, it was industry specific.

Q. Can you name other vaccines that were required to tighten up their labels?

A. Well, not just tighten up their labels but tighten up general controls in general. I will tell you that there was a major, a major turnover of the vaccine industry in those days as a result of the agency insisting on tighter perspectives. There were vaccines that were marketed that were taken off the market. None of them being Merck. Other companies, and we won't go into those details.

Q. Can you name a vaccine that was -- where label was tightened and controls were tightened in this period because of this agency effort?

A. I can't name one directly off

the top of my head, but it was general activity that was ongoing.
Q. Do you know what level of immunogenicity that was required of the MMR II vaccine?
MS. DYKSTRA: Objection.
THE WITNESS: So, again, not that I recall at the time itself but in reviewing the documents over the last several periods of time, what the agency was looking for was looking for an immunological assay that was capable of showing that the vaccine, when used at what they were now calling the end expiry value of 4.3, would be able to demonstrate at least a 90 percent seroconversion.
BY MR. BEGLEITER:
Q. Was that 90 percent including a 5 -- including some --
A. Variance.
Q. Some -- I'm trying to think of the word. Some confidence interval?
A. Confidence interval. It's in the report here. Confidence interval which is



the variance.
All biological assays and all assays in general by definition have confidence intervals.
Q. So the 90 percent was with the confidence?
A. 90 percent would have been the point estimate. You would then -- point estimate being the midpoint of the confidence interval.
Q. Do you recall what the label said about the --
A. I do not recall what the label said.
MS. DYKSTRA: When -- Bob, when you get a chance to take a break either before or after you finish --
MR. BEGLEITER: This is a one minute.
- - -
(Exhibit Emini-2, MMR II package insert, 01449029 - 01449040, was marked for identification.)
- - -
(A discussion off the record



occurred.)
- - -
BY MR. BEGLEITER:
Q. I've shown you Merck KRA01449029 through 9040, and ask you what this document is, if you know?
A. This appears to be the label or what is also referred to as the package insert for MMR II. What I cannot tell by just looking at it is which year this package insert came from.
Q. Let me -- if you go right to the very end, the very end, page 12.
A. Issued date is April 1999. Thank you.
Q. All I'm going to ask you about this document is the -- is what the label said about the seroconversion rate for the mumps component of MMR II. And if you go to the carryover paragraph from page 1 to page 2, I think that might have the answer.
MS. DYKSTRA: I'm sorry, do you want him to identify anywhere the label talks about seroconversion rate?
MR. BEGLEITER: No, I'm asking



him just basically to refresh his recollection.
THE WITNESS: Okay.
BY MR. BEGLEITER:
Q. Just ask you, having read the carryover sentence --
A. Yes, I have.
Q. -- is your recollection refreshed as to the SCR required of the vaccine?
MS. DYKSTRA: Objection.
THE WITNESS: This is not the SCR that is required. What it says here is that, very clearly, that "Clinical studies of 279 triple seronegative children...," and I'm reading the paragraph, "...11 months to 7 years of age, demonstrated that MMR II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles...," and then it tells you the measles, but I'll refer to the mumps, "...mumps neutralizing antibodies in 96 percent...of susceptible persons." That is simply a report of what was

observed in the clinical study that is being referenced. It is not a requirement.

BY MR. BEGLEITER:

Q. But this document, is this an insert for the vaccine?

A. Yes, it is.

Q. And this, as far as you know, is given to every medical center, physician who --

A. Whoever purchases the vaccine gets an insert because it's in the box.

Q. And when you answered 90 percent before, what were you reserving to there?

A. I was referring specifically to the context of the 007 clinical trial and what the agency, the FDA was looking for in terms of the quality of the assay that was being used to assess the immunological response to the vaccine. That's a different situation than what's in the label here. This label is reporting data from its original efficacy study. We need to recall that what you measure is a function of how you measure it. That the assay that was used back when this clinical study was originally conducted, and,



again, I need -- I don't know if it's appropriately referenced here so we can go back to see when the study was originally conducted, we'll have to read and take a look at it, but I'm certain it was many decades before the late 1990s because that was when the vaccine was first licensed. That assay was no longer in existence by the time of the 007 study. So a new assay had to be developed and the agency wanted the assay to be sensitive. What I mean by sensitivity, it needed to be able to discern a difference in the seroconversion rate that could be elicited by 4.3, 4.1 and 3.7. Those were the three comparators, right, that were being done. It had nothing to do with what was originally done many decades ago.

Q. So the 90 percent you're talking about which is post the confidence interval --

A. No, the 90 percent is, I presume, but the 90 percent, because in the documents I saw the number that I recollect was 90 percent, 90 percent is a measure of the assay sensitivity. So, for instance, if one wants to look at -- do a comparison, which is



what 007 was, of the ability of the vaccine at three different dosage levels, its ability to elicit a seroconversion response in young children, one wants as sensitive a vaccine as possible -- excuse me, as sensitive an assay as possible. If the vaccine were not capable of eliciting a seroconversion of at least 90 percent given the assay that you developed, you wouldn't be able to tell the difference between 90 percent or a few percentage points later, because typically the lower the midpoint of what you measure, the wider the confidence intervals and it becomes difficult to discern what's happening.

Q. Just to be straightened out, the 90 percent you're talking about is pre the confidence interval or post the confidence interval?

A. No, I view it as -- I interpret it as the midpoint of the confidence interval.

Q. So in other words, it could be from 95 to 85?

A. If the confidence interval --

Q. If it were 5 percent.

A. -- were 5 percent, it would be



referred to as 90 percent plus or minus 5 percent.

MR. BEGLEITER: We can have our break.

VIDEOGRAPHER: The time is 10:54. Going off the video record.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is 11:09. We're back on the video record.

MS. DYKSTRA: Dr. Emini, you asked him about the different arms in the 007 study and what the potencies were in the different arms. I think you may want to clarify what they were. He didn't have anything in front of him at the time, but he can clarify.

THE WITNESS: I mentioned they were 4.3, 4.1, 3.7. My apologies. The levels that were being tested were 4.9, 4.0 and 3.7.

BY MR. BEGLEITER:

Q. Now, in going back to the seroconversion rate for a moment, was -- did

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CBER ever communicate to you that they were looking for a 95 percent seroconversion rate?
A. To me?
Q. Yes.
A. No, there was no communication.
Q. Were you ever told by anyone at Merck that they were looking -- that CBER was looking for 95 percent seroconversion rate?
A. Not at all to my recollection.
Q. Now, when Protocol 007 was in development, did a decision have to be made about which strain of mumps vaccine -- which strain of mumps virus was going to be used for the assays?
A. Yes.
Q. And do you recall sitting here today what the candidates were for -- let me finish the question -- for the strain for the protocol?
A. For the assays?
Q. For the assays.
A. For the assays and protocol. There were two assays, one was a plaque reduction neutralization assay, the other was an ELISA assay as I said previously. Just so

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we're clear, we're always talking two assays here.
No, I don't recall what the candidates were other than the fact, and again, this came from my review over the last period of time of documents, other than the fact that the candidate had to be a so-called wild type virus. It could not be the vaccine virus itself.
Q. And were assays taken preliminarily of some of the wild type viruses?
MS. DYKSTRA: Object to the form.
THE WITNESS: I don't recollect the details of any work that was done along those lines.
BY MR. BEGLEITER:
Q. And just, again, if you don't -- with regard to these wild type viruses, was there an expectation from CBER as to what the seroconversion rate would be for those wild type viruses?
A. To my recollection, the only thing that CBER wanted to see was that the

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assay was capable of measuring a seroconversion rate that would be then statistically capable of determining a difference in seroconversion among the three levels of vaccine potency that were being tested in the protocol.
Q. But they weren't interested in the end result, they were interested only in the differences?
A. They were interested in the differences because that was the critical aspect. The three levels of potency that were being tested give rise to three -- if they would, would they give rise to three different seroconversion levels.
Q. Can you name any of the wild type vaccines -- excuse me, any of the wild type strains of mumps that were available?
A. No, I don't recollect them off the top of my head. The only one I can name is the one that was in actual use for the assay itself.
Q. And what was the name of that?
A. That was referred to as a low passage Jeryl Lynn strain.
Q. And that was the strain that was

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used by Dr. Hilleman to come up with the mumps vaccine?
MS. DYKSTRA: Objection.
THE WITNESS: So that was the -- it was -- no, it wasn't the exact one. This was a low passage Jeryl Lynn strain. So this was -- the way in which this was done is that the virus was originally isolated from Jeryl Lynn, who happened to be Dr. Hilleman's daughter actually, from -- was isolated from Jeryl Lynn and became known as the Jeryl Lynn virus. Then the virus was then passaged in cell cultures many, many, many times to attenuate it, in other words, to make it less capable of causing disease but yet still eliciting an immune response. I do not recall the exact passage of the Jeryl Lynn virus that then became the exact strain that is used in the vaccine. The low passage version was considered to be, appropriately so, a wild type virus, because of the low passage that was used for the purposes of the vaccine,

it was a virus that if one, in fact, put it into a child would more likely than not actually cause disease.

BY MR. BEGLEITER:

Q. To be clear, the Jeryl Lynn strain was the strain from which the mumps vaccine was developed. Isn't that right?

A. The Jeryl Lynn isolate, not the strain, isolate, was the isolate from which the vaccine was eventually developed. The exact strain that was used is a reflection of both the isolate, where it came from, hence Jeryl Lynn, and how many passages it had undergone in cell culture to attenuate it to make it the vaccine strain. So a low passage Jeryl Lynn strain is very different than the Jeryl Lynn vaccine strain.

Q. And was there a consideration of something called a cytopathic effect neutralization test being used as an assay?

A. Well, the way in which the neutralization assay was performed is that one takes the indicator virus, which in this case was the low passage Jeryl Lynn strain, one places it on a sheet of cells. The virus --



Q. It's all right if you want to give the answer, but my question was, was that considered?

A. The reason I'm answering it that way, that if you didn't do that, you couldn't do the assay.

Q. Was there a question about whether to use a CPE or a PRN as part of the neutralization?

A. I'm sorry. The reason I didn't answer the question was you weren't clear in that question. So it's -- but now I understand what you're asking. Not that I recollect.

Q. Now, what assay did CBER want, if you recollect?

MS. DYKSTRA: Objection to form.

THE WITNESS: I do not recollect those direct discussions with CBER.

BY MR. BEGLEITER:

Q. Did they want -- was it Merck's and your preference to use the ELISA assay?

MS. DYKSTRA: Objection to form.

THE WITNESS: There was a reference to use the ELISA -- if there



was -- I don't recollect the exact details of the discussions. What I can say is that both assays were used, the plaque reduction neutralization assay and the ELISA assay. To be clear, the selection of the assays were not conducted by Merck alone but was always in collaboration with the FDA, because the purpose was to answer a very specific question that the FDA asked us to answer and, therefore, it was a decision made by both organizations.

BY MR. BEGLEITER:

Q. Who ran the PRN test for Protocol 007?

A. So the PRN test was being run in David Krah's -- was developed and run in David Krah's laboratory.

Q. Who ran the ELISA test for Protocol 007?

A. I actually don't recollect if that was in David Krah's laboratory or a separate laboratory. That, I don't recollect clearly.

Q. Did you have an understanding --



withdrawn.

Do you have an understanding that CBER wanted a PRN assay to be conducted for this end expiry study?

A. Well, CBER agreed to the running of the PRN assay. So, therefore, I assume that they were comfortable with that decision which was made in collaboration with CBER.

Q. Well, did Merck agree with CBER when it first suggested a PRN assay?

A. No, I don't recollect the details of those initial conversations.

Q. Now, were you aware -- well, now, did CBER want a 95 percent -- I'm sorry if this is similar to the question I asked before, but did CBER want a 95 percent seroprotection rate against the wild type isolates?

A. I don't recall if CBER specifically wanted that number.

Q. And you don't recall whether or not -- or do you recall whether or not CPE was considered as one of the assays?

A. CPE is not an assay, so I don't know the question that you're asking.

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MR. BEGLEITER: I'm showing the witness --

- - -

(Exhibit Emini-3, 9/9/99 Memo, 00015686 - 00015689, was marked for identification.)

- - -

THE WITNESS: CPE refers to cytopathic effect. It's not an assay.

MR. BEGLEITER: I'm showing Dr. Emini Merck 00015686 to 89.

THE WITNESS: So what this refers to, it refers to an assay that is based upon virus elicited cytopathic effect, or CPE. But what I cannot tell from reading this document was they are the exact parameters nor the design of the assay itself.

BY MR. BEGLEITER:

Q. On page 2, I think you anticipated me, there's a committee that's established to "bring recommendation of which mumps neutralization assay (CPE or PR) should be used for future studies to the CAS in September '99." [As read] Right?

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A. Yeah.

Q. This was a committee in which you were the senior member?

A. Well, it's -- I don't recall -- I don't recall my exact membership on the committee back in '99.

Q. Are you saying that this is a mistake?

A. No, no, no. This says to bring the recommendation of the assay to the CAS. I don't remember if I was a member of the committee of the CAS, but I probably did bring the recommendation to the CAS.

Q. Among the four people that are listed, you, B. Buckland, Pete Kniskern and A. Shaw, you were the senior person?

A. Yes, I was the senior person.

Q. Do you recall whether or not a -- was a recommendation brought?

A. I do not recall.

Q. Go to the first page of this document. "DECISIONS" at the bottom. And it says, "At this point 2 independent assays have confirmed that the seroprotection rates against wild type virus isolates are not about

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95 percent, per CBER's expectation." [As read]

Does this refresh your recollection that CBER had an expectation that there would be a 95 percent seroprotection rate against wild type virus?

A. Well, I will take it in terms of what it says here, that CBER did have an expectation that it would be able to demonstrate a 95 percent seroconversion. This is an inappropriate use of the word "seroprotection." It's not the terminology that should be used.

Q. In looking at this document, does this refresh your recollection that you were a member of the CAS, the Clinical --

A. No, according to this document, I brought a recommendation to the CAS. I don't recall, as I said earlier, that I was a member of the CAS.

Q. Do you know what the -- do you have any recollection of what the independent assays were that confirmed that the seroprotection rates against wild type isolates were not about 95 percent?

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A. I don't recall other than what it says on this document.

Q. You can put that away.

MS. DYKSTRA: Are you through with Exhibit 3?

MR. BEGLEITER: Yes, we're done with it.

BY MR. BEGLEITER:

Q. Now, there came a time when a decision was made for the PRN assay to be conducted and the lab chosen was Dr. Krah's. Is that right?

MS. DYKSTRA: Objection.

THE WITNESS: Please repeat the question.

BY MR. BEGLEITER:

Q. Okay. There came a time when a decision was made to do a PRN assay. Is that correct?

A. Yes.

Q. And that was assigned to Dr. Krah, Dr. Krah's lab?

A. His assignment originally, again, based on documents that I reviewed, was to originally develop the assay.

Q. And had he developed any other PRN assays, to your recollection?
A. It was certainly within his level of expertise to have done that. I don't recall which specific assays he may have developed prior to this time.
Q. Do you know if he developed the assay for the head-to-head Priorix versus MMR II assay?
A. I do not recall.
Q. Now, sir, do you know when Merck started to develop the end expiry trial, about what year?
A. I don't recall directly. Again, on the basis of documents that I reviewed recently, the question came up with regards to whether or not 4.3 should reflect the end expiry value, so that would be roughly around the time that the consideration for it properly came up, so that would be in 1999, 2000, something along on those lines.
Q. In 1999, was there a -- withdrawn.
Do you know what the word "overfill" means as related to the mumps



vaccine?
A. It's a standard terminology within the industry. So what overfill means is to add more into the unit, whether it be a vial, a syringe, whatever the case happens to be, tied more into the unit than what would normally be required.
Q. And was an overfill performed in 1999?
MS. DYKSTRA: Objection to the form.
THE WITNESS: I don't recall the details.
BY MR. BEGLEITER:
Q. I'd like to hand you -- well, do you recall that an overfill occurred with regard to the mumps vaccine while you were in charge of biologics?
A. I don't recall the actual details, but I do recall, again, on the basis of documents that I reviewed, was that the decision was made to fill, not necessarily to overfill, so I'm being careful with the terminology here, to fill at a level of five logs.



Q. And what -- what would that equal in terms of the TCID50?
A. That would be 100,000.
Q. So that would increase from --
A. 20,000 to 100,000.
Q. Tell me, sir, were you involved with that decision at all?
A. I was not involved with that decision.
Q. Do you know who made the --
A. Not that I recollect, of course.
Q. Do you know who was involved?
A. I do not know who was involved, no.
Q. Did the filling to five log raise any safety concerns in you?
A. They did not at the time. I don't remember what my thoughts were obviously you know, 20 years ago, but I would not have raised any safety concerns then and don't raise any safety concerns now. Again, the decision was most likely than not taken with the concurrence of the agency.
Q. The amount of vaccine here goes from 20,000 to 50,000, it quintuples. Right?



A. 20,000 to 100,000.
Q. 20,000, I'm sorry, to 100,000, quintuples. Do you know whether it raised any concerns or not of you that to you whether or not any safety tests were taken, field or clinical?
A. No. I presume that there -- well, it -- there were -- one would need to go back and take a look at the original studies that were done when the vaccine was first licensed. And somewhere in those studies there's an indication of the levels of virus that were -- of vaccine virus that were tested in children at the time for safety purposes. But I don't know what those were.
Q. During your tenure at biologics, at the division, was there any consideration to increasing the fill again, that you recall?
MS. DYKSTRA: Objection.
THE WITNESS: I was only aware of this one.
BY MR. BEGLEITER:
Q. I didn't say it happened, was there a consideration of doing it, of filling in more?

A. I don't understand your question.
Q. Was there consideration of increasing the amount of virus by more than five log?
A. Not to my knowledge.
MS. DYKSTRA: I think the court reporter got something incorrect on the transcript. Do you mind if I just read it to make sure?
MR. BEGLEITER: Sure, go ahead.
MS. DYKSTRA: You asked him if the fill to five log raised any safety concerns and you said they did not at the time. I don't remember what my thoughts were obviously, you know, 20 years ago. Again, the decision was most likely not taken with the concurrence of the agency or taken with?
THE WITNESS: No, taken with the concurrence of the agency.
MR. BEGLEITER: Okay. That's fine. That's fair. That's how I heard it.
MS. DYKSTRA: Thank you. Just



wanted to make sure it was clear.
Thanks.
BY MR. BEGLEITER:
Q. Sir, I'd like to show you a document with Bates number 00615147 through 174. I'm going to show it to you, but I'm telling you, I'm not going to ask you any questions about the substance of it. This is what's called the authentication process. I'm going to ask you whether or not you received it. Okay? There will be several documents like this.
- - -
(Exhibit Emini-4, 10/2/02 E-mail with attachment, 00615147 - 00615174, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. All I'm going to ask you is whether or not you received this document in the course of your --
A. I have no direct recollection of having received this specific document, but given that it was addressed to me, I will assume that I received it.



Q. And you would have received it in the usual course of your employment with Merck?
A. I would have received it in the usual course of my employment, of course.
Q. You can put it aside. I'm not going to ask you any substantive questions about it.
So what's a warning letter from CBER?
A. It's exactly what it says. It's a warning letter from CBER in which the agency indicates specific deficiencies that it wishes to see corrected immediately. And it gives the recipient a relatively short period of time to put together a correction plan that the agency would then need to certify.
Q. And what could happen if CBER is not satisfied with the correction plan?
A. Again, it depends on what's the nature of the warning letter. If the warning letter reflects a manufacturing facility, they will close down a manufacturing facility. If it refers to a specific product, they can request withdraw of the product. It depends



on the details.
- - -
(Exhibit Emini-5, 2/9/01 Warning letter, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. Sir, again, I'm going to ask you a question, have you ever seen this document before?
A. Allow me a few minutes, please.
Q. Sure.
A. Again, I don't recall specifically having received this document, and there is no indication here that this was in any way addressed to me, so I don't know.
Q. But considering your position, would this have been something that would have been sent?
A. No, not necessarily. This was a note that was sent to Dr. Roberta McKee, vice president of vaccine and sterile quality operations. This would have been the Merck manufacturing division which is a completely separate decision of the corporation from the Merck Research Laboratories.

Q. Put it aside, sir.
Sir, do you know what a validation protocol is?
A. Yes, sir.
Q. What's a validation protocol?
A. A validation protocol is, again, it depends what the context is in which one is using the terminology, but for an assay, let's put it that way, for an assay validation protocol is a protocol that one conducts to validate the operational parameters of the assay, the variability of the assay, the variance of the assay, the reproducibility of the assay, a statistical determination of how one actually interprets the quantitative values that the assay generates. It's a statistically run and statistically predefined protocol that once those parameters are established for the assay, then essentially validates the assay. It's an old terminology. Terminology has changed since then. It's now referred to as assay qualification.
Q. Were there validation assays for Protocol 007?
MS. DYKSTRA: Objection. Form.



THE WITNESS: So, again, based upon my review, as would have been the case for any assay in support of a clinical study, the assay would have been validated, yes.
BY MR. BEGLEITER:
Q. Would it have been at least one for ELISA and one for the PRN assay?
A. Yes, we would do separate validations for each assay.
Q. What is vaccine biometrics research, what division of that -- is that?
A. That was a statistical group in support of vaccine research, vaccine clinical studies.
Q. Would you have reviewed -- or did you review any of the validation protocols for Protocol 007?
A. I have no direct recollection, but it is unlikely I would have reviewed the validation protocols. I would have relied on the, in fact, statistical group to determine whether or not an appropriate validation had been conducted. Validation is a statistical operation.



Q. Did you sign off on any validations --
A. Not that I recall.
Q. Would you recognize what a validation looks like for 007?
A. Probably so.
Q. I'm going to show you a fairly thick document but one that I'm only going to ask you to look at a few pages. It bears Merck number MRK-KRA0017036 to 114. Give it to the court reporter and give it to you.
MS. DYKSTRA: Exhibit 6.
- - -
(Exhibit Emini-6, FDA Response to MMR II, 00017036 - 00017115, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. Go to the third page which has contained 17038. Have you seen this letter before?
A. Not to my recollection.
Q. Do you know what AIGENT stands for, A-I-G-E-N-T?
A. I cannot -- again, I can't tell



you what the exact terminology stands for, but, again, on the basis of documents that I recently reviewed, it was in reference to the actual plaque reduction neutralization assay that was being used in clinical evaluation of 007.
Q. We've already discussed the study entitled -- I guess, rather the study titled, "A Study of MMR II at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age"?
A. Then it would be 007.
Q. Fine. This letter says that there's a summary of validation, and among other things, but all I'm going to ask you, sir, is to turn to page 17080. Actually turn first to 17076. You can look at it in combination if you wish with the next document beginning at 080 going to the end.
All I'm going to ask you, sir -- I'm not going to ask you for any questions about the substance of this document. I'm going to ask you whether or not this appears to you to be the validation protocol for Protocol 007 as it relates to PRN, the plaque

reduction neutralization?
A. Well, give me a second.
Q. Take a second.
MS. DYKSTRA: Take time if you need to look at the cover letter as well. I'm not directing you to look at anything, but take time to look at whatever time you need to make sure you're comfortable.
THE WITNESS: Yes, this does appear to be the validation protocol and the validation results for the assay.
BY MR. BEGLEITER:
Q. Going to the first page, this appears to have been sent to CBER on March 12, 2001.
A. On the cover page it is March 12, 2001, yes.
Q. Again, you don't recollect whether you actually reviewed this before you -- before it went to CBER?
A. Not my recollection, no.
Q. You don't recall whether you signed off on it?



A. I don't recall. It's timed. I don't recall.
Q. Okay. Fine.
MR. BEGLEITER: I'm going to hand the court reporter Merck 00052249 through 53, ask her to mark it. What's the number on this?
COURT REPORTER: 7.
THE WITNESS: 7.
MR. BEGLEITER: Okay. Emini-7.
- - -
(Exhibit Emini-7, 8/7/01 E-mail with attachment, 00052249 - 00052253, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. You are permitted to look at the whole thing, but I'm only going to be asking you questions about the cover e-mail and what's behind the cover e-mail, 483.
A. Okay.
Q. Now, the first question is, sir, did you receive this document in the usual course of your employment?
A. Yes, I did. It's addressed to



me, yes.
Q. Do you recall seeing this document?
A. Again, subsequent to reviews of documents over the last period of time, I do recall receiving this document, the first page which is the actual 483 document itself.
Q. You saved me a question. A 483, to be clear, is the sort of notice of deficiency that --
A. 483 is a notice of inspection observations that the inspector wishes to bring to your attention.
Q. And there was -- according to the second page which you said you recall, the inspection occurred on what day?
A. The inspection occurred on 8/6/01, August 6, 2001.
Q. This e-mail was sent to you by Karen McKenney on August 7th, the next day?
A. Well, the memorandum is dated August 6th. The e-mail is dated August 7th, yes.
Q. And sir, I just want to you to take a look at number 1.



MS. DYKSTRA: On the 483?
THE WITNESS: On the 483?
BY MR. BEGLEITER:
Q. I'll read it to you. Number 1 says, "Raw data is being changed with no justification, for example...," and then it gives a series of numbers which I'm not going to read to you. Do you have an understanding sitting here today of what that meant, what that referred to?
A. What that referred to was, again, remember 483 is a notice of observations that the agency or that the inspector specifically actually in the end wishes to have some explanation for. So if the inspector was not able to find at the time that she conducted this inspection was that there were changes being made to the data related to whatever assay she was looking at, that did not have clear justification noted when the changes were made.
Q. And do you know Mr. Krahling who was sitting here --
A. Yes, I did.
Q. -- sitting at this table? Did

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he warn you of this before August 7, 2001?
MS. DYKSTRA: Objection. Form.
THE WITNESS: I have no recollection of any discussions with Mr. Krahling related to this issue save one. Again, this was as a result of review of documents, and the document that I saw that indicated that at some point, and I don't remember what the date is, Mr. Krahling came to me to show me -- to express his concerns and presumably show me some data on which he had his concerns.
BY MR. BEGLEITER:
Q. And was that concern that data was being changed with no justification?
A. I don't recall the nature of that concern.
Q. You can put this away.
Well, I'll ask you, did you work on a response to 483? Did you review a response to the 483?
A. Yes, I reviewed. Again, no direct recollection, but, again, based on review of documents, I was involved in

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responding to the 483 and reviewing the responses to the 483, yes.
MR. BEGLEITER: I'll have the court reporter, please, mark this. I guess we're now up to 8, Emini-8. It's a document bearing Bates numbers Merck 481 to 539. I'd like the witness to look at it. It's being circulated to other counsel.
- - -
(Exhibit Emini-8, 8/20/01 Letter with attachment, 00481 - 00539, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. Okay. And, sir, do you recognize this document?
A. Yes. This would have been the formal response to the FDA to the four observations listed on the 483.
Q. And on page -- on the cover -- on the first sheet there's a letter. Is that right?
A. That is correct.
Q. Who signs that letter?

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A. I signed that letter.
Q. Your signature?
A. That is my signature.
Q. And, again, you can put this away, I have some questions to ask. I'm not going to ask any questions about that document, at least right now.
Well, the purpose of this document was -- the purpose of this document, was it to respond the 483 of August 6, 2001?
A. Right. The 483 was August 6th, the response went back on August 20th.
Q. And tell me, sir, what did you do between August 6th and August 20th that compiled information for you to respond to the 483?
A. Well, again, I have no direct recollection because of the period of time.
MS. DYKSTRA: I just caution you not to disclose any communications with counsel related to the response or anything you did to generate the response, but otherwise, you can respond.
THE WITNESS: Yes. No, that's

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fine. So the -- thank you very much. No, so the -- what I did is reflected right here in the responses. Worked with the team to pull together the responses that needed to be done.
BY MR. BEGLEITER:
Q. So did you commence any kind of investigation of what happened?
A. Of course.
MS. DYKSTRA: Objection to the extent that that involves counsel. You can answer yes and no and you can discuss any other investigation.
BY MR. BEGLEITER:
Q. Let me just -- I'll put a point on this. I'm not going to ask you any questions about what you may have said to counsel or counsel to said to you. Okay?
A. Fair enough.
Q. However, let me ask you the question, did you consult with counsel after the 483 was received by you?
A. I consulted with counsel, but, again, based upon the review of documents, again, of which were recently -- I recently

reviewed, I consulted with counsel immediately prior actually to the receipt of the 483. And consultation with counsel was in the context of --

MS. DYKSTRA: Just to caution you not to disclose the content of --

MR. BEGLEITER: Let him answer the question.

MS. DYKSTRA: You can say the time and the date, if you recall.

MR. BEGLEITER: Let him answer the question.

THE WITNESS: What I do recall was --

MS. DYKSTRA: Appropriately --

MR. BEGLEITER: I'm not asking for any attorney-client communication.

MS. DYKSTRA: He cannot disclose any communications.

BY MR. BEGLEITER:

Q. I'm not asking for any communication between you. I asked you whether or not you consulted with --

A. Yes, I consulted with counsel.

COURT REPORTER: Who am I



supposed to take?

BY MR. BEGLEITER:

Q. I'm sorry. I'll ask the question again.

Did you consult -- I'll ask it a little differently.

Did you consult with counsel after you received the 483?

A. I do not recollect that I consulted with counsel after I received the 483. Again, based on the review of documents, I believe that I consulted with counsel immediately prior to the receipt of the 483.

Q. Again, without telling me any communication, why did you consult with counsel prior to receiving the 483?

A. Again, based on the review of documents, I consulted with counsel immediately after I met had with Mr. Krahling, and Mr. Krahling brought his concerns to my attention.

Q. I see. So you remember that, but you don't remember whether or not you consulted with counsel after you received the 483?



A. That, I actually do not recollect.

Q. And do you recollect if counsel was involved in drafting the response which is -- I think it's Emini-9, the letter?

A. Emini-8.

Q. Emini-8.

A. Emini-8, yes. Normally counsel would not have been involved in these discussions. These are regulatory discussions. But, again, I have no direct recollection.

Q. As far as you know, everything in this document is correct, in Emini-8?

A. I signed it, yes, I believe it is.

Q. Now, sir, looking at Emini-8, was that the final response regarding the 483 or was there an additional response?

A. I don't -- regarding the observations on the 483, this is the response. I do not recall if there were subsequent communications. Oftentimes there are. And, in fact, I believe there probably are.

Q. Do you recall any teleconferences with CBER regarding your response?

A. Not an exact recollection of the



teleconferences, per se, but, again, on the basis of review of documents, there were teleconferences with CBER subsequent to this.

Q. You don't recollect anything regarding the substance of those teleconferences?

A. Only on the basis of what I reviewed.

Q. Well, what --

A. So on the basis of -- again, my recollection, only on the basis of what I recently reviewed, those were clarified -- I don't recall the specific details, but they reflected clarifying back and forth discussions between the agency and the company of the basis of the answers and to further clarify whatever additional questions that the agency might have. It's a pretty standard practice.

Q. Do you recall who you spoke with at the agency?

A. I don't recall even if I was present for that. The conversation would have been held between our regulatory liaison and the agency.

Q. Do you know a woman named Cathy Carbone, Dr. Cathy Carbone?

A. I know who she is. I don't recall if I spoke with her.
Q. Just eliminated a document.
Sir, going back a little bit in time, sorry to be out of chronological order, do you recall, again, about when, what year and when, what season the overfilling took place for the mumps vaccine?
A. No, I don't.
Q. Do you recall Merck being requested by CBER to give the seroconversion rates that it was getting on Protocol 007 to CBER sometime in 1999?
MS. DYKSTRA: Objection. Form.
THE WITNESS: I don't understand the question. Sorry. Please, one more time?
BY MR. BEGLEITER:
Q. CBER would from time to time ask you some results of some clinical trials, testing, whatever. Right?
MS. DYKSTRA: Objection to the form.
BY MR. BEGLEITER:
Q. Isn't that true, in your



experience?
A. It depends on the nature of what's being discussed and what it is. I mean, typically CBER would wait until the end of a study before asking for any data from a study.
Q. Do you recall with regard to Protocol 007, did they ask before the study?
A. I don't recall.
Q. Now, what relationship, what position did Mr. -- Dr. Scolnick have in the time that you were at the biologics?
A. He was the president of the research laboratories.
Q. He was -- at least in terms of a pecking order, he was above you?
A. We went through this already with Ford-Hutchinson. Yes.
Q. Fine. Who is Dr. Dorothy Margolskee?
A. So Dr. Margolskee was in the research laboratories. She had a general responsibility over vaccine-related medical and research questions, predominantly medical and regulatory questions. So she had, not



necessarily in terms of direct reporting relationship, but she had overall coordinating responsibilities. We'll go with that.
Q. And while you were in biologics, did you work with her?
A. Yes, I did.
Q. Did you work with Dr. Scolnick?
A. Well, Dr. Scolnick was the president of the research laboratories.
Q. Well, I'm saying you actually did things with him, discussed things with him?
A. Mostly in formal settings, yes.
Q. I'm sorry, informal or formal?
A. Mostly in formal settings.
MR. BEGLEITER: I'd like to show you Merck 1898768 through 72.
- - -
(Exhibit Emini-9, 10/31/99 E-mail with attachment, 01898768 - 01898772, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. We're calling it Emini-9.
A. Okay.



Q. Turning to page 69, 769, the bottom bullet point, "Mumps neutralizing antibody assay." Second sentence, "Prior to discussing the unanticipated low SCR for mumps with CBER, the results from sera from the head-to-head trial from MMR II and Priorix will be reviewed to confirm that this low SCR is observed in both products."
Do you see that?
A. Yes.
Q. Questions on this. First of all, do you have a recollection about whether there was an unanticipated low seroconversion rate for mumps on the MMR II product?
MS. DYKSTRA: Objection. Form.
THE WITNESS: So the discussion around this revolved around whether or not the assay -- now, remember, the assay was being redeveloped because the original assay that was used when the vaccine was first licensed no longer existed. The indicator strains didn't exist anymore, no one even knew what they were. So they didn't exist.
So going back to our previous

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discussion, the note was, from CBER, that this was -- presumably from CBER, certainly in agreement with CBER, that the seroconversion rate needed to be assessed in a plaque reduction neutralization assay or a CPE-based assay, either way, with a wild type strain yielding, all right, yielding a level of seroconversion that was approximately 90 percent as noted in the first sentence because of the need for sensitivity in the assay and reflecting the known field efficacy of the vaccine. What was occurring apparently was that -- not apparently but for a fact, again, based upon what's here, and I do recall this, what was known, what was observed was that with different wild type strains -- or wild type isolates, rather, of the virus, seroconversion rates were notably lower than 90 percent and, therefore, the assay was not giving a set of results that was reflective of the vaccine's known efficacy, and,

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therefore, could not be used for the kind of comparison we were discussing needed for the 007 study.

BY MR. BEGLEITER:

Q. Known efficacy referring to what was happening in the field?

A. Recurrent efficacy can only be determined in the field.

Q. Just straightening that out.

In the first sentence where it says, "...with JL as the test isolate...," is that Jeryl Lynn?

A. I presume it is Jeryl Lynn, yes.

Q. And using the clinical -- in the clinical testing, there was the seroconversion rates --

A. Was approximately 90 percent.

Q. And also but for Lo1, do you know what Lo1 stands for?

A. Lo1 probably is the designation for another wild type virus test isolate.

Q. You don't remember what that is?

A. I don't remember exactly what it is, but I'm sure that's what it is.

Q. That was 70 to 75 percent?

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A. That is correct.

Q. Again, the sentence I read to you, why wait for the results of the head-to-head MMR II and Priorix before telling CBER what the results -- the SCR results were?

MS. DYKSTRA: Objection. Form.

THE WITNESS: The only reason for doing that was to be able to essentially have an independent verification that the primary driver for the lower seroconversion that was being observed, okay, was a function of the assay itself. In other words, if you got two independent vaccines, both of which elicit lower seroconversion rates as measured using the Lo1 virus, one can -- and knowing that the field efficacy data pretty much supports, does for a fact support that both vaccines are effective, then -- because both are licensed vaccines in various parts of the world, then one can conclude that the assay that was being developed using the Lo1 virus, was not fit for purpose for the intended reason

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for the vaccine -- the assay was being developed for the 007 study.

BY MR. BEGLEITER:

Q. So what you're saying here is that because of the unanticipated low SCR for MMR II, you wanted to have or Merck wanted to have the results for the head-to-head to buttress what it was doing?

MS. DYKSTRA: Objection.

BY MR. BEGLEITER:

Q. To buttress the results?

A. That's not what I said. What I said was by having the data from sera from children that had received an independent licensed and, therefore, efficacious vaccine, because remember -- I'm going to take a step back. The purpose for developing the assay was to develop an assay that would measure an immunological response elicited by the vaccine that would correlate with the known, the known established efficacy of the vaccine.

So here we have an assay using the Lo1 virus that was given a seroconversion rate of 70 percent, yet we know the vaccine is much more effective than what would be

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reflected by that level. That would tend to suggest that there is something not, quote/unquote, correct about the assay in terms of what it was reflecting that the vaccine was actually doing. By having data from two -- from sera from children who received independently two known efficacious vaccines, the fact that both vaccines elicited immune responses that gave rise to a result that was roughly around 70 percent using the Lo1 virus, allows you to firmly conclude that and assay developed using the Lo1 virus is not fit for purpose and that it is incapable of giving you the kind of sensitivity that is required to answer the question that was being posed by the 007 trial.

Q. If -- I believe you're saying that the efficacy in the field answers the question as to the efficacy of the --

A. It is the only way to address efficacy.

MS. DYKSTRA: Object to the form.

BY MR. BEGLEITER:

Q. And why have --

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MS. DYKSTRA: I objected to the form of the question.

BY MR. BEGLEITER:

Q. Then if your conclusion is because of what's happening in the field that the mumps virus is fit for purpose --

A. The vaccine.

Q. Excuse me, the mumps vaccine is fit for purpose as it stood, then why have Protocol 007 at all?

A. The purpose for Protocol 007 was to provide the data that would allow both the company and the agency to define an end expiry number that it could then place in the label.

Q. And if that clinical study were to show a --

A. End expiry potency number.

Q. If that clinical study was to show that the potency had fallen below 90 percent, wouldn't that be something of interest to the CBER?

MS. DYKSTRA: Objection. Form.

THE WITNESS: Repeat your question because you're mixing words.

BY MR. BEGLEITER:

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Q. Let me ask it a different way.

A. Let's be precise.

Q. Let's ask it a different way.

The test was being conducted to see what the potency was at expiry. Isn't that right?

MS. DYKSTRA: Objection. Form.

THE WITNESS: The test was being conducted, which test, the study or the clinical study?

BY MR. BEGLEITER:

Q. 007.

A. The clinical study was being conducted to generate data that would support a vaccine potency level for mumps at the end of shelf life; so, therefore, the expiry potency level.

Q. But the conclusion you already had was that since it was efficacious in the field, that no matter what that number was, it was -- the vaccine was fit for purpose. Isn't that what you're saying?

MS. DYKSTRA: Objection.

THE WITNESS: The conclusion was that the vaccine that was being used

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from the time the vaccine was licensed up until the time that this entire discussion occurred, which was late '90s, early 2000s, that the vaccine that was being used in the field was indeed efficacious.

BY MR. BEGLEITER:

Q. And this study was designed to show that the vaccine was fit for purpose?

A. No. The study was designed to develop a number, to provide data that would support a number, a value for potency that could be placed in the label for determination of end expiry potency at the end of shelf life.

Q. And why was end expiry potency important to CBER?

A. It was important for control purposes. And what I mean by control purposes is so that there is a consistency and you can determine a consistency at which point -- in terms of shelf life. So if over time, if a particular batch of vaccine were to lose potency for whatever reason and were to drop below a given level, a given number which was

your end expiry potency, you could declare that, you know, there was loss of control potentially in the production of the vaccine or in the storage of the vaccine. Doesn't mean that the vaccine is no longer effective. That there was simply loss of control.

Q. So the premise for this Protocol 007 was that MMR/V, the mumps part of it at least, was effective?

A. Yes.

MS. DYKSTRA: Objection to the form.

BY MR. BEGLEITER:

Q. Premise going in?

MS. DYKSTRA: MMR/V wasn't in the study.

BY MR. BEGLEITER:

Q. Excuse me, MMR II.

A. MMR II.

Q. MMR II. Yes.

A. That the mumps component -- we'll stick with the mumps component. That the mumps component in MMR II --

Q. Yes.

A. -- was absolutely effective.



Q. And that's the premise going in?

A. That is the observed fact. It's effective.

Q. And let's just -- while we're on the subject, let's go to the first paragraph, MMR II end expiry. It says that -- first sentence tells you how many people, how many subjects are enrolled. Skip that. Then it says, "The primary study hypothesis of a..."

A. Seroconversion rate.

Q. "...seroconversion rate equal to or greater than 90 percent against wild type mumps...is unlikely to be met..." [as read]

A. Right.

Q. "...and therefore...should be revised either in terms of addressing the hypothesis or addressing the technical limitations of the assays used to date."

A. Right.

Q. And this is in October 31, 1999. Right?

A. Right.

Q. Do you know if by then there had even -- that the PRN had actually been set up to do any kind of assay work, any kind of



testing?

A. Well, according to this, the assays had been developed, that there was a PRN assay and the CPE assay, apparently both assays were being -- I'm reading what's in the rest of the document, that were being done. And they were being developed, you know, probably with the concurrence, not probably but for a fact, with the concurrence of the agency using a wild type virus. And with a wild type virus, and, again, reading through the rest of the document, one of the ones that was used, probably the initial one that was used was this Lo1 wild type virus. It was giving seroconversion rates that were much lower than 90 percent, approximately 70 percent. And that was not going to meet the agency's requirement for a sensitive enough test that would allow you to answer the questions posed by 007.

Q. Do you know if the agency was told, if CBER was told about the low SCR for Lo1?

A. Based on documents that I reviewed, these were discussions that were



going on in collaboration with the agency because the agency very much wanted an assay that would answer the question that would allow them to establish a value for end expiry in the label. An SCR of 70 percent, all right. So what we know is the following: We know that the vaccine is effective --

Q. My question --

MS. DYKSTRA: Let him answer.

MR. BEGLEITER: He's not answering my question.

THE WITNESS: I will get into the answer. Allow me to answer the question, please.

What we know is that the vaccine is effective, it's been given to children, to all the children in the study, and that the assay that had been developed using Lo1 was only yielding an SCR of 70 percent. That would not have been fit for purpose. That indicates that the assay, the assay is not fit for purpose. It's not allowing you to determine whether or not -- it was not allowing you to -- would not

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allow you, it would not prospectively allow you to determine whether or not there would be a difference in the seroconversion rate that would be statistically acceptable among the different, the three different potency levels that were being tested in 007. So, therefore, the discussion with the agency was how can we modify the assay that would give us an assay or assays of sufficient sensitivity.

MR. BEGLEITER: Can you read the question back, please.

- - -

(The court reporter read the pertinent part of the record.)

- - -

BY MR. BEGLEITER:

Q. Do you know if they were told specifically about what the low SCR was?

A. I do not recall what the specific conversation was. What I do recall was that there were ongoing conversations with the agency to generate an assay with sufficient sensitivity.

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Q. But you don't recall whether or not somebody said, you know, we've done an assay on Lo1 and the SCR is 70 to 75 percent?

A. What I do recall -- no, I don't recall that specific question.

Q. That's my question. Okay.

A. That specific discussion.

Q. Now, in terms of whether CBER was going to be -- whether CBER was going to be told about the unanticipated low SCR, back to the last paragraph on that page, when the results from the head-to-head trial with MMR II and Priorix was available. Was that discussed with Dr. Scolnick?

A. I don't recall.

Q. Was that discussed with Dr. Margolskee?

A. I don't recall.

Q. Isn't it a fact, sir, that the three of you discussed that and came to a conclusion this is what should be done?

MS. DYKSTRA: Objection to the form.

THE WITNESS: I have no recollection.

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BY MR. BEGLEITER:

Q. By the way, I don't know if I asked it. Did you receive this document in the usual course of your employment?

A. The document was -- let's see, am I here? Yes, the document was sent to me on October 31, 1999, and, therefore, I assume I did receive it.

MS. DYKSTRA: When is a good time to take a break? I don't know if you want to go another time, we can break for lunch.

MR. BEGLEITER: Let me just see what the latest one is. We can do it now.

MS. DYKSTRA: Okay.

MR. BEGLEITER: Have it now.

MS. DYKSTRA: We'll come back.

MR. BEGLEITER: Come back and then we'll go to lunch.

MS. DYKSTRA: That's sounds fine.

MR. BEGLEITER: Okay. Fine.

VIDEOGRAPHER: The time is now 12:16. Going off the video record.

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- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is now 12:31. We're back on the video record.

BY MR. BEGLEITER:

Q. What would have -- what, if anything, in the years '99, 2000, 2001 when you were with biologics, would have indicated to you that there was a problem with the efficacy of the vaccine?

A. Nothing at all.

Q. What if statistics in the field had been different?

MS. DYKSTRA: Objection. Form.

BY MR. BEGLEITER:

Q. Well, do it this way.

A. I don't know what that means.

Q. On what basis -- you've said, I believe, you testified -- if I put words in your mouth, please correct me, I'm sure you will.

What is the basis -- on what basis, what scientific basis do you conclude that in those years that you were biologic

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that the vaccine was effective?
A. Well, the original basis for the determination of the vaccine's efficacy or efficaciousness is a controlled clinical study. So that was the controlled clinical study that was performed that supported the original licensure of the vaccine back in whenever it was, the '60s, the '70s. So that was the placebo-controlled study.
Subsequent to that, your establishment of the -- one's determination of the continued effectiveness of the vaccine is that, you know, when the vaccine became widely used as a pediatric vaccine in this country, the mumps epidemics which tended to occur with certain regularity completely disappeared and those epidemics have not recurred since. The only way in which that would have happened is if the vaccine had, in fact, retained its effectiveness.
Q. Would a sustained outbreak short of an epidemic lead you to a different conclusion?
A. No, sustained outbreaks, the problem is there are a lot of variables

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associated with those. You don't know how many individuals were immunized, how, many individuals have not been immunized. Immunity wains, goes away with time. It depends on how long -- I'm slowing down, my apologies. It depends on how long those individuals have been immunized. It depends on a number of factors which it's the only -- the only thing that I personally would have taken as a clear indication of the loss of effectiveness of the vaccine, particularly given the fact that the vaccine is used in practically every child, there are unfortunately children who are not immunized as we know, would be an actual sustained epidemic.
Q. Did you -- let's go back to this document for a moment.
A. Which document?
Q. This document, the one you had before, I think it was 9.
A. Number 9?
Q. It's 8.
A. Number 8?
MS. MAHENDRANATHAN: It's 9.
MR. BEGLEITER: 9 is right.

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BY MR. BEGLEITER:
Q. In that first paragraph again, "The primary study hypothesis of a SCR greater than or equal to 90 percent against wild type mumps virus is unlikely to be met and therefore this should be revised either in terms of addressing the hypothesis or addressing the technical limitations of the assays used to date." [As read]
Your name is in this document, isn't it?
A. Yes.
Q. What do you understand "addressing the hypothesis" to mean?
A. The hypothesis of the study, so that would be the 007 study, and addressing the hypothesis of what the 007 study was designed to do which was to provide data to establish a number, potency number that could be used for end expiry. And if the assay is insufficiently sensitive to show statistical differences in terms of seroconversion rates, not effectiveness, seroconversion rates among the three levels that were being tested within the study, one could not appropriately address

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the hypothesis.
Q. And one way of addressing the hypothesis was in the choice of the viral strain to be -- of the isolate to be assayed?
A. Not to address the hypothesis but the choice of the viral strain was necessary to look at how one could devise an assay that would give sufficient sensitivity as a measure of seroconversion.
Q. And did that mean, going to the bottom paragraph, that Jeryl Lynn was a better choice for the assay than Lo1?
MS. DYKSTRA: Objection to the form.
THE WITNESS: The low passage Jeryl Lynn which was, as we discussed earlier, a representation of wild type virus, was selected because this particular strain, defined by both passage and isolate, the Jeryl Lynn isolate, was apparently capable of giving a much more sensitive representation of seroconversion, yes.
BY MR. BEGLEITER:
Q. Have you ever heard that the

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use -- anybody at CBER ever tell you that using the low passage Jeryl Lynn was -- for this assay was stacking the deck?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I do not recall that. But what I do recall is that these discussions of selection of -- that all of the discussions involving the actual design of the assays, both the plaque reduction neutralization assay, the AIGENT assay and the subsequent ELISA assay, were all discussions that were held in collaboration with the agency and with the agency's concurrence.

BY MR. BEGLEITER:

Q. Do you know if London-1 was tested using all three of the potencies?

A. I do not recall.

Q. So leaving aside the agency, there's a question I didn't ask you, but you've said it, you're sure it happened and --

A. That I recall.

Q. Can you tell me what day it happened?

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A. I cannot tell you.

Q. Who was there?

A. No, I can't tell you because these were ongoing discussions with the agency.

Q. So you can't identify the people at the agency. Maybe you can. Can you identify the people at the agency?

A. Not at this stage.

Q. Let me finish. Can you identify the people at the agency that said this is the appropriate thing to do --

A. Not at this stage, no.

Q. -- using Jeryl Lynn virus?

A. No, I cannot identify the individuals that were involved.

Q. Or any document that says it?

A. I cannot at this point identify a document.

Q. Who is Keith Chirgwin, Dr. Keith Chirgwin?

A. Dr. Keith Chirgwin was a member of the vaccine regulatory group.

Q. So he was someone -- was he on a par with you, below you, above you?

A. Well, he was not within my

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group. So he was in not in my reporting relationship. He's a member of the vaccine regulatory group who worked with Henrietta Ukwu who was the head of vaccine regulatory.

Q. Did you work with Dr. Chirgwin?

A. Since he was a member of the regulatory group, as part of overall broad collaboration of the vaccine research and development, yes, I did.

Q. Did you respect his opinion?

A. Yes, I did.

Q. I'm going to show you a document, 626382 through 626384. As you look at it, the first page does not have any e-mails to you. I'll save some time. So I'm only going to be focusing on the e-mail on the second page which I believe --

- - -

(Exhibit Emini-10, E-mail exchange, 00626382 - 00626384, was marked for identification.)

- - -

THE WITNESS: Sorry, please ask your question.

BY MR. BEGLEITER:

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Q. I'm just letting you know I'm not going to -- you're not on the e-mails beginning on the top third of the second page, so I'm not going to ask you any questions about those e-mails. Okay?

A. Okay.

Q. But I will ask you about the e-mail in which your name is in the cc. Do you see that?

A. Yes.

Q. It's from Dr. Keith Chirgwin.

A. Yes.

Q. It's dated November 17, 1999. See it? Okay. And let's talk about that, about that e-mail, that first paragraph.

A. Allow me time to read it, please. Okay.

Q. In that paragraph can you tell me what Dr. Chirgwin is addressing?

A. Well, Dr. Chirgwin is addressing the issue that we were discussing a moment ago, and that is whether or not there is relevance -- in the assay that is being developed in support of the 007 study, whether or not there is relevance to the use of wild

type strains of the virus. The argument he is making is that when one uses different wild type strains, not just the Lo1, there are large differences that are seen in seroconversion rates. And since the sera that are being tested are all the same sera, it would tend to suggest, not suggest, but clearly shows that the differences are due to the actual strains that are being used as the indicator strains in the assay.

So, therefore, he makes the conclusion that given that the vaccine effectiveness is what it is observed to be, very good vaccine effectiveness, since there are no sustained outbreaks, that the assay being developed with the different wild type strains giving not just low seroconversion rates but a wide variation of seroconversion rates is an artifact, if you will, of the wild type strains being used, and, therefore, not reflective of the vaccine's effectiveness.

Q. A couple of questions. First of all, he has a different point of view, would that be fair to say, on the relevance of the sustained -- of sustained outbreaks?



MS. DYKSTRA: Objection.

THE WITNESS: No, I would say that that is, in fact, the same point of view.

BY MR. BEGLEITER:

Q. Doesn't he say here, I'll read it, "...the low SCR with wild type does not correlate with the apparent field effectiveness of the vaccine and the low SCR with wild type has not resulted in sustained outbreaks, thus these low SCRs are not capturing the true protective efficacy of the vaccine." [As read]

A. That's exactly what I said before.

Q. Well, you drew a distinction, did you not, between epidemics and sustained outbreaks?

A. Well, his definition of sustained outbreaks, all right, and the way he's defining it here is equivalent to my definition of an epidemic.

Q. How do you know that?

A. Well, because what he's referring to is -- because an epidemiologist would all refer to it as exactly the same way.



What he's referring to -- what I refer to as an epidemic is a widespread sustained outbreak that would typically occur across all children of a given age who have received vaccine at the time that they were -- or received lots of vaccine that were presumably no longer effective at the time that they hit that age when they would normally receive the vaccine. So these children would all grow up at the same time and then you would see an epidemic within that age band. That is a sustained outbreak. We've not seen that with mumps.

Q. You're not trained in epidemiology, are you?

A. I am -- well, my training is very broad and, in fact, in my current role, okay, I do field effectiveness studies, yes.

Q. You know what Dr. Chirgwin of sustained outbreaks is?

A. Well, without having spoken to him, I interpret it the way I just mentioned.

Q. He doesn't in this -- you haven't seen anywhere where he says a sustained outbreak is blumpity-blump?

MS. DYKSTRA: Objection to the



form.

THE WITNESS: Of course not.

BY MR. BEGLEITER:

Q. Okay. Fine. Well, I want to make sure we're on the same thing, may have missed it.

And then in the last sentence, "If these arguments fail and CBER forces us to use wild type neutralization, then we will argue that 70 to 80 percent of SCR with Lo1 correlates with excellent field effectiveness and that therefore this is an acceptable SCR." [As read]

Do you see that?

A. Yes.

Q. Do you agree with that?

A. It's the only argument that one can make. So if the agency is insisting that the London-1 strain, which is what Lo1 apparently stands for, has to be used in the assay because it is a wild type virus, we know that the effectiveness of the vaccine is at a very high level, much higher than what would be reflected in an assay using the Lo1 strain which is on the order of, as noted here, 70 to

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80 percent, then the conclusion would be that what you are measuring in the assay at a level of 70 to 80 percent using the Lo1 strain is a reflection of the vaccine's known and observed field effectiveness.

Q. And coming back to the premise of what you just said, do you know what the agency, what CBER was requiring in terms of --

A. CBER was requiring --

Q. -- in terms of seroconversion rate?

A. CBER was requiring an assay of sufficient sensitivity. And based on the documents that I reviewed recently, they were requiring a level of sensitivity, of seroconversion rate of at least 90 percent as that would allow you a sufficient sensitivity to address the hypothesis that was being addressed in the 007 trial.

Q. The documents that I showed you this morning?

A. No, the documents that I reviewed with my counsel over the past several days.

Q. Do you know what the document

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is?

A. There were multiple documents. I can't recall off the top of my head, but there were multiple documents that referred to the need of having an assay with sufficient sensitivity -- there were multiple documents that referred to the need to have an assay that demonstrated at least 90 percent seroconversion.

Q. So the -- I think we'll get off the subject. Did Merck test the Protocol 007 serum samples against London-1?

A. I don't recall if the tests against London-1 were done with the Protocol 007 serum samples or with samples from other studies.

Q. So is it fair to say that in designing Protocol 007, that the assay that was chosen was an assay which gave Merck a likelihood of getting the seroconversion rate that CBER wanted?

MS. DYKSTRA: Objection. Form.

THE WITNESS: Both assays, the PRN assay and the ELISA assay were designed to give rise to seroconversion

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rates that could address the hypotheses of the 007 trial.

BY MR. BEGLEITER:

Q. Which included a 90 -- an equal to or greater than 90 percent seroconversion rate?

A. Which included a seroconversion rate of 90 percent, at least a seroconversion rate of 90 percent.

Q. What would a low seroconversion rate have meant to shelf life --

MS. DYKSTRA: Objection. Form.

BY MR. BEGLEITER:

Q. -- if anything?

A. Again, it's not what the seroconversion rate means to shelf life. It's what the difference in seroconversion rates might mean based upon a prespecified criterion when the results from the 007 trial would ultimately be evaluated and become available.

Q. This morning, I hope it's still morning, this morning you talked about how everything pharmaceutical decays over time?

A. Right.

Q. And stabilizers is sometimes put

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into vaccines --

A. Correct.

Q. -- to retard degradation?

A. Into any pharmaceutical product. Right.

Q. And we now know, you've told us, that there was a fill to 5.0 log?

A. Right.

Q. And the point of the end expiry test was to see whether or not that would be -- that it would meet, that the vaccine would meet CBER's requirements at the end of expiry. Right?

MS. DYKSTRA: Objection. Form.

THE WITNESS: No. What it would mean -- no. So CBER established a requirement that the 4.3 potency value in the label, the vaccine's label should appropriately be considered to be, should be considered to be, this was CBER's declaration, should be considered to be the potency value at the end of the vaccine's shelf life. That's what the agency declared.

BY MR. BEGLEITER:

Q. Who is Philip Bennett?
A. I don't recall his exact position within the company. He's not within the company. Actually I don't recall exactly.
Q. Did --
A. I really don't.
Q. Was there statisticians who would review at Merck the results of clinical trials?
A. Any clinical trial is a statistically driven study, yes. Yes.
Q. I'd like to show you this particular document which bears numbers MRK-0562218 and 19. Let me distribute it right now.

- - -

(Exhibit Emini-11, 3/14/01 E-mail with attachment, 0562218 & 0562219, was marked for identification.)

- - -

THE WITNESS: Okay.
BY MR. BEGLEITER:
Q. You see on page 2, the second page has a chart, a table. Do you see that?
A. Uh-huh.



Q. And this doctor makes the following statement with regard to that table.
A. Right.
Q. He says, "Following are the loss and variability estimates for mumps at various time points."
A. Right.
Q. "Our expiry dating needs to be 12 months in order to provide 95 percent confidence that a lot released at 5.0 will be above 4.3 at expiry."
Do you see that?
A. Yes.
Q. What does that mean to you?
A. That means by looking at the available stability data that was available to Phil Bennett at the time and then modeling that data on a statistical model, he comes to the conclusion that if we establish 4.3 as an expiry dating and you fill with a potency of 5, that there is -- that if you want to be guaranteed with a 95 percent probability, that you will be at the end of shelf life at 4.3 starting at 5, okay, then the length of that shelf life can be no more than 12 months.



Q. And if the shelf life instead was, as you speculate is possible, you didn't testify definite but it could be as much as two years, you said?
A. It could be as much as two years.
Q. That would be beyond the shelf life of the --
A. No, that would be beyond --
Q. Let me finish the sentence.
-- beyond the shelf life intended?
A. None of this declares shelf life. What this only says is that based on statistical modeling, if I start at 5 and want to end at 4.3 and I want to do that with a 95 percent probability, I probably should go no longer than 12 months.
Q. Now, if the expiry that CBER wanted could only be maintained for 12 months, wouldn't that mean that a shelf life afterward, after 12 months -- well, what would that mean to a shelf life that -- excuse me, withdraw the question.
If a determination was made by Merck that 4.3 log 50 dose would only support



12-month expiry using -- what would that mean to shelf life, if anything?
MS. DYKSTRA: Objection. Form.
THE WITNESS: Are you referring specifically to this note as a determination?
BY MR. BEGLEITER:
Q. No, I'm asking you as a general question.
A. If a determination were made, well, so if the agreement, if there is an agreement with the agency that the end expiry potency should be X, whatever the number is, and if a formal determination and a formal stability study shows that at a given time point you are highly likely to be below X, that does define your shelf life in general sense.
Q. Let me ask you some questions and then maybe we'll go to lunch.
Were you involved with hiring and firing people in your division?
A. I did not hire and fire directly. That was the responsibility of HR and the responsibility of my senior staff.

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Q. Was your signature necessary to hire someone?
MS. DYKSTRA: Objection.
THE WITNESS: It depends on the level of the individual that came in.
BY MR. BEGLEITER:
Q. Let's say Mr. Krahling here.
A. I don't recall what level he came in.
Q. How about terminating someone, did you have a responsibility to sign off on a termination?
MS. DYKSTRA: Objection.
THE WITNESS: It depended on the nature of the termination. But, again, most terminations were handled directly through HR and legal.
BY MR. BEGLEITER:
Q. How about when Mr. Krahling left Merck, did you sign off on a document?
A. I have no recollection.
MS. DYKSTRA: Let him finish the question.
THE WITNESS: I'm sorry.
BY MR. BEGLEITER:

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Q. I'd like to show you -- withdrawn. When Dr. Krah wanted to hire somebody, a virologist such as Stephen Krahling or someone else, was your approval necessary?
A. I have no direct recollection, but it would be highly unlikely that my approval would be necessary.
Q. Would he be consulting with you as to whether or not to hire someone?
MS. DYKSTRA: Objection.
THE WITNESS: The consultation would probably have been -- probably have been most likely with Dr. Shaw.
BY MR. BEGLEITER:
Q. Let's take a look at this. Merck 331424 to 33. This is Emini-12.
- - -
(Exhibit Emini-12, 10/10/00 Memo, 00331424 - 00331433, was marked for identification.)
- - -
THE WITNESS: Okay.
BY MR. BEGLEITER:
Q. My question to you is, does this refresh your recollection that you were

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involved with the hiring one way or another of Stephen Krahling?
A. It doesn't refresh my recollection of the day that this was received, but I will agree that this was sent to me, likely received by me and that I likely may have read it.
Q. In the last paragraph on the second page, "I therefore recommend offering one of our remaining technical positions to Steve."
Do you see that?
A. Yes.
Q. And did you act on that recommendation?
A. I don't recollect if I acted on that recommendation directly or discussed it with Dr. Shaw and allowed him to make the final determination.
Q. Did you receive this document in the usual course of your employment?
A. I will assume that I did because it was addressed to me.
Q. Do you have any reason why you wouldn't have received it, you know of no

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reason?
A. I know of no reason why I would not have received it.
MR. BEGLEITER: Let's have it as Number 13.
- - -
(Exhibit Emini-13, Resignation Authorization Form, 00582392, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. Okay. Doctor, is your signature on this page?
A. Yes, it is.
Q. And you signed in the usual course of your employment?
A. Yes, I did.
Q. And it's signed 12/20/01. Do you see that?
A. Yes.
Q. You indicated, I believe, a few minutes ago, again, if I got it wrong, please tell me, that you didn't sign off on every resignation or termination?
A. I said I didn't recollect if I

signed off on everyone's resignation. So I don't know -- I mean, this was obviously a -- could have been a process that was in place which I have no recollection of at Merck at the time that all resignations were signed off by the appropriate HR person that was the other signature on this and the head of the department would have been me.

Q. That person is Robert Suter?

A. From HR, yes.

Q. And he wasn't a doctor?

A. No.

Q. Do you know what position Mr. Suter held at HR?

A. The exact level of his position, I don't know. But he was assigned as the senior HR person to the -- to my department.

Q. How many -- was Steve Krahling's title virologist, to your recollection?

A. I don't recollect the exact title.

Q. What were the titles of the people who worked in -- who worked on Protocol 007 with Dr. --

A. I don't recollect the exact



titles. Too many companies in between and too many different titles.

Q. Do you have any recollection as to who worked in that lab other than Dr. Krah and Steve Krahling?

A. Recollections only came back when reviewing documents over the past several months and seeing various names being present.

Q. Okay. Let me just throw some names out and see if you recollect them. Mary Yagodich?

A. Yagodich I do recall, yes.

Q. What was her -- what do you recall about her?

A. I mean, to my recollection, under David Krah, so she was a member of David Krah's laboratory. My recollection is that practically everyone in the laboratory under David Krah had worked at the same level, but I can't attest to that being the fact. It could be, one could have been slightly higher, one below, I don't know.

Q. Do you know if she was his second in command?

A. I don't recall.



Q. How about Frank Kennedy?

A. Frank Kennedy, I did see the name when reviewing documents, but actually I have -- that's a recollection that hasn't even come back. I don't recognize it at all.

Q. How about Joan Wlochowski?

A. First name, please?

Q. Joan?

A. Joan. Joan Wlochowski.

Q. W-L-O-C-H-O-W --

A. Yes. Yes, I do recall. Yes, I do recall.

Q. We're talking together, it's going to drive her crazy.

A. My apologies.

Q. Joan W-L-O-C-H-O-W-S-K-I?

A. Yes.

Q. What do you recall about her?

A. Same thing. You know, same level with Mr. Krahling and then with Mary Yagodich, you know, in the laboratory. The laboratory operational staff under Dr. Krah.

Q. How many people worked in -- how many professionals worked in the laboratory?

MS. DYKSTRA: Objection.



THE WITNESS: I believe there were four or five.

BY MR. BEGLEITER:

Q. Tell me, sir, do you know during the time of Protocol 007 if any of the women working in the lab were pregnant?

A. I don't recall.

Q. Was there a rule in the lab that pregnant women couldn't work near live viruses?

A. That was a general rule, absolutely. Still is.

Q. Let me see if I can refresh your memory. I'm going to show you Merck 14744 through 747. We'll mark this now as 13.

MS. DYKSTRA: 14.

MR. BEGLEITER: 14.

- - -

(Exhibit Emini-14, 3/29/01 Memo, 00014744 - 00014747, was marked for identification.)

- - -

THE WITNESS: Yes, I do recall this memo. In fact, this is a memo that I did review recently now that I see it, yes. Thank you.

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BY MR. BEGLEITER:
Q. And did you receive this memo in the usual course of your employment?
A. Yes, I did.
Q. And does that indicate in the second page that Mary is the --
A. Mary Yagodich in seventh month of pregnancy.
Q. That's as of March 29, 2001?
A. Yes.
MS. DYKSTRA: Just for the record, I have two memos. Did you mean to give two memos?
MR. BEGLEITER: Are they both Mary Yagodich?
MS. DYKSTRA: They are both Mary Yagodich.
MR. BEGLEITER: I didn't mean to give you two but --
MS. DYKSTRA: They're different memos, though.
THE WITNESS: Yeah, they are different.
BY MR. BEGLEITER:
Q. The 746, I'll use that later.

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If you can hand that back to me, I appreciate it.
MS. DYKSTRA: Bob, can I have that copy back then, the one you're using?
MR. BEGLEITER: Yes. It should be during the course of the year 2000. That's how it should begin.
MS. DYKSTRA: Ending in 14744 as the Bates number?
MR. BEGLEITER: Yes.
MS. DYKSTRA: Thank you.
BY MR. BEGLEITER:
Q. You did receive this and acknowledge that she was pregnant March 29, 2001?
A. That's what it says.
Q. And does this also refresh your recollection about -- forget it.
MR. BEGLEITER: Can you mark 15702 to 03 as number 15, Emini-15?
- - -
(Exhibit Emini-15, 3/29/01 Memo, 00015702 & 00015703, was marked for identification.)

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- - -
BY MR. BEGLEITER:
Q. We used them. Sorry. I apologize. That should be stricken I believe. Well, we'll leave it marked, we'll use it anyway, but not right now. I wanted to show you something else.
A. Okay.
Q. This document would not indicate that Mr. Krahling was pregnant.
A. No, it would not.
Q. Jennifer Kriss, okay.
MR. BEGLEITER: I'd like to have marked 15719 to 15720.
- - -
(Exhibit Emini-16, 3/29/01 Memo, 00015719 & 00015720, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. So this memo involves Jennifer Kriss. Is that right?
A. Yes, it does.
Q. And who was Jennifer Kriss, do you know?

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A. Jennifer Kriss I recall as being a member of the laboratory.
Q. Dr. Krah's lab?
A. Dr. Krah's laboratory.
Q. This was sent to you in the usual course of your employment?
A. Yes, it was.
Q. Was she also pregnant?
A. According to the memo, she was in the fifth month of her pregnancy, and it's dated 29 March 2001.
Q. Going to the previous one, which was the one that was inadvertently marked involving Stephen Krahling but dated the same day.
A. Yes.
Q. Did you receive that in the usual course of your employment?
A. Yes, I did.
Q. Now, all of these are dated March 29th?
A. Yes.
Q. Talk about Protocol 005. Is that -- what is -- were any of these people working on Protocol 005?

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A. Well, it refers to Protocol 005. What I do not recall and don't know at the moment was whether or not Protocol 005 was the laboratory number for the assays that were being done in support of the clinical study in Protocol 007. That, I don't recall. So we would need to look at what Protocol 005 actually refers to.

Q. The point being is that if you look at any of those, can you tell whether or not these people were working on Protocol 007?

A. Well, all of these refer to the neuts of the mumps neut assay, and in one case it refers to 570 serum pairs were tested in emergency response to CBER's citation during the MMD. But it doesn't say, I can't tell you if it was 007 or something different. I cannot tell from this.

Q. You can't tell whether or not in that first paragraph, I believe they're all -- take a look at the one regarding Mary Yagodich, she was working on --

A. This refers to two sets of assessments, one was the development of an assay that was then used to assess the sera in

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the head-to-head clinical study of MMR II and Priorix, as we discussed before. It does not indicate whether or not that assay was actually run in the laboratory here or just solely developed, which normally would have been the case. The assay would have been run in a different laboratory. And then it also refers to data that needed to be generated to address a question that came up with respect to end expiry and shelf life to end expiry.

Q. And that would be 007. Is that right?

A. I can't tell exactly from the terminology used in this memo whether we're referring specifically to 007 or to something else. That, I don't recollect.

Q. Now, I thought I asked you before whether or not there were any other end expiry studies done other than 007 for mumps, and you said you knew of no others?

A. I don't recollect that there were any -- well, that there were any specific clinical studies that were done. There may have been assessment of sera to generate data in support of questions that may have come up

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by the agency with respect to end expiry, but I don't recollect the details of those assessments.

Q. Ms. Yagodich is in 14744. It says, "In the middle of this activity we received an FDA mandate to define an end-expiry dose of mumps virus in MMR II."

A. Where are you?

Q. The middle of 14744.

A. Right.

Q. Sir, doesn't that refer to the mandate which resulted in the Protocol 007?

A. It may, but I cannot, again, based on this language, make a direct determination.

On the second sentence it refers to "...an interim set of data in time for a projected meeting with the FDA." There was an interim analysis that was performed in 007, so this may refer to it.

Q. I'll put it to you this way: This is Yagodich, going to the Krahling one, can you think of any other protocol other than 007 in which this document would indicate he was working on?

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MS. DYKSTRA: Objection. Form.

THE WITNESS: I cannot, no.

BY MR. BEGLEITER:

Q. Same thing with Ms. Kriss, take a look at --

A. You mean other than the 007?

Q. Other than 007.

A. Other than 007, from the terminology in these memos, I can't conclude --

Q. I asked you another question. Can you think of any other protocol --

A. No, I cannot.

Q. Let me finish.

Can you think of any other protocol that they could have been working on other than 007?

A. It depends. It's the definition of working on that's causing me to hesitate. What do you mean by "working on," developing an assay or actually generating the clinical data using the assay?

Q. The latter.

A. Generating the clinical data using the assay. The only one I am aware of is 007.

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Q. Now, in the years that you were at biologics and vaccines, how often did Merck outsource clinical trials approximately?
MS. DYKSTRA: Objection. Form.
THE WITNESS: Outsource, sorry, you need more specificity. What do you mean by "outsource clinical trial"?
BY MR. BEGLEITER:
Q. Well, let me ask you this, go right to the subject. Do you know who Dick Ward is?
A. Yes, I know Dick Ward.
Q. Who is Dick Ward?
A. Dick Ward was a professor of virology. I don't know where he was at the time. When I knew him he was at University of Cincinnati, if I remember correctly.
Q. Do you know what hospital he was associated with?
A. I don't remember the exact title of the hospital.
Q. Have you ever heard of the Children's Hospital Medical Center in Cincinnati?
A. Yes, I have certainly heard of

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it.
Q. Is it a reputable hospital, medical center?
A. Well, yes, of course. Yes.
Q. Was there any thought about outsourcing to Dr. Ward any part of the clinical trial --
MS. DYKSTRA: Objection to form.
BY MR. BEGLEITER:
Q. -- of 007?
A. It was not to outsource the clinical trial. It would have been -- outsourced would have been the conduct of the assays in support of the clinical trial, to generate the data from the clinical trial.
Q. When you say "conduct of the assays," what are you referring to? What actual work is done to conduct the assay?
A. Well, it is the assay that -- the assays that are designed to generate the data from the clinical studies. So in the context of 007 that would have been the PRN assay and maybe possibly the ELISA. I don't recall if it was both or just one.
Q. Let's talk about the PRN. To do

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the assay, how is it accomplished? What would the virologist do to see if -- what the reaction was?
A. I can't tell you what the exact details were, but there were -- but there was clearly a standard operating procedure because, remember, the assay required to be validated, so what was validated was defined by the standard operating procedure. So whether a validated assay, by definition, doesn't matter where you run it and who runs it, it will generate the same set of data.
Q. Well, are you saying in all circumstances it would represent the -- it would result in the same set of data?
A. Only if one could validate that the laboratory that was run -- because in addition to validating the assay, the laboratory needs to be validated as well.
Q. If you were to have -- if you were to hire, retain, I don't know what the right word is --
A. Yes, I would validate the laboratory.
MS. DYKSTRA: Let him finish the

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question.
THE WITNESS: My apologies.
BY MR. BEGLEITER:
Q. It would be validated before the -- any part of the clinical trial was sent to that laboratory?
A. Yes.
Q. You wouldn't have a clinical trial, if that's the right word, the actual --
A. Samples.
Q. -- samples in a place where the validation had not occurred yet?
A. Well, you could have the samples in a place where the validation had not occurred yet. To actually run the assays using those samples to generate the data for the clinical trial purposes, typically, actually, you would not do that unless you were comfortable that the assay as well as the facility had been appropriately validated.
Q. So nothing would go to Dr. Ward's lab unless the facility itself was validated?
MS. DYKSTRA: Objection. Misstates his testimony.

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THE WITNESS: No. I don't recall if samples had been sent to Dr. Ward's laboratory, but, again, it is not whether or not the samples were there, it's whether or not they would be running the assay.

BY MR. BEGLEITER:

Q. So go back to something I asked you before. Were you contemplating using Dr. Ward's lab for any purpose regarding 007?

A. Not that I recollect, other than the review of the document showed that we were clearly apparently contemplating the use of Dr. Ward's laboratory as an additional laboratory or as the laboratory that would run the 007 samples.

Q. What documents were those?

A. Those were various documents and memo that I reviewed. I cannot tell you the specifics ones.

Q. You cannot because you don't remember or because you're --

A. No, I don't remember. I just saw them and gave them back. I did not retain anything.

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Q. Now, did Dr. Ward himself have a good reputation?

A. Dr. Ward definitely had a good reputation.

Q. And did the hospital have a good reputation?

A. The hospital has a good reputation.

Q. And you work at the Bill & Melinda Gates Foundation?

A. Yes.

Q. Does the Bill & Melinda Gates Foundation give grants to that hospital?

A. I don't know if we do or don't. We give lots of grants.

MR. BEGLEITER: This is 17 now. This does not have Bates numbers. I'll describe it as what appears to be a press release, dated Thursday, February 26, 2009, entitled "Cincinnati Children's receives $6.7 million grant from Gates Foundation to study influenza vaccine in pregnant women in Asia." This is before you got to the --

THE WITNESS: Well before, yes, by many years.

- - -

(Exhibit Emini-17, 2/26/09 Press release, was marked for identification.)

- - -

BY MR. BEGLEITER:

Q. If you take a look at that, is there any doubt in your mind that the Bill & Melinda Gates Foundation would have given a grant to the Children's Hospital of Cincinnati?

MS. DYKSTRA: Objection.

THE WITNESS: Well, they did give a grant.

BY MR. BEGLEITER:

Q. Okay. The place you're now working, that's a reputable institution?

A. An exceptionally reputable institution.

Q. And they wouldn't be giving grants to people that weren't reputable?

A. It depends on the nature of the work that needs to be done. Certainly reputable in the context for which the grant was given, the answer is yes.

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Q. Now, did you ever have a discussion with Dr. Krah and Dr. Shaw as to whether or not they would have -- well, do one at a time -- with Dr. Krah as to whether or not he would have preferred to do the PRN or have it outsourced?

MS. DYKSTRA: Objection.

THE WITNESS: I don't recall such a conversation.

BY MR. BEGLEITER:

Q. How about a conversation with Dr. Shaw?

A. I don't recall.

MS. DYKSTRA: Bob, let us know if it's a good time to break for lunch, either before or after you finish up.

MR. BEGLEITER: Give me another five minutes, then we'll go. Okay?

MS. DYKSTRA: Good.

BY MR. BEGLEITER:

Q. Let me ask it this way: Did you want Merck -- would you have preferred to have Merck do the PRN or have it outsourced when you first learned that CBER was requiring a PRN?

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MS. DYKSTRA: Objection. Form.
THE WITNESS: It doesn't matter. What matters is whether or not the validated assay can be run in a validated laboratory. It doesn't matter if it's internal or external. What usually drove the decision was usually a capacity decision. Assuming that there was appropriate validation.
BY MR. BEGLEITER:
Q. Capacity in what sense?
A. Capacity in that there are just so many people in a day and the facility is only so large and there are a certain number of samples that need to be run, so one can run them. Oftentimes a good reason for outsourcing an assay is because you need to have additional capacity to do it. But, again, the critical aspect of it is that the laboratory to whom you are outsourcing the assay is appropriately validated and can demonstrate that it can run the assay the way you would have run the assay.
Q. Let's go back to 14.
A. 14?

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Q. Yes, the Mary Yagodich. I'd like to read a sentence to you.
A. Please.
Q. The first sentence of the second paragraph.
A. Please.
Q. "The lab staff worked nights and weekends across the Thanksgiving, Christmas and New Year holidays in order to meet the deadlines imposed on them."
A. Yes.
Q. This is 2000 -- this memo is dated March 29, 2001?
A. Yes.
Q. "The plan for the remaining samples had...," Dr. Shaw emphasizes it.
A. Yes.
Q. "...had been to send them to an outside contract laboratory."
Do you see that?
A. Yes.
Q. Was the conditions in the lab among the workers having to work Thanksgiving and Christmas and New Year's a factor in deciding to send it to an outside lab?

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A. That would indicate that was a tight capacity, so, therefore, it would be have been, if appropriate, to send it to an outside laboratory to expand the capacity, yes.
Q. We've already discussed, I hope we remember this, that two of the members of the staff, Mary Yagodich and Jennifer Kriss were pregnant and couldn't be near the live vaccine.
A. And could not be near the live varicella.
Q. Right.
A. They could still work in the laboratory but not run the actual assays with the live virus.
Q. Right. So that you assured to. So weren't those reasons to outsource it, those reasons --
A. Any capacity.
MS. DYKSTRA: Let him finish the question so we can make sure the record is clear.
THE WITNESS: Sorry.
MS. DYKSTRA: That's okay.

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BY MR. BEGLEITER:
Q. So that was a reason to do it?
A. Yes.
Q. But a decision was made not to outsource. Right?
MS. DYKSTRA: Objection.
THE WITNESS: The decision was made not to outsource.
BY MR. BEGLEITER:
Q. That decision was made by you, was it not?
MS. DYKSTRA: Objection.
THE WITNESS: I don't recall if I made that decision or not. However, in reading the memo, it was indicated that the reason why the decision, that was the next sentence after the sentence that you note, not to outsource it was concern that the outsourcing laboratory, which presumably was Dr. Ward's laboratory, was not capable of reproducing the required precision that would be needed.
BY MR. BEGLEITER:

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Q. Where does it say capable?
A. Well, it just says --
Q. It says not be able to reproduce.
A. Well, I read it as capable. You may read it as not being able to reproduce the precision. So there was a concern obviously that they could not reproduce the precision.
Q. Didn't we discuss like a half an hour ago that if the lab was validated, two labs validated the same way doing the same protocols would come up with the same results?
A. If the assay is validated, yeah. If the assay and the laboratory are validated. So there was obvious concern over the validation of the laboratory.
Q. Where does it say that?
MS. DYKSTRA: Objection.
THE WITNESS: Where does it not say that?
BY MR. BEGLEITER:
Q. Okay. But where does it say it, sir?
A. Well, it doesn't say.
MS. DYKSTRA: Objection.

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BY MR. BEGLEITER:
Q. Go ahead, I'm sorry.
A. Just slow down for a second.
Q. Okay.
A. Tell me when you're ready. Ready. It doesn't say it, but in reading the documents, the suggestion was, and again, I have no direct recollection, to not to send it to Dr. Ward's laboratory either because it had not yet been validated and brought under time pressure to generate the data so, therefore, the decision was made to keep it entirely internally and to deal the best that one could with the capacity issue, which is what is reflected in these documents; or alternatively, to deal the best that we could with the capacity issue because there was concern over the quality of the data that would be generated in Dr. Ward's laboratory.
Q. What did you understand Dr. Shaw to mean when he said tightness of the data?
A. The precision of the data. Well, I'm sorry. My apologies. I'll take that back.
In the context of this memo,

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what he was referring to is the fact that the data generated using the samples that had been tested to date yielded values that were very tight with each other and, therefore, with a very narrow confidence interval. When you see that, it is imperative that you be certain, particularly if you're going to a different laboratory, that the validation of that laboratory be very good because the precision of the assay, which is the most difficult characteristic of an assay to control, is well controlled, particularly for a biological assay.
Q. Are you speculating here this afternoon that Dr. Ward's lab would not have had the proper validation?
A. What I am saying is that at the time that this decision was made and given the time constraints that were involved, that either there was a concern, that there was a concern either based on observation or simply based on principle, that Dr. Ward's lab might not be able to run the assay in a way that would ensure the same level of required precision.

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Q. Was the concern here also that could not -- that Dr. Ward's lab would not replicate what Dr. Krah's lab was --
A. No.
Q. -- coming up with?
A. That's not what I said. That is not the concern. The concern is whether the assay could be run with sufficient precision so that one would be able to achieve a data set -- remember, this is a biological assay, biological assays are very difficult to run with appropriate precision. That one would be able to achieve a data set with tight enough confidence intervals that would allow you to address the hypothesis of the 007 study.
Q. Have you seen any documents which say that Dr. Ward's lab was not capable of doing that?
A. I have not seen any documents, but it is -- the decision is not based on data that would suggest that one is not capable of doing it. The decision is made on the basis of whether or not there are data that show that one is capable of doing it. So the absence of such data and given the time

constraints could very much have led someone to make the decision not to transfer the assay and to keep it internally.

Q. Which lab was able to achieve the tight precision at Merck?

A. Well, again, it was from, again, reading that memo and Dr. Shaw's notation that the assay was run with the tight set of variant, and it was a validated assay, that we had what appeared to be reasonably good precision around the assay.

Q. By keeping it with Dr. Krah's lab, you could ensure that -- what the result was going to be, couldn't you?

MS. DYKSTRA: Objection.

THE WITNESS: No, you could ensure that the --

MS. DYKSTRA: Misstates his testimony.

THE WITNESS: -- assay would run consistently, could run with good accuracy and prescription, and would allow you to generate data that you could then cross compare across the three different arms of the study to



address the hypothesis of the study. It is not to ensure that you would get a specific set of data coming out.

BY MR. BEGLEITER:

Q. You're saying that Dr. Ward's lab, as far as you can tell from reading this document, was incapable of doing that?

MS. DYKSTRA: Objection. Again, misstates testimony.

THE WITNESS: No. I did not say that he was incapable of doing it. I said there was uncertainty that it could be done. But by definition, that uncertainty exists not just for Dr. Ward but for every other high level, highly trained virologist on the planet unless you generate active data to show that you can maintain the same accuracy and precision, which it is very difficult across laboratories running biological assays. So it's not specific for Dr. Ward.

BY MR. BEGLEITER:

Q. Do you know if Merck went so far as to have a contract with Dr. Ward's lab?



A. I don't recall if we actually had a contract or not.

Q. If there were such a contract, would that indicate that there was some thought that Dr. Ward's lab was capable of doing the kind of precision you're talking about?

A. No, because contracts can be established prospectively with the supposition that, you know, we'll actually execute the contract and actually pay for the work and do the work, you know, if we decide to use the individual. I've done contracts all the time that indicate -- before I determine whether or not I'm actually using somebody.

MR. BEGLEITER: Let me show you one document and we'll go to lunch. This is going to be 18.

- - -

(Exhibit Emini-18, E-mail exchange, 00448867 & 00448868, was marked for identification.)

- - -

BY MR. BEGLEITER:

Q. So your name is not on this?



A. No. Not in the top ones, no. The one at the bottom.

Q. It says, I had a long -- the one Alan Shaw to David Krah, I'm going to ask you whether or not this has any recollection to you. Do you recollect this?

A. No, I don't.

MS. DYKSTRA: Object. Let him read through this.

MR. BEGLEITER: Sure. Go ahead. I'm telling him what I'm going to ask him, that's all.

MS. DYKSTRA: Understood.

BY MR. BEGLEITER:

Q. So the date on this e-mail, the second one is November -- September 25, 2000. If you'll recall the dates on the ones that was sent to you on the personal memos that you saw were March 29, 2001. Do you see that?

A. Yes.

Q. So they're six months?

A. Six months roughly.

Q. And would you agree, sir, that there were problems in the lab at the end of September 2000?

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MS. DYKSTRA: Objection.
THE WITNESS: Well, what I read in this memo, again, no direct recollection other than what I'm reading here, is that there was -- all of this relates to the fact that we were talking about the potential for hiring additional people power for the laboratory, additional personnel for the laboratory. There was some concern that a hiring freeze was going to be put into place by the company which happened on occasion all the time. And there was a discussion going back and forth on this and I apparently had a discussion with Alan Shaw noting that one of the things that we probably needed to have a careful look at in David Krah's laboratory was the issue of turnover within the laboratory.
BY MR. BEGLEITER:
Q. In the third -- the fourth paragraph beginning, "We had a discussion of what the coming workload would be for our group," do you see that sentence?

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A. Yes.
Q. And the "we" is you and Dr. Shaw?
A. Yes.
Q. And "As I see it, the current major things are varicella support for Pharm R&D..." What's that? Do you know what that is?
A. That was support of the --
Q. Chicken pox.
A. -- pharmaceutical research and developing, this was at the time that the varicella vaccine was being developed so the laboratory was providing the biological support for that work. So that needed to be done.
Q. "...which should tail off over the next six to eight months..."
Do you see that?
A. Yes. Eight months would include March 29th.
Q. Transferring this I will say freaking, does that sound right to you?
MS. DYKSTRA: Objection.
THE WITNESS: Well, I don't know.

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BY MR. BEGLEITER:
Q. What do you think he meant by that?
A. What he was concerned about was that he was getting frustrated over all the time and effort that was being spent in the laboratory around the mumps assay in support of the 007 study. Because recall the laboratory was originally set up to be a research laboratory. They were working on varicella. There was a strong desire to pick up work on an influenza vaccine program as you can see is indicated here. And that the mumps assay between the work that was required for the development of the assay, to come up with an assay that would be suitable to address the hypothesis in 007 and then obviously was being contemplated at the time transferring the assay to Dick Ward's laboratory so as to alleviate his laboratory and actually having to run the assays was part of the heavy workload that was ongoing in the lab.
Q. So there was a capacity problem that was --
A. The same as we were saying

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before.
Q. There was a capacity problem at the lab. Go ahead, answer.
A. Yes, there was a capacity problem at the lab. My apologies.
MR. BEGLEITER: Let's go to lunch.
VIDEOGRAPHER: The time is now 1:39.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is now 2:36. This begins disc four.
BY MR. BEGLEITER:
Q. Good afternoon, Doctor.
A. Hello.
Q. What is an SOP, standard operating procedure?
A. Standard operating procedure.
Q. What is it in relation to what's in Protocol 007 or one of the other clinical --
A. A standard operating procedure can refer to any one of a number of different

things, but in the context of our ongoing discussion here, it would be a standard operating procedure that describes the procedure for the conduct of a specific assay and how to interpret the data from the assay, how to actually run the assay, how to do it, what you needed to control.

Q. Among other things, did it sort of set the rules for the assay?

A. It depends what you define by rules. What do you mean by rules?

Q. How the assay is to be conducted.

A. How the assay is to be conducted. Yes, it is the procedure for operating the assay.

- - -

(Exhibit Emini-19, 11/13/00 E-mail with attachment, 00009013 - 00009034, was marked for identification.)

- - -

BY MR. BEGLEITER:

Q. Could we hand Emini-19 to the witness. It's docket number -- Bates-numbered MRK 9013 through 9034.

This is a rather long document.



I'll just tell you you can read as much as you want, I'm not stopping you, but I'll be talking about the first page, 9013. I'll be asking you questions about that, and 9022. Aside from that, I'm not going to ask any questions. Well, that's not true. And also page 9017. Those are the only three pages I'm going to be making reference to.

A. Okay.

Q. So looking at the first page, 9013, did you receive this document, including the attachments, during the regular course of your employment?

A. It was addressed to me as one of the recipients of the e-mail. So yes, I did.

Q. It was received on November 13, 2000?

A. November 13, 2000.

Q. Great. Now, if you can turn to page 9022. I'll ask you to read, you can read it to yourself if you wish, a "Preliminary Subset Analysis." The first paragraph and then I'm going to ask you some questions about the preliminary subset.

A. Okay.



Q. Do you have any recollection of the preliminary subset?

A. I had no recollection from the time, no, only when reviewing documents.

Q. This paragraph indicates that there were approximately 1,980 subjects enrolled. Right?

A. Yes.

Q. From the subset, this was a randomly selected subset of approximately 600 subjects, about 200 per group. Do you see that?

A. Right.

Q. That doesn't ring a bell?

A. Other than what it says, no.

Q. It says, "Merck is still blinded to the treatment assignments." Is that --

A. Well, that's what normally would we do when you do a subset analysis so you don't suffer a statistical penalty.

Q. So in other words, when subset or the whole thing, blinding is required?

A. So when you do a subset analysis, prior to having -- prior to having analyzed the data to address the primary



endpoints of the study, right, so typically you would do this because this is a specific immediate question that needs to be addressed, as was the case here apparently, then you could do such a subset analysis. But what was very critically important was to maintain the blind of the study so that the statistician and the other personnel involved in generating the data, not involved in actually analyzing the data for the final endpoints of the study, are blinded to the treatment assignments. Standard procedure.

Q. A statistician in this case was not blinded -- was unblinded. You can't blind a statistician. Right?

A. No, you unblinded the statistician to do the subset analysis, but that would not the same statistician that did do the final analysis. The final analysis statistician would remain blinded.

Q. The sentence at the end of -- what is a treatment assignment?

A. The treatment assignment is related to the three groups of the study. Remember there are four potency levels --

excuse me, three potency levels?
Q. 4.9, 4.0, 3.7, is that what you said?
A. Yes.
Q. And then at the end it says regardless of -- the end of the paragraph that begins the statistician not associated with the conduct of the trial. In that paragraph it says, regardless of the outcome of the preliminary analysis, the sera from the remain set will be tested in a blinded fashion and all subject will be included in the final analysis.
A. That's correct.
Q. That's looking forward beyond the preliminary subset into the final -- into the completion of the assay?
A. Yes.
Q. Now, do you recall, looking at the document, what the day of the unannounced inspection we talked about before? I could remind you but maybe you remember. Do you remember the inspection that resulted in the 483?
A. Resulted in 483, yes.



Q. You want to look at that just -- you can fix the date, that's important.
A. I have to dig through here. Do you remember which one it was?
MS. DYKSTRA: Look at Exhibit 8.
THE WITNESS: Exhibit 8. There was one that actually had the 483 in it.
BY MR. BEGLEITER:
Q. On the second page?
A. That's the one you're referring to. That's the second page.
Q. The handwritten 483.
A. That would be 7. 7, yes.
Q. I'm asking you to look at it to confirm the date.
A. Confirm the date?
Q. Of the inspection.
A. That would have been August 6, 2001.
Q. At the time of the inspection going on, was anybody giving you any updates as to what was going on, anybody reporting to you on the inspection on that date on the 6th?
A. On the date of the inspection?



Q. Yes.
A. No. The inspector came in the morning as being the senior person related to the area that she wanted to assess. I was handed what is known as a Form 482, which is the announcement of the inspection. And then we made sure that we pulled together the people who needed to be pulled together and informed regulatory. Regulatory is responsible for interacting with the inspector during the inspection. I retired and was not called back until the inspection had been completed and the 483 had been prepared. To my recollection, of course.
MR. BEGLEITER: Have this marked, please, as Number 20, I guess. Let me just announce it. This is a document Merck 8835 through 8839. It's a four-page document, if you could mark it.
- - -
(Exhibit Emini-20, E-mail string, 00008835 - 00008839, was marked for identification.)
- - -



BY MR. BEGLEITER:
Q. My focus will be on your e-mail of August 7th, but you can read the whole thing. The first e-mail in the string.
A. Okay.
Q. And going to that -- did you -- are you the author of some of these e-mails?
A. Yes, I am.
Q. Did you receive all of them as part of your usual --
A. Let me see. Let me just check it to see.
Q. Take your time.
A. Yes, I either wrote or received.
Q. Going to the first e-mail, I see this is to Anthony Ford-Hutchinson and Peter Kim.
A. Yes.
Q. With cc's to various people. These people, Hutchinson and Kim, I think you answered this morning you weren't sure who was there, whether they were both your report -- the person to whom you reported at the same time?
A. So according to this note Peter

Kim was obviously there in the company since they sent him the message as well. So I would have been reporting to Tony Ford-Hutchinson who was, in turn, reporting to Peter Kim.

Q. Peter Kim was above him?

A. Was above him. And then, in turn, Peter Kim at that point since Ed Scolnick was still there, he had not yet retired, was reporting to Ed Scolnick.

Q. Who was the president?

A. Who was the president of the research laboratory, and Peter Kim eventually became president of the research laboratory when Ed Scolnick retired.

Q. What was your purpose in writing this e-mail, if you can recall?

A. The purpose in writing the e-mail is as noted in the e-mail, we had received a Form 483 with inspection observations from the FDA, and I felt it appropriate to write a note to my supervisors indicating the four observations as were noted in the e-mail that the inspector had made on the Form 483. And to note to my opinion of the nature of those observations and what we



were at least at that time contemplating to do subsequently. This was the day after the inspection.

Q. And just some abbreviations here. GMP is?

A. So GMP stands for good manufacturing -- formerly stands for good manufacturing practices. The terminology is also used generally to refer, at least at the time, to refer to appropriate defined procedures for conducts of -- for anything related to a potential product. So the term was used very generally, GMP. These days the term is much better defined.

Q. In the last paragraph you talk about the correlation being excellent between something and ELISA. Is the something the PRN?

A. The neut assay results and I presume that this was referring to the PRN, right, which was being run at the time.

Q. Was correlation something that was important to the FDA?

MS. DYKSTRA: Objection. Form.

THE WITNESS: Correlation was a



note -- well, there was --

BY MR. BEGLEITER:

Q. Your counsel is right, that wasn't a good question.

A. I know. Try it again.

Q. Is it your understanding that the correlation was important to the FDA?

MS. DYKSTRA: Objection. Form.

THE WITNESS: Correlation was important only insofar as these were two independent measures of an immune response to the vaccine. If we were to use both sets of data in order to compare the three different dose levels of the vaccine in 007, then a general correlation, didn't have to be perfect, but a general correlation would fall into the category of nice to have.

BY MR. BEGLEITER:

Q. It wasn't a correlation between the neutralization in assay --

A. And the ELISA.

Q. -- and the ELISA was not required?

A. It depends on what you mean by



"correlation." It is an exact correlation?

Q. Well, you wrote the e-mail. What did you mean?

A. So what I meant by "correlation" would be that in general if you're looking at a population of samples, right, not individual one-to-one samples, but you're looking at a population of samples, if the neutralization assay showed, let's say, 89 percent seroconversion, plus or minus a certain variance, that the ELISA looking at the same population of samples would also show within that variance an 89 percent seroconversion within the variance established by the assay.

Q. Why did you inform the supervisors that you're writing this e-mail to of that fact?

A. Well, because the question that this one was referring to was observation or what I was referring to as violation number one. Or which related to, and we can read it here, in that it potentially, that observation by the inspector potentially suggested that there might be an issue with the validity of the data because there had been changes that

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were made to the spreadsheet that contained the data but without noting the reason why the change was made. That was the basis of the observation. So, therefore, that automatically raises the issue to say are we certain that the data as they currently exist, or the data as they were originally derived, are they, in fact, reflecting the same conclusion. That's the observation.

So, therefore, the resulting data, what we did is that we took the data, we submitted it to the clinical statistical -- I'm reading directly from the memo. Correlated the neut assay results with that of an independently performed ELISA. The ELISA was being performed independently. And as a result, I noted that the correlation was excellent suggesting that there were no global problems. In other words, if changes were being made to the original data set that radically changed the conclusion of that data set, it might have a certain likelihood of showing a miscorrelation with the independently performed ELISA. So this was simply an initial indication of comfort taken

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that there wasn't a global issue with the data. It was not to say that what was done was correct. It just that it was not a global issue with the data.

Q. The ELISA test, the ELISA test and the neutralization assay, the ELISA assay and neutralization assay, they're different assays. Right?

A. Completely different assays.

Q. It also says it should be noted -- this in the last paragraph on page 839, "It should be noted that all samples were tested, per protocol, with the lab personnel blinded to sample identification."

A. That is correct.

Q. What does that mean?

A. That means that the lab personnel did not know whether or not the sample came from our number one or number two or number three. In other words, it did not know where the serum sample was taken and whether it was -- and which of the three dose levels of the vaccine that the individual from whom the sample was taken was inoculated with.

Q. Is that blinding important as far as you're concerned?

A. The blinding is essential in order to be able to do that, right, because it is intended to avoid bias on the part of the operator.

Q. If you go to the next e-mail, the one above it, also signed by you, you say -- and what you say at the end is "The points in this note will be captured by Alan Shaw in the draft of the responses of each of the individual notices of violation."

A. Yes.

Q. Do you see that?

A. Yes.

Q. That's, again, you're referring to 483 there?

A. Yes, the four individual points made in 483.

Q. You can read it if you want, but the point is that Alan Shaw was going to respond?

A. Alan Shaw was going to work on making a draft of the responses. Who ultimately responded formally? Probably it either came -- in this case it either came from me or it came from someone in regulatory in terms of the formal response. But the draft was being put together by Dr. Shaw.

Q. I notice something in the original message.

A. Which one?

Q. The one at the bottom of 838 was not sent to Dr. Shaw.

A. No, this was a message that was sent directly by me to my management.

Q. The e-mail we were just talking about where he says he's going to capture the points was also not sent to Dr. Shaw.

A. Okay.

Q. As a matter of fact, none of these e-mails were sent, except for one.

A. Except the reply that came back from regulatory.

Q. Except for Dr. Ukwu?

A. Ukwu, right.

Q. Let's get to that. Okay. So weren't you talking to Dr. Shaw on the day of the inspection and the day after the inspection, the days you were --

A. Certainly the day after --

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MS. DYKSTRA: Let him finish.
BY MR. BEGLEITER:
Q. Were you talking to Dr. Shaw on the date of the inspection and the day after and then after that?
A. I do not recollect directly, but I am certain based upon what we see here that I was obviously in conversation with Dr. Shaw certainly the day after. And depending upon when the inspector left, I don't know if we conferred that afternoon of the inspection.
Q. Everything you wrote in these two e-mails you believed to be true?
A. Yes.
Q. Do you still believe them to be true?
A. Based on what I see here, yes.
Q. Well, based on anything. Do you still believe them to be true?
A. Certainly I believe -- yes, I believe them to be true. I have no evidence to the contrary that they're not true.
Q. Okay. You also didn't send any of these e-mails to Dr. Krah. Isn't that right?

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MS. DYKSTRA: Objection.
THE WITNESS: These are e-mails that were intended for my immediate management.
BY MR. BEGLEITER:
Q. I understand that. But it was Dr. Krah's lab was the one that was inspected. I'm not saying you should have, I'm just saying the fact is you didn't send --
A. I didn't send them, no.
Q. Okay. Fine.
A. No.
Q. Okay. And did you discuss with Dr. Krah in the days after, the day of and the days two or three days after the inspection what happened in the inspection?
A. I have no recollection of the actual discussions themselves.
Q. But did you recall actually speaking with him?
A. I have no recollection of the actual discussions themselves. So by definition, I don't have a recollection of actually having spoken with him. Maybe we're saying the same thing.

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Q. No, no. You can recall that you spoke to somebody but not remember what you said.
A. I know, but what I said, my answer -- my apologies. My answer to your question is, I have no recollection of a discussion, per se.
Q. Why not?
MS. DYKSTRA: Objection.
THE WITNESS: Because I don't have one.
BY MR. BEGLEITER:
Q. No, no, no. Why don't you have -- well, you're saying you could have had a discussion with Dr. Krah but you just don't remember?
A. Well, yes, I could have had a discussion with Dr. Krah, but I just don't remember. Yes. I literally don't remember.
Q. Okay. Now, take a look at Alan Shaw's e-mail of August 8, 2001, at 9:36 p.m.
A. Which one is this?
Q. That's the cover page.
A. The cover page?
Q. The first page, 8835. The

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bottom one on that page.
A. Yeah.
Q. He suggests, "I would suggest that people from your group...," meaning Henrietta Ukwu's group. Right? "...plus Kati Abraham fix a time with Dave Krah and Mary Yagodich to make your audit."
A. Right.
Q. What audit are you talking about?
A. So, again, in reviewing the multiple back and forth communications that occurred with the agency after this initial inspection in the subsequent months, what clearly we conducted and then asked for was a general audit. First of all, there were audits related to ensuring that what had been observed by the inspector in the case of Dr. Krah's laboratory would result in -- first of all, would not result in any change to the interpretation of the data. That was fundamentally critical, so we conducted that assessment. We then also, you recall that some of these observations were observations related to operations in terms of how things

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were operating in the laboratory. So we conducted an audit to make certain that if those operations were, in fact, not being conducted the way in which the inspector noted to us, that we would take appropriate corrective action to make sure that that was the case. And on top of all of that, we also went on in addition to looking specifically at Dr. Krah's laboratory, we also took the opportunity to conduct a broader audit across all activities that were associated within the organization that ran under standard operating procedures to make sure the standard operating procedures were in place and that activities would be followed according to the appropriate standard operating procedures. Not an unusual set of activities.

Q. That resulted in the August 20th letter which number I don't have.

A. Which one is this now?

MS. DYKSTRA: Exhibit 8.

BY MR. BEGLEITER:

Q. Exhibit 8.

A. Take a look to be certain. This was the initial response, if I remember

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correctly. Yes, it was. This was the initial response to the agency that I responded to that addressed what we had done to reply to the observations that were made by the inspector.

Q. So were you under the impression when you wrote that letter --

A. Sorry, which letter, Number 8?

Q. Number 8.

A. Yes.

Q. -- that the Protocol 007 had been a blinded protocol except for the statistician?

A. That 007 had been a blinded protocol. Well, by definition it had been completely blinded. The only thing that was looked at, there was no indication whatsoever that the laboratory staff had any opportunity to unblind the samples.

Q. Do you know sitting here today that Dr. Krah himself was unblinded?

MS. DYKSTRA: Objection.

MR. BEGLEITER: I'm asking if he knows that, I'm not saying it's true.

THE WITNESS: I have no

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recollection. Let's have a look.

MR. BEGLEITER: I'd like to have marked for identification Merck 52243. It's a one page e-mail.

- - -

(Exhibit Emini-21, 8/9/01 E-mail, 00052243, was marked for identification.)

- - -

BY MR. BEGLEITER:

Q. If you can read -- I'm only going to ask you about paragraph 1. You can read anything you want to read.

A. This does not refer to sample blinding. This refers to the blinding of the counting of the plaques on the plate. It's a different situation than the one you were talking about.

Q. Well, was it appropriate for someone to be unblinded, for the head of the lab to be unblinded?

A. For counter-qualification, yes, that's perfectly acceptable.

Q. Is that anywhere in the SOP?

A. I don't recall if it was

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specifically in the SOP, but typically someone needs to be unblinded for a qualification to be appropriately conducted. The individuals who were blinded were the individuals who were looking -- that were actually running the counters with the individual samples. Remember what the counters are doing, that this is individual counting of the plaques on the assay. So they were blinded to each other's results. He knew which ones were the actual value numbers because he was using, as he notes here very clearly, "...the workbook printout as a guide to check for extravariable/single dilution positive samples."

So basically they would be -- so he was aware what the numbers were and then essentially asking you count them, you count them, you count them, and he was assessing based upon what the original numbers were, the variation that occurred if you counted them or you counted them or you counted them.

Q. The plates he was talking about were the plates that actually where the assay was conducted. Is that right?

A. This would be the plates in which the assay was conducted, yes.
Q. And his knowing what those plates showed in terms of plaques, that wouldn't bias him?
A. No.
MS. DYKSTRA: Objection.
THE WITNESS: It depends on what he was doing. In this particular case he was doing counter-qualification. So there is no bias associated with that. This was so that he could conduct an independent assessment of the variability that was occurring among three different potential readers. Probably as a result of, you know, having taken a careful look again to determine what the variability of the counting procedure was.
BY MR. BEGLEITER:
Q. Did you inform supervisors who you sent your e-mails to on the 7th and 8th that, in fact, that Dr. Krah had been unblinded on the counter-qualifications?
A. No, because it was not relevant



to the overall inspection issue.
Q. Well, did you -- you had represented to your supervisors that, in fact, there had been blinding?
A. Yes.
Q. Now, could the blinding, since Dr. Krah would know the pre-positives, post-positives, pre-negatives, would know that -- would know who was what, wouldn't that -- couldn't that bias the taker of the test?
A. No, it says here, if I read this correctly, it says, "...we are blinded for our counter qualification...for the rechecks of the current assays that I have done. I have not been blinded since I was using the workbook printout as a guide to check for extravariable/single dilution positive samples." So he was checking to see if there were extra variable/single dilution positive samples, the values that were being generated were the blinded values being -- were the values that were being blindedly assessed by the blinded counters. He was not changing any numbers there himself.



Q. I didn't -- I asked a question about blinding. I'm saying there was a workbook printout.
A. Yes.
Q. As a guide to check extra variables/single dilution positive samples?
A. Right.
Q. So in other words, Dr. Krah knew what the single -- where the single -- which ones were in single dilution positive samples. Is that right?
A. Right.
Q. And that could tell him whether or not they were pre-positives or not. Isn't that right?
A. No. I don't see how that would be possible.
Q. You mean having a printout that tells you what each plate, what the plates --
A. It does not identify the sample. It's simply says these are the numbers that were counted. It does not identify from whom or from which individual the sample came from. That was information that would only be available to the blinded statistician. The



samples are blinded by code.
Q. Then explain this to me. For the majority of the plates, the pen marks were left on the plate for initial recheck to see if plaques were over or undercounted, i.e., each pen mark -- was each pen mark associated with an identified plaque?
A. Right.
Q. And if there was a difference noted, the spots were removed and the plate was recounted.
A. Right.
Q. Is that appropriate to do, to remove the spots?
MS. DYKSTRA: Objection.
THE WITNESS: If you don't remove the spots, you can't recount because you won't be able to see the plaques so you have to remove the spots.
BY MR. BEGLEITER:
Q. Who asked them to recount?
MS. DYKSTRA: Objection.
THE WITNESS: I don't recall who specifically asked to do the

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recounting. I don't recall who specifically asked. I can tell you --
BY MR. BEGLEITER:
Q. I take it from that that you have no recollection of asking him?
A. I have no recollection of asking him personally to do the recount.
Q. You have no recollection of discussing with Dr. Shaw either?
A. I have no direct recollection of discussing it with Dr. Shaw. But this would have been part of the procedure to assess the quality of the data.
Q. Shouldn't the fact that there was a recheck going on be something that Dr. Shaw should have known?
MS. DYKSTRA: Objection.
THE WITNESS: He may very well have known and probably did know it. I just don't recall ever having -- 20 years later having the conversation with him.
BY MR. BEGLEITER:
Q. But it wasn't important enough to write an e-mail to you to tell you that it

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was going on. Is that what you're saying?
MS. DYKSTRA: Objection. Mischaracterizes his testimony.
THE WITNESS: No. He just -- first of all, I don't recall if he did write me an e-mail because we haven't reviewed every single e-mail that went back and forth between myself and Dr. Shaw. But this activity was going on. It was undoubtedly part of the operational audit and reassessment of the data since it was questioned in terms of how the original data were generated or at least how they were recorded, not necessarily generated but how they were recorded. That's perfectly standard.
BY MR. BEGLEITER:
Q. Was CBER told about the rechecking --
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. -- by you?
A. Not by me directly. My communications with CBER were formal

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communications, so there were discussions that were ongoing as normally would be the case between regulatory and CBER as a result of the inspection. And part of the effort probably involved, based upon what I read here, a rechecking of the data and the actual counts that were done to determine if there was a complete -- if there was an issue in terms of following the SOP and if the numbers which had been changed without explanation in that original spreadsheet, if one does it again, does one come up with the same set of conclusions.
Q. In Exhibit 7, which is the 483, contains the 483, number 1 we already read, raw data is being changed with no justification.
A. Right.
Q. For example. Okay.
A. No justification may mean that no justification was noted on the document, not that there was no justification. Big difference.
Q. And then two days later, three days later, August 9th, Dr. Krah says that he was unblinded as to counter-qualifications.

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Do you think that something -- withdrawn.
Did you believe this was something that should have been told to the FDA?
A. No. Because they're not correlated with each other. He was doing a counter-qualification which was to ascertain, since they were going to recount the plates and the plates were apparently being recounted by multiple individuals, so you go through this qualification process to see -- because remember, these are manual counts. They rely on human judgment. So, therefore, if analyst number one did it and analyst number two and analyst number three, and they, according to the memo, were all blinded to each other in terms of what they were actually counting, in other words, analyst number two was not looking over the shoulder of analyst number one. Everything was done blindly. So analyst number one would do a set of counts, analyst number two would do a set of counts and analyst number three would do a set of counts. They would sit there, okay, and then a third party, presumably a statistician, would sit

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down, look across the counts and determine, okay, so what are the actual counts and how close are they in their actual counts. Now, when one does that, there is sometimes -- and this is a qualification effort that was ongoing, so these are qualifications. Remember, this is like a validation. It's to determine whether or not your eyes count X number of plaques to my eyes also count X number of plaques, if there is a big difference between what you count and I count, then we have an issue here. Whose numbers do we believe? Do we believe your numbers. Do we believe my numbers. So, therefore, it requires at that point to sit down, do some training, do some assessments so as to coordinate, if you will, how you interpret what you see and how I interpret what I see. You can only do that if then there's another party that really looks to see are there large variabilities. And that apparently is what Dr. Krah was doing. So what he's referring to is the blinding of the -- blinded to the actual plate counting that was going on. This is not blinded -- blinding related to the

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designation of the actual samples being tested.

Q. Could you tell from the counting sheets which pre or post samples were associated with the specific trial?

MS. DYKSTRA: Objection.

THE WITNESS: Well, by definition -- so one could make the assumption that if, in fact, there was a high degree of neutralization, chances are that this was an immunized individual. But remember they're all immunized individuals in this trial. These children received different potency levels of the vaccine. They were largely immunized. So, therefore, if you're blinded to which group the sample came from, it will have no impact on the final outcome of the trial because that's something that's going to be assessed by the unblinded statistician at the end of the study. Then associates a given value with a given sample from a given arm of the trial. This is done to avoid

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unintended bias.

BY MR. BEGLEITER:

Q. What is done to avoid unintended bias?

A. The blinding. The blinding is done to avoid unintended bias.

Q. And do you know sitting here today whether or not Dr. Krah had access to the pre-positive samples?

MS. DYKSTRA: Objection.

BY MR. BEGLEITER:

Q. Access to know which samples were pre-positive, I should say.

A. One -- pre-positive.

Q. Yes.

A. Please define pre-positive.

Q. You don't know what it means?

A. No, I think I know what you're asking, but I'm not certain, so I'm asking you to be more precise, please.

Q. I'll ask it a different way rather than get into an argument.

What Dr. Krah was doing would allow him to know what the count was, what the plaque count was per child. Isn't that right?

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MS. DYKSTRA: Objection.

THE WITNESS: That would not allow -- this would not allow him to know that, no.

BY MR. BEGLEITER:

Q. If he had a notebook that had that information, he would already have known it. Correct?

MS. DYKSTRA: Objection.

THE WITNESS: Only if the workbook contained the actual designation of the sample and where it came from. The actual designation of the subject to the sample.

BY MR. BEGLEITER:

Q. Have you ever seen the workbook?

A. I have not seen -- I don't -- well, no, I can't answer. I don't recollect having seen this workbook or not having seen the workbook. I do not.

Q. Now, sometime before the unannounced inspection, you had spoken to Mr. Krahling? We discussed this already today. You had a conversation with him.

A. Right before the unannounced

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inspection, yes.
Q. Somewhat fairly close to the unannounced inspection. Right?
A. Yes.
Q. Didn't he tell you that there were -- what did he tell you about the way the counts were being done in the lab?
MS. DYKSTRA: Objection.
THE WITNESS: So the only recollection I have of that, right, was a notation in a document that I saw over the last few days, right, that indicated that Mr. Krahling had shown me -- had shown me data suggesting that there were changes being made to the data, pretty much essentially what the inspector noted in the 483 report.
That is the best of my recollection.
BY MR. BEGLEITER:
Q. What document was that?
A. So this was a document, if I recall correctly, that was a document, it was an e-mail largely redacted but with a handwritten notation.
Q. What did the handwritten

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notation say, if you recollect?
A. This was somebody who had written to me or made a note of the fact that Mr. Krahling had shown me some data. I don't recollect the exact terminology.
Q. And who did Mr. Krahling accuse of changing the data?
MS. DYKSTRA: Objection.
THE WITNESS: I do not recollect the details of the conversation.
BY MR. BEGLEITER:
Q. Didn't Mr. Krahling accuse -- withdrawn.
Did Mr. Krahling make the accusation that the changing of data was done in Dr. Krah's lab?
MS. DYKSTRA: Objection. Asked and answered.
THE WITNESS: I don't recall the details of the conversation.
BY MR. BEGLEITER:
Q. By the time you received the 483 -- by the time you read the 483 and thought about it and did your e-mail the next day, did you consider the fact that there

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might have been some inappropriate changing of data in Dr. Krah's lab?
A. The possibility always exists and when someone comes to me, and this has been consistently true of anything I've always done, comes to me with a -- we'll call it an allegation that there might be something which is improper, then one typically refers this to an independent third party to do the assessment. What I can tell you and will tell you is that I did refer this to legal counsel in the company.
Q. Did you consider removing Dr. Krah even temporarily from the laboratory?
A. There was a -- I don't recall my thoughts at the time but there would have been no reason to do so until the third-party investigation would have been completed. Also what I didn't recall, I really don't recall at the time is whether or not there were actually activities still going on at the time. In other words, additional assays going on at the time. If there had been none going on, then we would have stayed at status quo, stopped everything and just waited for the independent

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assessment to be completed.
Q. Would that have been an appropriate thing to do?
MS. DYKSTRA: Objection.
THE WITNESS: That would normally being the appropriate thing to do.
BY MR. BEGLEITER:
Q. You don't recall if that was done or not?
A. Well, what did occur -- what did occur was immediately thereafter, as it turned out, the inspector showed up, was within a few days, the 483 was issued, the point was made directly on the 483. Therefore, what we normally would have done independently of that anyway was just went on in response to this case, to the 483.
Q. You didn't directly ask Dr. Krah about the allegation --
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. -- changing the date?
A. I am certain that we may have had some conversation related to it, but

normally once this is referred to a third party for assessment, you allow the third party to conduct their assessment independently of any interaction with the third party because it would not have been appropriate.

Q. Was Dr. Krah ever asked by you -- who is the third party you're talking about here? Would that have been legal counsel?

A. So the -- it was legal counsel and -- may I? And then I had my --

MS. DYKSTRA: Just legal counsel.

THE WITNESS: Just legal counsel. We'll leave it at that.

MS. DYKSTRA: Stop at that for privilege issues.

THE WITNESS: Privilege issues.

BY MR. BEGLEITER:

Q. The very last sentence in that paragraph, let me read -- there's two sentences.

A. Please.

Q. "For the majority of the plates,



the pen marks were left on the plate for an initial recheck to see if plaques were over or under-counted (i.e., was each pen mark associated with an identified plaque)..."

A. Right.

Q. ...and if there was a difference noted, the spots were removed from the -- removed and the plate was recounted. Do you see that?

A. Yes.

Q. In the next sentence Dr. Krah says something. "This may introduce a bias, but the changes have been both up and down (although largely up due to missed counts)," the last word is in the parentheses.

What do you understand him by saying that "this may introduce a bias"?

A. Well, by statistical definition, every time you count something more than once, there's a certain probability that you will introduce a bias. And that the criteria that's used for counting the first time, and even in one's own head, can be very different than the criteria that was done the second time. So what then -- so then typically what



happens, particularly when one is using human judgment to count plaques, if you count it multiple times, you're going to get potentially multiply different sets of numbers. So that may, as he noted, introduce a bias. But as he noted from a statistical perspective, at least by eye, there were as many increases in numbers as there were decreases in numbers. So when one does a statistical assessment in the end, it will come out in the wash.

Q. And Dr. Krah to this very day never told you about this rechecking?

MS. DYKSTRA: Objection.

BY MR. BEGLEITER:

Q. Is that your testimony?

A. No, my testimony is I don't recollect having a discussion with Dr. Krah.

Q. If there is even a possibility of introducing a bias, do you believe that the FDA should have been informed of that possibility?

MS. DYKSTRA: Objection.

THE WITNESS: The FDA would automatically have been informed when



they looked at the reanalysis in comparison with the initial assessment, because the statistical assessment would have indicated the presence of a statistical bias. So that happens automatically.

BY MR. BEGLEITER:

Q. So you said "would have," but you don't know?

A. If the statistical analysis, and, again, subsequent -- looking at my reply to the agency, there was no indication of an inadvertent or advertent bias.

Q. This statistical analysis, do you recall ever seeing this statistic analysis prepared by Dr. Krah somewhere in this lab?

A. Not by Dr. Krah. It would have come from the statistical group. In fact, it's probably embedded in the full reply to the agency and in subsequent discussions.

Q. We talked before about there being at least two kinds of validation. I'm not giving it to you yet.

A. He's not going to give it to me.

Q. Two kinds of validations, one

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for the assay and one for the lab itself?
A. Laboratory, yes.
Q. Are there any other kinds that you're aware of?
A. Well, validation -- both the terms validation and qualification are general terms. So they relate to any set of activities in which there is a requirement for accuracy, precision and ability to interpret the quantitative results, whether it be a laboratory, whether it be an individual, whether it be an assay. As an individual you can be qualified and validated as well.
Q. Who did the validation for Protocol 007, the PRN part of the test?
A. Well, the data for the validation would have been generated by the laboratory that developed the assay.
Q. Dr. Krah's laboratory?
A. That would have been Dr. Krah's laboratory, yes.
Q. Okay. And did CBER request the validation results for the neutralization assays you were going to use?
A. I don't recall offhand, but I

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would be very surprised if they had not requested. It's a standard request from the agency.
Q. Was the asset conducted before or after assays were completed?
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. Excuse me. Was the assay conducted before or after the validation was completed?
A. I don't recall offhand.
Q. Would that be something that would be inappropriate, to complete the validation before the --
A. It's not.
Q. Let me finish the sentence.
A. I'm sorry. My apologies.
Q. -- before the validation was completed?
A. I apologize.
It is not a requirement.
Q. Didn't you indicate before, we were talking about Dr. Ward, that you would have wanted his lab to be validated before he was given the task of doing the clinical -- of

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analyzing the assays?
A. Yes, but that was my requirement. That was the requirement, but it is not a formal requirement -- so let me explain. It is not a formal requirement that validation or qualification be completed, be completed prior to the actual conduct of the assay. It is a requirement that it be completed prior to the analysis of the data from the assay. So if you develop an assay and you do not complete the validation prior to actually running the samples and you run the samples at risk because you're doing the validation either afterwards or in parallel, it's your risk. Because once you run the samples, and if the assay turns out not to be appropriately validated following the validation protocol, then you put the entire test and entire data set at risk.
Q. Excuse me for one second.
In the case of 007, was the validation experiments done by the same group, same lab that was doing the assay, the PRN?
MS. DYKSTRA: Objection.
THE WITNESS: I cannot recall

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directly, but that would normally be the case.
BY MR. BEGLEITER:
Q. It would normally be the case that the same lab would do both, the validation testing and the testing itself?
A. Yes.
Q. Can you go back to 20? The last page, 8839. When you write, "It should be noted that this assay was being performed by the research personnel who developed the assay and in the research laboratory..."
A. Yes.
Q. ...in which the assay was developed. Typically, the assay should have been transferred --
A. Would have been transferred, not should have been transferred.
Q. "...to a testing lab following this development."
A. Yes.
Q. Isn't that referring to the validation testing?
A. No, because recall, you have to validate so you do it two different ways.

Typically what you would do is that you would, if laboratory A, in this case, the research laboratory were to develop the assay, then they would perform a validation. Terminology used today is qualification. Means the same thing.

So they would normally perform it to determine the assays, as we said, precision, accuracy, reproducibility. When an assay that is a validated assay is then transferred from one laboratory to another laboratory, the assay is revalidated to make sure that it behaves the way in which it behaved when it was first developed. So you would wind up basically revalidating the laboratories. So what normally would have been done in this case is the research laboratory would have developed the assay, would have qualified the assay, would have sent it to a testing laboratory, either internally or externally, and then the assay would have been requalified in the context of that testing laboratory probably at the same time that you would validate the laboratory itself.



Q. Wasn't -- didn't CBER want it -- want to review and concur with the validation protocol before the testing?

MS. DYKSTRA: Objection.

THE WITNESS: Again, it is -- the reason why I'm hesitating in answering your question is that that is not a formal requirement. CBER may ask to view a validation protocol, a validation data prior to the actual running of an assay. However, and this has happened to me on multiple occasions, CBER will also say go right ahead, if you want to run the assay prior to the time that we looked at the validation, but you run it at your own risk.

BY MR. BEGLEITER:

Q. Does CBER usually approve or concur with the validation?

A. CBER would have to approve -- would have to concur that the validation was done correctly and that the numbers that were being reported from the assay, that the way in which one would interpret those numbers by



both the lab running the assay and CBER would be the same.

Q. Let me show you 682341 to 682345.

- - -

(Exhibit Emini-22, List, 00682341 - 00682345, was marked for identification.)

- - -

MS. DYKSTRA: Do you have copies?

MS. MAHENDRANATHAN: Yes.

BY MR. BEGLEITER:

Q. The only question I'm going to have is what is this? Do you recognize this type of document?

A. Yes. What this document is, is a document in which the operator of the assay will report their observations.

Q. And this is part and parcel of actually doing the assay?

A. This is part and parcel of performing the assay, yes.

Q. Does it have a date on when this was performed?



A. 9th of February, 2001.

Q. And do you know when the validation protocol was given to --

A. I don't recall.

Q. Let me finish the question. When the validation protocol was given to CBER?

A. I apologize. I do not recall.

Q. I should point out on that document, 2341, at the bottom it says, "Mary Yagodich, December 12, 2000," at the bottom. Do you see that?

A. It says, "December 12, 2000," at the bottom.

Q. Right. Let me show you again Exhibit 6. You have that in front of you?

A. 6?

Q. Yeah.

A. Yes.

Q. And go to page 17080.

A. Yes.

Q. And that shows -- what is this document, that 17080?

A. This is a document to Dr. Krah

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from the statistical analysis group that is -- refers to the validation of the plaque reduction neutralization assay. And it refers to the validation results. Just bear with me a second, let me go look. Yes, this refers to the validation results, yes.

Q. Of the PRN?

A. Of the PRN, plaque reduction neutralization.

Q. If you go to the second page of the exhibit, there's a letter.

A. Of the overall exhibit, yes.

Q. Yes, the whole entire exhibit. And that letter is dated March 12, 2001?

A. That is dated March 12, 2001.

Q. So it's some two months plus after Exhibit 23 was prepared. Is that right?

A. Exhibit 22.

Q. Exhibit 22 was prepared.

A. Yes.

Q. And it's your statement that that was perfectly okay?

A. Yes.

Q. But at the risk of Merck?

A. But it is at the risk of -- it

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is at the risk of the company. As, again, validation is required and accepted by the agency prior to the time that the data that you see here in Exhibit Number 22 can be analyzed by the statistician in the end. But the actual generation of the data, that occurs at your risk. So if you're not willing to take the risk, you wait until the validation is completed and accepted by the agency. If you believe that your assay is validate-able or qualifiable, means the same thing, then if you are pressed for time, you can take the risk of running it. The risk, of course, being that the validation may not work out or the agency may not except the validation.

Q. So my question to you is, were you informed that Dr. Krah was taking this risk for Merck?

MS. DYKSTRA: Objection.

THE WITNESS: I do not recollect being informed either that he was or that he was not. I don't recall.

BY MR. BEGLEITER:

Q. Do you recall anyplace in which any conversation, any document, anyplace in

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which the FDA, CBER were told that assays were completed before the -- excuse me, the assays were conducted --

A. The assays --

Q. Let me start again.

Do you recall from anyplace, whether it's a document, a conversation in memory, that CBER was told that assays were conducted prior to CBER receiving the validation protocol for concurrence?

A. I do not recall a direct communication with CBER noting exactly what you said, but it's self evident.

Q. Do you recall CBER being told when the individual assays were conducted?

MS. DYKSTRA: Objection.

THE WITNESS: I do not recall, but it's in the workbook, the dates.

BY MR. BEGLEITER:

Q. The workbook, you're referring to Exhibit 23?

A. Exhibit 22.

Q. 22. Was the workbook given to the FDA?

MS. DYKSTRA: Objection.

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THE WITNESS: I don't recall if the workbook was given to the FDA, but I do know that this was part of the data, I presume, I don't know if it was exactly this data, but part of the data that the FDA inspector came to observe and upon which she noted the concern over the apparent changes without written justification.

BY MR. BEGLEITER:

Q. That wasn't my question. My question was whether the FDA would -- CBER was told?

A. As I said -- I'm sorry.

MS. DYKSTRA: I said let him finish.

BY MR. BEGLEITER:

Q. That CBER was told that assays were completed prior to the -- to sending the -- to Merck sending the validation protocol to CBER?

MS. DYKSTRA: Objection. Asked and answered.

BY MR. BEGLEITER:

Q. Well --

A. I do not have a direct recollection of such a communication.
Q. I believe I asked you this morning whether you signed any of the validation protocols for PRN 007. Let's take a look at 33 -- 337307.
I'm asking the reporter to mark for identification 337307 through 337313.
- - -
(Exhibit Emini-23, Plaque Reduction Neutralization Assay for Mumps, 00337307 - 00337318, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. So what is this document?
A. This is -- allow me a moment, please. These are signature pages on the front end of the document related to Plaque Reduction Neutralization Assay, Analytical Validation Protocol Version 2. I don't know exactly which plaque reduction neutralization assay was being referred to here. This is the AIGENT assay according to this document which is the anti-IgG neutralization assay.



Q. This is the assay that we have been discussing, yes, the PRN?
A. Yes.
Q. And do you see your signature on it? Well, do you see your signature on any of these sheets?
A. Yes, I do.
Q. And you signed it what day?
A. The 22nd of February 2001.
Q. And you had no comments?
A. I had -- specifically says none.
Q. So, sir, you'll notice we talked about the validation protocols being sent to the -- being sent to CBER in March of 2000 -- March of 2001? Going back to that document.
A. I need to go back, please.
MS. DYKSTRA: Exhibit 6.
BY MR. BEGLEITER:
Q. Exhibit 6, the cover letter March 12th.
A. The cover letter was March 12, 2001, yes. And the results of the validation were completed on February -- the memo from the statistical group that was being referenced is dated February 27, 2001.



Q. What page are you looking at, the number at the bottom?
A. My apologies. I'm looking at page 17080.
Q. Going back -- so when you signed it, when you signed this document -- withdrawn.
What does your signature on this document mean?
MS. DYKSTRA: Exhibit 33. 23.
THE WITNESS: 23, that is correct. It means that I am in concurrence with the plan to conduct the validation as indicated in the documents, number 23.
BY MR. BEGLEITER:
Q. The plan to conduct the validation?
A. The plan to -- yes. This is the validation protocol. So Number 23 is the protocol that describes how the validation will be conducted.
Q. That's why if you turn to page 315 --
A. 15?
Q. Yeah. Let's say purpose. Let



me read to you the sentence in the -- the second sentence. The data rising from this validation study will be used to 1, 2, 3, 4, 5, do you see that?
A. Yes.
Q. So that means it hadn't been done yet?
A. That is correct. This is the protocol for conducting --
Q. On page -- the next page, 316, at the bottom "Assay Validation Experiments," the second sentence -- the first sentence, "The plaque reduction neutralization assay will be performed...." And then the next sentence, "The validation experiment will include...." So this is all speaking in future tense?
A. Yes, of course.
Q. Do you know when it was completed?
MS. DYKSTRA: Objection. Form.
THE WITNESS: Well, the -- sorry.
MS. DYKSTRA: Objection. Form.
THE WITNESS: I'm sorry. Well,

my only answer to that comes from looking at the document in your Exhibit Number 6 which was a response to the agency and going to page 80 which was the data that was the completion of the validation assay dated approximately -- dated exactly seven days later, on February 27, 2001.

BY MR. BEGLEITER:

Q. On the document that you signed, is that a template or is that something that was drafted just for this assay?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I -- well, clear what's your question, sir, you were referring to what? Are you referring to --

BY MR. BEGLEITER:

Q. The signature page.

A. You're referring to the signature page?

Q. Yes.

A. So we reference the signature page, well, it is specific for this assay insofar as the names on the signature page are



present.

Q. Going back --

A. Because they were specific obviously to the laboratory and the reporting relationships.

Q. Going to 23 it says Jerry Sadoff N/A. Do you know what that mean?

A. Jerry Sadoff was -- had responded. He was in the clinical research group. N/A means he was not available.

Q. If he was listed on this document for a signature, shouldn't his name -- shouldn't he have -- he eventually signed off?

MS. DYKSTRA: Objection.

THE WITNESS: Not necessarily so. It all depends upon what the company was using as an acceptable representation of review and signature.

BY MR. BEGLEITER:

Q. Even though there was at least seven days between the time you signed it and the time that the experiments were completed?

A. Right, but it's also acceptable to sign post facto, too, as long as -- the



only thing that the signature page indicates is that there is approval, as long as no comments are made by the individuals who sign. That the validation protocol as written is acceptable and can, in fact, be used to validate the assay as described. Again, there is also a risk factor associated with this because if it is approval after the validation is actually -- if an issue is raised by any of the individuals that were being asked to review. If an issue was raised after the actual validation protocol is run, then one has to go back and one has to do it all over again.

Q. The document Number 23 has a box on the top, it says, "Initial Review," it's bolded and there's a box.

A. Yes, I see it.

Q. And then to the right of that there's "Final Review" in grayish letters.

A. Yes.

Q. What is the initial review?

A. I don't recollect offhand what the difference between the initial review and final view. This is a four-page document, so



the initial review and final review would most likely be exactly the same.

Q. You're speculating now?

A. I am totally speculating. It's a four-page document, pretty straightforward to review.

Q. Do you know if you ever signed off on a, quote/unquote, final review?

A. I don't have any recollection.

Q. If you take a look at page 7314, the very bottom there's Karen Hencken's signature. I believe above the word "Comments" there's something that looks like a check mark?

A. Yes.

Q. Do you know if she had any comments?

A. I don't know. I can only go by what she has here which was there was nothing there.

Q. This was a validation protocol for a clinical trial using clinical samples for children. Is that correct?

A. This was a validation protocol for an assay that would be used to generate

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data from a clinical study.
Q. Did you understand that the validation protocol authorized the experiments to be conducted in a GLP compliant lab?
MS. DYKSTRA: Objection.
THE WITNESS: All validation studies and all clinical assay studies are to be conducted in laboratories that follow good -- GLP refers to good laboratory practice, it means a different thing today than it did then, but...
BY MR. BEGLEITER:
Q. Yes. And, in fact, was Dr. Krah's lab a GLP compliant lab?
A. The laboratory -- the GLP compliance required the presence of SOPs and the requirement to follow SOPs, so my answer to that question would be yes.
Q. Is there a certification for GLP?
A. There is no formal certification as far as I'm aware for GLP.
Q. And a clinical trial involving clinical samples in children must be conducted

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according to a -- to good clinical practices. Isn't that correct?
MS. DYKSTRA: Objection.
THE WITNESS: The conduct of the clinical trial has to be by good clinical practices, yes, which are again, you know, clear specifications in terms of what that means.
BY MR. BEGLEITER:
Q. Do you know if Dr. Krah's lab was a good clinical practices laboratory?
A. Dr. Krah was -- good clinical practices refers to the conduct of the clinical trial, the interaction with the subjects of the trial, what one does with those interactions, issues of institutional review board approvals, issues of ethics. It does not relate to the laboratory. It does not relate to the laboratory. It relates to the conduct with the subjects in the study.
Q. Let me see if we can get this straight. The same lab with the same personnel and SOP were used to develop, validated and perform the assays. Right?
A. In the case of the 007 study,

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yes.
Q. And did you ever sign any validation of Dr. Krah's lab and personnel to run a -- to run the clinical samples pursuant to GCP?
A. Again, GCP does not refer to the laboratory or to the laboratory operations. What is being used in some of these documents in a very loose fashion is the term GLP which refers to good laboratory practices. In general what this refers, and this is typical of all laboratories that run clinical assays, is that they run a validated assay and that the laboratory's operations are run under specified standard operating procedures.
Q. Do you know if the personnel in Dr. Krah's lab had been trained to perform assays under GMP or GCP?
A. If the individuals followed the standard operating procedures and ran the validated assay in the way in which the assay was defined by the SOP in a validated fashion, that would have been acceptable.
Q. But you don't know if, in fact, that occurred?

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A. If there was what, formal training?
Q. Yes.
A. I do not recollect if there was formal training involved, but it is not a requirement.
Q. Well, I thought you said that it was a requirement for a GLP?
A. That standard operating procedures be followed. Now, whether or not one actually has a formal training for that or not is another story.
MS. DYKSTRA: Let me know when it's a good time to take a break.
MR. BEGLEITER: I'm almost finished with this subject.
I'll hand the court reporter Merck 780051 through 54.
- - -
(Exhibit Emini-24, E-mail exchange, 00780051 - 00780054, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. You didn't receive this document,

did you?
A. I did not, no.
Q. I'm asking, do you know who Robin Mogg is?
A. I do not recall directly. I recognize the name, but I do not recall the individual.
Q. How about Joseph Antonello?
A. Joseph Antonello was a member of the statistical group.
Q. This document purports to give the dates of the asset runs, isn't that correct, regarding -- purports to give the dates of the asset runs?
A. Of the assay runs.
Q. Assay, I'm sorry.
A. Asset refers to something else.
MS. DYKSTRA: I'm sorry, Bob, is there a question pending?
MR. BEGLEITER: I'm sorry, I thought he was still looking at it. I think he is still looking at it.
MS. DYKSTRA: I'm sorry, your question was?
MR. BEGLEITER: I'm showing him



the document. Before I ask any question, I'm going to give him a chance to look at it, the document.
MS. DYKSTRA: Okay. I was asking whether there was a question pending. I wasn't sure.
MR. BEGLEITER: There's no question pending.
THE WITNESS: Okay. Thank you.
BY MR. BEGLEITER:
Q. And does this show in Protocol 007 the dates, at least, of some of the assay runs?
A. This shows the dates, if I read this correctly, it's pretty sparse, relates to the assay runs that were performed in the context of the assay validation.
Q. And the earliest for the pediatrics were August 21, 2000. Is that right?
A. According to this, it would be for what it says here, August 21, 2000. But I don't know what that entry refers to.
Q. Can you explain to me -- do you have any explanation as to why the validation



wasn't completed and sent to CBER until March 12, 2001?
MS. DYKSTRA: Objection.
THE WITNESS: Why it was not sent?
BY MR. BEGLEITER:
Q. Yes.
A. I can't tell you why it was not sent other than to say there was no requirement to send it.
Q. Well, it's about a seven-month period from the first pediatric run until it goes to --
A. I don't know what this pediatric run refers to. I really don't. The only thing that I can ascertain from this were the validation runs that were run from -- the so-called adult runs at the top that were run from the 18th of January to the 26th of February 2001. So that would have -- those would have been runs that were run -- studies that were run, you know, roughly at -- but these are adult runs. So this refers to assay runs. Whether or not they're directly related to the validation or not, I cannot tell from



this.
Q. There's no question, though, that the validation could have been done prior to when it was done?
MS. DYKSTRA: Objection. Form.
THE WITNESS: Well, anything can be done at any time.
BY MR. BEGLEITER:
Q. That's true. What about -- I mean, the fact that we -- I showed you an assay that was run in December. I'm trying to understand why maybe you -- you tell me that it wasn't necessary --
A. It was not necessary.
Q. -- but I want to understand why it was that assays were done and then the validation went in?
A. Well, when -- so I will give you a hypothetical circumstance under which one would normally do that. Hypothetical circumstances could be one in which an assay is developed. One is confident about the parameters of the assay. There is a time pressure of some sort to generate the data from the assay. Following the procedure of

performing a formal validation and then sending the data and then obtain concurrence to the agency prior to actually doing the run takes time. Now, from a risk perspective, that's the least risky approach, because if there is a disagreement with the agency, then one has the opportunity to go back and modify the assay, redo the validation, whatever the case happens to be. But once the assay samples are run, the actual study samples are run, you can't go back and do it over again. So, therefore, you take a risk.

So if there's a time constraint and I need to update it by a certain time, what one would do is to validate the assay in parallel, more or less in parallel with running the actual clinical samples, it could be more or less, because it would be a little bit before, it could be a little bit after. The only point is you would not complete the validation prior to actually generating data on the actual clinical samples.

Q. Do you recall if there was a time constraint with 007?

A. Well, there were time constraints



related, but I don't know if they were related to this. There were time constraints associated with generating data from that so-called interim analysis to have a look at the seroconversions that were present that -- that the seroconversions that were elicited in subjects who received vaccine of certainly the two lower potency values that were being assessed in the study.

Q. Because children had received vaccines below the 4.3 spec, is that what you're saying?

MS. DYKSTRA: Objection. Form.

THE WITNESS: Because there was a -- again, I do not recollect exactly, but whatever it was there was a desire to generate data. I really don't recollect the discussions, but there was a desire clearly to generate data to assess the seroconversion as measured by the assay in those two lower potency values.

BY MR. BEGLEITER:

Q. You don't know sitting here today why there was any kind of time



constraint?

A. Specifically why there was any kind of time constraint, in specific discussions that I had recollect today, the answer is no.

Q. Now, you mentioned that there were -- I promised you we could break, so let's break.

VIDEOGRAPHER: The time is now 4:02. We're going off the video record.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is 4:17. We're back on the video record.

BY MR. BEGLEITER:

Q. Doctor, was it generally understood at Merck -- withdrawn.

Your view that Merck could do the assay, test the assays and then do the validation, was that written somewhere? Is there any kind of rule for that that we can look at?

A. Is there any written rule that



I'm aware of? No.

Q. So where do you get the idea that it's appropriate for -- it's permissible?

A. It's permissible. I mean, it's standard, it's standard practice. I've had other examples, not necessarily when I was at Merck, but in my subsequent employment, I'll leave it at that, where we've done the same thing, run assays at risk before there is agreement with the agency on the validation.

Q. Shouldn't you have approved this at risk running?

MS. DYKSTRA: Objection.

THE WITNESS: Not necessarily formally approved it. I may have approved it informally. I just simply do not recollect.

- - -

(Exhibit Emini-25, 1/4/02 E-mail with attachment, 00579518 - 00579521, was marked for identification.)

- - -

BY MR. BEGLEITER:

Q. I'm going to show you a document that's been marked Emini-25. It's Merck

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579518 through 521. You'll find it an easy read. It's been mostly redacted.
A. Okay.
Q. First of all, did you receive this document in the usual course of your employment with Merck?
A. If it was sent to me, I'm looking for that right now.
Q. Look at five lines from the top.
A. There's many names there. Yes, there I am. So, therefore, the answer to your question is yes.
Q. And it says, "Attached are the minutes of the December 12 meeting of the Critical Assay Subcommittee. Thanks Joan." [As read] Who is Joan Staub?
A. Joan Staub was -- she had multiple positions within the organization. So -- and she was in the, if I remember correctly, in the project management group, or the program management group, whatever it was called.
Q. Now, behind that is an e-mail dated January 4, 2001. I won't ask you any questions regarding this.

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A. Please don't.
Q. Turn to the second page. "Update: CBER Audit of Mumps Neutralization Data."
Do you see that?
A. Right.
Q. Now, I'm going to read to you the first sentence. As a result of the data audit, CBER believes that we used technical -- clinical trial sera to develop the assay and that we changed the assay after we looked at the data. Do you see that?
A. Yes.
Q. This is a very -- would you agree this is a pretty strong accusation?
MS. DYKSTRA: Objection.
THE WITNESS: No, it's not an accusation. It says that CBER believes that we used clinical trial sera. Remember, it depends on the context in which the individual wrote the statement. The way I would interpret this is to say that CBER has a concern that the assay could have been changed after we looked at the data Joan

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derived from the clinical trial sera.
BY MR. BEGLEITER:
Q. If that were, in fact, done, that would be a pretty serious scientific violation?
MS. DYKSTRA: Objection.
THE WITNESS: That would be probably something you consider to be inappropriate, yes.
BY MR. BEGLEITER:
Q. More than inappropriate. That would be a violation of the ethics of scientists?
MS. DYKSTRA: Objection.
THE WITNESS: Well, ethics is a strong term. I would call it, I would call it inappropriate and not something that one would normally do or should normally do.
BY MR. BEGLEITER:
Q. And did that happen?
A. Not to my recollection. In fact, that did not happen.
Q. You believe it didn't happen?
A. I believe that it didn't happen

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for the reasons noted here.
Q. "We can document, using D. Krah's...," that's Dr. Krah, right, "...notebook, that we developed the assay with laboratory sera and we can build an argument that the assay was validated before we started running."
A. That was Joan Staub's opinion on the matter.
Q. Well, the opinion here is that it was -- withdrawn.
This indicates that it would be a useful thing to build an argument that the assay was validated before the assay started running. Isn't that right?
MS. DYKSTRA: Objection.
THE WITNESS: That was Joan Staub's opinion because this is a note written by her.
BY MR. BEGLEITER:
Q. So she has an opinion and you have an opinion?
A. And other people may have had other opinions.
Q. Right. Okay.

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A. So this would certainly not be my perspective.
Q. Now, do you know what a summary report is of a validation protocol?
A. Exactly what it says. It is a report of the validation study that was done.
Q. Was one done for Protocol 007?
A. I don't recall if -- well, there was a report -- there was a report that we noted in my reply to the CBER 483 from the statistical group, I believe that's what you're referring to.
Q. Did you write that summary report or did somebody else?
A. No. That would have been written by the statistical group.
Q. Is that Mr. Antonello's group?
A. That would have been Mr. Antonello's group.
Q. Going back to 23, a document that you signed at least on the second page of it, I just want to make sure I understand this. The third sentence at the top, "It is understood that these experiments will be performed in a GLP compliant laboratory to

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ensure the validity of the data." Okay. And was it your testimony that in order to be a GLP compliant laboratory you needed an SOP?
A. You needed to operate in the context of existing, approved and filed standard operating procedures, yes. And they could relate to any one of a number of different factors in the laboratory.
Q. Okay. Isn't GLP reserved for testing in the experimental non-clinical research arena?
A. The way the terminology is used today, yes. It is used specifically to refer to that. Back in the day, 20 years ago, the terminology was used much more loosely.
Q. Do you know what Form 1572 is?
A. I don't recall off the top of my head, no.
Q. Is there a form that a principal investigator and the study sponsor are required to sign committing to conduct the study under accepted norms including GCP compliance, not just with regard to the subjects but with all testing? Does that ring a bell?

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MS. DYKSTRA: Objection.
THE WITNESS: Okay. Yes.
BY MR. BEGLEITER:
Q. You know about that?
A. Well, it would be a standard operation to be conducted but that refers to the clinical investigator. The way he described it specifically to the clinical investigator and the testing referred to there would be testing performed by the clinical investigator.
MR. BEGLEITER: Let's get this one. 126340. Let's have it marked. It's 24. I'm asking the court reporter to mark as an exhibit Merck 126340 through Merck 126351.
- - -
(Exhibit Emini-26, 2/5/02 Letter with attachments, 00126340 - 00126351, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. Your name is not in this document. Are you familiar with the forms that are attached here?

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A. Allow me a moment.
Q. Investigational New Drug Application.
A. That is your standard IND form that goes with all correspondence associated with an open IND, as was the case here. And then there's a form related to the statement of investigator. In this case it was a protocol amendment related -- I'm just reading what's in the memo. And the note related to a new clinical investigator, new clinical side being brought on board, into the study.
Q. To your knowledge, was a 1572 form filled out for MMR II Protocol 007?
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. If you know.
A. I don't know -- so this is a Form FDA 1572 but relating specifically to this single investigator, April Palmer, MD.
Q. Notice on the front page it does make reference to Protocol 007. It gives the title of it.
A. Yes, that's right. And presumably this form would have been filled

out by all the other investigators involved in the study as well.
Q. And does this form contain a commitment that the study sponsors required -- is committed to conduct the study under accepted norms including good clinical practice compliance?
A. Would you, please, point that out to me?
Q. Under "COMMITMENTS"?
A. Yes.
Q. "I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects."
Do you see that?
A. Yes, I do.
Q. Are you familiar with 21 CFR part 50?
A. I am not specifically familiar with the details of that particular part of the CFR.
Q. Move on.



A. Again, these are commitments that relate specifically by Dr. Palmer to Dr. Palmer.
Q. You mentioned a couple of times you had a conversation with Steve Krahling before the unannounced inspection?
A. Again, not direct recollection of the conversations themselves, per se, but upon review of documents.
Q. Now, we discussed before, I don't know whether you agree or not, that there were some problems in the lab with personnel and the way the lab was being run.
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. Actually in e-mails where there was some criticisms?
A. Yes, there was, that's right. You showed me e-mails where there was some criticism.
Q. And did there come a time when you invited Dr. Krah's lab to come to your office to meet with them?
A. Again, I have no recollection of the event.



Q. Was this a regular occurrence where you would bring in entire labs, people and have discussions with them?
MS. DYKSTRA: Objection.
THE WITNESS: It would not be an unusual occurrence.
BY MR. BEGLEITER:
Q. And was the lab in a different building from your office?
A. I recollect that the laboratory was in the same building as my office. It would have been building 16.
Q. Did there come a time when you met with them, with Dr. Krah's -- excuse me, with the lab personnel in Dr. Krah's laboratory and advised them to follow Dr. Krah's orders?
MS. DYKSTRA: Objection.
THE WITNESS: As I mentioned, I have no recollection of direct -- of any such meeting -- of any meeting, period.
BY MR. BEGLEITER:
Q. Do you have any recollection of discussing bonuses with any members of



Dr. Krah's lab?
MS. DYKSTRA: Objection. Asked and answered.
THE WITNESS: I have no recollection.
BY MR. BEGLEITER:
Q. Do you have any recollection of discussing double bonuses with people in Dr. Krah's lab?
A. That's the same question. I have no recollection.
Q. Now, you saw documents where Dr. Shaw advised you that people in Dr. Krah's lab were working very hard --
A. Yes.
Q. -- including nights, weekends and holidays?
A. Yes.
Q. Did you ever tell anybody, whether it's the entire lab or just individuals, that there was a fall of 2001 deadline to get Protocol 007 completed?
MS. DYKSTRA: Objection.
THE WITNESS: I have no recollection.

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BY MR. BEGLEITER:
Q. Whether you told them or not, was there any kind of deadline, whether imposed by CBER or self imposed by Merck?
A. Well, again, based upon review of the documents and overall what was happening at the time, did it, in fact, appear to be a deadline, yes.
Q. My question was, was it a self-imposed deadline or was something that CBER wanted?
A. That I cannot answer because that I really don't know the answer to. I don't know if it came out as a result of a discussion with CBER or if the company decided that it needed to be self imposed for some reason.
Q. What kind of stresses did that cause to get this thing, to get it done by a certain date?
MS. DYKSTRA: Objection.
THE WITNESS: You have to be more specific than that. Stress is --
BY MR. BEGLEITER:
Q. Do you recall what the deadline

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was to get Protocol 007 completed?
A. Would I surmise it that the deadline -- no, I don't know what the exact deadline was, but that there was certainly a date in order to be able to get results by a given day.
Q. And you don't --
A. I can't give you a specific date because I don't remember.
Q. Can you give the reason why that was done at all?
A. As I said, other than the -- it was there, I don't recall the reason for it.
Q. When did you first meet Steve Krahling?
A. I gather, to the best of my current recollection, it would have been right after he joined the laboratory.
Q. Did you visit the laboratory?
A. I recall being in the laboratory on a couple of visits, but I cannot recall the context.
Q. Did there come a time when Mr. Krahling contacted you for any purpose?
A. Again, upon --

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MS. DYKSTRA: Objection. Asked and answered. Go ahead, you can answer.
THE WITNESS: Thank you. Upon, again, review of documents, I was shown a memo that Mr. Krahling had written to me concerning HR and personnel-related issues in the laboratory, or observations that he had that concerned him.
BY MR. BEGLEITER:
Q. Who did you get the memo from?
A. If I remember correctly, it was directly from Mr. Krahling.
Q. Who brought you the memo?
A. Oh, I can't -- I don't recall. It may have been sent by e-mail. It could have been an e-mail actually. I don't even remember.
Q. You mentioned Bob Suter. Did you discuss Mr. Krahling with Bob Suter at any point?
MS. DYKSTRA: Objection.
THE WITNESS: I may have. Again, I cannot recollect the specific

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event where I sat down with Mr. Suter to discuss Mr. Krahling.
BY MR. BEGLEITER:
Q. Did you discuss Joan Wlochowski with Mr. Suter?
A. I have no recollection of the specific event.
Q. How long had you worked -- withdrawn.
Was Bob Suter, Mr. Suter assigned to your division?
A. I recollect that Mr. Suter was the senior HR support person for my department, yes.
Q. Did he set up a meeting between you and Mr. Krahling?
A. As I said, I don't recollect having a specific discussion with Mr. Suter about Mr. Krahling. So I obviously have no specific recollection of such a meeting.
Q. Well, the question wasn't asked about whether you had a conversation. You said did he set it up. He could have set it up by e-mail.
A. I don't recall.

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Q. Did he make a recommendation to you that there be a meeting between you and Mr. Krahling?
MS. DYKSTRA: Objection.
THE WITNESS: Again, I do not recall.
BY MR. BEGLEITER:
Q. But you do recall there was a meeting --
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. -- with you and Mr. Krahling?
A. Upon review of the documents there was a suggestion that there was a meeting, yes.
Q. Which documents did you review that suggested that?
A. There was -- if I remember correctly there was a document that was sent by -- to me by Mr. Suter actually. There was a notation on the document relating to the fact that Mr. Krahling had shown me, though I don't know who made the notation, it was a handwritten notation, Mr. Krahling had shown me data that caused him some concern.

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Q. Caused Mr. Suter some concern?
A. Caused Mr. Krahling some concern.
Q. Mr. Krahling. Okay.
Do you recall what the category of data was?
A. I do not recall the exact data that was -- or what was shown to me.
Q. Was a meeting ultimately set up in your office?
MS. DYKSTRA: Objection.
THE WITNESS: Well, again, to my recollection, that was data that was shown to me, that was shown to me by Mr. Krahling. So this was the event that I was referring to earlier that then led to my contacting counsel.
BY MR. BEGLEITER:
Q. Was that meeting a scheduled meeting in the sense that it wasn't a surprise?
MS. DYKSTRA: Objection. Form.
THE WITNESS: I have no recollection. I don't have specific recollection.
BY MR. BEGLEITER:

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Q. I mean, did he come to your office unannounced?
A. I don't have specific recollection.
Q. What did Mr. Krahling bring with him to the meeting?
MS. DYKSTRA: Objection. Asked and answered.
MR. BEGLEITER: No, he --
BY MR. BEGLEITER:
Q. Go ahead.
A. Only what was noted on the note that I reviewed, right, that he showed me some information, some data. I don't remember the exact terminology. So, again, I have no specific recollection of the nature of what I was shown.
Q. How long did this meeting take?
A. I have no recollection of the meeting here, per se, so I can't tell you how long it took.
Q. You don't recall the meeting but you're convinced that there was a meeting?
A. Only because it is documented, the documents suggest that there was a meeting

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and it led to an event afterwards, a follow up.
Q. Did the document contain your version of a meeting with Mr. Krah?
A. This was a document sent to me, again if I recall correctly, from Mr. Suter. Again, since I have no clear recollection of the meeting or what was seen, my only recollection is, in quotes, my recollection in quotes is what is in the document.
Q. And from that document does it appear that that document contains your version of what happened at that meeting?
A. I don't recollect the meeting so the answer to the question is I don't know.
Q. Whether you recollect the meeting or not is not my question. My question is whether or not did it appear to contain your version of what happened sometime. Maybe meeting is the wrong word.
A. Well, it was Mr. Suter's version of it because -- but, again, this was a handwritten note on the side of this memo and I don't recall, nor am I certain that I really know who wrote that note.

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Q. What was the subject of the memo?
MS. DYKSTRA: Objection. Form.
THE WITNESS: I don't recall the exact subject of the memo. I do recall that it was also a heavily-redacted memo. So obviously there were other things in that there had nothing to do with mumps.
BY MR. BEGLEITER:
Q. So you can't recall if there's a meeting but there's a memo which talks about --
A. There having been one.
Q. -- there having been one. Okay. And did Mr. Krahling bring with him any counting sheets? I'm asking you --
A. I don't recall.
Q. Trying to refresh your memory. Did he bring with him any counting sheets?
A. I don't recall.
Q. Did he bring with you a mock control plate?
A. I don't recall.
Q. Did he bring with you any kind

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of cell plate?
A. I don't recall.
Q. Did Mr. Krahling ask you to examine the monolayer on the plate and tell him how many plaques he saw?
A. I don't recall. This is 17 years ago.
Q. Do you recall what Mr. Krahling asserted that was -- do you recall what Mr. Krahling asserted that was going on in the lab which he thought was improper?
MS. DYKSTRA: Objection. Asked and answered.
THE WITNESS: I don't recall the details. But obviously whatever was asserted led me to bring it to the attention of counsel immediately thereafter.
BY MR. BEGLEITER:
Q. Was Mr. Suter in the -- did the memo that you saw indicate that Mr. Suter was in the room and overheard anything, any conversations between you and --
A. Not that --
Q. Let me finish. And

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Mr. Krahling?
A. No.
Q. In terms of temporal terms between the time of when you went to seek legal advice, we can fix -- can we fix the date on that? When did you seek legal advice? Again, I'm not asking for the legal advice. I want to know when you sought it.
A. It was obviously immediately thereafter because the FDA inspection occurred, if I remember correctly, it was only roughly a week, maybe two weeks thereafter. I don't recall, so it was immediately thereafter. So my seeking of legal advice occurred between the time I spoke with Mr. Krahling and the time that the FDA inspection occurred. I suspect very strongly it occurred almost immediately after Mr. Krahling came to me.
Q. Did you suspect that Mr. Krahling was the cause of the inspection?
A. No. No. I mean, it -- did I make the connection at the time? No, I actually -- I remember very clearly in my own mind, this I remember clearly, not making that

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connection, interestingly enough.
Q. You thought to yourself that this is not because of Stephen Krahling?
MS. DYKSTRA: Objection. Say that again.
BY MR. BEGLEITER:
Q. I'm trying to accurately paraphrase what he said.
A. I remember clearly. The thought may have occurred to me, although, you know, subsequent to that, but on that day that the agency inspector showed up, that did not cross my mind at that time. That was likely because I was very focused on the fact that an agency inspector had shown up, and we needed to get everybody together to do what needed to be done.
Q. Before that date, how often in your career had there been an unannounced visit from the FDA?
A. Well, it would not have happened to me because very rarely would a research laboratory have been put into a position of running the assay the way in which this was done.

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Q. I'm only asking about you. Prior to the unannounced visit on August 6, 2001, how often had there been an unannounced visit to one of the labs under your supervision?

A. Under my supervision?

Q. Yes.

A. Never before. This was the first time.

Q. Was this a startling event for you?

MS. DYKSTRA: Objection.

THE WITNESS: Well, it was an event that one remembers. That event I remember clearly associated with that one. Whether it would be startling, probably not because unannounced FDA inspections of ongoing clinical studies and/or of ongoing production facilities are not unusual. It happens all the time because we had a laboratory under my supervision that was involved in the conduct of a clinical assay in support of a clinical study and having an unannounced inspection from the agency

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was startling only because the agency showed up unannounced, but it was not an unusual event, if that was your question.

BY MR. BEGLEITER:

Q. Had you ever been -- had any laboratory under your supervision ever before been accused by the FDA of changing data?

MS. DYKSTRA: Objection.

THE WITNESS: No. But it never -- the opportunity for such an accusation if it were ever to be made never existed, but it existed with regard to a Protocol 007 only because there was the laboratory actually running the assay.

BY MR. BEGLEITER:

Q. Which was a rare event. Who else would run the assay if not for the laboratory?

A. It would be either an external testing laboratory or another testing laboratory within the facility or a testing laboratory responsible for clinical assays over in the manufacturing division for the

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studies that they supported. What was unusual, if you want to use that terminology, was the fact that we were running these clinical assays in a laboratory, Dr. Krah's laboratory, that was originally designed to support assay development, to support research. But unannounced -- going back to your previous question, unannounced agency inspections related to any product, product under development, product that was licensed and produced, happens all the time.

Q. Let's go back a second. So it was unusual, to use a word I think you were using, for the lab that developed the assay to actually do the assay testing, conduct the assay?

A. Normally that would not be the case, and as noted in one of the documents that you showed me earlier today, it was noted in there that normally we would have transferred the assay onto a testing laboratory.

Q. Typically?

A. Typically. Typically, usually.

Q. We've already gone over why that

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wasn't done.

A. We've gone over why that wasn't, because there was time pressures.

Q. Did you see a lawyer after -- a Merck attorney, again I don't want to know what he told you or you told him, but with regard to the unannounced visit, unannounced inspection, did you seek advice?

A. I do not recollect.

Q. Let me be clear. Going back a second. You went to see a lawyer after you -- after something happened with Steve Krahling, whether it was a meeting or something else, you're not sure. It was a meeting that is recorded?

A. It's a meeting that's recorded. I don't recollect the specifics of the meeting.

Q. Did you at that point -- again, before the announced visit, did you at that point consider terminating Mr. Krahling?

A. Oh, I don't recollect at all having ever thought that at that point. The reason why I went to counsel was because in response to what Mr. Krahling presented to me,

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and I felt that I should bring it to counsel. I'm going to leave it at that.

MS. DYKSTRA: Just caution you not to get into privilege.

MR. BEGLEITER: I'm not going to ask him.

MS. DYKSTRA: I wasn't cautioning you. I was cautioning the Doctor.

THE WITNESS: She was yelling at me.

BY MR. BEGLEITER:

Q. Were you accompanied to counsel by Dr. Krah or Dr. Shaw or did you go yourself?

A. I don't recall the specifics.

Q. Did you discuss Mr. Krahling's interaction with you with Dr. Krah?

A. Did I discuss -- with Dr. Krah. I don't recall.

Q. How about with Dr. Shaw?

A. I do not recall the specifics. I don't recall. I don't recall if I had the meeting. I don't have the specifics of the meeting. Again, it was 17 years ago.

Q. And do you recall -- I'd like to

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just make sure I know exactly what words, as best you can remember, what you have -- what Mr. Krahling orally, in writing, whatever, communicated to you about what was going on in the lab.

MS. DYKSTRA: Objection. Asked and answered.

THE WITNESS: Only by what was in the memos that were shown me. There was the original communication which, as best as I can tell, was solely by memo, whether it was by memo or by e-mail, whatever the case happens to be, in which Mr. Krahling referred specifically to HR-related issues. It was solely HR-related issues at that point. And then sometime subsequent to that, there was a subsequent meeting in which whatever Mr. Krahling showed me, and, again, I don't remember the specifics of it, led me to approach counsel.

BY MR. BEGLEITER:

Q. Does that memorandum that Mr. Suter apparently put together --

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A. That was reporting the second meeting.

Q. Right. What do that --

A. Or the second interaction.

Q. What do you recall that memo said about what Mr. Krahling had told you?

A. Just what I said. There was a handwritten notation on the memo. It was a wholly redacted memo. It was a handwritten notation, and I don't know who wrote the notation. Again, just for clarity, I don't know whether it was Mr. Suter or anybody else who wrote the notation noting that Mr. Krahling had showed me, if I remember -- if I remember correctly, had showed me some information that caused concern, or that was concerning to Mr. Krahling.

Q. Was there, after the unannounced inspection, did you commence any kind of internal -- withdrawn.

After that unannounced inspection, was there any internal investigation that was conducted?

A. Well, we conducted a full audit as noted in the response that went back to

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CBER approximately 20 days later. These are all standard procedures that one follows to address the observations of the inspector. And also oftentimes what one does is one goes beyond that to say, okay, so this is what the inspector saw, therefore, we will address what the inspector specifically saw. What we will also do is conduct a broader assessment to make sure that even though the inspector didn't shine a light on something else, that everything else is also operating the way it's supposed to operate. So it's not unusual to do that.

Q. Was there a witness' interview?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I was not involved in the overall audit so I can't tell you.

BY MR. BEGLEITER:

Q. I didn't ask you whether you were involved. I asked you whether to your knowledge --

A. To my knowledge.

Q. To your knowledge were witnesses interviewed?

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A. I don't recollect.
Q. Were you interviewed by anyone?
A. I actually don't recollect.
Q. Again, I'm not asking what was said to counsel. Wasn't what you said to counsel --
A. No. You're talking about the post 483.
Q. No. I'm talking -- well, what I'm asking -- I'm not going to ask what was said, but did your counsel interview you?
A. I do --
MS. DYKSTRA: Objection.
THE WITNESS: But I don't recall.
BY MR. BEGLEITER:
Q. Did you ever advise Mr. Krahling not to call the FDA about any problems he had in the lab?
A. Not to my recollection.
MR. BEGLEITER: Take a break now, and then I think we can -- I'm trying to see if I can wind it up. I'm not promising.
VIDEOGRAPHER: Time is now 4:53. We're going off the video record.

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- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is now 5:16. We're back on the video record.
BY MR. BEGLEITER:
Q. Doctor, during the assay, the PRN assay in Protocol 007, did Dr. Krah's lab find that there were lots of vaccine that were out of compliance with the label, if you remember?
A. Not that I -- well, you have to define the word "compliance" for me.
Q. Well, where the end expiry was below 4.3?
A. I don't recall.
Q. You said there were three arms of the test, right, 4.9, 4.0 and 3.7.
A. That were being tested in the 007 clinical trial, three potencies of the vaccine.
Q. Did the lab find that any other lots were below 4.0?
MS. DYKSTRA: Objection.
THE WITNESS: The study 007 was

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not looking at individual lots. Sorry, I don't understand your question.
BY MR. BEGLEITER:
Q. There was a preliminary subset. Is that correct?
A. There was an earlier subset looking at a subset of sera, yes.
Q. And during the course of this test, was MMD, did MMD do its own testing to determine if there were lots that were below 4.0?
MS. DYKSTRA: Objection.
THE WITNESS: My apologies, but you're talking about two different things here which is confusing the question.
BY MR. BEGLEITER:
Q. Make it simple. With regard to in the 2000-2001 period, did MMD, Merck Manufacturing Division, do any testing to see if any of the lots that had been sent down to -- for use had below 4.0, had a below 4.0 spec?
MS. DYKSTRA: Objection.
THE WITNESS: I do not know of

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specific data from MMD. I would not have seen it and I don't know.
BY MR. BEGLEITER:
Q. Let's show it to you.
- - -
(Exhibit Emini-27, 2/26/01 E-mail, 00549510 - 00549535, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. I'd like to show you what's been marked as Merck 549510 through 549535.
I'm actually going to ask you to focus on the very first paragraph under "Ed" on the first page.
A. Okay.
Q. And first of all, is this a document that you received in the usual course of your -- is this a document that you received in the usual course of your employment at Merck? Let me ask the question, is the document that you received in the usual course of your employment at Merck?
A. Yes, it is.
Q. And tell me, sir, in that first

paragraph, the first sentence, "We have been assisting MMD in responding to CBER questions re mumps end-expiry by performing an interim analysis on 600 children participating in the mumps end-expiry study (200 per group, studied at mumps potencies of 4.9, 4.0 and 3.7)."

Do you see that?

A. Yes.

Q. That study, was that study part of the Protocol 007?

A. Yes.

Q. Now, did that study in the preliminary subset indicate that lots below 3.7 were not -- did not meet the requirements of immunogenicity?

MS. DYKSTRA: Objection.

THE WITNESS: No, that is not the result. The result is indicated right here in the memo. It says in the last paragraph on that first page, all the way down at this bottom, it describes the neut assays. It says, "By the neutralization assays, ...and end-expiry of 4.0...," remember this was one of the three levels that were



tested in 007, "...meets CBER's demand...," as was noted here, CBER's perspective criteria for 90 percent seroconversion rate. So 4.0 is fine. While the 3.7 log titer misses, right, with 88.2 percent seroconversion rate but a 95 percent confidence interval of 82.3 to 92.6.

Now, going back to our earlier conversation from today, this is not an assessment of efficacy. Rather what this is, is a measure of the ability of the vaccine at these three different tested potency levels to elicit a measurable immune response as measured by the assay. CBER obviously placed a criterion around what they would accept as given the assay of an acceptable seroconversion rate, criterion that was established on the basis of, I'm not exactly certain what, but they established it at 90 percent, that that's what they wanted to do, and they did it. You will note that the confidence interval crosses 90 percent.



BY MR. BEGLEITER:

Q. It then says --

A. It then says, Jerry, that would be Gerald Sadoff, and I feel 3.7 is medically okay and would be defensible to the office of compliance. And based on the data, I would agree.

Q. The last sentence of that paragraph under "Ed" it says, the last two sentences, "The less than 3.7 lots are of particular concern; the 3.7 to 4.0 lots are likely defensible with some additional work." And then it says, "All 106 lots are a compliance issue."

Do you see that?

A. Right. So I don't know what the -- I believe the 106 lots are referring to the lots that they believe at end expiry may be below. It's unclear from what's written here. Maybe below that declared level which the agency had declared at 4.3. The data, I'm reading the penultimate sentence in the first paragraph, the 3.7 to 4.0 lots are likely defensible. And given the data at the end of this page, I would agree, they are defensible



because the data are not ostensibly different between 4.0 and 3.7.

The reason why the 3.7 lots are of particular concern, less than 3.7 lots are of particular concern is that there are no data on the level of seroconversion that would be -- that would occur because the study only went down to 3.7 lots, so what would happen at 3.5, 3.4, any lower number, there are no data. So it's classic unknown lines.

Q. But there was data at 3.7 and 4.0. Is that correct?

A. Right there, yes.

Q. So I'm asking about the -- I'm talking about the lots which were between 4.0 and 3.7. Those are the -- aren't those the lots, 106 lots which are a compliance issue?

MS. DYKSTRA: Objection.

THE WITNESS: The wording is unclear, but it may refer that -- those 106 lots may refer to those lots between 3.7 and 4.0.

BY MR. BEGLEITER:

Q. You got this e-mail on February 23, 2001?

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A. Okay. Yes.
Q. And did you do anything about that after learning that 106 lots may be a compliant -- are a compliance issue?
A. That is a matter of regulatory discussion between the company and CBER. There was nothing for me to do.
Q. Do you know how many doses there are in 106 lots?
A. I don't know how many doses are in a lot.
Q. You weren't consulted on what to do with those 106 lots?
MS. DYKSTRA: Objection.
THE WITNESS: No, because I would not have been consulted. The data are very clear and I would not disagree with the conclusions here. The 106 lots, what we know from the 007 data from the initial analyses that were done, is that at 3.7 the seroconversion rate has a confidence interval that crosses 90 percent. So statistically there is no difference in the seroconversion rate on a potency of

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4 or a potency of 3.7, which is why -- which is why there was the statement here saying that Jerry, who was in medical at the time and Dorothy Margolskee together agreed that 3.7 is medically acceptable and defensible, and she says it twice.
BY MR. BEGLEITER:
Q. But I'm talking about the lots between 3.7 and 4.0.
A. That's the one I'm talking about.
Q. So there is no --
A. There are only -- I'm sorry.
Q. Do you know what the FDA was informed of this?
MS. DYKSTRA: Objection.
THE WITNESS: In continuous communications I don't know personally whether or not the agency was informed but these were the kinds of things we shared continuous communications between the agency and the company. And given that this was a question, existing question of where to establish

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the end expiry number, and remember the number had been established by the agency at 4.3 initially simply because it was simply the number that was in the original label that you showed me this morning and therefore the agency said this should probably be the end expiry number, without there being any data supporting whether it should be that number or a lower number or for that matter a higher number, which is why the 007 was being conducted, in that sense a formal compliance accepting 4.3 as representative of the end expiry number which is the way the agency interpreted it in the initial communications, then by definition, they are these lots that are below 4.0, certainly below 4.3, are a potential compliance issue, but not a medical issue.
BY MR. BEGLEITER:
Q. If it was -- how do you know that? How do you know it's not a medical issue? How do you know what the consequences

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are -- withdrawn.
How do you know what the conferences are of selling -- of using vaccine below 4.1?
A. Look at the data right here. So what do we know. We know that the vaccine has retained field effectiveness. So we know the vaccine is effective even though there clearly, as is noted here, 106 lots that are between 3.7 and 4.0, with that number of lots with the number of doses probably involved in that number of lots, if this was ineffective vaccine, you would have had a large outbreak of mumps. It was never seen.
So you have 106 lots that fall between 3.7 and 4.0 field effectiveness. The agency was clearly comfortable with that conclusion because 007 is based on the basis that the vaccine's effectiveness still exists. So now the question is where for control purposes do we put the end expiry number in the label.
So they're using seroconversion as a surrogate measure of vaccines immunological potency. All the way down to

3.7, so that would encompass these lots obviously between 3.7 and 4.0. All the way down to 3.7, the seroconversion, 95 percent confidence interval gave a rate that is statistically not different than the number observed at four logs.

Q. If the label says 4.3, which it did, we talked about that this morning.

A. Right.

Q. And at 4.0 to 3.7, there's an understanding at Merck that these are -- there's a compliance issue with regard to those 106 lots. Right?

MS. DYKSTRA: Objection.

THE WITNESS: Relative to the label.

BY MR. BEGLEITER:

Q. Yes, relative to the label.

A. Just be clear, compliance can mean many things.

Q. So whether or not it's medically or not medically a problem, let's assume it's not medically --

A. You --

Q. It's probably medically, but...



A. You can't say it's probably medically, you don't know either.

Q. The lots were being sold as being compliant with the label, weren't they?

MS. DYKSTRA: Objection.

THE WITNESS: The lots were being sold, I cannot answer that question whether or not the supposition was that they were compliant with the label or whether the vaccine was considered to be effective. That is an assessment that is made not just by the company but by -- also by the FDA. The FDA formally releases lots of the vaccine.

BY MR. BEGLEITER:

Q. Let's move on to AIGENT.

You don't know what happened with those 106 lots, do you?

A. I do not.

Q. Those 106 lots would have been used in the late '90s or early 2000s. Is that right?

MS. DYKSTRA: Objection.

THE WITNESS: Presumably, but I



don't know.

BY MR. BEGLEITER:

Q. Do you know that there have been outbreaks over the last several years?

A. There have been, yes. But there have been outbreaks of other vaccines related to diseases as well. So there's nothing to conclude.

Q. You were in favor of using antihuman IgG in Protocol 007 AIGENT PRN. Right?

A. That was a conclusion that was drawn between the company and the agency.

Q. I'm talking about you. That was the question. You were in favor of it?

MS. DYKSTRA: Objection.

THE WITNESS: I was in favor of it because of the nature of what the assay was being designed to do. And I recollect that even prior to the review of the documents, that the original recommendation to use the anti-IgG actually came from the agency.

BY MR. BEGLEITER:

Q. Do you know what document that



is?

A. No, I just have a recollection of the event, that the recommendation came from the agency and within review of documents I saw it as well, but I have an independent recollection.

Q. Were you present when the agency said it was okay to use AIGENT?

A. I cannot tell you under which circumstance I was informed of that, but I do recollect discussions that's where -- that this was an agency-related recommendation.

Q. Sorry, that was a bad question. I mean, were you present when the agency first suggested that AIGENT be used?

MS. DYKSTRA: Objection.

THE WITNESS: That the anti-IgG be used in the assay?

BY MR. BEGLEITER:

Q. Right.

A. I do not recollect the circumstance.

Q. What was the purpose of using antihuman IgG?

A. It is a general method to

increase the sensitivity of a virus neutralization assay when the virus neutralization assay is designed to specifically measure virus neutralizing antibody.

Q. So it makes the testing more sensitive, is that it?

A. It makes the testing more sensitive.

Q. And is that a -- by adding the antihuman IgG, is that an artificial way of making the neutralization assays sensitive?

A. I will only answer that question in the context of the definition of the word artificial. The entire assay and all of its components by definition are artificial to the assay.

Q. How about very artificial?

MS. DYKSTRA: Objection.

THE WITNESS: That's a non-answerable question.

MR. BEGLEITER: I'd like to show you a document marked Bates numbers 549462 through 470. Have it marked Exhibit 28.



- - -

(Exhibit Emini-28, 2/26/01 E-mail with attachment, 00549462 - 00549470, was marked for identification.)

- - -

BY MR. BEGLEITER:

Q. I'm going to focus on a paragraph on page 471, the bolded paragraph towards the top.

A. Okay.

Q. Is this a document that you received in the usual course of your employment at Merck?

A. Yes, it is.

Q. Let me read the first sentence. "In talking with Emilio, the neutralization assay is very artificial because of the IgG added; to avoid too many seropositives, very high initial dilutions were required." Do you think you're the Emilio referred to in this sentence?

A. Since I was the only one with that name at the company at the time, I believe so, yes.

Q. So this is a document written by



Dorothy Margolskee?

A. Yes.

Q. So did she accurately relate that in her discussion with you, that somehow the neutralization assay is very artificial because the IgG -- was the IgG added?

A. Well, very is a quantitative term and I didn't write that, Dorothy Margolskee wrote it, so I can't tell you what the context in her mind was when she wrote it. I will agree, as I said a moment ago, that the assay, in all of its components is, quote/unquote, artificial as it is designed to measure only what it is designed to measure. So what did I mean by that?

Q. Answer the question because I was going to ask you that.

A. So this assay was designed to measure virus neutralizing antibody. The effort was made to conduct the assay in such a way that would give rise to a high level of sensitivity. So if you look at the three different dose levels that were studied in the 007 study, the highest dose level was 4.9 logs, so this is well above even the 4.3 that



was listed in the original label of the vaccine. The reason why it was done at 4.9 logs was that the argument is made that we know probably it's highly likely that this is clearly an effective potency level for the vaccine. Simply because going back to the original studies that were done, the original control studies done way back in 1960s with the mumps vaccine, it was done at a potency level, presumably at approximately 20,000, because that's what came in the label. So 4.9 is above the 4.3, more than a half log above, more than a half log above.

So, therefore, the argument is we would like to have an assay that measures seroconversion at the 90 percent level for at least that 4.9 log level that's being tested, right, because then we can benchmark what we see at 4 and what we see at 3.7 using a very sensitive assay. So the assay needed to be designed to have a sensitivity of 90 percent.

Now, is what is being measured, that immunological response that is being measured, is that the actual immunological basis for the vaccine's efficacy? That is not

known. Even to this day it is not known. But it is considered to be a surrogate measure of the immunological response to the vaccine and, therefore, a surrogate of effectiveness. But remember it's a surrogate. True effectiveness can only be established out in the field. So, therefore, what was done under these circumstances, the assays by definition is artificial.

So what was the first thing that was done? The first thing that was done was to find a wild type strain that gave the original assay a level that began to approach 90 percent. Hence the moving from the London-1 strain to the low passage Jeryl Lynn strain. So that was a change. It's designed to change the assay to reflect a certain biological response that you want to measure at a given level. The addition of the anti-IgG falls along the similar lines which is an additional step that one put in to enhance the likelihood that you would see that virus neutralizing antibody responses.

So in the same sense that switching to the low passage Jeryl Lynn strain



is artificial because it is a function of the assay, the same thing is true for the addition of the anti-IgG.

Q. So it's a way of -- so it's another way of getting results that agree with what's going on in the field. Is that what you're saying?

A. It is another way of getting results using, at a level of sensitivity that would allow you to distinguish any differences in the ability of the vaccine at the three tested dose levels in 007 to elicit an immunological response as measured by the assay.

Q. So this was all the -- the two things you're talking about, the wild type, Jeryl Lynn being used over, let's say, the London-1 and using antihuman IgG --

A. Right.

Q. -- after the initial testing did not meet what CBER was looking for?

MS. DYKSTRA: Objection.

THE WITNESS: In terms of sensitivity.

BY MR. BEGLEITER:



Q. Okay. And the way of making it sensitive and the way of getting the results that CBER was looking for was to add the anti-IgG and use the wild type Jeryl Lynn?

MS. DYKSTRA: Objection. Form.

THE WITNESS: With their concurrence because they wanted an assay that was sufficiently sensitive to distinguish among the three different potency levels being tested in 007.

BY MR. BEGLEITER:

Q. I'm going to show you three documents, and the only purpose is for authentication. Identify whether you received these documents in the usual course of your employment. I'm not going to ask you substantive questions.

A. Yes.

- - -

(Exhibit Emini-29, E-mail exchange, 00549497 & 00549498, was marked for identification.)

- - -

MS. DYKSTRA: Do you want to



give me all three, maybe I can stipulate to the authenticity?

MR. BEGLEITER: Well, if you give them back to me, I'm not going to use it. I thought this was a document that had your name on it. I apologize. If you could give it back to me, I'd appreciate it.

THE WITNESS: This one?

MR. BEGLEITER: Yeah. Oh, I see. I see.

I'm sorry, we are going to use it. We are going to use it, I'm sorry. It's getting late in the afternoon. We are going to use it.

BY MR. BEGLEITER:

Q. So I'd like you to take a look at this, sir. Your name is not on it, but the very first sentence -- this is, by the way, document 549497 through 498. The first line reads: I have given Emilio...60 cases -- 60 case numbers to re-test (the 42 failures plus 17 marginal positives).

MS. DYKSTRA: Can we have a copy?

BY MR. BEGLEITER:
Q. "I believe he will try to re-test them with both ELISA (wild-type mumps) and the wild-type neutral." [As read].
Are you the Emilio referred to here?
A. I believe I am, yes.
Q. Okay. Put it away.
I'm going to give the court reporter Merck 68264 through 68271, ask her to mark it, please. 30.
- - -
(Exhibit Emini-30, 11/10/00 E-mail with attachment, 00068264 - 00068271, was marked for identification.)
- - -
BY MR. BEGLEITER:
Q. Sir, I'm just going to ask you on this document whether you received this in the usual course of your employment?
A. Yes, I did.
Q. Put it away.
MR. BEGLEITER: If you guys give me five minutes, one last look and see if there's any more questions. Take a



short break.
VIDEOGRAPHER: The time is 5:46. Going off the record.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is now 5:50. We're back on the video record.
BY MR. BEGLEITER:
Q. Sir, isn't it true that every submission that Merck sends to CBER must be audited --
MS. DYKSTRA: Objection.
BY MR. BEGLEITER:
Q. -- as far as you know?
A. As far as I know. That's standard practice, yes, of course.
Q. Who is supposed to audit CBER submissions?
MS. DYKSTRA: One second. I don't think the Doctor has his microphone on.
BY MR. BEGLEITER:
Q. Your voice carries.
Who is supposed to audit CBER



submissions?
A. To the best of my recollection, the auditing responsibility is either with regulatory or a quality assurance group within regulatory.
Q. And what does auditing require?
A. Auditing typically requires -- any auditing typically requires that if you're reporting on numbers or statements of fact, that there are data, that there are actual original data sources that you can trace to.
Q. Who is actually -- did you audit submissions that Merck made to CBER about Protocol 007?
A. Did I audit?
Q. Yes.
A. No, I would not audit it. No, auditing is a very formal function.
Q. Did you ensure that quality assurance audited Merck's submissions regarding --
A. I don't recollect -- sorry. I don't recollect if I specifically requested auditing for -- on quality assurance for CBER submission, but that normally would have been



done by the regulatory group.
Q. Okay. So it was their prime responsibility, the regulatory group, not yours?
A. CBER submission is a regulatory document and, therefore, it is the responsibility of the regulatory group.
Q. Do you know if CBER was ever sent audit results?
MS. DYKSTRA: Objection.
THE WITNESS: I would not know that.
BY MR. BEGLEITER:
Q. Talking about with regard to Protocol 007.
A. I am not aware.
Q. What state do you reside in?
A. The State of Pennsylvania.
Q. Do you plan on moving?
A. Not by tomorrow I'm not, no. I mean, it's an open question. Do I ultimately plan on moving? I don't know.
Q. I'm someone who doesn't like to ask people's home address on a deposition.
MS. DYKSTRA: I will provide

that to you if you need it.
MR. BEGLEITER: You'll agree to provide it to me if I need it?
MS. DYKSTRA: If you need it.
MR. BEGLEITER: Thank you. I have no further questions.
Your witness.
MS. DYKSTRA: Thank you.

- - -

EXAMINATION

- - -

BY MS. DYKSTRA:

Q. Dr. Emini, I just have a couple of clarifying questions based on your testimony today.
I'm going to mark as Emini-31, I believe.
A. 31.

- - -

(Exhibit Emini-31, 12/1/99 Letter with attachment, 01201 - 01209, was marked for identification.)

- - -

BY MS. DYKSTRA:

Q. Dr. Emini, do you recall -- this



is a December 1, 1999, letter that Merck submitted to CBER. Correct?
A. Yes. Yes, it is.
Q. Do you recall Mr. Begleiter asked you whether or not Merck disclosed to CBER the various seroconversion rates that Merck had obtained using different strains including the Lo1 strain of the virus?
A. Yes, I do.
Q. And if you look at page 2 of this document, can you explain to me what is referenced in the first paragraph that says, "Merck's experience" and Table 2, the chart?
A. So the first paragraph refers to a pilot study that was sera from children who had been vaccinated with MMR II and assay, with assays that were either using the Jeryl Lynn strain, the low passage Jeryl Lynn strain presumably and the London-1 strain as the target strains in the assay. And initial results of the experiments as stated and as shown on Table 2 suggested that the measured seroconversion rate using the Jeryl Lynn strain was on average 91 percent. And you can see the individual numbers here from the three



different series that were tested. And for the London-1 strain was approximately 69 percent when averaged across the two serum series that were tested.
Q. What did Merck's practice, in your experience, in connection with the development of 007 for Merck to be candid and transparent as it is here with the agency?
A. It was in my experience that they were candid and transparent consistently with the agency throughout all of the discussions that we've been referencing today.
Q. You can put that document aside.
I'm going to ask you to pull back Exhibit 6. It was already marked Exhibit 6. Focus your attention on page 1, which is -- Bates label on the bottom is 17043. Again, this is a March 12, 2001, letter from Merck to CBER. Correct?
A. This is correct, yes.
Q. I just want to confirm, you had received questions during your questioning around the company's use of passage 8 of the Jeryl Lynn strain. Do you recall that?
A. I don't have a specific



recollection of the discussion.
Q. Do you recall the discussions with Mr. Begleiter?
A. Yes, I do, certainly.
Q. Do you recall he asked you about the use of the anti-IgG?
A. Yes, I do.
Q. I just want to focus your attention on the first paragraph of the CBER submission. Let me know if this -- either you can read this to us or tell us whether this refreshes your recollection that Merck confirmed with CBER, number one, that CBER suggested the use of the anti-IgG, and that CBER agreed to use passage 8 of the Jeryl Lynn strain in 007.
A. The first paragraph states clearly that "The newly developed plaque-reduction neutralization assay...," although you've been referring to it as the PRN assay, "...using a wild-type mumps strains has been optimized for use in the evaluation of sera from the Mumps Expiry Trial...," this is Protocol 007 as noted. Because the intent was to use a sensitive assay for the reasons

we discussed previously.
Assay description and the standard operating protocol procedure was submitted to CBER as background for the November 29, 2000, conference. And as suggested by CBER during the meeting held on March 13th, the assay sensitivity for measurement of virus neutralizing antibody has been optimized by addition of the antihuman IgG. It notes that the assay relies upon immunostaining to reveal plaques since the virus used in the assay is not ostensibly cytopathic. And, therefore, also it's agreed with CBER during the March 13, 2000, meeting we have chosen the lowest available passage, that would be passage 8.
MR. BEGLEITER: You're reading very quickly.
THE WITNESS: It's verbatim -- my apologies. I can read it again more slowly.
So as I said, "As agreed with CBER...," again, "...during the March 13, 2000, meeting, we have chosen the lowest available passage



(passage 8) of the Jeryl Lynn strain of mumps as being appropriately representative of a wild-type mumps virus strain."
BY MS. DYKSTRA:
Q. This paragraph in the submission to CBER is consistent with your recollection that CBER first suggested the use of antihuman IgG and that they agreed that passage 8 of the Jeryl Lynn strain was appropriate for this assay?
A. It agrees with my recollection of CBER's recommendation to use the antihuman IgG to increase the sensitivity of the assay, again, for the reasons we discussed previously. And with regarding -- I did not have a specific recollection of why the Jeryl Lynn strain was chosen, but that was, recollection occurred, if you will, as a result of looking at documents over the past several days.
Q. Thank you. I'm going to also go back and ask you to look at what was marked Emini Exhibit 11 today. This is a two-page document from -- the first one is from Phil



Bennett and the second e-mail on the page is from Keith Chirgwin. Do you have that in front of you?
A. This one?
Q. Emini-11.
A. 11.
Q. Might be --
A. No, no. It's just getting a little confused here. My apologies. Yes, 11.
Q. So you -- do you recall -- separate and apart from looking at the words on this document, do you recall discussions with Phil Bennett around his stability or any stability modeling he may have done?
A. I do not have a specific recollection of discussions with Phil Bennett.
Q. In the context of determining whether shelf life of the vaccine should be, how does the company determine that and what would they rely on at this point in time -- let me strike that.
You recall you had discussions with Mr. Begleiter around CBER's recommendation and approval to raise the minimum release potency of the vaccine to 5.0



log10 TCID50. Correct?
A. Yes, I do.
Q. In connection with that increase in potency, what would the company do to determine the appropriate shelf life of the product?
A. Well, what would normally be done in the context of an appropriate shelf life is that one would conduct formal stability studies which is, I believe, what I answered before, formal stability studies that would entail actual measurement of virus potency at different time points in realtime with in this case vaccine that had been stored at the accepted storage temperature of the vaccine, which is 28 degrees Celsius.
Q. So is that similar to saying that the company would -- it would be preferable or more reliable for the company to rely on actual stability potency assay results over time versus a stability model in determining appropriate shelf life?
MR. BEGLEITER: Object to the form.
THE WITNESS: Both the company

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and the agency, yes.
BY MS. DYKSTRA:
Q. Thank you. I wanted to just clarify something that -- you had a question during your examination around whether or not you recall where the ELISA assay was conducted. Dr. Krah ran the PRN assay in your building. Correct?
A. Yes, in his laboratory in my building, in the building in which I had my office, yes.
Q. Do you recall that Merck also had a Wayne facility?
A. Yes, I do.
Q. Does that refresh your recollection where the ELISA assay may have been conducted?
A. Again, based on documents that I was shown, yes, the Wayne facility by this time had been put into place and ELISA assay was performed there. The Wayne facility had been put into place specifically to be a physically separate facility for the conduct of clinical assays, or assays in support of clinical studies.

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Q. If you could also pull back Emini Exhibit 7.
A. Exhibit 7.
Q. It's an August 7, 2001, e-mail from Karen McKenney which attaches the 483 and a memo dated August 6, 2001, from Karen McKenney, Kelly Pardue and Cathy Wadsworth.
A. Yes.
Q. I want to focus your attention on the second two pages which are the memo dated August 6, 2000, with the relined "FDA Inspection of Virus and Cell Biology for Mumps End Expiry Plaque Neutralization Assay."
A. Yes.
Q. Can you tell me, do you know who the people on the "from" line are, McKenney, Pardue and Wadsworth, what department they're in?
A. I recall Cathy Wadsworth, I believe that they were either in quality assurance or somehow involved with regulatory, but I'm not completely certain.
MS. DYKSTRA: Can I pause just for a second?
Mr. Krahling, do you mind

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departing just for this, it's the AEO document? Thank you.
BY MS. DYKSTRA:
Q. You said you thought they were in quality assurance. Is that correct?
A. I believe. I don't have an exact recollection.
Q. Can you just describe to me the type of memos these are and whether or not these are routine memos and the purpose of this type of documentation of an FDA inspection?
MR. BEGLEITER: Objection to the form.
THE WITNESS: So these are routine memos that are -- that refer, that provide information and also to the file of what transpired in discussions that occurred during an FDA inspection.
BY MS. DYKSTRA:
Q. And are they -- what is the purpose of them, of these memos?
A. The purpose of these memos is to provide a record of the nature of the

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discussions, to provide a record of specific documents that were provided to the agency or to the inspector at the inspector's request, and to inform management of the relevant personnel of the nature of what transpired.
Q. On the last page of the memo, it says, "COPIES PROVIDED," and a list of documents. Is that correct?
A. Yes.
Q. Would it be the responsibility of the people in QA who prepare this memo to include everything that was provided to the FDA?
MR. BEGLEITER: Objection to form.
THE WITNESS: It would be the responsibility of whomever was asked. What this memo indicates is that these copies were provided, whether they came directly from QA or they came from someone else. But what the memo notes is that all of these copies of these documents were provided to the inspector.
BY MS. DYKSTRA:

Q. Just a couple of more documents we'll look at briefly. If you can look at Emini -- what was marked Emini Exhibit 8, please.
A. Yes.
Q. That is an August 20, 2001, letter from you to CBER in response or following the August 6th inspection. Correct?
A. Correct.
Q. In this letter you have provided answers, and I want to focus your attention on page 1 of 3 under Observation number 1 which is document Bates-labeled 482.
A. I'm sorry, the page notation, yes. Thank you.
Q. And I want to focus your --
MR. BEGLEITER: What page are you on?
MS. DYKSTRA: I'm sorry. The document labeled 482 at the bottom.
THE WITNESS: 482 at the bottom.
BY MS. DYKSTRA:
Q. I want to focus your attention on one, two, the third paragraph which begins, "We take seriously the issue of data integrity."



A. Yes.
Q. You recall Mr. Begleiter asked you about Dr. Krah's and/or anyone else's counting or recounting of the assay plates in the PRN assay. Do you recall those questions?
A. Yes, I do.
Q. In this statement to the agency you relate an assessment of the uncorrected and corrected results. Do you see that?
A. Yes, I do.
Q. Can you explain to me what this paragraph means and how you interpret this or what you recall of it?
A. Well, the correction as referred to here would have been the correction that was noted by the inspector when the 483 was issued, the first observation of the inspector, that there were some data numbers that had been corrected but without there being a written justification for the correction. So that obviously opens the question as to why this was done and why was the correction made.
So part of the answer here, of course, is that, you know, obviously one's



concern is that there may be an issue of data integrity or not, so we conducted the set of audits to show that that was not the case. But on top of that, and this is routinely done as well, which is to say let us make the assumption that the corrections, that refers to those corrections that were made without justification, should not have been made. And what if one analyzes the data using the original uncorrected data. And what does one get. Does one actually see a substantial difference either one way or the other. And what one is looking for, in fact, is a difference that might in some way favor the outcome of the study obviously. So that's what one looks for. But as we're seeing here, is that the overall seroconversion rates, in fact, ostensibly didn't change. Overall seroconversion rate on the analysis turned out to be the original analysis with the uncorrected data -- excuse me, with the corrected data, the original analysis resulted in the 92 percent seroconversion rate with a 95 percent confidence interval as noted between 89.6 percent and 94.3 percent. By



reanalysis where one goes back to the original numbers, the overall seroconversion rate was 92.6 percent with a confidence interval of 90.2 percent to 95.1 percent. So what that indicates, given the significant overlap between -- among the two confidence intervals is that whatever changes were made and whatever the basis was, because it wasn't noted, did not change the results. If anything, if one was looking to potentially raise the seroconversion level to a higher number, the effect of the corrections which were made which were not justified in the document actually lowered the seroconversion numbers.
MS. DYKSTRA: I'm going to mark two more documents. I believe we're on Emini-32.
- - -
(Exhibit Emini-32, 10/10/01 Letter, 01631027, was marked for identification.)
- - -
BY MS. DYKSTRA:
Q. Dr. Emini, if you can look at

what's been marked as Emini-32, which is an October 10, 2001, letter from Manal Morsy to Cathy Carbone at CBER, Bates-labeled 1631027. I want to ask you whether or not, number one, this refreshes your recollection with respect to your questioning today around Dr. Ward at all and/or -- just ask that.

Does this refresh your recollection, this document with respect to what Dr. Ward's lab -- what role Dr. Ward's lab had in connection with 007?

A. According to this memo, the only immediate connection was that, as Dr. Shaw explained in the reading now, the one, two, three, four, fifth paragraph down, Dr. Shaw explained that the only positive and negative controls sera samples were provided to Dr. Ward. So these would typically be the samples that would be provided to do an initial assessment of the quality of the data from the laboratory to determine whether or not the results that Dr. Ward would obtain would be similar to the results that were obtained in the Merck laboratory. And as he notes, the results for the control samples,



which is what those were, are consistent with the Merck results. Dr. Shaw explained that all the raw data from Mr. Ward's laboratory had been provided to Ms. Debra Bennett from the agency during her last visit to the research laboratories, and the specific data were given the geometric mean titers for the two sera representing high and low value are contained in the validation report which was also previously supplied to CBER.

We believe this was probably, I believe, I believe that this was probably in response to a question from the agency as to whether or not there were potential or significant differences between the values that would have been generated in Dr. Ward's laboratory as opposed to the Merck laboratory, Dr. Krah's laboratory and the results of the data that were presented or submitted to the agency is that that was not the case.

Q. The serum samples -- the sera samples that were provided to Dr. Ward's lab were not the 007 clinical sera samples, but control samples used to, I guess, validate the lab prior to actually running the clinical



study?

A. Known negative samples and known positive samples, yes.

Q. And known negative and known positive mean what?

A. These are samples where you know that the known negatives do not contain the antibody that you're measuring. They're known to that because you've assayed them many times in different tests. The known positive samples are samples from individuals who have a range of antibody responses to what you're measuring, which in this case is the mumps virus.

Q. And known meaning based on other assays, not Protocol 007?

A. Based on other assays. It is known that they should register as positive. The objective of the doing the study is to see what number came out and to correlate that number with the numbers obtained between the two laboratories of Dr. Ward's and the company.

Q. I'm going to show you one last document which I've marked as Emini-33.



- - -

(Exhibit Emini-33, 4/8/01 Letter, 0000328 - 0000331, was marked for identification.)

- - -

BY MS. DYKSTRA:

Q. It's a little bit lengthy, April 8, 2001, it looks like a letter to you signed by on page 4 Stephen Krahling, Bates-labeled RELATOR_000033 looks like 8 -- 328, 329, 330, 331. Can you take a look at this and let me know what you recall, if anything about this document or generally about Mr. Krahling's complaints to you regarding HR issues in Dr. Krah's lab?

A. So this is the document that I reviewed prior to today and that I believe referred to in my previous testimony that had been shown to me and by which I recall that I did, in fact, receive this document from Mr. Krahling in which Mr. Krahling documented rather extensively his perspective that the, call it, the HR environment within Dr. Krah's laboratory was, in fact, in his opinion problematic.

Q. And I see in the second paragraph he comments around highly personal relationships with female employees and personal gifts. Do you see that?
A. Yes, I do.
Q. And in the third paragraph he raises issues around work schedules. Do you see that?
A. Yes.
Q. And in the last paragraph, again, no vacation mandates and schedules?
A. Yes.
Q. And we can go forward in the other paragraphs, just confirm that they also raise other HR-type concerns?
A. All are HR environmental issues yes.
Q. Do you recall -- strike that.
You noted that you had seen a document that reflected that you met at some point in time just prior to the agency's FDA 483 inspection in August 2001, that you had met with Mr. Krahling where he raised an allegation of something different than HR, something of concern to him?



A. Yes.
Q. You don't remember specifically that meeting, but you remember seeing a document that referenced that meeting?
A. That was a note from Mr. Suter to me from HR.
Q. When you had that meeting referenced in that document with Mr. Krahling, you stated that you immediately contacted counsel.
A. Yes.
Q. Correct?
A. Yes.
Q. Other than that meeting that was referenced in the document where you contacted counsel, did Mr. Krahling ever raise to you any concerns regarding any fraud or misconduct, I'm distinguishing that from HR complaints, about the running of protocol in any way?
A. Not to my recollection.
Q. Had he raised the complaint around misconduct in the lab at any point in time, is it fair to say that you would have done just what you did when he raised his



complaint at the end of July, that you would have contacted counsel?
MR. BEGLEITER: Objection to the form.
THE WITNESS: As evidenced by my action that I took in contacting counsel after the meeting that I had with Mr. Krahling in which he showed me his concerns over the data, the answer to your question would be yes.
BY MS. DYKSTRA:
Q. But other than that meeting, you don't have any recollection of Mr. Krahling raising to you anything other than HR concerns?
A. I do not.
MS. DYKSTRA: I have no further questions.
MR. BEGLEITER: Can you give me a few minutes?
MS. DYKSTRA: Sure.
VIDEOGRAPHER: The time is 6:16. Going off the video record.
- - -
(A recess was taken.)



- - -
VIDEOGRAPHER: The time is now 6:37. This begins tape six.
- - -
FURTHER EXAMINATION
- - -
BY MR. BEGLEITER:
Q. Doctor, I'd like you to turn back to Exhibit 6, page 17043.
A. 43.
Q. Yes. Actually if you go -- 17043. Do you know who wrote paragraph A that you read from?
A. Who physically wrote it? No, I do not.
Q. It says here, "As suggested by CBER during the meeting held on March 13, 2000, the assay's sensitivity for measurement of virus-neutralizing antibody has been optimized by addition of anti-human IgG."
A. Yes.
Q. So my question is, do you know independent of this paragraph who at CBER made that suggestion supposedly?
A. No, I do not.

Q. Do you know whether CBER agrees with the sentence?
MS. DYKSTRA: Objection.
THE WITNESS: Well, it was CBER's suggestion and recommendation, and then discussions were held continuously with CBER. So CBER was certainly aware that this was happening, and if they had a suggestion, they would have entered it.
BY MR. BEGLEITER:
Q. Doctor, my question is, did you know if the person who wrote this got it right?
MS. DYKSTRA: Objection.
THE WITNESS: By definition I cannot know that.
BY MR. BEGLEITER:
Q. Thank you.
A. By definition.
Q. Let's go to Exhibit 31. That's the document you used to discuss the London-1 isolate?
A. Yes.
Q. Do you know at what potencies



the London-1 isolate was tested at?
MS. DYKSTRA: Objection.
THE WITNESS: Please define "potency."
BY MR. BEGLEITER:
Q. If you don't understand the word potency, I'm just going to go on to the next question. You don't know what the word "potency" means?
A. I don't know what the potency means in context of your question. You said at what potencies was it tested, are you referring to the potency --
Q. In other words -- I understand. The 007 data was testing at three potencies, were they not?
A. At three potency levels, yes. In the context of 007 study, yes. No, I do not -- so to answer your question --
Q. You do not know?
A. I do not know because I do not know what the serum series specifically refer to.
Q. So you can't tell whether or not London-1 here was subject to the same --



withdrawn. Let me just go on to the next one.
Let's go to Exhibit 32. Do you have that in front of you?
A. Yes, I do. Yes.
Q. Is there anything in this letter which explains to you why Dr. Ward's lab was not used for Protocol 007?
A. No, that was not the intent of this letter.
Q. How do you know what the intent was?
A. Well, because -- I am inferring the intent of this letter because what is being reported here is that using the control sera, the data from Dr. Ward's laboratory were identical and were comparable, I'm looking for the exact word that was used here, to the data from the Merck laboratory are consistent with the Merck results was the terminology that was used. So the intent here presumably was to show that the two assays, you know, could be consistent. This was not a validation study, this was just simply a determination looking for consistency.
Q. So this would be a reason to



corroborate the use of Dr. Ward's lab, wouldn't it?
MS. DYKSTRA: Objection.
THE WITNESS: It would be a reason for stating that if one wanted to -- well, no, again, this was not a formal validation. That would depend on the validation of the assay in Dr. Ward's laboratory, and it would depend on the actual validation of the laboratory itself.
BY MR. BEGLEITER:
Q. There are reasons why it would -- why you could or you couldn't, but I'm saying this letter isn't a negative to using Dr. Ward's lab?
A. No, it is not directly a negative.
Q. Directly a negative?
A. Directly a negative.
Q. What do you mean "directly a negative"?
A. I'm sorry, directly meaning it does not directly state don't use it or the data don't directly state you cannot use it.

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Q. Let's go to Exhibit 8. With regard to 007, sir, do you know -- do you have a definition of pre-positive?
A. Sorry, are you reading in a specific place?
Q. I'm not reading anything.
A. Just a question, sorry. You said Exhibit 8, my apologies. A definition of a pre-positive?
Q. Yes.
A. So my definition of a pre-positive would be a serum sample from someone who had not received the vaccine or had not been exposed to the virus in the course of natural infection.
Q. Does pre-positive imply that there is some, for example, some plaques in a cell plate that just a small number of plaques before -- withdrawn.
Does it imply that there are some plaques in a cell plate before the subject has -- before mumps has been introduced into the plate?
A. The plaques in a cell plate are a function of the indicator virus that one

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places in the cell plate. It does not refer to the pre-positive sample, per se.
Q. So pre-positive would be a sample in which the child in this case would not have -- did not have mumps?
MS. DYKSTRA: I'm going to object because this is beyond the direct examination.
MR. BEGLEITER: This is exactly what it's going to.
MS. DYKSTRA: Well, it doesn't seem like it's going to, because I didn't talk about pre-positive. So I'll give you a little bit of latitude, but then I'm going to object.
MR. BEGLEITER: You can object, but it relates to this on page on Exhibit 8. So that's exactly where I'm going to. I'm asking a foundation question.
BY MR. BEGLEITER:
Q. So my question, again, is, make sure we understand it, a pre-positive is one where someone would look at the cell plate and exclude it from the study because it was

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pre-positive. Isn't that right?
MS. DYKSTRA: Objection. Form.
THE WITNESS: So the use of the terminology pre-positive in that regard, that is referring to an individual who you believe not to have been vaccinated, no record of vaccination or no record of natural exposure to the virus and yet when the assay is run, there was an indication of antibody, plaque reduction neutralizing antibody present.
BY MR. BEGLEITER:
Q. Okay. And the pre-positives are usually excluded from the testing. Isn't that right?
MS. DYKSTRA: Objection.
THE WITNESS: It would depend on the level of the pre-positivity. If you had such a pre-positive, you would not be able, using the assay, to discern whether or not the individual seroconverted subsequent to immunization because there was already antibody apparently present prior to

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immunization.
BY MR. BEGLEITER:
Q. Let's go back to Exhibit 8. I'll ask you whether or not there was any indication here that pre-positives were considered in coming to the conclusions that were come to?
MS. DYKSTRA: Are you referring just to the paragraph?
MR. BEGLEITER: The paragraph that you read on page 482.
THE WITNESS: I'll read it again. There is no indication given what is stated in this paragraph that there were any considerations one way or the other related to the concept of pre-positivity.
BY MR. BEGLEITER:
Q. What would be the impact of pre-positive on the corrections that were related in this paragraph?
MS. DYKSTRA: Objection. Form.
THE WITNESS: I can't answer that question because it would depend on what samples were individually

corrected and what the nature of that correction was and what that entailed, so I can't answer the question. I don't know.

BY MR. BEGLEITER:

Q. Did you tell CBER of the impact on pre-positives?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I was not directly involved with any discussions with CBER around that question.

BY MR. BEGLEITER:

Q. Who did this reanalysis that's mentioned in this paragraph?

A. This reanalysis was performed by the statistical group, as it would have been performed.

Q. So they didn't have the cell plates in front of them?

MS. DYKSTRA: Objection.

THE WITNESS: What they had in front them were the two sets of data, the original so-called uncorrected data and then the subsequent corrected data.

BY MR. BEGLEITER:



Q. What this paragraph relies on is the integrity of that data?

A. What this relies on are -- well, all analyses rely on the integrity of data by definition, yes.

Q. On Exhibit 8, again, did -- was there ever a point at which undiluted IgG was added to the PRN test for Protocol 007?

MS. DYKSTRA: Objection.

THE WITNESS: I have no way of knowing that.

BY MR. BEGLEITER:

Q. You don't know?

A. I don't know.

Q. I do have a question, it's a follow up for today. Just one question. It's a yes or a no.

Is there a way for Merck to determine who purchased 106 out of compliance lots?

MS. DYKSTRA: Objection. Form.

THE WITNESS: I would not know if there is a direct way of doing that.

BY MR. BEGLEITER:

Q. That would be --



A. That would be the manufacturing division and the marketing division, not us.

MR. BEGLEITER: Thank you. Thank you, Doctor.

MS. DYKSTRA: Thank you.

VIDEOGRAPHER: The time is 6:48. This concludes the deposition of Emilio Emini.

- - -

(Witness excused.)

- - -

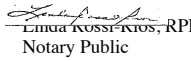
(Deposition concluded at 6:48 p.m.)



CERTIFICATE

I do hereby certify that I am a Notary Public in good standing, that the aforesaid testimony was taken before me, pursuant to notice, at the time and place indicated; that said deponent was by me duly sworn to tell the truth, the whole truth, and nothing but the truth; that the testimony of said deponent was correctly recorded in machine shorthand by me and thereafter transcribed under my supervision with computer-aided transcription; that the deposition is a true and correct record of the testimony given by the witness; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WITNESS my hand and official seal this 19th day of June, 2017.



Linda Rossi-Rios, RPR, CSR
Notary Public

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.



ACKNOWLEDGMENT OF DEPONENT

I have read the foregoing transcript of my deposition and except for any corrections or changes noted on the errata sheet, I hereby subscribe to the transcript as an accurate record of the statements made by me.

_____
DR. EMILIO EMINI

SUBSCRIBED AND SWORN before and to me this ____ day of _____, 20___.

_____
NOTARY PUBLIC

My Commission expires:



ERRATA SHEET

IN RE: USA ex rel. vs. MERCK

DATE: 6/6/2017

| PAGE | LINE | CORRECTION AND REASON |
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_____ _____
(DATE) DR. EMILIO EMINI

# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 116

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

| | | |
|---|---|---|
| UNITED STATES OF AMERICA ex rel., STEPHEN A. KRAHLING and JOAN A. WLOCHOWSKI, Plaintiffs, | : | CIVIL ACTION NO. 2:10-04374(CDJ) |
| vs. | : | |
| MERCK & CO., INC., Defendant. | : | |
| IN RE: MERCK MUMPS VACCINE ANTITRUST LITIGATION | : | Master File No. 2:12-cv-03555(CDJ) |
| THIS DOCUMENT RELATES TO: ALL ACTIONS | : | |

** CONFIDENTIAL **

December 22, 2016

Videotaped deposition of FLORIAN SCHODEL, MD, taken at the offices of Spector Roseman Kodroff & Willis, 1818 Market Street, Suite 2500, Philadelphia, Pennsylvania 19103, beginning at 9:05 a.m., before LINDA ROSSI-RIOS, a Federally Approved RPR, CCR and Notary Public.

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- - -



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EXHIBITS





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(None)

QUESTIONS MARKED

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(None)



- - -

VIDEOGRAPHER: We're now on the record. My name is Russ Strain representing Veritext Legal Solutions.

The date today is December 22, 2016. The time is approximately 9:05 a.m. This deposition is being held at Spector Roseman, 1818 Market Street, Philadelphia, PA. The caption of this case is In Re: Merck Mumps Vaccine Antitrust Litigation, filed in the US District Court for the Eastern District of Pennsylvania, Case Number 2:12-cv-03555. The name of the witness is Dr. Florian Schodel, MD.

If counsel at this time will, please, introduce themselves for the record?

MR. KELLER: Sure. Jeffrey Keller from Keller Grover on behalf of Relators.

MS. ZINSER: Diana Zinser, Spector Roseman Kodroff & Willis for plaintiffs.



MR. MACORETTA: John Macoretta from Spector Roseman for private plaintiffs as well.

MR. KRAHLING: Steve Krahling, Relator for the United States of America.

MR. HOWARD: Tim Howard for Merck.

MR. SULLIVAN: Tom Sullivan from Morgan Lewis for Merck.

MR. LOVELAND: Daniel Loveland from Venable for Merck and Dr. Schodel.

MR. SANGIAMO: Dino Sangiamo from Venable for Merck and Dr. Schodel.

VIDEOGRAPHER: Counsel on the phone.

MR. BEGLEITER: Bob Begleiter, plaintiffs.

VIDEOGRAPHER: The court reporter is Linda Rossi of Veritext. Will the court reporter, please, swear in the witness?

- - -



FLORIAN SCHODEL, MD, after having been duly sworn, was examined and testified as follows:

VIDEOGRAPHER: Testimony can now proceed.

- - -

EXAMINATION

- - -

BY MR. KELLER:

Q. Dr. Schodel, can you state your name for the record?

A. My name is Florian Schodel.

Q. Have you ever been known by any other name?

A. No.

Q. Can you tell me your business address?

A. 1623 Pine Street in Philadelphia.

Q. Have you ever had your deposition taken before?

A. Not in a US court.

Q. When you had your deposition taken outside the US, when was that?

A. I don't remember. A long time ago.

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Q. I asked that. We'll go over some of the --

A. More than 20 years.

Q. Okay. We'll go over some of the -- was that for one of your employers or was that a personal matter?

A. No, personal matters.

Q. Let me go over some of the ground rules to remind you. I'm sure your counsel has sort of walked you through this, but it always helps to kind of go over it before the deposition so it's fresh in your mind.

You've -- your testimony today is under oath under the penalty of perjury. At the end of this deposition the court reporter is going to do a great job of writing down everything that you say, that I say and anybody else in the room says. You'll have a chance to review that and make any corrections that you think are appropriate, but I will remind you any changes you make to the transcript we'll be able to comment at trial. Okay?



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A. Okay.

Q. Since the court reporter, though she's amazing, can really -- only really capture words, though, she can't say -- if you get up and ran out of the room, she'll write down witness ran out of the room. Try to answer the questions with words, you know, instead of saying uh-huhs and uh-uhs, yes or no would be -- we'll have a much cleaner record if you could do that. Is that fair?

A. No problem.

Q. Great. I'm going to be asking you questions and you're going to be answering the questions. If you don't understand my question, please let me know; otherwise, we're all going to assume that you understood the question. Is that fair?

A. I will not answer a question I can't understand so obviously I will ask you.

Q. Perfect. As long as we have the same understanding.

We don't want you to guess or estimate unless specifically requested. We want to know what your best understanding of



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things so if you don't have a good understanding or if you can't answer the question except by guessing or estimating, please let us know. Is that fair?

A. That's fair.

Q. As you can tell, the court reporter, again, takes down everything that we say and it's helpful, though I don't think we'll have a problem, is to not talk over each other. Allow me to finish asking the question, though you're already probably going to know what the rest of my question is when I start it, I may pause in the middle as I try to formulate a question, just give me the opportunity to finish the question before you answer. And I'll try to do the same thing instead of asking you the next question before you answer, fully answer, just so we get a nice clean record at the end of the day. Because when the record comes out, it's going to have a question and an answer, and if we talk over each other, the question gets broken up, because she just writes down whatever people are saying when they're saying it.



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Dr. Schodel, do you have a personal lawyer?

A. For this particular case?

Q. Generally, overall.

A. Not in the United States.

Q. Do you have an attorney for your consulting firm?

A. For my firm?

Q. Yes.

A. No.

Q. Who is representing you today?

A. They already stated it. The firm Venable.

Q. Is Morgan Lewis representing you today?

MR. SANGIAMO: That's Mr. Sullivan's firm as well.

THE WITNESS: Are they?

MR. SANGIAMO: Yes.

THE WITNESS: They are.

BY MR. KELLER:

Q. Did you sign a retainer agreement with them?

A. No, I did not.

Q. Are you paying them any fees?
A. No, I do not.
Q. Have they ever represented you in the past?
A. No, they have not.
Q. So they only represent you for the purposes of this lawsuit and your deposition today?
A. That's correct.
Q. Yes?
A. Yes.
Q. When did you first speak to your counsel for the purposes of this deposition?
A. For the purposes of this deposition we spoke in the beginning of this week.
Q. Were they retained at the beginning of this week?
A. No. A little earlier.
Q. Do you know when earlier?
A. No.
Q. Was it within the past month?
A. Yes, probably.
Q. How many times have you spoken





to your counsel for the purposes of this deposition?
A. Well, directly for the deposition, we've only spoken this week. We have a general discussion earlier.
MR. SANGIAMO: Doctor, it's important that you not disclose the content of those prior discussions. So your answer is okay but wait for Mr. Keller's next question.
BY MR. KELLER:
Q. And you said you had a general discussion. I'm not going to ask you what you discussed, I just want to know when you discussed -- this general discussion you had prior to this week, do you recall when that was?
A. I don't recall exactly. I could look it up in my calendar, I had a lot of discussions. I think my first knowledge of the case was triggered by --
MR. SANGIAMO: I'm sorry, go head.
THE WITNESS: -- somebody called





me and then I got in touch with Merck which was maybe half a year ago, but I don't really remember.
BY MR. KELLER:
Q. And when you -- somebody from the plaintiff's side of this lawsuit contacted you. Correct?
A. Contacted me. And they contacted me in a way that met -- that I thought it was a Merck lawyer because he did not state in the beginning of the phone call who he was representing and started asking me questions. And started asking whether I would be willing to appear as a witness in this case that I didn't know anything about. And it sounded very strange to me. So finally, I asked whether he was representing Merck. He told me that he was not. And by that time I told him that I would talk to Merck and not continue this conversation.
Q. Do you recall -- so you called somebody at Merck. Did you call -- who did you call at Merck?
A. To tell you the truth, I don't





remember anymore. I don't -- I could probably try to -- I don't remember anymore. But I tried to find somebody at Merck who was responsible for, and then I eventually got to the people who were dealing with this.
Q. Did you speak to the legal department at Merck?
A. They eventually contacted me back, but they were not my first contact because I wouldn't have known whom to call there.
Q. The person who you spoke to at Merck who wasn't one of Merck's lawyers, do you recall what you discussed with them?
A. No, I didn't actually discuss anything other than I was contacted by a law firm in regards to a court case that Merck seemed to be involved in and that I wanted Merck to get in touch with me and figure out what needed to be done.
Q. Did somebody from the legal department at Merck reach out to you?
A. Yes.
Q. Do you recall who that person

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was?

A. Tia Clarke.

Q. Can you spell the last name?

A. No. But I can try.

C-L-A-R-K-E maybe. Could be K without an E.

Q. Fair enough. If you identify people's names, just for the court reporter's sake, if you -- especially if they have a spelling that is difficult, it may be helpful just to spell it as you go. You're going to have to do it eventually. She's going to ask you anyway.

A. In that case I simply don't know. It's probably C-L-A-R-K-E.

Q. Close enough. Just so that we have -- even if it's phonetic, it's helpful to have the names.

And then you said that you -- do you recall how long you spoke to Ms. Clarke?

A. No, I think that was just an exchange of e-mails.

MR. SANGIAMO: Dr. Schodel, just make sure you just answer his question. His question was do you



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know how long you spoke to --

THE WITNESS: I'm not even sure I spoke to her at all.

BY MR. KELLER:

Q. Do you recall how long -- did you speak to anybody in the legal department at Merck?

A. No.

Q. Did Merck refer you to one of your lawyers that your -- that are representing you here today?

A. Yes, eventually.

Q. Then you said that you spoke to somebody -- other than this week, have you spoken to anybody else at Merck regarding this lawsuit?

A. No.

Q. Have you spoken to anybody else other than your lawyers regarding this lawsuit?

A. Yeah, my wife. I told her that I had to spend the last days before Christmas giving a deposition.

Q. Did you discuss with her any of the details?



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A. Bloody detail. No, of course not.

Q. Fair enough. And then you said this week you spoke to your lawyers about preparation for this deposition. Correct?

A. Yes.

Q. And when this week did you speak to them?

A. Monday.

Q. Monday.

A. Was it Monday? Yeah.

Q. Did you meet them in person or on the phone?

A. Yes. Or was it Tuesday? I don't know. I think -- I mean, I have a lot -- had a lot of stuff on my plate this week. It may have been another day of the week. Tuesday.

Q. Your best recollection. I'm not going to hold you to Monday or Tuesday. So either Monday or Tuesday you met with them in person. Do you recall how long you met with them?

A. Most of the day.



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Q. Most of the day. Did they show you documents?

A. Yes.

Q. Do you recall how many documents?

A. No. Many.

Q. Many. Is many more than 10?

A. Yes.

Q. Is it many more than 100?

A. No.

Q. More than 20?

A. Probably.

Q. Less than 50?

A. I don't know.

Q. And you reviewed those documents?

A. Yes.

Q. And did any of those documents help refresh your memory about what was in those documents?

A. Yes.

Q. Do you recall which of those documents refreshed your memory as to what was in those documents?

MR. SANGIAMO: I'm going to interpose an objection. I'm going to

instruct Dr. Schodel not to answer that question.

BY MR. KELLER:

Q. Are you going to follow your counsel's advice?

A. When you find out as you ask me about specific documents, which I do remember and which I don't remember, I couldn't give you a list off my head which ones I remember or don't remember. But there were some -- some of them were e-mails that I had written and I had not remembered them if I hadn't seen them.

Q. Fair enough. Other than that full day that you met with your counsel in preparation for this deposition, have you done anything else in preparation for this deposition?

A. No. No.

Q. Did any of the documents that you looked at, did they surprise you in any way?

MR. SANGIAMO: Dr. Schodel, I'm going to instruct you not to answer





that question. That's invading the attorney/client privilege and work product doctrine, legal doctrine. So I'm instructing you not to answer Mr. Keller's question.

BY MR. KELLER:

Q. Are you going to follow your counsel's advice?

A. Yes, I do.

Q. Was there anybody else present at that meeting either Monday or Tuesday that weren't lawyers?

A. One more lawyer who is not here right now.

Q. So they were all lawyers?

A. Yes.

Q. There was nobody from Merck present at that meeting?

A. No.

MR. KELLER: Do we have Dr. Schodel's CV? I'm going to mark as Exhibit 1 a CV of Dr. Schodel that was produced to us this morning.

- - -





(Exhibit Schodel-1, Curriculum Vitae, was marked for identification.)

- - -

BY MR. KELLER:

Q. Exhibit 1 is a document entitled "CURRICULUM VITAE" which was produced this morning by your counsel, Dr. Schodel. Is this your CV?

A. Yes, it is.

Q. Is it current?

A. Yes, it is.

Q. Any reason to believe that the information here is not accurate?

A. No.

Q. I just want to go over a couple of things about your educational background. Can you just give me a quick summary of what the degrees you have?

A. Yeah, I have a degree in medicine which is an earned doctorate. So I wrote a thesis in immunology. I have also an earned doctorate in microbiology which is a second doctorate in medical microbiology for which I wrote another thesis and I have





the -- it doesn't exist here, it's a habilitation which is a right to become a professor and teach.

Q. Can you describe for me what your understanding of an immunologist is?

A. An immunologist is somebody who analyzes immune responses in living organisms.

Q. That's what you're trained in?

A. That's one of the things I'm trained in, yes.

Q. Do you consider yourself an immunologist?

A. No.

Q. No?

A. No, I consider myself a physician.

Q. Have you ever used your immunology background as part of any of your job duties?

A. Yes, of course.

Q. Have you used your immunology background as part of your job duties at Merck?

A. Yes.

MR. KELLER: Let me mark as

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Exhibit 2 --

- - -

(Exhibit Schodel-2, LinkedIn profile, was marked for identification.)

- - -

BY MR. KELLER:

Q. Exhibit 2 is a document that we pulled down off of LinkedIn -- I'm sorry, that we pulled in off of LinkedIn, which has a summary of some of your educational and work background. Is the information on this document correct?

A. I have to read it first.

Yes, it seems to be correct. I mean, I'm just referring to the summary. All the other stuff, yeah.

Q. Sure. If there's something in here as we -- if we go through this that you say that -- you see that's incorrect, feel free to let me know that.

In the first sentence it says that you have 20 years of large pharmaceutical biotech industry and academic experience of leading teams in the development of vaccines





and biologies. Is that correct?

A. Yes, only that by now it's probably longer.

Q. How much longer is that?

A. It's about 30 years now.

Q. 30 years, okay.

Your company that you founded, what's the name of that company?

A. Philimmune.

Q. What kind of consulting do you do at your company?

A. I provide advice on developing biologics or vaccines primarily on the clinical side, what kind of clinical trials should be run to meet criteria for licensure and how something works. I provide some advice as to strategy on what compounds based on data may be worth developing and what the likely regulatory pathway would be for getting them licensed in different jurisdictions.

Q. Is one of those jurisdictions the United States?

A. Yes.

Q. So you have a -- you consider





yourself to have a good understanding of the regulatory environment in the United States for getting a vaccine license?

A. Yes.

Q. And that's one of the services you provide to your clients?

A. Yes.

Q. And that's part of your 30 years of experience?

A. Yeah.

Q. When you say "clinical trials," can you give me your understanding of what clinical trials you're referring to?

A. Well, any clinical trial which means any trial that puts a compound into humans and tests what happens, whether that's safety in Phase I, whether it's safety and immunogenicity or whether it is other endpoints for the purpose of licensure.

Q. When you say "endpoints," what do you mean by "endpoints"?

A. Endpoints are in the end what you measure to determine whether something is safe or efficacious.





Q. When you say "efficacious," what do you mean by "efficacious"?

A. Efficacious means that it prevents a disease.

Q. I apologize to have you define a lot of these terms, they seem very rudimentary, I do that to make sure that we're all on the same page.

A. Perfectly fine.

Q. Have you ever done any work with your consulting company for Merck?

A. A single time I have, yes. A single time I have.

Q. So they're a client?

A. They're not a current client.

Q. Do you hope to do more work for them in the future?

A. I can't speculate.

Q. Would you like to do more work for them in the future?

A. I would like to do work for anybody who needs me.

Q. Including Merck. Correct?

A. Including Merck.

Q. Let me go back to your Exhibit 2 which is the -- your LinkedIn page. In the second paragraph to the bottom it says, "Florian joined MRL in 1996...." Do you see that?

A. Yes.

Q. And MRL, what does that refer to?

A. Merck Research Laboratories.

Q. ...as Director of Clinical Vaccine Research leading EU vaccine clinical trials in the clinical development of rotavirus, measles, mumps and rubella vaccines. Do you see that?

A. Yes.

Q. What does EU stand for?

A. The European Union.

Q. Do you recall what clinical trials you worked on during this time frame that you were working for Merck in Europe with respect to the mumps vaccine?

A. Those are several questions in one. With respect to the mumps vaccine, I don't remember any trial in the EU, although





there might have been an EU arm so I don't really remember details of the trials. I know that there was a -- that the end expiry trial was being performed, but whether it was performed in the EU, I don't remember.

Q. And "the end expiry trial," can you describe what you mean by that?

A. That was a trial to determine whether a lower dose of mumps at the end of its shelf life would still yield the same immune response as a higher titer obviously.

Q. So is the purpose to see whether or not -- if Merck sold the vaccine at a lower dose, whether or not that would protect kids in the same way that a higher dose would?

A. No, that's a --

MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: I think that -- so you're sort of leading into something which is not -- the premise is wrong. It's not a matter of whether was Merck selling something that -- at a lower dose. Merck wasn't planning to sell





something at a lower dose. But by that time the labeling philosophy had changed or was about to change, hadn't quite changed yet, both from an FDA perspective and from a company perspective. The old labels originally just stated a number which was found to be efficacious in a clinical trial, whatever that number was. Some of these numbers became compendial, by the way. Then over time the understanding started to be that a vaccine needed to maintain that number that was stated in the label throughout the shelf life. So that was a change. And because that was not the case when mumps was originally licensed 40 years ago, Merck had to make sure that whatever was in the vaccine throughout shelf life maintained its efficacy. So that the label statements would be as of the current understanding which had changed.





So Merck wasn't trying to sell anything different. It was always selling the same thing. It was just providing additional -- actually being quite diligent in providing additional information about the clinical behavior of the vaccine it was selling.

BY MR. KELLER:

Q. When you say "compendial," can you describe what that means?

A. Yes. There are some compendia that define concentrations or potencies of certain things like the pharmacopeia. And in some cases they provide numbers for vaccines. So, for example, in the European Union there is a compendium that states essentially, I don't know the exact text, but that states essentially that a mumps vaccine will have 3.7 logs of mumps virus.

Q. In that 3. --

A. So that becomes a -- rather than something that a company has tested, that becomes a leading requirement for a

vaccine to have that number in it.
Q. So in the US, do you recall it being a higher number?
A. I don't recall the US having a compendial statement at all.
Q. Do you recall that in the US that the label required that the mumps vaccine have a certain potency?
A. Yes, but with the caveat what I just said, understanding of what that meant had changed over time.
Q. Gotcha. But it did have a certain potency?
A. Yes, but originally --
MR. SANGIAMO: Dr. Schodel, make sure you let Mr. Keller finish his question.
I'm sorry. Could you restate your question, please, Jeff?
MR. KELLER: Sure. Can you read it back?
- - -
(The court reporter read the pertinent part of the record.)





- - -
BY MR. KELLER:
Q. But you understood that the label in the United States did have a certain required potency for the vaccine?
MR. SANGIAMO: Object to the form.
THE WITNESS: Yes.
BY MR. KELLER:
Q. And the question was whether or not that potency had to be not just at release but also at the end expiry of the vaccine. Correct?
A. That is correct.
Q. When you say "potency," can you define for me what you mean by "potency"?
A. Potency is -- I mean, it's defined in the CFR, but potency in this particular case means a certain quantity of virus that leads to a biologic effect in an in vitro assay. In that case it's a plaque neutralizing reduction assay. So it -- a plaque -- it's a plaque assay, neutralizing reduction is the antibody assay. It's a





plaque -- it's a plaque assay, so many units in there that when you put them in cell culture, they produce holes in the cell culture which are counted as plaques.
Q. So when you say, "a plaque assay," are there different plaque assays?
A. Yeah. There are all kinds of different assays to measure potency. They could be fluorescent assays. They could be -- it's just -- they're just measures to quantitate the amount of a live product.
Q. So the plaque assay, is that a plaque reduction neutralization assay?
A. No, that's the antibody assay.
MR. SANGIAMO: Object to form.
You can answer.
BY MR. KELLER:
Q. So the plaque assay there is used for potency, is that -- it's just identifying how many viruses are in each dose. Correct?
A. How many live viruses are in each dose. And it's not -- the assay is not as important as the -- I mean any assay could





be validated to show that it does the same thing as long -- and as long as it's shown to do the same thing, it would meet those criteria. But it's, of course, defined in defining documents. I don't remember exactly what Merck did there.
Q. So there's protocols that set for how these assays are run. Correct?
A. Yes.
Q. And those assays are validated some --
A. Yes.
Q. -- to a certain extent. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Let me strike the question.
These assays, these potency assays are validated. Correct?
A. Yes.
Q. Who does the validation?
A. That is not my responsibility but I think it's the manufacturing department

that validates the release assay.

Q. You said that the label philosophy had changed at a certain point during your tenure at Merck regarding the end expiry versus whether or not, if I understand you correctly, the release potency would be the same or different from the end expiry potency. Correct?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Do you understand my question?

A. The first part yes. The second part no. So the first part has a change. Yes, it has changed. It has nothing to do with Merck. It has changed overall for the whole industry. The second part wasn't clear to me.

Q. Sure. When you say it's changed for the whole industry, can you describe what you mean by that?

A. Well, that in general the idea of how -- what the guarantee in the label had evolved and the science had evolved. I think





most labels were written 40, 50 years ago with a description of the product that did not include either maximum release or minimum release potencies but just simply a number.

Q. And then that changed from a regulatory standpoint?

A. It changed both from a regulatory and from a company standpoint in the sense that it was clarified what these things mean.

Q. So there is a clarification between -- you say clarified, clarified by who?

A. Ultimately by the agencies.

Q. So in the case of the US, the FDA?

A. Yes.

Q. Were you involved at all in any of the discussions with the FDA regarding this change in requiring a maximum and minimum potencies?

A. Not explicitly but implicitly, yes.

Q. When you say "implicitly," can





you describe what you mean by that?

A. Well, because as that became the requirement for new products, every new product that would be licensed had to meet these kinds of expectations and, therefore, there was always a discussion as to what the data were to support these numbers.

Q. So this change that occurred, do you recall when that change was?

A. Not specifically. But I think it evolved in the time period between 1990 and 2000 roughly, and then the years thereafter.

Q. And so this change in the requirement, do you recall Merck having any discussions that you became aware of with respect to this requirement of having an end expiry potency?

A. Yes.

Q. Were you involved in those discussions directly with the FDA?

A. No, not -- certainly not initially. As specific protocols or filings were discussed, I may have been part of some of those discussions.





Q. Were you involved in the end expiry study that we talked about earlier?

A. Yes, on and off.

Q. Did you help develop original protocols?

A. No.

Q. Do you know who developed original protocols?

A. I know it on the biometric side but not the clinical side.

Q. Who about on the biometric side?

A. Tim Schofield. At least that was my recollection.

Q. Do you recall -- what role did you play at all in this end expiry study?

A. Well, I was supervisor of the physicians who were responsible for mumps where I was directly responsible for a short time for anything that had to do with MMR or MMR/V. But that changed various times. So at times I had physicians report to me who were responsible for MMR or MMR/V.

Q. And MMR/V, that's ProQuad. Correct?

A. ProQuad, yes.
Q. Let me just sort of frame the time frame on this. You said at some point your duties changed. You were a supervisor of folks, doctors that were responsible for MMR II. Correct?
MR. SANGIAMO: Mr. Keller, are you okay with Dr. Schodel looking at his CV --
BY MR. KELLER:
Q. Absolutely. Whatever helps refresh your memory, that's fine.
A. That wouldn't give you the information and I have to say that I don't remember the exact timing anymore because that was -- in the time frame between the end of '96 when I started and roughly '98, I was on and off. I was assuming more responsibilities. MMR was certainly not the focus of my work. It was much more rotavirus and a number of things and clinical trials in Europe. But over time I got more of that responsibility as well.
When the formal reporting lines




changed, I really don't remember. And then I wasn't at Merck for about two years. And when I came back -- I still worked for Merck as a contractor or consultant but only on one approach, it had nothing to do with MMR. In that time period between '98 and 2000 I didn't work for Merck on the MMR.
Then when I came back, MMR was initially not under me. I think it was still under Jerry Sadoff. And it may have been Scott Tyler or Mike Severino who were the responsible physicians not reporting to me. And then at some point after 2000, maybe 2002 or so, 2001, 2002, I became formally responsible for these vaccines.
Q. So according to -- I'm looking at your LinkedIn summary of your work experience. It has you starting at Merck Europe in 1996 through November of 1998. Were you working in Europe or were you working in the United States?
A. Half and half.
Q. And then in November 2000 -- and you left for a company outside of Merck and




then came back in November 2002 -- 2000, sorry, and where you held executive director of vaccine integration through March of 2002. Do you see that?
A. Yes.
Q. What is vaccine integration?
A. Vaccine integration was a department at the time which was created in anticipation of a number of vaccine filings, quite a few, which made sure that the different departments of Merck collaborated in putting together the right data for the filings.
Q. Is that more focused on new vaccines versus existing vaccines?
A. No, it was responsible for certain aspects of both. For example, we developed a way how to write the CTD in electronic form. So it had various -- it had a direct clinical team which was very small. And that was more focused on new things, but then it had a larger role across different departments.
Q. Let me just sort of back up so I




can understand what your actual duties were at Merck and then we can sort of walk through.
When you started in 1996 through that 1998 time frame as a director of clinical vaccine research, what were your duties? We can limit it really -- let me ask that generally. What were your duties generally?
A. In general, I had a small group that was responsible for the operational aspects of clinical trials in Europe. So working with the CROs, working with the investigators, making sure that we had the sites ready and so on. So more operational work.
I was also the liaison to the joint venture with Sanofi Pasteur in Europe and sat on the clinical development team for Hexavac which was a vaccine that we co-developed with Sanofi at the time. That was a major part of my responsibilities, and I represented Merck on that team for clinical issues.
Then in the US, as I mentioned earlier, I was primarily responsible as a

monitor for the new rotavirus vaccine, so I developed a clinical development plan for RotaTeq. And those were really the main responsibilities. That's what I spent most of my time on, between --

Q. So your role with respect to the MMR vaccine was very limited during this time frame?

A. At that time, my role was limited, yes.

Q. The rotavirus vaccine, did you conduct clinical studies with that vaccine?

A. Yes. Yes.

Q. What were the studies -- what were the assays that were run in that, with that particular vaccine?

A. Well, I mean, there were a number of ELISAs run to measure antibody titers and functional assays to measure neutralization of viruses as well.

Q. When you say a functional assay, could you describe what you mean by a functional assay?

A. A functional assay would be an





assay that is a neutralization assay that basically mixes the virus with the antibodies in a test tube and see whether the virus activity on a cell log gets reduced.

Q. So it either kills it or stops it from growing. Is that fair?

A. Yes. It could. Yes. Or stops it from entering a cell.

Q. Gotcha. So in this, the neutralizing assays that you did for the rotavirus, was that a plaque reduction neutralization assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: First of all, I didn't do these assays.

BY MR. KELLER:

Q. Fair enough.

A. So I was responsible for the clinical part. And secondly --

Q. Let me back up.

A. Secondly, there were different formats tried. I don't even remember anymore exactly which one which was in the end. I





think they were microneuts, but I don't --

Q. Okay. Fair enough. What is the difference -- is the ELISA a functional assay?

A. No. It's a binding assay.

Q. Binding assay. What do you mean by "a binding assay"?

A. Measures whether an antibody is bound to a substrate which could be a cell, could be an antigen that is fixed in the plate.

Q. And so what is the -- an ELISA assay, how is that reported in terms of reporting?

A. The ELISA assay reports, it has a substance added to the test tube which by virtue of an enzyme is converted from one form to the other and then changes color. And that color change is measured. So if a lot of antibody is in there, the antibody is tagged with an enzyme. A lot of enzyme in the tube and that enzyme causes a color change and the color change is measured.

Q. So your -- it's an optical test to identify a number of optical units. Is





that a fair way to say it?

A. Yes, although most tests are optic because you have to look at them. So when you count them, that's an optical test, too, in a way.

Q. Gotcha.

A. But this is one where you measure color change specifically. So the change of light absorption.

Q. How is that reported?

A. Many different --

MR. SANGIAMO: Jeff -- excuse me. Jeff, you're saying how is that reported?

MR. KELLER: Yes.

MR. SANGIAMO: Okay.

THE WITNESS: It can be reported just as an optic density change at a given dilution. That would be the simplest form. It can be reported as a titer, a titer being defined by certain criteria.

BY MR. KELLER:

Q. So when it's done as a titer, do

they usually typically report that as a seroconversion?

A. Those are two different concepts. Seroconversion means that a serum that previously was negative or lower by defined measure becomes now higher in content of antibody as measured by an ELISA or any other assay for that matter. So that's not --

Q. That's a way to use ELISA -- utilize a test is to report --

A. The ELISA test would be what you measure. The seroconversion would be what you calculate out of that.

Q. How would you determine when you're calculating what you're measuring, whether or not it's a seroconversion or not?

A. Well, you compare pre and post. So a seroconversion means that a serum that previously contained no or little antibody contains now some antibody above a certain threshold. Or a serum that contained a quantity of antibody in the first test now contains ten times more antibody. So it contains more by some defined measure as any





which way you define that.

Q. So either you can do it by a fold factor or a cutoff. Is that correct?

A. That is correct, yes.

Q. And when you do it by a cutoff -- did you ever hear the term "serostatus cutoff"?

A. Yes.

Q. What does that mean?

A. It means that a number in that particular assay under standardized conditions determines whether you have a higher likelihood to be negative or positive. In other words, it divides a cohort of people into those that have -- likely have and likely do not have antibodies.

Q. How do you determine whether -- what that serostatus cutoff is?

A. By using negative and positive sera.

MR. SANGIAMO: Object to the form. You can answer.

BY MR. KELLER:

Q. Can you describe that process?





MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: Yeah. You find a collection of sera that by a comparator assay have been -- or by history have been known not to have been exposed by whatever you're measuring. And you run your new assay and you see how it classifies. It's a classification comparison if you want. That's at least one way of doing it. There are other ways that you can use.

BY MR. KELLER:

Q. So that -- is that called a control?

A. No. No, it's not. A control would be something that you run within the assay to determine whether the particular assay run has actually worked the way you predict it to work.

Q. And so the way to determine it by a factor, how does that work?

MR. SANGIAMO: Object to the form.





THE WITNESS: Well, the factor is -- it depends on how you define it. There's many ways of defining a factor. If you -- we're still talking about a serostatus cutoff factor. Right? Just to clarify the question. What factor are you talking about?

BY MR. KELLER:

Q. Let me just clarify that. I believe you testified that there's two ways, at least two ways to identify a seroconversion, one is by doing it by a cutoff and the other way was doing it by a factoring --

A. Oh, you mean that kind of a factor?

Q. Yes.

A. Well, the factor again can be determine in different ways. The most commonly used ones are the very classic one which comes out of sero dilutions which basically uses two dilutions as a factor, so that's the famous fourfold rise. That's has been introduced because in dilution

experiments twofold is something that can generally reliably be pulled apart. A single dilution is hard to tell apart and you make an error, so it's too variable. Twofold is generally something that you can easily hold apart. In an era long gone in which most assays were done by sero dilutions, the fourfold has become more and more a standard. Even it's not a perfect standard but it is an average standard that works reasonably well for that particular purpose. It's really an old concept coming out of sero dilutions. The other I think --

MR. SANGIAMO: I'm sorry, Doctor. Mr. Keller, what was your last question?

MR. KELLER: He wasn't done. Let him finish answering, then you can go back and --

THE WITNESS: It was about the different ways of determining a factor or the different factors. So one was the fourfold. The other one would be one in which you determined the





variability of the assay and determined a factor that clearly surpasses the variability of the assay at a given quantity. And, therefore, it's actually a better way of determining a factor in a way because it tells you, say, for example, your assay is very -- has a very low standard deviation and you can easily determine the twofold difference. Then a better cutoff would be whether something is changed by twofold from the start. You can easily imagine that it depends on the units and it depends on the accuracy of the assay.

BY MR. KELLER:

Q. So doing a fourfold analysis is another way to determine if your cutoff is correct or not?

MR. KELLER: Why don't you just read the question back.

Let me strike the question. I'll say it over.

BY MR. KELLER:





Q. Is one way to identify if the cutoff that's used to determine seroconversion in an ELISA assay to check it against a fourfold analysis to see whether or not that cutoff is correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: No. The two are different concepts.

BY MR. KELLER:

Q. But they're both -- the two concepts are different ways of showing the same thing. Correct?

A. Not exactly.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. How is that -- how are they different?

A. One is an absolute number that with a high likelihood differentiates a group into two different states, positive or negative or having antibodies or not having antibodies. The other one is simply a





measure derived from the presumed variability of an assay saying you can likely differentiate the two but they can be both positive, for example. I mean, a fourfold rise could be something that's already positive and becomes -- so they're really different concepts.

Q. When you talk about the absolute number, that's having a set serostatus cutoff as a number. Correct?

A. That's right.

Q. When you say a highly -- "a high likelihood," is there a percentage at which you would expect that you'd have that probability of it being the number that would most closely resemble -- let me strike that.

What do you mean by "a high likelihood"? Is there a percentage --

A. It depends on the circumstances.

MR. SANGIAMO: Object to the form.

THE WITNESS: It depends on the circumstances. It could be anything you predefine. I mean, you can

define -- you can, for example, predefine that you want to have a 95 percent likelihood that a serum you stated within that example is seropositive rather than seronegative. You could define and have a 80 percent likelihood or a 50 percent likelihood. Whatever you want to define. And the definitions then translate into what your cutoff would be.

BY MR. KELLER:

Q. Gotcha.

MR. SANGIAMO: Doctor, it would be helpful if you just pause before you start to answer Mr. Keller's question. Give me a chance to evaluate whether I need to object or not.

THE WITNESS: Okay.

BY MR. KELLER:

Q. When you say that -- in those numbers, the 95, 85 or 50 percent, are those -- are those typically written in a protocol or how are those determined? Are they





determined before you run the -- before you run the assay or is it something that you learn from running the assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: They could be either. It depends for what purposes you are defining them. If you have already pre-established a serostatus cutoff, for example, out of a validation experiment and you've used whatever criteria you've used, you could now run a prospective control of that serostatus cutoff with any given set of samples. With any given set of samples you would expect it to be a little different and you could say, okay, does this serostatus cutoff that I have predefined in this new experiment reliably differentiate the negatives, the likely negatives from the likely positives.

BY MR. KELLER:

Q. Is there a -- sort of an





industry standard for doing, you know, immunogenicity testing with ELISA as to what percentage you would want to see as a likelihood of the cutoff being correct?

A. No.

Q. Is there a rule of thumb?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't know.

BY MR. KELLER:

Q. If you're using an ELISA assay that relies upon a serostatus cutoff that's being used for purposes of determining whether or not what you're testing will ultimately protect somebody from getting sick in the future based on that antigen, is there a standard that comes to your mind or a percentage that comes to your mind that you'd like to see in terms of the accuracy of that serostatus cutoff?

MR. SANGIAMO: Object to the form.

THE WITNESS: There are too many assumptions in your question. And let





me just deconstruct them one by one.

BY MR. KELLER:

Q. Sure.

A. So the first assumption is that the assay is directly correlated to protection. I'm just leaving it there because you don't know that it in most cases.

The second one is that there is a given predetermined percentage that should be one way or the other the way I understood your assay. And that is it really also depends on the circumstances.

Q. Let me ask you, if there's no correlate of -- let me back up. You say a correlation of protection. What do you mean by that?

A. A correlation of protection would be a measure by which you could predetermine whether somebody is protected or has a very high likelihood of not acquiring a disease. It's different from -- leave it at that.

Q. So if -- you said that's one of the criteria, whether or not there's a

correlate of protection and the other was if there's a predetermined percentage that you're looking for. How are those two related, if they're related at all?

A. Well, if you have a very strong correlate of protection, let's use the case of hepatitis B for example where 10 million international units is fairly well defined and accepted as a correlate, and then a second premise would be that you know that a vaccine elicits a very high level of protection with that correlate, then you want to make sure that the accuracy at which you determine it is also pretty high. So it's in the 90 and above percent range. That is, you know, it depends on how reliable the assay is obviously because the correlate can't be very precise if the assay to measure is not very precise. And it depends on how well you know that the correlate actually really correlates. Now, if there have been prospective randomized double blinded efficacy trials in which a correlate has been clearly and unequivocally established, that's





sort of that best kind of data to have, exists in very, very few disease. Where that exists, you have a very high standard of expectation on an assay that would mimic that kind of a correlate.

Q. Gotcha. When you say -- when you talk about precision, what do you mean by precision, "precise"?

A. Well, there is a definition which I'm probably not able to exactly reproduce.

Q. Your best understanding.

A. It means that the -- and I don't know the exact biometrically definition of precision, but it means that the assay can reproducibly and accurately reflect the analytical truth.

Q. Of what you're testing?

A. Of what you're testing.

Q. From the standpoint of an ELISA assay, you would want to have an ELISA assay that's precise that it's only counting, for example, in the mumps case, mumps antibodies versus any other antibodies that may be in





that blood sample. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's true for any assay, yes.

BY MR. KELLER:

Q. When you say "any assay," would that be true for a plaque reduction neutralization assay?

A. In principle, yes.

Q. You said that -- you mentioned that there's very few correlates of protection that you're aware of. Can you identify if there's any correlates of protection in the mumps, measles, rubella vaccine?

A. Yes, there is one for measles which is not quite straightforward because it was run in an assay format that is no longer run by anybody. And it has been differently transcribed into different numbers. But it's the only one that has a very clear, established, recognized correlate.

Q. So there's no clear established recognized correlate for mumps or rubella?





A. No.

Q. You say that when the -- for measles it's comparable because the assay format has changed over time. What do you mean by that?

A. Well, that -- I don't recall the exact way how this was established originally, but I remember that it was established in a series of cases that were linked to the preexistence of antibodies in the serum of people who became cases. And there was a cutoff established which was originally based on a neutralization assay and then translated into an ELISA. And there is debate as to how that translation actually was done and whether the ELISA number shouldn't be different from the number that is yet defined in a lot of literature. So there's -- some people reported 120 number and others reported 255. The 255, I think, is better researched.

Q. So when you say -- when you're comparing -- is what they did with that neutralizing assay when they compared it to

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the ELISA assay, is that called -- did they correlate those two assays together?

A. You could call that a correlation, yes.

Q. Is there other ways to compare two assays to see if they get the same result?

A. Yes, by what you just mentioned previously, for example, by their power to distinguish different groups, negatives and positives. Do they distinguish the same groups, do they categorize them the same way.

Q. When they do that, is that called a correlation analysis?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Or some other term?

A. I don't know whether -- what specific term is really used for that.

Q. When you say that they're comparing the two groups, if the two groups -- can you describe that process, how you do that?

A. Well, if you have a group, say,



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of a given number of positives, a given number of negatives and they measure them in the two assays and you put them in a 4-by-4 table in which you see essentially how the different assays classify them, you will see those that are positive in both assays, that are negative in one and positive in the other or negative in both assays. And then you can -- it's more -- I would call that a concordance testing rather than a correlation testing.

Q. And those concordance testing, how important is that that the information match up and how important is it to the extent they don't match up?

MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: All assays are artifactual. They're all a specific creation of measures to approximate, to approximate the true biological nature of what you're measuring. So you're measuring two different assay systems. You would expect them not to



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be completely concordant because you're measuring different things. It depends on the circumstances how important it is for your conclusion from that that they are exactly the same or not. It also depends on how variable they both are. For example, if you compare one relative variable or even fragile assay to one that's very well established and very robust, you may find different correlations every time you do the correlation.

BY MR. KELLER:

Q. Gotcha. So when you're doing this concordance assay, you're looking at the result that are concordant and you're looking at what's also the discordant. Correct?

A. That's correct.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Is there a standard way to describe those discordant rights as false positives or false negatives? Do those terms



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sound familiar to you?

MR. SANGIAMO: Object to the form.

THE WITNESS: That -- well, that is a way they are sometimes described, but that assumes that you know the truth, which is sometimes neither here nor there. Sometimes they're just simply different and you have to find out why they're different if it's important. But it doesn't necessarily mean that there's a false negative or a false positive.

BY MR. KELLER:

Q. Is there a --

A. But if you take one for the truth and the other one for the experiment, then, yes, you can use those terms.

Q. So in the case where you're in the measles context, you are -- the folks in those assays were doing a concordance analysis between a neutralizing assay and an ELISA assay. Is that correct?

A. I'm not sure that they ever did

that. I'm not sure what they ever did. I just found that in some of the papers that were written relatively shortly after the observation, that there was a certain titer that correlated with a low likelihood of becoming a measles case, all of a sudden that switched to ELISA titers and the ELISA titers may or may not have been really the same numbers. So I think this is not a formal concordance testing, at least I'm not aware of it. It is more an error in transcription.

Q. I see.

A. And then later on actually the 255 was based on a -- to the best knowledge at the time an effort to correlate the ELISA as it was then run with the old data in the literature.

Q. And that correlation, how is that correlation used for purposes of -- from a regulatory standpoint?

A. I don't know exactly. Because just to remind you, the basis of licensure for these vaccines is generally noninferiority which is not an absolute





cutoff alone. So how was it used for regulatory purposes, I don't think it was --

- - -

(Interruption.)

- - -

MR. SANGIAMO: Mr. Keller, if anyone enters the conference, they ought to say who they are, but I would also appreciate if people not enter and then leave. And perhaps if anyone wants to enter, they can contact someone here find out when there's a break and they can enter during a break and announce themselves at that time.

MR. BEGLEITER: I'll do that. The reason why I got cut off, I don't think the witness is speaking into a microphone, not being picked up by the microphone. I was trying to see if I could get a better way of hearing. I apologize for the disruption. I would ask that maybe he speak a little louder.





MR. KELLER: Hey, Bob, it's Jeff. I'm just going to put the microphone closer -- the Polycom closer to you -- to the witness so you can hear. Let's carry on.

BY MR. KELLER:

Q. You said that typically you're looking -- the regulatory folks are looking for noninferiority. Can you define what you mean by that?

A. Yeah. Noninferiority would be noninferiority of say, for example, a seroconversion rate. And if a vaccine A has a seroconversion rate of X and vaccine B which contains supposedly the same components or is supposed to elicit the same protection as a seroconversion rate; B, the noninferiority would be defined by immunizing people, measuring the antibodies, creating the difference between the seroconversion rates and building a confidence interval around the differences in seroconversion rate and postulating that. That is not greater than a given number. For example, 10 percent





or 5 percent, whatever is appropriate. That would often be the criterion for declaring that something is noninferior and an extension of that similar, even though what's really being tested is not inferiority, that could apply to concomitant use in which you give it with another vaccine or it could sometimes, more rarely, but sometimes also apply to the de novo licensure of the vaccine.

Q. When you're talking about -- you mentioned a 4-by-4 table as part of a concordance analysis. Can you define what you mean by that?

A. Just a table that classifies the positives by one assay, the positives by the other assay, the negatives by one assay, the negatives by the other assay and how that overlaps.

Q. And how are those -- for purposes of comparing, for example, an ELISA to a plaque reduction neutralization assay, how would you -- is that a typical form you would expect to see in a concordance analysis

of those two assays?

MR. SANGIAMO: Object to the form.

THE WITNESS: Yes, something like that. You would find some kind of an analysis that would tell you to which extent the assays not so much measure the same thing as classify people the same way, which is concordance.

BY MR. KELLER:

Q. So when they classify the same way or they discord it in the way they classify things, have you ever worked on a concordance assay between a plaque reduction neutralization and an ELISA in your --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- professional experience over 30 years?

A. I have not really run the assay lab, so I have not worked on any concordance assays. I have, of course, seen them.





Q. When you say you've seen them, can you describe how you came about to see them? Let me just strike that.

What do you mean by see them?

A. I've seen the results of whatever the lab did to provide the data and then I sometimes try to understand them.

Q. And these 4-by-4 tables, how are they useful?

A. Well, they tell you what percentage of results are the same and what results are different, what percentage are different in a classification assay, in a classification exercise I should say. So you find out whether an assay, two assays classify things the same way. You would not expect them generally to do that exactly. In some cases they do it pretty well and other cases not so much.

Q. And for the ones that you've reviewed with regard to a plaque reduction neutralization assay and an ELISA, have you ever seen one done for the mumps virus -- mumps vaccine?





A. Yes. Yes.

Q. So you've seen a concordance analysis comparing a plaque reduction neutralization assay and an ELISA assay?

A. Yes.

Q. Do you recall seeing a 4-by-4 chart for that?

A. Yes, I think I do, but I don't remember the details.

Q. In that assay, do you recall -- why would the percentages of discordant results in that assay be important?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, because they give you a general idea whether the classification is the same.

BY MR. KELLER:

Q. When you say "the classification," what do you mean by classification?

A. Of positives and negatives in the assay.

MR. SANGIAMO: Jeff, we've been going about an hour and ten minutes.





If you reach a good breaking point --

MR. KELLER: We can take a break.

VIDEOGRAPHER: Off the record at 10:13. This will end disc number one.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: Back on the record at 10:25. Beginning of disc number two.

BY MR. KELLER:

Q. Dr. Schodel, when you moved from the clinical -- the director of clinical vaccine research in Europe to the executive director of vaccine integration, did you physically move to the United States?

A. Yes.

Q. And that was in November of 2000, around there?

A. Yes.

Q. And when you -- and you testified earlier that your job duties didn't change substantially, just that you had more supervisory responsibilities when you went

from the executive director of vaccine integration to executive director of biologics in vaccine clinical research. Is that correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't think I said that.

BY MR. KELLER:

Q. Let me ask you the question. Did your duties change when you changed positions?

A. When I came to the US, I -- yes, my duties did change. I no longer had the EU clinical trials. I still was involved with the joint venture but much less frequently. And I had this vaccine integration role that I described to you previously, which I did not have before.

Q. You also testified that you had some role with respect to the end expiry study for the mumps vaccine. Correct?

A. Did I have a role? No, I did not have a direct role in that study at all.




I have not designed it. So, no, I did not have a direct role. But some of the people at points reporting to me had a direct role.

Q. And then they would report to you what was happening with that study?

A. Among other studies, yes.

Q. With particular to that end expiry study, did they ask you for any of your advice?

A. In all probability, yes.

Q. And did you review any documentation related to that study?

A. Probably, yes.

Q. Did you have any -- did you have any role whatsoever before you moved from Europe to the United States on that end expiry study?

A. I have a vague recollection of -- as a direct role, no. I have a vague recollection of discussions during the time I was in Europe for Merck but not in the interim periods. Neither information nor any role.

Q. And so when you're -- when you




came to the US in this executive director of vaccine integration position, did you stop having responsibilities with regard to vaccine clinical research?

A. No. I still had responsibility for vaccine clinical research but primarily at that particular time, initially, primarily on varicella-containing vaccines.

Q. That was part of the ProQuad application?

A. ProQuad, Zostavax, yes. And varicella itself, Varivax.

Q. You said that you worked for the joint venture in Europe for some of the -- did you work on the joint venture in getting the MMR vaccine approved in Europe?

A. Certainly not the initial approval because that had been approved way before I came. But in subsequent approvals I may have occasionally been a part of the discussions with the joint venture. Most likely because I was on the oversight committee, so called JDVMC.

Q. And so the -- are you aware that




Merck ultimately changed its label with regard to its end expiry potency?

A. Yes.

Q. Okay. Do you know whether or not they changed a label with regard to its end expiry potency in Europe as well?

A. I don't remember. But there is a compendial specification in Europe.

Q. In that compendia, do you know if that was changed similar to what was done in the US in terms of end expiry potency?

A. Not to my knowledge.

Q. Do you recall submitting the results of Protocol 007 -- let me strike that.

The end expiry study we're talking about, you understand to be Protocol 007. Correct?

A. Yes.

Q. When I say "Protocol 007," you understand that to be the end expiry study. Correct?

A. Yes.

Q. So Protocol 007, do you know if

that was ever submitted to the EMA for purposes of changing the label?
A. You have two parts of the question.
Q. Let me start over. I'll make it simpler.
Do you know if Protocol 007 was ever reported to the EMA?
A. It would have been reported, yes.
Q. Why would it have been reported?
A. Because there is a general -- I think it might even be a law that the -- or at least there's guidance that any clinical studies with licensed vaccines have to be reported.
Q. Do you know what the CDC is?
A. Excuse me?
Q. The CDC?
A. Yes, I do know what the CDC is.
Q. Did you have any -- did you ever have any communication with the CDC?
A. Yes.
Q. In what context?




A. For example, the ACIP.
Q. Did you ever speak in front of the ACIP?
A. Yes, I have asked questions there for sure.
Q. In regard to the MMR vaccine?
A. No, I don't think so.
Q. Did you ever have any conversations with the CDC regarding Protocol 007?
A. No, I don't remember that either.
Q. Do you recall Merck ever reporting the results of Protocol 007 to the CDC?
A. They were published, so I guess that certainly -- they certainly could have read them. Whether they were independently reported to the CDC, I wouldn't see why, but I don't know.
Q. Where were the results of the Protocol 007 published?
A. I don't remember, but it's -- I think they were published.




Q. And you understand that Protocol 007 had reported on two different assays. Correct?
A. Yes. Correct.
Q. One assay was the ELISA?
A. Yes.
Q. The other assay was a plaque reduction neutralization assay?
A. Yes.
Q. That PRN -- when I say PRN, you understand that to be plaque reduction neutralization assay?
A. Yes.
Q. That PRN assay had been modified. Are you aware of how the assay was modified?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not in all detail, but I do remember that the FDA had urged Merck to run an assay that was different in format than the assay they were at that time running.
BY MR. KELLER:




Q. In this -- were you at that meeting when that was discussed?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't remember.
BY MR. KELLER:
Q. You say that the assay was modified. Do you remember whether or not it was modified with the use of rabbit anti-IgG, antihuman -- strike that.
Do you recall whether the PRN assay that was modified was modified with the use of adding rabbit human IgG?
A. That is my understanding now, but I didn't remember that quite frankly. I wasn't sure whether it was that or a complement anti-IgG.
Q. And complement is different from rabbit anti-IgG?
A. Yes, it is. Yes, it is.
Q. Have you ever heard of anybody using rabbit antihuman IgG in a plaque reduction neutralization assay?
A. Yes.

Q. Where did you hear that from?
A. It's in the scientific literature.
Q. When was that literature written?
A. It's old. I think it comes out of NIH or FDA. I don't remember anymore.
Q. That was done in the early '70s. Does that make --
A. Probably right.
Q. Do you recall any -- had Merck ever used this method of using a rabbit antihuman IgG?
A. I don't know.
Q. You don't know. Have you ever seen any other manufacturer use it?
A. I have been told that it has been used by other manufacturers, but I don't remember seeing it.
Q. Who told you that?
A. I don't remember.
Q. Was it GlaxoSmithKline in their MMR vaccine that they used rabbit anti-IgG?
A. I think they did, yes, but I'm not sure.




Q. Do you know how -- when did you learn about this?
A. I don't know. I mean, it could have been through a publication, it could have been through hearsay.
Q. Do you recall ever speaking to somebody at GlaxoSmithKline regarding the use of rabbit anti-IgG in a plaque reduction neutralization assay?
A. No.
Q. Have you ever -- did you ever look at the validation documents regarding the PRN assay in Protocol 007?
A. The Merck one, yes.
Q. Do you recall reviewing the analysis of what impact the rabbit antihuman IgG had on that assay?
A. No.
Q. Are you familiar what effect the rabbit antihuman IgG does have on neutralization?
A. Not in detail.
Q. What's your understanding?
A. I would have to speculate. So it's not very useful.




Q. Is it based on your 30 years' experience working with clinical studies including plaque reduction neutralization assays and ELISA assays?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. We're entitled to your best understanding.
MR. SANGIAMO: But not speculation. Right?
BY MR. KELLER:
Q. Not speculation.
A. Well, I couldn't offer anything but speculation because at the end of the day I have not run any assays with the addition or without the addition of IgG. So I wouldn't know the effect.
Q. Let me ask you differently. Do you recall any discussions -- do you recall reviewing any documentation at Merck that criticized the use of the rabbit anti-IgG in that assay?
A. No, not specifically.




Q. Do you recall any -- you say not -- what about generally?
A. Well, what do you mean with generally? I mean --
Q. Do you recall any documents that generally --
A. I said -- I was answering specifically your question whether I recall any documentation on the use of rabbit anti-IgG. And, no, I do not.
Q. You said specifically. I just want to know --
A. That was the specificity. Not -- I mean, do I recall assays on -- discussions on PRN, yes. Do I recall specifically the use of anti-IgG? No. In fact, I didn't even remember it until recently.
Q. Gotcha. Do you recall ever seeing any -- having any discussions at Merck where they -- where somebody criticized the use of anti-IgG?
A. It's the same -- it's sort of the same difficulty, no, not in that way.

Q. And do you recall any discussions about the use of rabbit anti-IgG, its effect on the PRN assay?
A. No.
Q. You said that you reviewed some information, scientific information that was published a long time ago regarding the use of rabbit anti-IgG in a plaque reduction neutralization assay. Do you recall gaining any understanding other than that publication?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Do you understand my question?
A. I'm not sure -- I'm not sure if I do.
Q. I'll rephrase it then. Other than the review of that early scientific paper that you testified to earlier regarding the use of rabbit anti-IgG in a plaque -- in a PRN assay, do you recall gaining any understanding other than that paper from any other source?
MR. SANGIAMO: Object to the form.




THE WITNESS: As I said, I specifically did not have -- I don't remember having specific discussions about the use or nonuse of rabbit IgG in the assay, I mean, as opposed to the assay.
BY MR. KELLER:
Q. Based on your 30 years' experience in running and overseeing clinical studies, do you have an understanding how the use of rabbit antihuman IgG would affect a plaque reduction neutralization assay?
A. Well, in a general sense, adding a factor to an assay might increase its sensitivity. It might decrease its robustness or increase it. So it could go either way.
Q. When you say "sensitivity," what do you mean by that?
A. It's the ability to pick up small amounts of antibody from a background.
Q. Gotcha. And when you say "robustness," what do you mean by that?
A. The repeatability so the




other -- in other words, if you run it several times, do you get the same value, is it -- does it have a high standard deviation or not.
Q. How would the rabbit antihuman IgG affect the robustness?
A. It's a biologic reagent, so one of the ways it would potentially affect it is that it could vary over time.
Q. Would it have any impact on -- do you understand the term "specificity"?
A. Yes, I do.
Q. And with respect to specificity, is -- do you understand the term as it's to be used in a PRN assay?
A. Yes.
Q. What's your understanding of specificity with respect to --
A. It's the ability to distinguish between a signal that is caused by what you want to measure, antiviral immune response as opposed to something else, something that is in the serum, something that could be against another virus or whatever.




Q. So specificity for a plaque reduction neutralization assay, you would be looking at whether or not the neutralization was caused by something other than the -- in the case of the mumps assay, the mumps vaccine versus some other -- let me start that over.
In the case of a plaque reduction neutralization assay, when you look at specificity, if you're testing mumps, you'd want to make sure that the neutralization was caused by the mumps vaccine as compared to some other antibody or any other effect. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's true for any assay. You always want to make sure that you're actually measure what you want to measure and not something that is influenced by something else. It could be influenced by serum alone or by other viruses or by schmutz. I mean, it's the -- the possibilities are endless. So whatever you're

measuring, you want to make sure that you reliably measure what you want to measure.

BY MR. KELLER:

Q. So in a plaque reduction neutralization -- like, for example, in Protocol 007 when they did a plaque reduction neutralization assay using the mumps vaccine, when they -- do you know whether or not they validated and tested whether or not that assay was specific and what percentage of specificity it had?

A. I do not remember that the percentage of specificity was specifically analyzed in the validation protocol. I do remember that the assay was validated and the validation was accepted by the FDA.

Q. Do you know whether or not -- do you recall any discussions at Merck regarding the specificity of the -- of Protocol 007's PRN assay?

A. Vaguely. As with any assay, you would have -- you would have potentially specificity issues.





Q. Do you recall if there were specificity issues with this particular PRN assay in Protocol 007?

A. Well, I don't know that the specificity, as I said, has ever been analyzed, so I can't tell you for sure.

Q. Do you recall there ever -- Merck ever doing any analysis as to whether or not the use of the rabbit antihuman IgG had any impact on the specificity of the PRN assay in Protocol 007?

A. No, I do not.

Q. Do you ever have an opinion yourself about that?

A. It would be speculation because I wouldn't have a comparison so I wouldn't know what specificity to expect in comparison because the analysis hasn't been done, so I really can't tell you.

Q. I see. Do you have any, based on your 30 years of experience, have any understanding as to whether or not the use of the rabbit antihuman IgG could have an impact on specificity of that assay used in Protocol





007?

A. As any reagents in an assay, it likely would have an impact on specificity.

Q. But you're not aware of Merck ever analyzing what that impact was?

A. No. And I certainly don't know if they have done it. I just don't know.

Q. You just don't recall?

A. No, I -- well, yeah, I don't recall it, I don't know.

Q. Would you --

A. I mean, it's possible that they've done it and they haven't told me. It's always possible that I forgot it, but I don't know.

Q. Would you be surprised with the use of the rabbit antihuman IgG that they wouldn't have tested this specificity --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- since you're adding that into a -- into the test that you're doing?

MR. SANGIAMO: Object to the





form.

THE WITNESS: Would I be surprised? I think as part of the -- as part of the assay analysis, it might be reasonable to do it. I would not be too surprised if that particular analysis had not been done.

BY MR. KELLER:

Q. Have you, as part of your research in looking -- strike that.

Do you recall there being any discussion at Merck that the use of the rabbit antihuman IgG had a significant fold increase in the neutralization of that assay?

A. Well, again, I've already said that several times. I don't -- I do remember that Merck, under guidance from the FDA, tried to make particularly sensitive assay, but I don't remember any discussion as to the IgG.

Q. Sure.

A. So I just don't know.

Q. Gotcha.

A. I was not involved in that.

Q. In your 30 years of experience, would it be a concern to you if the use of rabbit antihuman IgG would increase the neutralization by a hundredfold?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, because all the assays are relative and have to be validated in and by themselves. I mean, a hundredfold increase of something, you know, PCR assays are sometimes a lot more sensitive than other assays, but it might have less specificity because it's easier prone to contamination. So in principle, no.

BY MR. KELLER:

Q. So would you expect when Merck validated the PRN assay with the antihuman IgG, that they would have somehow tried to control for that affect on specificity?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, you're





assuming that they have analyzed and indeed -- and that specificity and then they would have to control for it because it wasn't what was expected. So there's too many assumptions in there.

BY MR. KELLER:

Q. Gotcha. Let me ask you differently then. Do you know whether or not Merck used a serum negative control versus a mock control in their PRN assay in Protocol 007?

A. No.

Q. Do you know what difference that would make with respect to the use of rabbit anti-IgG in terms of determining whether or not the use of that addition would change the specificity of the vaccine -- of the assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, I don't.

BY MR. KELLER:

Q. When you have overseen the running of plaque reduction neutralization





assays in the past, you've overseen those assays used in other context. Correct?

A. No, not correct.

Q. You've never reviewed the protocols of the plaque reduction neutralization assay before?

A. They were not run in my lab. I have -- I mean, in the course of my life, I've seen protocols. I've seen validation protocols and I've seen validation results. But -- and I've read them. But I wasn't the one who wrote them or put them in place.

Q. Gotcha. And as part of your consulting duties since you left Merck, have you ever discussed with one of your clients these are the plaque reduction neutralization assays?

A. With several, yes.

Q. Did you review those protocols?

A. No, not in detail. In general. My advice is usually more strategic.

Q. In any of the plaque reduction neutralization assays, protocols or discussions that you've had in your 30 years





of experience, have you ever discussed whether or not to use a mock serum control versus a serum control?

A. Yes.

Q. What is the difference, reason why you'd use one or the other?

A. In fact, I've discussed using various kinds of mock serum or serum controls. They all have their pros and cons. A none negative serum control has the advantage that it is in the right matrix serum that you want to measure in, but it doesn't necessarily represent all sera. A mock depleted serum control in which the specific antibody has been depleted by absorption has the advantage that you're measuring in a matrix in which it would normally be the analyte but it has been artificially removed. It's also artificial but it has some other advantages. Then there are other mock controls which appear to mimic the composition of serum without being serum themselves, for example, by adding albumin and other things. They have the advantage

FLORIAN SCHODEL, MD - CONFIDENTIAL

that they're highly reproducible. But the disadvantage that they're not as close to all the kinds of things we do know in serum.

So there's all kinds of different ways of creating these controls. I've seen many of them applied. I don't recall any major problems with any of them as such other than that with any of these controls containing serum, it's difficult to figure out exactly what you have to control for because sera are variable. In other words, you have one control, but you can't control for all the things that are in sera other than specific antibodies.

Classic one is that, for example, if a serum is bloody, you generally don't use it because it has live erythrocytes in it. That influences some assays, not others. So that's a wide field. They have to be appropriate for the assay. It doesn't necessarily mean that one is better than the other.

Q. Let me ask you a question about that in a little more detail. Do you have any





understanding as to how rabbit antihuman IgG would interact with serum that may have other antibodies in it?

A. No, I don't.

Q. You don't. Do you recall any discussion at Merck regarding how the rabbit antihuman IgG would interact with serum?

A. I simply don't recall any discussions with rabbit anti-IgG.

Q. Fair enough. Fair enough.

Let me ask you a question about --

A. By the way, it's because I see the transcription, it's rabbit as in the animal, not rabid as in the infected -- sorry.

Q. Let me ask you a question a little more scientific. What does antihuman IgG bind to?

MR. SANGIAMO: Object to the form.

THE WITNESS: It binds to human IgG, immunoglobulin G, an epitome on immunoglobulin G or several epitomes





on -- it depends on whether it's a monoclonal antibody or polyclonal serum, it will bind to different things on immunoglobulin G.

BY MR. KELLER:

Q. Does it also bind to other antibodies?

A. That's not something that I can answer in general because it depends on how it's been made and how it's been absorbed. So if -- depending on whether it is made with IgG as the immunizing principle and it's not cross absorbed, it might bind to other antibodies or not. It really depends on what it is.

Q. What human antibodies have IgG in it, what percentage, if you know?

A. It's the predominant antibody in serum.

Q. So antihuman IgG would bind -- let me back up for a second. Let me come back to that in a minute. Let's keep pushing forward. Let me ask you a couple of questions.





In a PRN assay, you've testified that specificity is important to make -- to make sure that the neutralization that you're getting in that assay is actually caused by the antigen that you're testing for. Correct?

A. That's correct.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. So is there a standard or a rule of thumb that you're aware of for plaque reduction neutralization assays as to what you'd want to see in terms of specificity?

A. No. No.

Q. If there was only 10 percent specific, so 90 percent of what it was neutralizing wasn't the antigen you were testing, that would be a concern, wouldn't that?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, it depends on the circumstances. If that's as good as you could get, then you would

make sure that the 10 percent are always the same 10 percent. But that's a bit of an extreme example.

BY MR. KELLER:

Q. Well, in the Protocol 007 PRN, they are reporting in seroconversion, correct -- let me strike that.

For Protocol 007, do you know what the endpoint was for the PRN assay?

A. It was -- I don't have a perfect recollection. I think it was the seroconversion rate, and the major endpoint that I remember, because that's why the protocol was done, was the comparison of the seroconversion rates between the different lower titered cells --

Q. So how would specificity --

A. -- to the control.

Q. Strike that. Strike that.

How would specificity affect seroconversion rates in this particular Protocol 007 PRN assay?

A. That's a really interesting question. I can't really answer it, but it




would certainly not affect the comparison because you would expect the specificity to be always the same. Since the major point was the comparison, it wouldn't really affect the major point of the trial.

Q. Well, in Protocol 007 they tested the market product potency.

A. Right.

Q. Correct?

A. Right.

Q. They tested the intermediate potency?

A. Right.

Q. And low potency. Correct?

A. Right.

Q. So do you recall there being a concern that in testing Protocol 007 through a PRN assay, that the seroconversion rate that reported would possibly impact the label for the seroconversion reported in the label?

A. No.

Q. So is it fair to say that the specificity of -- in the Protocol 007's PRN assay could impact the percentage that's




identified as seroconversion?

A. That's more the sensitivity that would impact that rather than the specificity, as long as the specificity is always kept at the same level.

Q. Right. But if you're test -- if the purpose of Protocol 007 -- let me ask you, was -- the endpoint of Protocol 007 was to test to identify a seroconversion rate. Correct?

A. The endpoint was to make sure that the lower titered cells would have at least as good as be noninferior to the marketed control.

Q. But my question is, if the seroconversion rates that are being tested, if that assay is -- has a specificity that is low, let's use 50 percent as a number, it's in the middle, if 50 percent of the -- if the assay is only 50 percent specific, that means 50 percent of the neutralizing -- neutralization that occurs is based on something other than the mumps vaccine. Correct?

MR. SANGIAMO: Object to the




form.

THE WITNESS: You have to see that in the design. So I don't know how a low specificity would affect the seroconversion rates because that's more determined by the sensitivities I said. And as long as the specificity is the same in all three cells, you would still have a valid comparison of whether they were noninferior.

So here in the design and in the question of this protocol, I'm not concerned about the absolute seroconversion rate. I'm concerned about which -- does it fall off somewhere. If you give less than you normally give, would that make it less potent. It's a different comparison, therefore, specificity doesn't in my mind directly influence it.

BY MR. KELLER:

Q. I see. But it does directly influence whether or not that seroconversion number would -- let me ask you a question.

In the original Hilleman assays that were conducted where they approved the mumps vaccine, these used seroconversion as a means to show how well the vaccine would work in protecting kids from getting sick from the disease. Correct?

A. Well, it was sort of the other way around. They had at that time because mumps was frequent, still the luxury of doing controlled studies in the population that was exposed to mumps, and primarily what they measured was whether the vaccine would prevent cases of mumps or not. Sorry. And then, of course, they also measured immunogenicity, and it turned out that the seroconversion was probably even underestimating the level of protection that they saw. But there was never a clear correlate established between the two.

Q. So if Merck -- do you know whether or not Merck ever represented -- let me strike that.

So your -- just so I'm clear, your testimony is that specificity wouldn't





matter in this particular assay because you're only testing whether or not the lower doses matched seroconversion in the higher doses. Correct?

A. It wouldn't matter for the outcome of the study, yes.

Q. I see. Would it matter if the outcome was determine whether or not the kids would get -- be protected by the vaccine?

A. Well, first of all, that's not the question of the study. And secondly, no, because an assay in itself does not -- does not -- especially if no correlate has been established, does not give you a certainty that you're protected or not. That's the difficulty with something where no correlate has been established. One of the reasons it has not been established is that there is not a known titer at which you have absolutely no certainty of -- absolutely no chance of getting mumps. You can have antibodies and you can still get mumps.

Q. So if there was a correlation between a plaque reduction neutralization





assay and protection from disease, then would specificity matter in that assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's too absolute a question. In other words, in a comparison it still wouldn't matter. In a comparison of two things that are different and used as just for the sake of the comparison. So for the purposes of 007 that wouldn't matter.

BY MR. KELLER:

Q. Would it be something that would be important for a regulator to know?

MR. SANGIAMO: Object to the form.

THE WITNESS: If the regulator wanted to ask that question, obviously it would be important for them to know, but that's not a question that I remember ever having been asked.

BY MR. KELLER:

Q. You don't think it's important





whether or not when you're looking at something that's correlated to immunity, correlated to protection of a disease by a vaccine, whether or not in a plaque reduction neutralization assay, in fact, that a percentage of what's being neutralized that is used to report seroconversion was based on something other than the vaccine?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't understand your question.

BY MR. KELLER:

Q. Sure. I'll back up a second, try to break it down for you.

Your testimony specificity is irrelevant -- let me strike that.

Is specificity -- was specificity irrelevant in Protocol 007, the PRN assay?

A. Largely, yes, because it's a comparison. So the absolute -- and I don't know the exact specificity, that's why I can't really answer it. But because of the

comparative nature of the study, it was not a study to predict the likelihood of cases of mumps occurring but a study to compare different potencies of mumps. For that particular purpose it was irrelevant.

Q. Do you know whether or not Merck ever represented that its Protocol 007 study was correlated to protecting kids from getting sick?

A. No, I don't remember that. And I -- no, I don't.

Q. Would that change your testimony as to whether or not specificity of the PRN assay was relevant?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, it would not.

BY MR. KELLER:

Q. Still not?

A. It would not because the same lack of specificity would be true for all -- would be true for all cells. In other words, if they behaved the same, there's no reason to expect that they would correlate




differently with the likelihood of getting disease.

So in other words, even if the assay wasn't perfect, as no assay is, if they were the same in all three cells, even if there was a correlation, the correlation would still be the same for all three cells. It doesn't matter. So the concept is different.

Q. If Merck was conducting -- let me strike that.

If the PRN assay was going to be used to set what the seroconversion rate was for the label, for that purpose, would that have -- would the specificity have -- be important for that analysis?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can't really answer that question. I mean, the reported number in the label is a number given -- that was an assay result at a given time when the vaccine was licensed. And at that time it was truly reported as whatever




it was. So I don't see how specificity would be -- would enter into the label.

BY MR. KELLER:

Q. Do you recall there being any discussions at the time that you were at Merck where there was a concern that if Merck reported seroconversion rates lower than what was reported in its label, that it would have to reduce or change its label to reflect those new results?

A. I don't remember a discussion exactly around those lines, but I do remember -- and I don't remember whether I heard them myself or heard of them, discussions with the FDA where the FDA expressed a desire that the seroconversion rates in the label be reflected by an assay that was run to test the vaccine.

Q. Let me sort of break this down a little bit. If your -- if the assay was -- if you had to report the seroconversion rate that was reported in the Protocol 007 in its label as -- would that affect your analysis as to




whether or not the specificity of what was neutralized would have been relevant for that analysis?

A. No. I don't really -- I don't really see the connection. I mean, what you're talking about is more sensitivity than specificity.

Q. Well, let me break it down into smaller bits. You testified earlier that specificity in a plaque reduction neutralization assay is identifying whether or not the neutralization that occurs happens from the antigen you're testing. Correct?

A. That's correct.

Q. And if a percentage of that neutralization comes from something other than the antigen, that means -- that's what specificity is discussing. If it's 50 percent specific, 50 percent of what's being neutralized is caused by the antigen being tested and 50 percent is being caused by something else. Correct?

A. Yeah, that's correct.

Q. And so --

A. But we don't have an analysis that the --
Q. Let me just kind of go through this so I understand it.
And so if --
MR. SANGIAMO: Wait a minute, Jeff. He was -- let him finish with his answer.
BY MR. KELLER:
Q. Are you done?
A. No, I wasn't. We don't have an analysis that suggests that the assay had a 50 percent specificity to start with.
Q. Assume it did for the purpose of this discussion. And so in that situation, what effect does neutralization have on the reporting of seroconversions in a plaque reduction neutralization assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not sure I understand. What effect does neutral --
BY MR. KELLER:




Q. Yeah, when a plaque reduction neutralization assay reports in a seroconversion, it's reporting the number of plaques that have been -- that are identified in a dish. Correct?
A. Yes.
Q. And so what the plaque reduction neutralization assay is doing, it's looking at a dish prevaccination and comparing that to a dish postvaccination after a certain period of time. Correct?
A. Right.
Q. So if the neutralization that occurs is caused by 50 percent something other than the antigen that you're testing, that could have an impact on an overstate seroconversion, couldn't it?
A. It depends on the circumstances. You have to -- just to give you an example, if you have -- to stay with this kind of a general assumption, if you have a pre-titer of say 1 to 8, and then you have a post titer of 1 to 256, for example, now you take 50 percent of that, then you would be having




a pre-titer of 1 to 4. And the pre-titer of 1 to 4, assuming that everything is linear, would go to half of 1 to 256 or 128. That would still be a seroconversion. So it would -- in that case it would have no impact whatsoever.
Q. But in the case where the --
A. So you're making a wrong assumption. Your assumption, and I'm not quite sure where that happens, but that example should make it clear to you that even an assay in which not all the reported numbers come from the specific part of the assay but there is also contribution of a nonspecific part can still be highly sensitive and sufficiently specific to report a seroconversion rate.
Q. So what happens when the numbers are compressed, you know, you're looking at around that seroconversion cutoff, you have numbers that are much closer to the cutoff, that 50 percent criteria?
MR. SANGIAMO: Object to the form.




THE WITNESS: Well, again, that's making too many assumptions. Then they would also be -- if everything was linear, they would also be still linear. It would still be in the same direction.
MR. SANGIAMO: Sorry. Let me --
MR. KELLER: Just so I'm clear, let me --
MR. SANGIAMO: No, no, no. I've been letting this go for a while. You're asking -- Dr. Schodel is not being presented as an expert witness in this case. He's here as a fact witness. You're asking a whole lot of hypothetical questions. He's answering them, I've been letting it go. I think we're getting close to the time where it's time to start moving on.
BY MR. KELLER:
Q. Just so I'm clear, Dr. Schodel, it's your view that specificity was irrelevant to the Protocol 007 PRN assay?

MR. SANGIAMO: Objection. Asked and answered.

THE WITNESS: No, that's not exactly what I said. I said that for the degree of specificity, as long as it was the same or similar was irrelevant for the primary endpoint, the analysis of the comparison.

MR. KELLER: Let's do this, let's -- let me mark as Exhibit 3 --

- - -

(Exhibit Schodel-3, Immunological Correlates of Vaccine-Derived Protection Fondation Mèrieux Conference Center 'Les Pensières' Veyrier-Du-Lac, France article, was marked for identification.)

- - -

BY MR. KELLER:

Q. This is a document, an article written by you, Dr. Schodel, "Immunological Correlates of Vaccine-Derived Protection...," and then it appears that this was presented at a conference in France. And I will not even try to give the rest of the title in French.





But do you recall comparing this?

A. Yeah, this was basically a summary of that meeting.

Q. Dr. Plotkin gave a lecture about correlates and surrogates. Correct?

A. Uh-huh.

Q. Do you recall that particular seminar?

A. I've heard him -- not that particular one, but I've heard Stanley speak many times about correlates, yes.

Q. In this introduction you write, "It is often not feasible and occasionally not ethically justifiable to run placebo controlled clinical trials for efficacy. Hence, correlates of vaccine induced protection have an important role in the discovery, development and life cycle management of vaccines (for example changes in the manufacturing process, concomitant use with vaccines, extension of the age range of the indication)."

Do you see that?

A. Yes.





Q. When you wrote that, did you believe that statement to be correct?

A. Yes, I still think it's correct.

Q. Under "Terminology" you write in the third paragraph, "I'd suggest that the term immunological correlate of protection is reserved for such correlates where immune measures in a validated assay have been shown to correlate with protection from infection and/or disease in controlled trials in a statistically meaningful manner."

Do you see that?

A. Yes.

Q. Do you believe that statement to be true?

A. Yes.

Q. So correlates of protection, that's an important -- let me strike that.

Typically you look at a correlate of protection in a situation where you can't do a clinical study because of ethical reasons. Correct?

A. If one is available. You typically look at a correlate of protection





where a correlate of protection has been established. Sometimes you have to do it without one because there hasn't been one established.

Q. So as you -- it's your testimony earlier that for MMR the only correlates of protection that you're aware of is with measles. Correct?

A. That's the best established. Even that, as I pointed out, there are some issues.

Q. When you say "correlate of protection," do you mean that -- is that the same as correlate of effectiveness?

A. No.

Q. What's the difference?

A. Well, effectiveness is a concept which combines real world exposure to a drug or a vaccine and outcomes that are observed. It is usually not prospective, it can be prospective and the controls are not randomized controls. So what you look at is a population effect in people who are vaccinated as opposed -- like as an example,

for opposed to people who are not vaccinated. But there are many other factors why people aren't vaccinated, and so the groups are hardly ever exactly identical. So effectiveness is much less precise measure of whether a vaccine as such works or is efficacious than efficacy. It is on the other hand by some felt to be a measure of real life usefulness. But it has many, many factors that go beyond any of the things we've discussed here.

Q. So have you ever seen the term correlate with efficacy?

A. Yes.

Q. And what does that mean based on your understanding?

A. Well, that means that a laboratory measure can predict whether somebody is protected or not. In that regard, measuring that laboratory measure can help you ascertain whether a drug vaccine, whatever else will likely protect or not -- likely protect or not protect against the disease. But that's measured in an efficacy





setting. Efficacy means that you have a well-defined randomized controlled trial with enough endpoints and it's all set up in the right way.

Q. Are you aware of whether or not Protocol 007 was ever described as a correlate of vaccine effectiveness?

A. No --

MR. SANGIAMO: Object to the form.

THE WITNESS: -- I'm not aware of that.

BY MR. KELLER:

Q. Did you ever --

A. If it had been described that way, I might be a bit surprised.

Q. Are you aware of Protocol 007 ever being described as a correlate of vaccine efficacy?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, I'm not aware of that.

BY MR. KELLER:





Q. Would that surprise you as well?

A. Well, depends on who made that statement.

Q. If Merck made that statement.

A. Somewhat. It's not an efficacy study.

Q. Did you ever make that statement?

A. I don't remember it, no.

Q. Did you ever make the statement that Protocol 007 was a correlate of vaccine effectiveness?

A. I don't think so.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. You would be surprised if you did?

A. I would be surprised if I did.

Q. Because correlates of vaccine effectiveness and correlates of vaccine efficacy, those are two different ways that show that a vaccine actually protect the kids from getting sick. Correct?

A. In the efficacy, yes, that's





clearly primarily the vaccine. In the effectiveness it is societal factors other than the vaccine as well so it's not as direct a measure of the vaccine.

Q. Would you consider if somebody made the statement that both of those existed with Protocol 007, that that would be considered a correlative with protection?

MR. SANGIAMO: Object to the form.

THE WITNESS: No. It was not set up to do, to measure efficacy or effectiveness. I mean, MMR is a highly efficacious and effective vaccine but the measure for that is different.

MR. KELLER: Let me mark as Exhibit 4.

- - -

(Exhibit Schodel-4, E-mail string, Bates MRK-KRA01648951 - 01648956, was marked for identification.)

- - -

BY MR. KELLER:

Q. Exhibit 4 is a document that bears Bates stamp numbers KRA01649851 through 956, and it's a series of e-mails.

Doctor, if you could take a moment to review the e-mails, it will save us time rather than me trying to read this stuff into the record. Just take a moment. Let me know when you're done.

MR. SANGIAMO: It's a long e-mail thread, Jeff. No expectation he would have been done already.

MR. KELLER: I understand.

THE WITNESS: I think I have a -- I will see whether I may need to go back because there's a lot of stuff in there.

BY MR. KELLER:

Q. That's okay. I just wanted to have you -- so you have an understanding of sort the context of this e-mail. This e-mail -- there's a series of e-mails that were written before it was -- before you were e-mailed as part of this e-mail chain and instead of me going through everything that




happened before the e-mails came to you, I thought it was helpful to have you review it.

But if you look on the third page, which is 1648953, there's an e-mail from Joan Staub on June 19, 1997, to Henrietta Ukwu and Barry Garfinkle and there's a series of other people on this e-mail including David Krah, Alan Shaw, Jerry Sadoff. And this is regarding mumps issues. In here this e-mail, though you're not on this, it's in the chain of e-mails that was ultimately sent to you, there's a statement that says Henrietta -- let me back up for a second.

Who is Joan Staub?

A. Joan Staub was a project manager at Merck.

Q. Was she a project manager on MMR II, if you recall?

A. I don't remember. But since she's sending these e-mails, she had probably some project management responsibilities.

Q. Who is Henrietta Ukwu?

A. Henrietta Ukwu at the time was the regulatory person for vaccines at Merck.




Q. And Barry Garfinkle?

A. Henrietta was on the clinical side, Barry was on the manufacturing side. He was the quality person of it. I don't know whether he was regulatory or quality for vaccines on the manufacturing side.

Q. Here Joan Staub is saying, "Henrietta/Barry, The suggestion from the MMR Competitive Defense Task Force was to actually run a clinical trial with Mu at expiry since SB will be filing in Germany and is expected to come on the market in 1998."

Do you see that?

A. Yes.

Q. This MMR competitive defense task force, were you a member of that?

A. I don't remember that.

Q. Do you remember what that task force job was or role or purpose?

A. Probably to make sure that MMR meets all criteria and can stay on the market. Remain competitive. I don't know.

Q. Do you recall there ever being -- do you recall ever seeing any




documentation from this task force?

A. I'm not seeing one right here apparently. So that's the last time that I remember one. I didn't even know the thing existed.

Q. Fair enough. Was it -- during the time that you were at Merck, was it Merck's practice before meetings of its committees that it would send out an agenda in a background paper what was to be discussed at that meeting?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't know whether I can make a general statement like that. There were all kinds of general meetings. Some meetings were very formalized, and, yes, that was done. Other meetings were very informal and, no, that was not done.

BY MR. KELLER:

Q. In this e-mail when it says Mu, you understand that to be mumps. Correct?

A. No, it's MMR. Mu, yes. Mu is

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mumps. Yeah. Okay.

Q. And SB, that's Smith --

A. Smith Beecham probably, yeah, sure.

Q. And that's Glaxo Smith today. Correct?

A. Yeah. Yeah.

Q. Do you know whether or not -- so here there is a discussion here about running a clinical trial with mumps at expiry. Do you see that?

A. Uh-huh.

Q. Do you recall giving an opinion about what that clinical trial would look like during this time frame? I know it's a long time ago.

A. No, I don't specifically remember this one. But, you know, there's a -- in general, there's always a debate if you want to know whether something works at end expiry as to whether -- how you should do that. And I -- if somebody had asked me an opinion on how to do that, I would certainly have weighed the pros and cons of doing





dilutions over aging over various other things.

Q. Gotcha. Here in the last sentence to Ms. Staub's e-mail, she has, "Any downsides to this...other than the obvious?" Do you see that? Do you understand what she meant as to what the obvious downsides were?

MR. SANGIAMO: Objection. Calls for speculation.

THE WITNESS: I have no -- I have no idea what Joan thought at that time.

BY MR. KELLER:

Q. Okay. Do you recall --

A. It's not obvious to me.

Q. -- understanding what the obvious downsides would be of running an end expiry study of mumps?

MR. SANGIAMO: Object to the form.

THE WITNESS: The first thing it cost money. The second one would be that you might not meet the criteria of the study and then you would have





to figure out what to do.

BY MR. KELLER:

Q. When you say not meet the criteria of the study, end up with a seroconversion rate lower than what was in the label?

A. No. It could be all kinds of things. I mean studies, clinical studies have their problems. You could not have enough participants or valid assay points to make any statement.

Q. Sure. If you look on page 2, there's an e-mail on the 27th of June, 1997 from a Joline Fontaine to you, Dr. Schodel. Do you see that?

A. Uh-huh. Which one is this? This here. Where is it?

Q. It's on --

A. She said, "what do you think of the studies proposed below?"

Q. Correct. Who is Joline Fontaine?

A. I'm not 100 percent sure, but she may have been another Merck employee. I





do remember the name, but what her exact function was, I don't remember.

Q. Sure. In here you -- in the e-mail that came after that where you responded on June 30, 1997, you say here, Dear Joline, If we decide to address the at expiry mumps titer versus immunogenicity issues by clinical trials, I think we should A, not compare to at release for the obvious risks; and B, not titrate the virus, because that risks to change the ratio of mumps and measles and rubella with possible ensuing changes in interference.

Do you see that?

A. Uh-huh.

Q. What were you talking about? Do you recall writing this e-mail?

MR. SANGIAMO: Mr. Keller, I'll just ask you to let him read the rest of that e-mail if he has not read it already.

MR. KELLER: We'll get there. I'm just asking if he recalls writing this e-mail.

MR. SANGIAMO: The question is, do you recall writing the e-mail?

THE WITNESS: I don't, but I can certainly recall if I reread this again my kind of argumentation here.

BY MR. KELLER:

Q. Sure. Take whatever time you need. Let me ask you the question, then you can see if you can answer it, if you have to reread it.

What did you mean when you decided to address that expiry mumps titers versus immunogenicity issue?

MR. SANGIAMO: You should read the remainder of the e-mail.

BY MR. KELLER:

Q. Or is that versus or is that as? It's confusing to me.

A. So there are two -- there are at least two issues in trying to post hoc determine an end expiry titer. Some are linked to the -- well, it's at least three. Some are linked to the general risk of running clinical trials and some are linked





to the -- to what you compare it to. And obviously many vaccines, if you compare them at the high titer, they have -- initially, will have a higher immunogenicity at release which I'm not sure is actually true for mumps. I don't think it is. But for varicella, for example, it's very well known. So if you compare, if you compare the release, the release titers and they're very high to the end expiry titers which are lower, you will see a difference which is fine, but it's a real difference.

The second one is how do you actually prepare such a material. And the third one is how do you measure it. And that goes both for the product side and for the clinical side. So in the preparation, we've always made MMR pretty much the same way. It's the same kind of cell culture, it's the same kind of harvest site, it's the same way of blending the viruses. Those viruses are not innocuous to each other. They do stuff to each other when you mix them. We certainly found that out when we did ProQuad.





There's a lot of publications on that.

So if you were to hold everything the same but change one of the components, you actually change the whole. So you're no longer comparing the same vaccine. It's not a good way of determining the end expiry. So that's one of the factors.

Let me think about what the other factors were. The other factor is the uncertainty of actually knowing exactly what titer of what you have in there because every release assay has variability. And I remember one thing that when this was finally done, which I was not part of, the -- Merck put in a heroic effort to actually determine the exact titers of the mumps component in the MMR that it had specifically created for the trial to compare, as you said before, the medium dose and lower dose to the normal release dose. That was very important because if you just pick a lot that's somewhere sitting in your refrigerator and that had been analyzed, because they analyze





the release assays, happen when the lots are made, so, you know, they may have been analyzed, I don't know, two years ago. The way the assay ran then, you may have a number that is not contemporaneous and it does not reflect the truth of the comparison. Again, we're talking about comparisons. The comparisons is what really matters. So I was also nervous that if you -- in this e-mail, that if you were to construct something like that and not come up with a format of testing that really increased the variability -- decreased the variability of the release assays, that not only would you create an artificial situation, you would potentially amplify it by the uncertainty that is inherent in every assay and in every assay depending on the form that it's run.

Q. Why wouldn't you want to have an artificial situation?

A. Why would I not want to? Because it wouldn't reflect what I put out on the market. And I have been putting out in the market for 40 years. It wouldn't reflect

the safety, effectiveness and efficacy record of the vaccine. It would be something completely contrived.

Q. So you wanted to make sure when you -- when they were -- if you were going to do this end expiry study with different potencies, that the potencies that you were testing with were as accurate as possible to that potency that --

A. On one hand as accurate as possible and on the other hand reflecting the material that's actually out there on the market, not something that is just made up in the lab and then put into people.

Q. Gotcha. So in this e-mail you talk about the obvious risk, is that the obvious risk you were talking about?

A. Yeah.

Q. Was there a concern that the results, if you ran this assay, would be lower than what was identified in the label?

A. No. This was not -- I'm not dealing with the label here. I'm just dealing with comparisons. So there was no




concern about the label. The concern was simply that this would not reflect the situation that we wanted to test.

Q. Here you write, The trial should only compare seroconversion rates to acceptable historical seroconversion data after immunization with lots at expiry, thus making sure that even lower titers meet the standards (the problem here is whether the assays our lab are willing to run are generally accepted by the agencies or the scientific public at large, short of publications I have my doubts).

What assays were you talking about?

A. Well, so that's the first set of assays on the product which to make sure that they're accurately reflecting what's on the product. Then the other one is that the assays that are -- whether that's the ELISA or the PRN, that are currently run are up to snuff by the standards of when this happened. Not assays that were run in 1970 or 1965 when Maurice did his original licensure of MMR.




So what I was thinking of is simply the impact of time on regulatory expectations. I mean, we have a lot of -- these are old products, they've been extremely successful in the market. They've been very safe, they've been given to hundreds of millions of people and they've worked. We have a low, very, very low burden of disease in this country because we use this, different to almost everywhere else in the world. So the last thing you want to do is now store it. A set of comparisons with such a record and distract from that record by running something which is not ideally controlled and very different from what was done in 1960-something. However, standards have evolved. That was the reference here to the regulatory agency. So you have to come up with something which works.

Q. So the fact that when Maurice Hilleman did the original studies back in the 1960s, there's a expectation, at least a regulatory expectation, that current modern assays would be used for these types of tests.




Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: Yes, of course, but -- they were modern, but, you know, I was modern in 1956.

BY MR. KELLER:

Q. So in 1997, modern for 1997. Correct?

A. Yeah.

MR. SANGIAMO: Jeff, we've been going about an hour and ten minutes. Are you at or close to a breaking point?

MR. KELLER: Let me just finish this document and then we can move on from there.

BY MR. KELLER:

Q. This concern you talked about here, the changes in interference, was there interference with the ratio of virus in the MMR II vaccine between the different antigens?

MR. SANGIAMO: Object to the form.

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THE WITNESS: I don't know. I was -- there was a theoretical concern.

BY MR. KELLER:

Q. Have you ever seen any documentation that talks about -- let me strike that.

When you were working on the ProQuad licensing applications, did -- was there any discussion about interference between the mumps, rubella and measles antigens in the ProQuad?

A. No, varicella.

Q. It was varicella?

A. Yes. So that, of course -- and that's published that that interference had led to the very long half towards ProQuad licensure because the viruses had to be appropriately re-titrated. It didn't change the MMR component but it did change the varicella component.

Q. Do you recall any discussion at Merck that there's interference between measles and higher the amount of measles





that's added in a dose, the lower the potency of the mumps?

A. No, I do not. As I said, the example I just gave you is the ProQuad example, that one I knew about, but not what you're saying.

Q. You weren't aware of that?

A. No. Or at least I don't remember it.

Q. If you look on the next e-mail from Keith Chirgwin to you and Ms. Fontaine, who is Keith Chirgwin?

A. Keith Chirgwin was in the regulatory group. I don't know what his role was at that time, but he eventually basically succeeded Henrietta Ukwu and became the head of vaccine regulatory.

Q. If you see in the middle of Mr. Chirgwin's e-mail --

A. Which one is that, on the first page?

Q. 1468951 on the first page.

A. Okay. Okay.

Q. Dated June 30, 1997, at





6:39 p.m. Mr. Chirgwin writes --

A. Where is this? So this is from me to -- or is this from -- no, this is --

Q. From Keith Chirgwin. You got it. To you and Ms. Fontaine. Do you see that, June 30th?

A. This is from me to --

Q. No, from Keith Chirgwin to you.

A. There's something wrong.

MR. SANGIAMO: It says from.

BY MR. KELLER:

Q. From Keith Chirgwin. I'll go through that in a second. It's a weird e-mail.

A. There's something wrong here because this is a message I sent to Keith obviously from the text.

Q. Right.

A. But --

Q. Looks like he's cutting and pasting into his e-mail.

A. Maybe he wrote it and just -- I don't know. I'll have to read it and see.

Q. It looks like Mr. Chirgwin had





taken something that you had written previously, though it's not in any e-mails that we've been able to find, and then responded below that. I was wondering if you look at the part that's attributed to you, Dr. Schodel, do you recall writing this particular section?

A. I have certainly not written this. This is not something I would write. It's just not my style of writing and I don't remember this. So this is something that he pasted in there. In my --

Q. In here it appears that either he wrote it or where he got this information, he says -- this e-mail says, What worries me is there is no clearly defined standards and we may be waking sleeping dogs up as they say (especially since I get no clear picture of whether our assays are generally acceptable. I get a wide spectrum of answers to the acceptability of ELISAs only).

Do you see that?

A. Yes.

Q. Do you recall there being a

discussion with respect to doing an end expiry study in this time frame, that Merck wanted to use just an ELISA assay for its end expiry study?

A. I don't remember that. I don't think I've written that, so -- but on the other hand, I -- it's a reasonable question as to whether the ELISA alone would be acceptable and reasonable. That question --

Q. Why would that be a reasonable --

A. Well, the ELISA is a much better controlled assay than the PRN. By its nature it can be. So it's just a more reliable assay.

Q. So the -- here the opposite is the concern is that whether the acceptability of ELISA alone versus some other assay. So why would that --

A. Well, there was a --

MR. SANGIAMO: Object to the form. Actually, Jeff, did you finish your question? You said so here the opposite is the concern is that whether in the acceptability of ELISA




alone --

MR. KELLER: I'll rephrase it. Let me strike it.

MR. SANGIAMO: Thank you.

BY MR. KELLER:

Q. From the wording of this e-mail it appears to me the opposite, that there was a concern that there wouldn't be an acceptance to the use of ELISA alone, and I'm asking you whether or not -- what you understand that to mean?

A. So those are not opposites.

MR. SANGIAMO: Object. I'm sorry, Doctor. Objection. You're asking what the author meant, or are you asking his interpretation of those words?

MR. KELLER: His interpretation, yes.

MR. SANGIAMO: His interpretation.

THE WITNESS: So let's first talk about acceptability. Acceptability would mean acceptability to regulatory agencies. I can't speculate on what




is or is not acceptable to regulatory agencies. By that time there was still a strong desire by at least the FDA to see virus neutralizing titers, functional assay titers for this particular virus. That is not -- and so they are not opposites. I mean, the -- it does not mean that the ELISA is not more reliable and better standardized. It is simply that the expectations may have been different at that time.

BY MR. KELLER:

Q. Well, an ELISA assay only counts antibodies. Correct?

A. Yes, it does.

Q. It doesn't count whether or not those antibodies protect the kid from getting sick?

MR. SANGIAMO: You have to let him finish his answers. He didn't just now.

THE WITNESS: But it does detect antibodies reliably.




MR. KELLER: Let's take a break.

VIDEOGRAPHER: Off the record at 11:41. This will end disc number two.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: Back on the record 11:55. Beginning of disc number three.

MR. KELLER: For the record I'd like to mark as Exhibit 5 a document.

- - -

(Exhibit Schodel-5, 2/23/01 E-mail with attachment, Bates MRK-KRA00549510 - 00549535, was marked for identification.)

- - -

MR. KELLER: For the record, Exhibit 5 is a document that bears Bates stamp number KRA 549510 through 535. There is some documents in the middle that aren't Bates numbered but they are Bates numbered in the way they are produced to us, we just

couldn't print them out with Bates numbers. So 549518 -- oh, I wasn't able to do it. Which is just the attachments to this e-mail. So I will represent to you they are Bates numbered in there. Are there Bates numbers in yours?

MS. ZINSER: Yes.

MR. KELLER: Good, good, good.

Strike my last statement.

BY MR. KELLER:

Q. Exhibit 5 is a document that bears Bates numbers KRA 549510 through 535. And I will ask you, Dr. Schodel, you are identified as receiving this document and its attachments on February 26, 2001, from Dorothy Margolskee. I'll ask you, do you recall receiving this e-mail and the attachments?

A. No, but I probably received it if it says so.

Q. Do you have any reason to believe that you didn't receive it?

A. No.

Q. Do you have any reason to




believe that you didn't review the attachments?

A. No. I think I probably read them.

Q. In the attaching e-mails from Dorothy Margolskee -- who is Dorothy Margolskee during this time frame, what was her position?

A. Dorothy was still my boss at the time. She -- I can't tell you what her exact title was but she had essentially all of vaccine development on the MRL side under her.

Q. Was she on the manufacturing side or the laboratory side?

A. The laboratory side.

Q. This e-mail on February 23, 2001, was sent to an Edward Skolnick. Who is Edward Skolnick in this time frame?

A. Ed Skolnick was the head of MRL.

Q. Was he the president of MRL?

A. Yes.

Q. Also cc'd -- do you know who Douglas Greene was?




A. Uh-huh.

Q. Who is that?

A. Doug at the time was the head of clinical.

Q. Clinical?

A. Yeah.

Q. Clinical research?

A. Clinical research within MRL. So he was reporting to Ed.

Q. And was it typical to send e-mails to Ed Skolnick during this time frame, once the information was important?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: I'd have to speculate. Of course. I mean, he was somebody who took a lot of interest in details.

BY MR. KELLER:

Q. And here it was cc'd to Jerry Sadoff, Henrietta Ukwu, Emilio Emini, Keith Chirgwin, Michael DeAngelo -- Michael Angelo and Michael King. Who is Emilio Emini?

A. Emilio Emini was the head of




the basic research group.

Q. Was his group --

A. In MRL.

Q. -- the one running Protocol 007?

A. No, his group was the one that was running the neutralization assay.

Q. So his group was --

A. And possibly the ELISA as well. Pretty certain the ELISA as well.

Q. So his team was the one actually running the assays that were part of Protocol 007?

A. Not the assays on the protocol side -- on the product side, but the assays on the clinical side.

Q. Correct. For part of Protocol 007, they were doing the PRN assay testing. Correct?

A. Yes.

Q. They were doing the ELISA testing as well?

A. Yes.

Q. So it was running in the labs that he controlled?

A. Yes.
Q. Who is Michael Angelo?
A. Michael Angelo was in manufacturing. I don't know what his exact role was, but I think quality.
Q. What about Michael King?
A. Also manufacturing.
Q. In the first paragraph, Ms. Margolskee writes to Mr. Skolnick, "We have been assisting MMD in responding to CBER questions re mumps end-expiry by performing an interim analysis on 600 children participating in the mumps end-expiry study (200 per groups, studied at mumps potencies of 4.9, 4.0 and 3.7)."
Do you see that?
A. Yes.
Q. Do you recall Merck conducting a preliminary subset analysis of Protocol 007's PRN assay?
A. Yes.
Q. Do you know why it ran that assay -- did a preliminary look at the results?




A. I'm not sure, but it may have been due to CBER questions.
Q. Was it common to unblind a study in the middle of it to take a look at the results of a subset?
A. This is making an assumption. I don't know how much unblinding was done. Unblinding had all kinds of different levels of detail.
Q. Why --
A. Interim analysis would be run based on the data then available. And it could be done in a blinded or in an unblinded fashion. And it could be group unblinded or individual unblinded. So there's all kinds of details. I don't know what the details are here.
Q. Do you -- why are assays blinded -- strike that.
Why would a plaque reduction neutralization assay be blinded?
MR. SANGIAMO: Object to form.
THE WITNESS: Every assay would be blinded in the lab to make sure




that the lab doesn't know what group it belongs to to avoid any potential bias.
BY MR. KELLER:
Q. And --
A. You're -- I mean, are you assuming that the lab was unblinded to the individual assays? There's nothing would suggest that.
Q. So it's your testimony that when the preliminary subset analysis was run, that the lab was not unblinded to the results of that assay?
MR. SANGIAMO: Objection.
THE WITNESS: What do you mean with unblinding? I mean, unblinding would -- so the lab was, of course, not blinded to the results of the assays they run because they run the assay and they report the data. But they would not know who the sera comes from. So that's the important part. They wouldn't know whether it comes from one group or the other group as




well. And the analysis is done by statisticians so it's not the lab who does the analysis.
BY MR. KELLER:
Q. You said the reason that you would do blinding was to protect against bias. Correct?
A. Right.
Q. And so you said that for the plaque reduction neutralization assay it was important to blind the folks doing the assays as to the different potency groups. Correct?
MR. SANGIAMO: Objection.
THE WITNESS: Yeah.
MR. SANGIAMO: Are you asking him about -- questions about decisions that were made about Protocol 007 and the running of the assay in Protocol 007 --
MR. KELLER: I'm asking questions about --
MR. SANGIAMO: -- or are you asking in general -- let me finish my question. Are you asking for general

expert testimony or are you asking for --

MR. KELLER: Dino, you can object and that's it. Speaking commentaries are not appropriate.

MR. SANGIAMO: Well, I've let you go a long time with these hypothetical questions. I think at a minimum you need to clarify for the witness --

MR. KELLER: Instruct the witness not to answer then. Stay out of my deposition, Dino.

MR. SANGIAMO: I think you need to make it clear what you're asking.

BY MR. KELLER:

Q. Dr. Schodel, are you aware of how Protocol 007 was blinded?

A. No.

Q. For plaque reduction neutralization assay would you expect, based on your 30 years of experience and participating with these protocols, that the groups of -- the three different potencies would have been blinded to




the people doing the assays?

MR. SANGIAMO: Object to the form.

THE WITNESS: Like any other assay that goes into the lab that would be blinded. Priority blinded studies are generally given blinded into the lab.

BY MR. KELLER:

Q. Would you have expected there to be blinding as to whether or not it was a pre or postvaccination sample?

MR. SANGIAMO: Object to the form.

THE WITNESS: Not necessarily. Because of the timing as to when the assays are run. If they're run parallelized, they may have been blinded. If they're run as they come in, they would not have been blinded because they come in at a certain time, not perfectly blinded, but they still would not specify that.

BY MR. KELLER:




Q. What are the benefits of blinding the prevaccination versus the postvaccination --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- based only your experience?

MR. SANGIAMO: Object to form.

THE WITNESS: I'm not sure there are any.

BY MR. KELLER:

Q. Somebody running the assays for a plaque reduction neutralization, the prevaccination serum you'd expect to see a whole lot of plaque in those samples. Correct?

A. Yes, that's correct.

Q. And in the postvaccination group you would expect to see fewer plaques. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's correct.

BY MR. KELLER:

Q. So if the person counting the assays or counting the plaques to determine




how many are in each of those dishes, if they know it's a prevaccination versus a postvaccination, that could introduce bias into their counting, couldn't it?

MR. SANGIAMO: Object to the form.

THE WITNESS: Depends on how it's otherwise controlled.

BY MR. KELLER:

Q. How else could it be otherwise controlled to prevent bias?

A. By an SOP.

Q. So how would an SOP prevent bias if the person counting the plaques know which ones are the prevaccination serum and which are postvaccination?

A. They don't know.

MR. SANGIAMO: Object to the form.

THE WITNESS: They don't know that. They can only speculate on it because they're not told that this is pre or postvaccination. They wouldn't know, for example, whether it's a

postvaccination sample with a low titer or a prevaccination titer -- prevaccination sample with a high titer, which also exists. So they simply wouldn't know.

BY MR. KELLER:

Q. Is that from your personal knowledge or are you just -- or is that a general statement?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't know exactly what the lab did in this particular case, but it's --

BY MR. KELLER:

Q. If the folks running the lab were -- knew which samples were prevaccination serum and postvaccination serum and were running whether or not they were seroconverting as the assay was going on, would that cause you concern from a bias standpoint?

MR. SANGIAMO: Objection.

THE WITNESS: That's making too





many assumptions. They don't generally know and I don't see the interest they would have in the lab to have any impact on that. I mean, all they do is count holes and record them. And they have to -- actually the plates that are counted are kept. So if they were to count wrong, yet another control because you can go back and count again.

BY MR. KELLER:

Q. That's the reason why you count the plates, so that they could be used as a quality control?

MR. SANGIAMO: Object to the form.

THE WITNESS: In principle.

BY MR. KELLER:

Q. Are you aware of --

A. Or take a photograph.

Q. Are you aware of anybody destroying the plates in Protocol 007 before the assays were completed?

A. I was never in the lab neither





physically nor -- I have no idea about these things.

Q. Do you know who David Krah is?

A. Yes, I know David.

Q. What is your opinion of David Krah?

MR. SANGIAMO: Mr. Keller, you're not letting him finish his answers.

THE WITNESS: Highly qualified scientist, very personable.

BY MR. KELLER:

Q. Did you ever hear of anybody calling him a fraud?

A. No.

Q. Did you hear anybody stating that he committed fraud in a clinical study?

A. No.

Q. That would surprise you?

A. Yes.

Q. Did you ever see the preliminary results from Protocol 007, this interim analysis of 600 kids?

A. Well, according to the e-mail I





did. I'd have to say that I didn't -- it was not in the front of my mind for the last --

Q. Gotcha. So let me direct your attention --

A. -- almost 20 years.

Q. -- to 549517.

MR. SANGIAMO: Jeff, you got to let him finish. You know you're doing it. You got to let him finish.

THE WITNESS: It's okay.

MR. SANGIAMO: She got it. She got the additional testimony.

BY MR. KELLER:

Q. So let me direct your attention to 549517.

A. 549517.

Q. Do you see that?

A. Okay.

Q. And are these the preliminary results of Protocol 007 of those 600 kids?

MR. SANGIAMO: Objection. Answer if you know, Dr. Schodel.

THE WITNESS: What it says here is that they are the draft results of

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the preliminary subset analysis.

BY MR. KELLER:

Q. Here under the topic it says, Jon Hartzel biometrician vaccine, do you know who Jon Hartzel is?

A. Yes, I do.

Q. Is it your understanding that Mr. Hartzel is the one that ran this analysis?

A. The statistical analysis, yes.

Q. And who did Mr. Hartzel work for at Merck Research Labs during this time frame?

A. He works for Merck Research Labs.

Q. Do you know who he reported to?

A. Probably -- I don't really know. Probably Joe Heyse.

Q. And do you know who Joe Heyse reported to?

A. Ultimately Doug Greene, I think. But, again, I'm not sure. So the better answer would be I don't know.

Q. Let me direct your attention to page 549519, and tell me if you --

A. 549 --



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Q. 519. This is a group of documents --

A. 518 here.

Q. -- through 535 entitled, "MMRII 007 Subset Analysis PRN Assay Listing for Subjects Initially Seronegative."

Do you see that?

A. No. Okay. Here we go.

Q. What do you understand this document to be?

MR. SANGIAMO: For the record, I don't think Dr. Schodel has been given the chance to read the cover e-mail. So I want that noted before he answers the question.

BY MR. KELLER:

Q. This was attached to the e-mail that you receive. Correct?

MR. SANGIAMO: In 2001.

THE WITNESS: In 2001 and it has a lot of pages. So let me at least get to the page before I tell you whether it tells anything to me other than that you told me a page. So what



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do you want to know?

BY MR. KELLER:

Q. What does this document represent to you? What is it reporting?

A. It looks like a table.

Q. Is it reporting by potency group 4.9, 4.0 and 3.7 for each of the subjects identifying the titers and whether or not they seroconverted for the preliminary subset analysis of Protocol 007?

A. I don't see the grouping here. What I do see is serostatus attributions. It has the report. It has that here.

Q. So this is the unblinded results of the preliminary subset analysis. Is that correct?

A. It's at least partly unblinded. It's unblinded by group allocation.

Q. And it identifies each kid that was tested by their titers and whether or not they seroconverted. Correct?

MR. SANGIAMO: Objection. Answer if you know.

THE WITNESS: It doesn't



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identify them. It just lists their values in a row. That's different from identifying them because it doesn't give an identifier to which kid that might be.

BY MR. KELLER:

Q. Right. It identifies the results for those approximately 600 kids. Correct?

A. As far as I can tell, it identifies the results in these two assays here.

Q. And it identifies the prevaccination titer and the postvaccination titer. Correct?

A. Yes, that's true.

Q. It also identified whether or not the child seroconverted. Correct?

A. I assume so because it says sero is probably not in one, but I have to speculate because it doesn't say that here.

Q. Do you know whether or not these documents -- these documents are also provided to Dr. -- to Ed Skolnick as well as part of

this e-mail?
A. They would appear to have been because unless something else was attached to the e-mail sent to me.
Q. So this was also provided to Emilio Emini who was head of the lab that was running the PRN assay?
A. That's correct.
Q. If you go to the first page of the e-mail that was sent to Mr. Skolnick and forwarded on to you, Doctor, Emilio goes on and says, On the basis of this analysis and what is currently calculated by MMD as mump stability in MMR-II (obtained from analyses of recent MMD stability lots since the summer of 1998), there are MMD "lots in question" that have been released in the past 2 years.
Do you see that?
A. Yes.
Q. And so do you know what they're referring to as this recent stability, MMD stability, do you recall there being a stability analysis of these lots since 1998 to current?




MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall that one specifically, but there is always lots on stability.
BY MR. KELLER:
Q. So what is Merck looking at -- when you say lots are on stability, what do you understand that Merck is looking at with regard to testing lots on stability?
A. Well, it's -- a part of a regulated product manufacturing is that you put a certain sample of lots on stability, routine stability testing and you determine whether they maintain stability through shelf life. The analysis of that which takes into account the totality of the data will tell you whether it does or does not meet the stability criteria.
Q. So here it says, "These lots may still be in circulation with 24 month end-expiry...that fall below 3.7 (6 lots) or between 4.0 and 3.7 (100 others)."
You understand that 3.7 and 4.0




represent log potency. Correct?
A. Yes.
Q. The less than 3.7 lots are of particular concern; the 3.7 to 4.0 lots are likely defensible with some additional work. 106 lots are a compliance issue.
Do you see that?
A. Uh-huh.
Q. Do you recall at this time frame that the end expiry potency was 4.3 log?
A. No, I don't.
Q. Do you understand what is understood -- what is meant here by "a compliance issue"?
A. Well, compliance issue might be that if Merck had data that the lot did not meet the then expectations of the FDA in terms of potency through shelf life, that lots would have to be recalled.
Q. So do you recall there being a discussion at Merck during this time frame about recalling those 106 lots for being below the end expiry requirement in this letter?
A. I don't recall that. That's




something you would have to ask the manufacturing guys. But in all probability there was a discussion that's referenced here as whether these lots are -- whether these are just individual outliers without any significance or whether they are a reason to recall.
Q. So if a lot is released below the end expiry specification, under what circumstances would regulations, federal regulators FDA require those lots to be recalled, if you know --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- during this time frame?
MR. SANGIAMO: As he said, answer if you know. And object to form.
THE WITNESS: Yeah, it's not an absolute, there's not an absolute rule. It would depend on an analysis of -- we're not talking about lots that are released under specifications.

They were released under specifications. And at the time the end expiry rules were evolving. Individual time points of the stability study because of the variability of the assay can always fall under specifications. And the model is a model. There would have to be additional research being done in the lab in manufacturing to determine whether the actual lots were actually meeting expectations or not, and then there would have been to be a discussion as to what, if they weren't meeting expectations, what that would mean and whether it would be better for the vaccinees to go through a recall and revaccination or whether it was -- whether there were enough data to defend the product as it was released.

BY MR. KELLER:

Q. Was there a -- when an issue like this would come up where the product





would be -- do you understand the term "out of specification"?

A. Yes.

Q. What is that -- what's your understanding of that term as used at Merck?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, it --

MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: It in general means that a product at some point doesn't meet the expected specifications.

BY MR. KELLER:

Q. That could be the end expiry specification?

A. If that end expiry specification is formally set and if it -- yes, then theoretically it could be that.

Q. Have you ever seen the term "compliance issue" used at Merck before other than in this document?

A. Yeah. In all pharmaceutical companies you talk about -- sometimes about





compliance issues, yes. It's a lose term. It doesn't mean all that much.

Q. It doesn't mean all that much, compliance?

A. Well, it means that there is -- that -- obviously compliance means compliance with all relevant rules and regulations. And so there's a wide spectrum of things that compliance issue can mean. It can mean that you need additional data to figure out whether you're in compliance with rules and regulations or it can mean that you've discovered that something is outside of rules and regulation and then you act upon it.

Q. Do you know whether or not Merck ever reported these 106 lots that are compliance issue to the FDA?

MR. SANGIAMO: Objection. Calls for speculation.

THE WITNESS: I do not know.

BY MR. KELLER:

Q. If Merck's 106 lots were out of compliance with the specification, would you have expected Merck to have disclosed that to





the FDA?

MR. SANGIAMO: Objection.

THE WITNESS: I don't know whether they were out of compliance, and as I said, I don't know.

BY MR. KELLER:

Q. At the time of Protocol 007 they were doing testing, they were testing three different potencies, correct, 4.9, 4.0 and 3.7? Correct?

A. That's correct.

Q. The 4.9 was the dose that released -- the dose was released to the market. Correct?

A. That's correct.

Q. And the 4.0 and 3.7 were below what that current end expiry was that they're required to comply with. They were trying to -- back up.

Protocol 007, purpose of Protocol 007 was to lower the end expiry dosage that was identified in the label. Correct?

A. I don't recall -- I don't

recall it with that precision. I think it was a quite substantial effort to establish the data for a scientifically supported end expiry label in the label. With the changes in labeling philosophy, that we have discussed initially when we started this interview.

Q. If you look on -- under the "First, the neuts data," neuts, that means, that represents -- is that -- do you understand it to mean the neutralization data from the preliminary subset analysis of Protocol 007?

A. Yeah.

Q. In the second bullet point it says, "By the neutralization assay, an MMR-II mumps end-expiry of 4.0 meets CBER's demand for a 90% seroconversion rate floor...."

Do you see that?

A. Yes.

Q. Did you understand that CBER was requiring a 90 percent seroconversion rate floor?

A. Unfortunately I don't remember





that MMR, but...

Q. ...while the 3.7 log titer misses (88.2 percent seroconversion, with 95 percent CI of 82.3 to 92.6 percent).

Do you see that?

A. Yes.

Q. CI, that's -- what do you understand CI to represent?

A. Confidence interval.

Q. 95 percent confidence interval, that was the criteria upon which you -- this document identifies Protocol 007, the criteria that was being required by the FDA?

A. Yes.

Q. Here it says, (Jerry and I feel 3.7 is medically okay and may be defensible to the Office of Compliance; see below). Lots which have 24 months end expiry titers below -- lower than 3.7 lots would not have data from this study to support the shelf-life.

Do you see that?

A. Yes.

Q. What is your understanding with





respect to the statement "medically ok"? What are they looking at here with respect to these 106 lots and whether or not they're medically okay? Do you have an understanding?

MR. SANGIAMO: Objection. Calls for speculation. I also want to note he's still not given a chance to read this document.

THE WITNESS: I really don't know what they meant precisely. It's a pretty loose term. As you know, the compendial specifications in the EU is 3.7. It's also pretty clear when you look at the data, that even though the number seems to be lower than the ones for 4.0 and 4.9, it's still a pretty high number of seroconversions. So there's not a reason to assume -- since there is not direct correlation between titers and protection, there's no reason to assume that it would be clinically less efficacious.

BY MR. KELLER:

Q. So then what is the purpose of





having -- doing an analysis of seroconversion if -- let me strike that.

So is it your testimony that it may be medically okay for kids who got vaccines that had end expiries below, in this case, 4.0 and because the seroconversion rate was close to the 4.0 and the 4.9?

MR. SANGIAMO: Object to the form.

THE WITNESS: That was not the totality of my argument but a part of it. I would say that it would still be -- provide a substantial level of protection against all components in the vaccine.

BY MR. KELLER:

Q. Well, here Merck is -- CBER is demanding a 90 percent seroconversion floor for purposes of Protocol 007. Do you see that?

A. That's what I read here, yes.

Q. Do you know why FDA set 90 percent as a seroconversion floor?

A. I can't speculate as to why the

FDA set 90 percent as an absolute number floor.

Q. And so just so I back up, is Merck -- it looks -- it appears to me from reviewing the parts that we've gone over, that Merck is using as its defense of whether or not the lots that have been released at below 4.0 and at 3. -- between 3.7 and 4.0 are relying upon the data from the preliminary subset of Protocol 007. Correct?

MR. SANGIAMO: You mean this one bullet point that I'm reading?

MR. KELLER: Yes.

THE WITNESS: I don't think that that's the entire argument. And I don't know the entire argument. What you see here, to the extent that I remember this, is an effort to use the data as data supporting the argument. But it doesn't mean that that's what Merck relied on for anything.

BY MR. KELLER:

Q. But it appears that there -- as at least one data point to determine whether




or not these lots are medically okay and defensible with the Office of Compliance -- let me strike that.

The Office of Compliance, that's the FDA. Correct?

A. I don't know. It's not -- this is a strange term. I don't really know what that is. It's probably an office within the FDA, but I'd have to speculate.

Q. So is it fair to say that at least for this part of the argument, analysis for whether or not these lots are medically okay, Merck is relying upon this preliminary subset results of Protocol 007?

A. I would not word it that way. I think Merck is looking at the subset analysis to provide current data as to how the vaccines are behaving relative to each other. It does not entirely rely on anything in that study to say that the lots are okay, or not okay for that matter.

Q. I see. And so you say how they behaved together. So what your -- is it your position that because in Merck's preliminary




subset of Protocol 007, the 4.9 dose group had a seroconversion rate of 94 percent, 94.1 percent and the 3.7 group had a seroconversion rate of 88.2 percent, and that those are highly -- or so close in number that all that matters is how those numbers compare to each other and not the actual results of whether or not they -- let me strike that. That's a terrible question.

How do you understand -- you testified that they're comparing -- they're using it to compare how the different groups performed to justify that these lots released at end expiry of 3.7 are medically okay. Can you explain that to me a little more detail? I'm not sure I understand it.

MR. SANGIAMO: Object to the form.

THE WITNESS: So I would see this very differently. This is -- testing them in a clinical trial is more an exercise of willingness to provide data on a future end expiry dose that will be written into the




appropriate manufacturing documentation. It -- the trial was not run with the intent of justifying anything in that regard.

So when you then look at the data, you see that actually all three groups provide very respectable seroconversion rates, and it would probably be hard to tell them statistically apart even though they appear different which often deceives the eye because you see a number, it is a different number. But if you look at the confidence intervals, they're overlapping. So I'm not sure that even just looking at this little fragment, which is not even the complete study, it's incomplete numbers, you would be able to tell them apart. So they're all behaving fairly well. Which provides additional information that's relevant to the question as to whether low titered -- or lower titered lots might

be clinically acceptable doesn't mean that that's what you would use in your label because you have an excess of caution, you make sure that you're always above a certain threshold. But actually what this provides to me is reassurance that even a somewhat lower titered vaccine is still performing quite well.

BY MR. KELLER:

Q. And in you're relying upon the seroconversion rate for that?

A. No, I look at the whole thing. I look at the titers and the seroconversion rate. And I don't have the ELISA titers in front of me unfortunately, which are even more important because the ELISA has less variability. And I don't have the complete analysis. So you're talking about an interim analysis. But in the meantime, the complete data would be much more helpful to actually look at the complete data set rather than just an interim set. That was just what was known at the time.





Q. I see. I apologize if I'm a bit confused. Let me ask you this question: If here Merck is relying upon the seroconversion numbers of the preliminary subset as support and comfort that doses that have an end expiry of 3.7 would be medically okay when you testified earlier that the -- Merck never tested the specificity of its plaque reduction neutralization assay that you're aware of.

MR. SANGIAMO: Object to the form. Actually there's no question yet. Is there a question?

BY MR. KELLER:

Q. My question is, if the specificity of these plaque reduction neutralization assays was low, wouldn't that affect the seroconversion rates that were reported across all three dosage ranges?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. And underestimate seroconversion -- overestimate -- I'm sorry, overestimate seroconversion?





A. I think you gave the answer into your relatively convoluted question yourself. I'm not sure I can even follow it entirely. But the answer was at the end when you said that they were all similar. That basically tells you that sensitivity of the assay is not the major factor in determining whether these lots are different or not.

Q. Well, the 3.7 that's derived was derived in a different assay. That was derived from a potency assay, not a plaque reduction neutralization assay.

A. Yeah, but when they're put in people, they behave relatively similar. It doesn't matter whether I have a number here of 70 percent seroconversion or 90 percent seroconversion and a titer that's slightly lower or higher. I compare the three cells. And if the confidence intervals overlap, I tell you I can't tell them apart which means they're all potent in the clinic. The absolute numbers don't tell me anything.

Q. So it's your view that seroconversion is irrelevant for purposes of





analyzing what happened in Protocol 007 --

A. No.

Q. -- the PRN assay?

A. That's not what I said. And you're trying to lead me into saying something which I absolutely did not say. I did not say that seroconversion was not important. I said that it is similar between the groups. It is not important for predicting efficacy. That's what I said.

MR. SANGIAMO: Jeff, it's 12:32.

MR. KELLER: That's fine.

VIDEOGRAPHER: Off the record at 12:32.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: Back on the record at 1:29.

BY MR. KELLER:

Q. Doctor, can you put Exhibit 5 back in front of you? Let me direct your attention to 549511. In the middle of the page it says, "Background/Impact Assessment" --

A. Wait. Wait a second. 5495 --
Q. 511.
A. Okay.
Q. It's the second page of the document.
In the middle of the document it says, "Background/Impact Assessment on Marketed Product." Do you see that?
A. Uh-huh.
Q. In the middle bullet point it says, In the meantime, there has been continuing discussions with CBER re mumps end expiry titers. In response to recent CBER inspection from the Office of Compliance to MMD, manufactured mumps stability data was re-examined. In that analysis, it appears that mumps stability has been somewhat less (i.e. around .2 logs faster over a 24 months period; a total of around 1.0 log lost over 24 months) for lots manufactured at least since the summer of 1998.
Do you see that?
A. Yes.
Q. Were you aware that based on




Merck's then current mumps stability models, that it was projecting an approximate 1.0 log loss over the shelf life of its product?
MR. SANGIAMO: Object to the form.
THE WITNESS: I may have been aware of it. As you know, I didn't work in manufacturing, so this wasn't exactly my line of business.
BY MR. KELLER:
Q. Do you recall any discussion at Merck regarding the stability models that projected a one log loss over 24 months?
A. Not in any detail.
Q. What generally do you understand those conversations to take place?
MR. SANGIAMO: Objection.
THE WITNESS: I was not involved in the modeling exercises so I wouldn't -- it wouldn't have been discussed with me. I mean, what would have been discussed with me is more the interpretation of clinical data.
BY MR. KELLER:




Q. Do you recall there being discussions of the 1.0 log loss over 24 months to be at issue with Merck's complying with its end expiry specifications of its label for the mumps component?
A. Not that specifically.
Q. You just generally recall that?
A. I generally recall that when there were data like the ones that are suggested initially of lots on stability not being above a certain titer that there was sometimes a discussion about that. I don't remember any detailed discussion about the modeling piece.
Q. Do you recall any discussion about anybody who criticized the model that Merck was using at Merck within Merck's employees that calculated this projected 1.0 log loss at 24 months?
MR. SANGIAMO: Objection. Form.
THE WITNESS: No.
BY MR. KELLER:
Q. If you go back to the document, the second bullet point it says, "Given this




new analysis, lots manufactured since...1999 are still fine with the overfill and 24 month end-expiry titers projected at or above 4.0."
Do you see that?
A. Yes.
Q. Do you recall what they're talking about for the overfill?
MR. SANGIAMO: Objection. Calls for speculation.
THE WITNESS: I can read this and tell you what an overfill would be, but I'm not sure -- I don't remember the details.
BY MR. KELLER:
Q. What's your understanding of an overfill?
A. Overfill would be that you fill in more vaccine than you have previously at least by that assay.
Q. Do you recall that in September of 1999 Merck and CBER -- or CBER required and Merck agreed to overfill its minimum release specification to 5.0?
MR. SANGIAMO: Object to the

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form.

THE WITNESS: Not in that detail but now that -- you know, this makes sense in the context.

BY MR. KELLER:

Q. So in the last bullet point on this page it says, Unfortunately, with the faster mumps potency loss rates seen since at least summer of 1998, there are released lots which, at 24 months, are projected to be below 4.0 (100 lots) or 3.7 (6 lots). This will be a compliance issue with the Agency.

Do you see that?

A. Yes, I see that.

Q. Do you understand that to mean the agency is the FDA?

A. It could have referred to the FDA or to other agencies as well.

Q. During this time frame, did you understand that the -- at this time the label required that at end expiry there would be 4.3 log?

A. I think this was just -- this was still in the -- I don't remember exactly



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whether at this time the label was already defined as an end expiry label as it was later on understood to be, whether it was a release label essentially.

Q. Do you remember at some point the end expiry log being set at 4.3?

A. I'm not -- I'm a bit murky on the details here. It probably was, but I'm --

Q. If -- when this says -- when this e-mail that was sent to the president of Merck in February of 2001 says this will be a compliance issue with the agency, who at Merck would decide whether or not to disclose this information to the agency?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's not my responsibility. I didn't know.

BY MR. KELLER:

Q. In this document they're talking about whether or not 3.7 will be medically okay and maybe defensible with the Office of Compliance. Do you know who would make the



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decision whether or not 3.7 would be medically okay during this time frame?

A. Well, Jerry Sadoff was probably -- and Dorothy Margolskee were probably making the assessment as they said here.

Q. Here back on 549512, in the case -- "In case you want the details, Attachment #4 is a line listing of the lots - note column 5, which is the release dose per lot" --

A. Where are we here?

Q. On page 3 of the document which is 549512.

A. Page 3, okay. And where?

Q. Just where I left off reading. I'm just reading the next --

A. Again.

Q. In case you want the details, Attachment 4 is a line listing of the lots - note column 5, which is the release dose per lot and assume a 1 -- around a 1.1 log fall over 24 months. Do you see that?

A. Yeah, I see that.



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Q. If you go to 549518 of this document, it actually doesn't have a Bates number on it, but when we printed it out, the Excel printed with a number. This was also part of that document. It's a document entitled: "Total Doses on Low Mumps Titer Lots within Expiry." Do you see that?

A. Uh-huh.

Q. Here it says that US Doses Distributed in 2002 has 12,765,787. Do you see that?

A. Yes, I see that.

MR. SANGIAMO: In 2000.

BY MR. KELLER:

Q. In 2000, right.

Is it fair to say that based on this attachment that what they're identifying here is the number of doses released in the US that had low potency below the 4.0 spec?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, I can't really see that here. It says, "Total Doses on Low Mumps Titer Lot within Expiry."

So they would have been within expiry.
I'm not sure -- this is not -- there's not sufficient labeling here for me to tell what these are.

BY MR. KELLER:

Q. Fair enough. If you look at the rest of the spreadsheet that's attached it identifies for each lot, lot number, release potency, expiry potency, package number, and at the back of it it will identify the number of lots that have been released for each -- number of doses in each lot. Do you see that?

A. Well, I'm not familiar with these kinds of tables, so I -- I can see what's labeled here. This is not --

Q. Do you recall --

A. There's a line total doses here but there's nothing in it.

Q. That's after the first page. I can represent to you without going back and adding them up --

A. This is not -- this is obviously spread out over several pages and does not -- these are not labeled. So it's




package doses, but I'd have to go back and forth and relate them to something, if they're even related.

Q. Let me ask you a question. Do you recall during this time frame any discussion about there being 10 or 12 million doses that fell below the specification in the label for end expiry?

A. Well, that's a lot of assumptions. So what we're talking about so far was a model, a stability model. It was not saying that the doses fell below anything.

Q. Well, it's projecting that if doses would fall below --

A. That's very different. That's very different. That's a model is a model is a model.

Q. Okay. Here Dorothy Margolskee, she's a fairly senior executive at Merck. Correct?

A. Very senior.

Q. Very senior. So she's representing that this will be a compliance issue with the agency. Correct?




A. That obviously was her opinion.

Q. But you don't recall any discussion about a compliance issue of tens of millions of doses below end expiry projections that were made by this model?

A. Not as you word it. I do recall a discussion about mumps potency and I do recall that there were discussions with the agency as well, but I certainly don't recall that anybody said -- certainly the agency would be the one to tell us that there were X number, million number of doses that were out of compliance or released at the wrong titer.

Q. When you say that there was discussions about mumps potency with the agency, were you involved in those discussions?

A. Probably not, certainly not as far as they concerned -- involved manufacturing issues.

Q. Were you involved in any discussions where there was a discussion as to what to tell CBER about these 106 doses at 4.0 and lower?




MR. SANGIAMO: Object to the form.

THE WITNESS: What do you mean with what to tell CBER? We would have shared data with them.

BY MR. KELLER:

Q. Did Merck tell CBER about these 106 lots?

A. How am I to know? As I said before, that was not my responsibility.

Q. I understand that. Do you recall any discussions regarding whether or not to tell CBER about these 106 lots?

A. No, I do not. That was also not my responsibility.

Q. Okay. Fair enough. Do you recall any discussion about 227 lots that were below 4.3?

A. No.

Q. Do you recall any discussion about 227 lots with respect to anything?

A. The number doesn't strike a bell at all.

MR. KELLER: Let me mark this

next exhibit as Exhibit 5.

MR. SANGIAMO: 5?

MR. KELLER: 6. I'm sorry. Strike that.

Let me mark this next exhibit as Exhibit 6.

- - -

(Exhibit Schodel-6, E-mail chain, Bates MRK-KRA00549497 & 00549498, was marked for identification.)

- - -

BY MR. KELLER:

Q. For the record, Exhibit 6 is a document that bears Bates stamp number KRA 549497 through 498. It's a series of e-mails. I'll direct your attention to the e-mail that starts at the bottom of 5497 -- 549497 and runs on to the second page at 498. This one is from Timothy Schofield to Dorothy Margolskee, and it's talking about the "Low Months Target Lots within Expiry."

A. Note that I was not copied on this e-mail.

Q. Right, I see that. The e-mail





above that is from you. Do you see that?

A. That's right.

Q. Here it appears that you were responding to the e-mail that was below. So it looks like if you look at the February 22, 2001, e-mail from Mr. Schofield to Margolskee, it was subsequently forwarded to you about 40 minutes later. Do you see that?

A. Okay. Now I get it. I just didn't understand.

Q. Fair enough. I'm glad you pointed that out to me.

If you look at Mr. -- who was Mr. Schofield again, what was his position?

A. He was the head of biometrics at the time.

Q. He was a statistician?

A. Yes.

Q. And Jonathan also?

A. Not a clinical statistician. A biometrics person. So he was dealing with not clinical issues but manufacturing issues, analytical issues.

Q. I see. Mr. Antonello, Joseph





Antonello, who is that?

A. He was working in his group. He was also biometrician. Also not somebody who dealt with clinical statistics, but somebody who would work with the lab to validate assays and so on.

Q. Did Mr. Hartzel and Mr. Antonello work together?

A. I think actually Jonathan Hartzel was in the clinical statistics group, to which exact -- I mean, I was not in either of these two groups, so they may have worked together or not, I don't know.

MR. SANGIAMO: Jeff, these guys are both doctors.

MR. KELLER: Sure.

BY MR. KELLER:

Q. Dr. Hartzel, he's the one that was -- who worked on the planning subset data, correct, the unblinded subset data for Protocol 007?

A. I don't know that for sure. He may have been the statistician associated to the study all of the sudden but whether he





has actually worked on that set of data other than summarize it, I don't know. There may have been other people in the background who worked on it. I did -- you're asking me things that I wouldn't know.

Q. Sure. In here, in this e-mail from Schofield to Margolskee, Schofield says, "Dorothy, Here's the spreadsheet I was working from. A couple ideas:

"1. I spoke with Joe Antonello who is doing the evaluation of the validation data...." Do you see that?

A. Yeah.

Q. Do you understand that this is the validation data for Protocol 007?

A. No, I didn't.

Q. You don't know?

A. You're telling me now.

Q. He suggested that we look at the dilution response profiles to see if the negatives were "marginal," or strictly flat. In addition, it could be interesting to see what the rates would be at 40 percent neutralization.

Do you see that?
A. Yes.
Q. He's talking about a neutralization assay. Correct?
A. It would seem from here, because he mentions 40 percent neutralization, but out of context I wouldn't know.
Q. Fair enough. Number 2 he says, "Would there be a better probability of success in retesting the failures (and some marginal positives) in the wild type neut."
Do you see that?
A. Yes.
Q. The wild-type neut, that's Protocol 007's PRN assay. Correct?
A. Uh-huh. I mean, this is a bit of jargon, so I -- in seeing the name, that's what I would expect, but I'm not sure. I don't know what he refers to exactly because he can do a wild-type neut with any wild-type mump strain.
Q. So when they're talking about better probability of success in retesting that failures, how would you get a better




probability of success by retesting failures in a wild-type plaque reduction neutralization assay?
MR. SANGIAMO: Objection.
THE WITNESS: Well, failures in this context here, you know, means failures of performing in the assay so they are not -- so you don't have a valid data point for this particular sera which is, of course frustrating. They humanize people. They are sera. They've been analyzed, but for whatever reason the control was wrong, the cells were old, something else didn't work, so they're failures, test failures. Now the question is what are the values in these sera and you can --
BY MR. KELLER:
Q. You say the controls, do you recall there being any discussion about testing the failures in the preliminary subset of Protocol 007, the ones that didn't seroconvert?




A. I'm not sure what he means with failures here, whether those are failures that are failures because they are -- don't yield useful values or they're failures because they were wrongly classified, I'm not so sure.
Q. Sure. If you look at the e-mail from you the same day, only an hour and a half later, again, cc'ing Hartzel, and in here you write, "Dear Tim, I think esp. 2 would be useful...." Esp. means especially 2?
A. Yes.
Q. What did you mean by "esp"?
A. Yes.
Q. So here you're saying retesting of the failures would be useful. Correct?
A. Well, no. What I'm saying -- yes and no. So what I'm saying really is it would be useful to have more data, more valid data. I'm making an argument that if you have a postimmunization -- a preimmunization titer that seems higher than the preimmunization titer -- the other way around. The preimmunization titer that seems




higher than the postimmunization titer, there's something funny going on. If you don't have data, you're actually -- you should retest and figure out whether there was something wrong.
Q. I see.
A. But, of course, you wouldn't do a retest just on those. Just the advantage of doing a retest is that it would also include those where you -- where something biologically not plausible is happening.
Q. So would you not test vaccine failures in a PRN assay? Why don't you just --
A. I'm still not sure whether we're talking about vaccine failures or not. Nobody says vaccine failures.
Q. Let's go to the next e-mail from Jonathan Hartzel to you, Dr. Schodel, which happened about two minutes later. It says, this is from Hartzel, "I have given Emilio...," and that's Emilio Emini. Correct?
A. Uh-huh.
Q. He's running the lab that's running Protocol 007. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: He was in charge of the lab.

BY MR. KELLER:

Q. About 60 case numbers to retest (the 42 failures and 17 marginal positives).

Do you see that?

A. Yes, I see that.

Q. I believe he will try to retest them in both the ELISA (the wild-type mumps) and the wild-type neut.

Do you see that?

A. Yes, I see that.

Q. Those are the two arms of Protocol 007. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't really know what these failures refer to here, whether they're failures in the overall protocol that could be including the control arm or whether they would be any of the cells. This





is just an assay issue. You have serum samples in there which are low and sometimes look like they can't easily be interpreted, like the ones below which have been higher before they get immunized and then they're lower, which is sort of strange. So you wonder what's going on.

BY MR. KELLER:

Q. So during the middle of this protocol, you're having the lab go back and retest results from the protocol, whether they're control failures or vaccine failures, but you're retesting data that's --

A. I'm not having anybody do anything. I did not direct anything or I just expressed an opinion as to what kind of data I would like to see. So in other words, where it would be useful to get data now I -- you know, you can't just willy-nilly retest stuff. So there has to be some protocol followed, and that's the lab's problem, not mine. I'm just reacting to whether this data makes any sense.





Q. So let me just direct your attention to -- back to Exhibit 5, which is the Margolskee e-mail. And an attachment at 549517, which is the preliminary subset summary that Jonathan Hartzel is identified on. Do you see that?

A. Yes.

Q. Now, if you look at the seroconversion failures from the 4.9, the 4.0, the 3.7, you'll see that there's ten failures of the 4.9, there's 12 failures --

A. Wait a second. Where do I see those?

Q. Looking at the percentages of seroconversion, 159 over 169, 167 over 179, 149 over 169. That's how they're calculating seroconversion, the total number by what percentage of those seroconverted. Correct?

MR. SANGIAMO: Object to the form. Dr. Schodel, do you see the data to which Mr. Keller is referring?

THE WITNESS: I see the data, but there's -- you're making an assumption that I don't know which





ones are test failure. What I do see here is the response rates that are indicated here.

BY MR. KELLER:

Q. Right. So there's 169 kids in the 4.9, 159 of those seroconverted. Right?

A. 159 of 169, that's right, yeah.

Q. If you actually run the number, that's 94.1 percent. Does that make sense?

A. Yeah, that makes sense.

Q. So if you look at the failures, 159 out of 169, 10 kids didn't seroconvert for 4.9, 12 didn't seroconvert for 4.0 and 20 didn't seroconvert for 3.7. Do you see that?

A. Yes.

Q. That adds up to 42, doesn't it, sir?

A. Yeah, it would.

Q. So does that help you to understand the 42 failures that are listed here that were given to the research lab that's doing Protocol 007 to retest the 42 failures?

A. It also includes 17 margin

positives. I hadn't made that connection, but it may explain it.

Q. Why would you test in the middle of an assay -- let me back up a second.

If the assay had not been completely validated at this point, based on your supervising clinical studies throughout your 30-year career, what justification could be done for going back and testing the failures --

MR. SANGIAMO: Object to the form. Calls for speculation.

MR. KELLER: I'm not done, Dino.

BY MR. KELLER:

Q. -- for testing the failures in the middle of a clinical study before you validated the study?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: There's a lot of inherent assumptions in there. First of all, what does validating the study mean?

BY MR. KELLER:





Q. Validating the protocol of Protocol 007 for the PRN assay --

A. How would you do that?

Q. Don't they validate those assays before they run them?

A. That's not the protocol. That's the assay. The assay, I believe, was validated.

Q. Was it validated before the assay was started?

A. I would assume so, but I don't know.

Q. Is that typically done?

MR. SANGIAMO: Object to the form.

THE WITNESS: You're asking me to speculate about what the lab did. It was not my responsibility.

BY MR. KELLER:

Q. Sure. But is it fair to say that in February 22nd, 2001, the lab was going back and retesting the failures from the seroconverting failures of Protocol 007?

MR. SANGIAMO: Objection. Calls





for speculation.

THE WITNESS: I don't know that from the e-mail. It was obviously discussed. But whether they did it, I don't know.

- - -

(Exhibit Schodel-7, 3/1/01 E-mail, Bates MRK-KRA00549218 & 00549219, was marked for identification.)

- - -

BY MR. KELLER:

Q. For the record, I've marked as Exhibit 7 a document that has previously been marked by Morsy --

MR. SANGIAMO: Exhibit 12.

BY MR. KELLER:

Q. -- Exhibit 12 which bears Bates stamp number KRA 549218 through 219. Doctor, I'd like you to take a minute to look at this and see if you recall receiving this e-mail. I'll represent that you're on one of the listed.

A. I'm obviously copied on that. I was -- you know, it's an invitation for a





meeting. So I -- since I'm copied on it, I probably received it and I probably -- I don't remember this meeting at all. This was a few years ago.

Q. That's fair. This was an e-mail dated March 1, 2001, from Keith Chirgwin to a whole host of people including yourself. Correct?

A. Yes.

Q. The topic was "URGENT Mumps expiry - Tomorrow's Teleconference." Do you see that?

A. Yes.

Q. In the first -- there's a point that says number "1-Preparation for RMC discussion on March 8." Do you see that?

A. Yes, I see it.

Q. Do you know what RMC is?

A. I don't remember that acronym anymore. It was some research management committee or something, but I'm making this up because I'm not sure what it means. There's a lot of acronyms at Merck.

Q. Do you know what a recall

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committee meeting is?

A. Huh?

Q. A recall committee meeting is?

A. This is -- I don't think this is a recall meeting. But I don't know.

Q. Fair enough.

A. Recall meeting? I don't know. I don't think so.

Q. I'm just asking if you --

A. No.

Q. Number 2 says, "Preparation for CBER stability discussion later this month." Do you see that?

A. Yes.

Q. Under "Agenda" it says, "MMD: Follow-up discussion with CBER - lots out of compliance." Do you see that?

A. Yes.

Q. It has Roberta McKee, Mike King and Mike Angelo. Do you see that?

A. Yes.

Q. Were those the people responsible for determining whether or not to disclose the lots out of compliance issue that we talked





about?

A. As I said before, I don't know who was responsible, if there was a responsibility indeed. Roberta McKee was in regulatory on the CMC side, so on the manufacturing side, and Mike King was manufacturing, and Mike Angelo was in quality control and manufacturing as well.

Q. These lots out of compliance, since this is contemporaneous with the memo that Ms. Margolskee -- is it Dr. Margolskee?

MR. SANGIAMO: Dr. Margolskee.

BY MR. KELLER:

Q. Dr. Margolskee sent to the president of Merck as well as a bunch of other folks, do you understand that to be the same 106 lots she was talking about?

A. I don't know.

Q. You don't know. If you look on the next page under "Clinical," number 1 it says, "Clinical support for end of shelf life titers." Do you see that?

A. Yes.

Q. Under 5 it says, "Jerry Sadoff."





And under 6 it says you, Dr. Schodel. Do you see that?

A. Yes.

Q. Number 2 it says, "plans for assessment and possible need for rescue." What did you mean by that? What do you understand that to mean?

MR. SANGIAMO: Objection.

THE WITNESS: I have no idea.

MR. SANGIAMO: The question is what do you understand that to mean?

MR. KELLER: Yes.

THE WITNESS: Assessment -- I mean, rescue would mean revaccination, I guess, if there was any rescue needed, but I don't know what was meant here.

BY MR. KELLER:

Q. You don't know. Okay. Fair enough.

MR. KELLER: Mark Exhibit 8.

- - -

(Exhibit Schodel-8, PowerPoint presentation, Bates MRK-CHA00086318,





was marked for identification.)

- - -

BY MR. KELLER:

Q. For the record, Exhibit 8 is a document that bears Bates stamp number 86318, and it's a three-page presentation document. And I'll tell you from the metadata produced, this is dated March 3, 2001. And my note identifies this as being used at the 3/8 teleconference.

A. Is that the entire presentation?

Q. Yes. Can you tell me if you recall ever seeing this presentation before?

MR. SANGIAMO: Dr. Schodel, you don't have to accept Mr. Keller's representation that he just made to you about being the entire presentation and the date. I'm not saying he's wrong, but you don't have to accept it.

MR. KELLER: Are you saying the metadata is false?

MR. SANGIAMO: No, I'm not saying that it is false. I haven't

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seen the metadata. Sitting here right now, I can't -- I don't know what the metadata says.

THE WITNESS: I don't remember the details, but I can read it, of course.

BY MR. KELLER:

Q. Sure. Focus on the first page.

A. Okay.

Q. Stability data do not support current end of shelf life (4.3 log). Do you see that?

A. I see that.

Q. Does this help refresh your memory at the time of this presentation that the shelf life label claim was 4.3 log?

A. That's what is stated here.

Q. Do you recall there being a meeting that discussed that the stability data did not support the current end of shelf life label claim of 4.3?

MR. SANGIAMO: Objection.

THE WITNESS: I now remember that I was in a meeting with this





topic because you just showed me the agenda so, yes, I do, I can read.

BY MR. KELLER:

Q. Do you recall any discussion that happened at that meeting?

A. Not in any detail.

Q. Does this help refresh your memory of seeing this document in the past?

A. No.

Q. The second bullet point says, "Further increase in release potency is not feasible...," and it says, "...(target 5.2)." Do you see that?

A. Yes, I see that.

Q. Do you recall any discussion during this time frame of March of 2001 about looking at whether or not Merck could overfill even further than what it did in 1999?

A. I don't recall such a discussion, but I would support the statement.

Q. The last bullet point, "Therefore we must provide clinical data to support a decrease in the labeled potency." Do you see that?





A. I see that.

Q. That data, that's Protocol 007 with a release -- with a potency below 4.3, either 4.0 or 3.7. Correct?

A. I'm not sure entirely because this is a different time here. This was -- when did this happen? I mean --

Q. The date on the document says -- the metadata which is the computerized data that comes --

A. We're talking about 2001.

Q. Yes.

A. Which was when that protocol was being run. Right?

Q. Correct.

A. So it's not -- it wasn't planned for that purpose.

Q. But was it used for that purpose?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Let me back up. What was the purpose of -- you say it wasn't planned for the purpose. What was the purpose Protocol





007?

A. I said that before. It was to provide clinical data to support what now had changed in the labeling expectations, a scientifically supported end expiry number.

Q. And so in what they were -- what was in Protocol 007 was a release dose of 4.9 and two lower doses. And two of those lower doses were below 4.3. Correct?

A. That's correct.

Q. So they were trying to change the label to reduce the potency claim in the label from 4.3 to either 4.0 or 3.7. Correct?

A. Yeah, but you're bringing these two things that are both timely and logically not necessarily related into relation. The protocol was run for what I said it was run for. Now the data were available. So when there was a -- at least an impression of an issue with a stability model, of course, the data as any other data out in the market, were used to understand the behavior of the vaccine across its potency range. That's a post hoc use of the data. It is not why this

was run, because quite obviously -- I mean, this happened in 2001, the protocol was already under way, so it was not planned or designed for this particular purpose.

Q. But it certainly increased the importance of that protocol having a reduced potency from 4.3 to either 4.0 or 3.7. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: At least temporarily, yes, because now there were data that could be supplied which -- and often not available in these kinds of situations.

- - -

(Exhibit Schodel-9, 9/28/01 E-mail with attachment, Bates MRK-KRA00561416 - 00561421, was marked for identification.)

- - -

BY MR. KELLER:

Q. Let me mark as Exhibit 9 a document bearing Bates stamp number 561416 through 21. And here there is a -- it's an e-mail with an attachment. The e-mail is from





Jonathan Hartzel to a laundry list of folks including you, Dr. Schodel.

Can you tell me, if you take a minute to take a look at this and tell me if you recognize the e-mail and the attachment as well?

A. There's a lot of information in here, so while I can quickly read it, it doesn't mean that I'll be able to answer to all details.

Q. Do you recall seeing this e-mail and attachment?

A. Not this specific one, but I do remember that a discussion about the ELISA cutoff at some point happened.

Q. That discussion about the ELISA cutoff, we're talking about the cutoff of the wild-type ELISA assay used in Protocol 007?

A. Uh-huh.

Q. What is a cutoff?

A. A cutoff is a number that with reasonable certainty distinguishes between positives and negatives.

Q. When you say "between positive





and negative," is that for purposes of the ELISA assay used in Protocol 007, used to determine whether or not the results are treated as a seroconversion?

A. Yeah, it would be for the purpose of a seroconversion and to determine whether somebody has preexisting antibodies or postvaccination antibodies. The two are linked, of course.

Q. You talked earlier, there's two ways to analyze ELISA assays. One was by using a fixed cutoff and the other one was using a fold criteria?

A. Right.

Q. Fourfold criteria?

A. Right.

Q. So is it fair -- let me just kind of go through this e-mail. Here the subject is CBER background ELISA. During the CAS -- strike that.

"During CAS and at some follow-up meeting, some additional clinical information was request to address some areas of concern."





The CAS, that's the clinical assay subteam committee. Correct?

A. I think so, yeah.

Q. Were you a member of that?

A. Yes.

Q. Were you the head of that committee?

A. At some point, yes.

Q. During this period --

A. Or co-chair anyway.

Q. During the September of 2001 were you the co-chair or head of this committee?

A. Probably. Not so good with the time exactly.

Q. What was the purpose of this committee?

A. Was to review the status. The major purpose was an operational one. It was to make sure that we actually could do the assays that we needed to be done in time. So we had a lot of assay throughput because of Gardasil, because of ProQuad and so on. So we had tens of thousands of assays that were

not being done in time. We had to come up with a better way to manage that. That was the major purpose why we started this committee and then we on occasion also looked at specific questions around the assays as they concerned any one of the participants, whether that was clinical or regulatory or the lab.

Q. So do you recall a discussion at the clinical assay subcommittee regarding the setting of what standard would be used to determine a seroconversion with the ELISA assay used in Protocol 007?

A. No. I do vaguely remember that the discussion that is represented here happened that it was set, and that I don't think we had pre-discussed how to set it in that particular committee. At least I don't remember it. And that CBER wanted more information about its behavior in classifying sera and that information was provided. Then the information that was available was discussed obviously as it is attached here.

Q. So here in these the second --





these areas where it says, "...to address some areas of concern," it says, "This information was not to be sent to CBER, but was for our own understanding." Do you see that?

A. Yeah.

Q. So was that typical at Merck, to discuss information that would be a concern and not provide that information to CBER?

A. There was nothing to provide to CBER because the area of concern is the debate that was ongoing at CBER at the time as well as to whether an absolute cutoff was okay or whether you should apply fourfold criteria and all kinds of permutations in between which can cause more confusions than anything else. The same discussion about Varicella and about other assay. I don't recall any specific issue with mumps. And, of course, in addressing these kinds of -- in CBER there were two schools of thought. There were those who wanted to have fourfold criteria and those who were okay with the cutoff and had been taking part in these cutoff discussions and how they were to be





used.

So we had similar discussions about a number of assays. So the concern was whether we could come to a common understanding. In order to do that, we had to look at the data. That's not something that was not shared with CBER because it wouldn't have been shared with CBER. In fact, the e-mail below tells you that it has actually been faxed to CBER. So data was faxed to CBER --

Q. That's a different -- that attached something different.

MR. SANGIAMO: Mr. Keller, you got to let him finish his answers.

MR. KELLER: Sure.

MR. SANGIAMO: So what's the pending question?

THE WITNESS: But the value of the -- I mean the data themselves would have been discussed internally before they were sent off. Besides these are -- these are -- this is all based on just assay data that have not





been cleaned or screened so they would never been used for clinical submission. They would not be -- they would not send to an agency data you do not consider final data because they have not been cleaned or screened. That would be actually not in compliance. So why should they be shared with CBER. There's no reason to.

Now I have to share something with you. I need a break.

MR. KELLER: Sure.

VIDEOGRAPHER: Off the record at 2:11. This will end disc number three.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: Back on the record at 2:19. Beginning of disc number four.

BY MR. KELLER:

Q. Dr. Schodel, if you look on the

e-mail that you received attaching this Mu Dist plus Mu Me Pre-Pos Rates.doc, it says, Attached is a memo which contains information on the distribution of 6 week mumps titers based on mumps wild-type ELISA assay (with special interest in those falling between 10 and 40).

Do you recall discussions regarding whether or not setting the serostatus cutoff for the ELISA arm of Protocol 007 as to whether or not the serostatus cutoff should be set between those ranges of 10 and 40?

MR. SANGIAMO: Object to the form.

THE WITNESS: I do not recollect such discussions.

BY MR. KELLER:

Q. Do you know -- so you don't know the special interest in those fall in between those 10 and 40 range?

A. No, you asked me a different question. So ask the question again.

Q. Sure. Do you recall -- so you





don't recall what the special interest identified in this particular e-mail the writer had with respect to the cutoff arm between 10 and 40?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can deduce it from the rest of the e-mail. So could you. It goes back to this discussion of whether a fourfold rise is important or it should be applied on top of a serostatus cutoff. Because these things were not completely worked out by the time of this meeting, we had to take into account what would happen if a fold rise would apply even though the serostatus cutoff in our eyes was the right thing to do.

BY MR. KELLER:

Q. I see. Was there a concern, do you recall -- you said that you're deducing from that. Do you recall any specific conversations at Merck during this time frame





regarding the setting of the serostatus cutoff at a range between 10 and 40?

A. No.

Q. Do you recall there being any discussion about the serostatus cutoff of 10 being too low?

A. No.

Q. Do you recall there being any concern that CBER would want to see a higher serostatus cutoff?

A. No, not in this particular way. You have to go back to what we discussed before which is the mixing of these two criteria.

Q. Gotcha. So at this point in time there hadn't been a determination as to what criteria would be used, whether the serostatus cutoff, a fixed cutoff or one with -- that's based on a fourfold criteria. Correct?

A. No. It had been determined that a serostatus cutoff would be used. So a fixed cutoff. That is what was submitted to CBER and what was -- how the assay was run.





CBER on the other hand, was apparently still struggling with the concept and some people wanted, in addition, to apply a fold rise criteria. That message was the serostatus cutoff because now you have to figure out what would that mean in terms of classification because you're not changing your serostatus cutoff but you're adding a different criterion and it changes how you classify things.

Q. So if you hit a serostatus cutoff of -- if you set it at, for example, ten, there was a concern that you'd also have a fourfold increase between the pre and the post?

A. That's right. And if you were to do that, then obviously you would lose quite a bit of the population that fall in between these two because you could no longer determine whether they were seroconverting. So that would change the population in your trial.

Q. And the people that were leaning towards doing a fourfold analysis were the

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folks at CBER. Correct?

A. It came back several times from CBER. I think it's more -- I don't know exactly who it was, but I think it's more the old school thought of because that's what we've done all the time. And then eventually it changed.

Q. Let's turn your attention to the attachment to this e-mail which is 561418.

A. Yes.

Q. Here it says, "Distribution of 6-week Mumps Titers Using the Mumps Wild-type ELISA Assay." Do you see that?

A. Yes.

Q. This wasn't attached to CBER. Correct?

A. I don't know --

MR. SANGIAMO: Object to the form.

THE WITNESS: -- whether it was attached to CBER, so I couldn't tell you.

BY MR. KELLER:

Q. It's not in the listing of the





e-mail that's below --

A. As it states in this e-mail here, these are uncleaned and screened data so they would not be submitted as such to CBER.

Q. Here it says, "M-M-R® II Protocol 007 and ProQuad® Protocol 012 are currently the only studies in which the new mumps wild-type ELISA assay has been performed."

Do you see that?

A. Uh-huh.

Q. These were a new assay. Correct?

A. Yes.

Q. "For this assay the seroprotective level is defined to be 10 Ab units."

Do you see that?

A. Yes.

Q. When it says "seroprotective," what do you understand that to mean?

A. Well, that's actually a little bit of mislabeling. It's the seropositive level.

Q. I see. So it's not identifying





whether or not it can protect a kid from getting -- the kid has more --

A. There is no absolute cutoff that the would protect anybody. Even a higher titer wouldn't necessarily protect them.

Q. So the cutoff is not tied to whether or not -- for this ELISA assay, whether or not it will protect kids from getting mumps. Right?

A. No. No.

Q. Subjects who have titers of than less than 10 Ab units are considered negative. Do you see that?

A. Yes.

Q. So those folks, if you have a 10 Ab cutoff -- if you had -- if the results of this assay were below 10 Ab, that would be a seroconversion failure. Right?

MR. SANGIAMO: Object to the form.

THE WITNESS: No. If you have a titer initially of 8 and you have 200 afterwards, that's a seroconversion.





If you have a titer initially of 12 and you now have a titer of 8, that's not a seroconversion.

BY MR. KELLER:

Q. That's a pre-positive?

A. That's where a problem potentially could be. Or if you have a titer of 8 and 8, that's also not a seroconversion. But anything goes from below 10 or above 10 is a seroconversion.

Q. Gotcha. And that's what -- you're converting -- the blood is converting from one state to another. Correct?

A. That's right. That's why it's a classification, it's a little different from the fourfold criteria.

Q. So here in this document it says, There is some concern that CBER may require a fold rise in titers (from pre-negative to postvaccination) in order to demonstrate that seroconversion has occurred. So that a subject who has a prevaccination titer of 9.9 and a postvaccination titer of 10.1 (the difference being within the

variability of the assay) would not be considered a seroconverter.

Do you see that?

A. That's correct.

Q. But for the end result was that a fourfold analysis wasn't done. Correct?

A. No.

Q. So under Merck's analysis, if their prevaccination titer and their wild-type ELISA assay was 9.9 and postvaccination titer was 10.1, that would be a seroconverter?

A. Yes.

Q. When it says that is the difference being -- "the difference being within the variability of the assay," is that -- does that mean that those results could switch each time you ran the assay?

A. That's right. But, of course, they do that in both ways, because it's the variability of the assay. So you will also have people who are pre-positives. In other words, they're not considered, and then they become seronegative.

Q. If the analysis show that they





were all going in one direction, would that cause you concern?

MR. SANGIAMO: Objection to the form.

BY MR. KELLER:

Q. Like the variability, if, you know, instead of being -- balancing out -- the disgruntle results balancing out --

A. It's a theoretical question. In any assay if everything goes in one direction, you would try to analyze why that is. It doesn't necessarily mean it's wrong. There could be reasons for it. But it's something that you want to look at. But it doesn't apply here.

MR. SANGIAMO: Objection to the form of that last question. Thank you.

BY MR. KELLER:

Q. Do you recall doing any analysis as to the results of Protocol 007 to see whether or not the fourfold criteria would have changed the results?

A. I don't remember that. But in





general I think when such requests came in, we would do an analysis of what it would do to the results. But there is an additional difficulty with that. It's not just that it changes the results. It also changes the population that you identify because now everybody who is between 10 and 40 falls out. So there's a number of things, number of consequences to consider. So all the people who actually have responded but at a lower rate are no longer considered. Not that that's -- it's not a big population here, but...

Q. But isn't the purpose of setting the -- here it says seroprotective level, but the serostatus cutoff is to identify some immunological response in the blood to the antibodies that would lead to a conclusion that the kid will be protected from getting the mumps virus?

MR. SANGIAMO: Object to the form.

THE WITNESS: Those are two different concepts. First of all, the





primary and most important part is that you said a cutoff in a way that it relatively reliably and repeatedly allows you to distinguish between two different populations, those that have seroconverted and those that have not seroconverted. The question as to whether that's related to protection or not is not one that entered here at all because there is no efficacy study attached to it.

BY MR. KELLER:

Q. Right. CBER didn't require any sort of analysis to sort of link the serostatus cutoff to something that relates to the vaccine at that level protecting the kid from getting sick?

MR. SANGIAMO: Object to the form.

THE WITNESS: There is no efficacy trial that that could have been related to. However, on the population basis, a vaccinated population has a very low likelihood

of acquiring mumps.
BY MR. KELLER:
Q. What's your basis for that?
A. Epidemiology, look at the curves. There's almost no mumps in the United States.
Q. How do you explain the outbreaks that occurred in 2006, 2009 and currently?
A. It's not perfect protection but it's a protection that has reduced the level by several hundred folds.
Q. You do have to admit the vaccine is not performing as well as it did in the past?
A. No, I don't have to admit that at all.
Q. You think it works perfectly the same as it did back when Dr. Hilleman ran those assays?
A. Yes, I do.
Q. Do you sit here today and think that the vaccine protects 96 percent of the kids who get the vaccine?
A. That's -- I don't know that




exact number. But it certainly -- whatever the number was then, which has some uncertainty around it, too, because of how the trials were run, I would consider under the same circumstances that to be still the same.
Q. I see. Have you seen any studies conducted by Merck that showed that the vaccine performed significantly lower than 96 percent --
A. That the vaccine performance --
Q. -- by neutralizing studies? Let me strike that.
Have you ever seen any assays conducted at Merck with respect to the mumps vaccine by a plaque reduction neutralization assay that showed the seroconversion to be below 80 percent?
A. Not a formal study, no.
Q. If it's not a formal study, then what kind of study did you see?
A. I remember that both from conversations within Merck but also from conversations with people at the NIH and




other institutions, that different mumps strains react differently in the neuts assay. So if you use a different strain and if you use different conditions, you can see seroconversion rates that are different with the same set of sera. It has nothing to do with Merck. That's just a general fact of the neutralization assay.
Q. Who do you recall speaking with at NIH?
A. Rubin, Dr. Rubin.
Q. And when was that?
A. Oh, I don't know.
Q. Last year?
A. No, no.
Q. 20 years ago?
A. It was certainly more around the time of the -- of an outbreak probably or an investigation into an outbreak.
Q. So in the 2006, 2009?
A. Yeah, that may be the right time.
Q. In regards to 2006 or 2009?
A. No, I don't. I said 2009




certainly not.
Q. Sometime around 2006?
A. Yeah.
Q. Were these studies ever conducted by Merck or studies conducted by CBER?
A. What do you mean by "these studies"?
Q. These discussions you talked about, were those studies --
A. Well, at the time --
MR. SANGIAMO: Just a minute, Dr. Schodel, let Jeff finish his question.
BY MR. KELLER:
Q. These studies, these conclusions that different viruses will have different seroconversion rates based on a plaque reduction neutralization assay, were these assays that you discussed, were these run by Merck or were they run by somebody else --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:

Q. -- when you talked to Mr. Rubin, Dr. Rubin?
A. I think both at Merck and at the NIH there were mumps neutralizing assays performed with different strains. At the time there was a question as to whether outbreaks might be due to strains with different characteristics, different genetic sequences, different virulents. So various labs tried to figure out what the basis of these apparently high out attack rates in certain populations were. And in the context of that other strains were tried as well.
Q. Do you know which strains were tried?
A. No, no idea.
Q. Let me direct your attention back to Exhibit 9 in the attachment 561418. Here it says in the second paragraph, "Due to the characteristics of the mumps wild-type assay, it will be very difficult to accurately read titers below 10 Ab units."
Do you see that?
A. Yes.




Q. If the serostatus cutoff is set at 10, is there a concern that that assay can't read below 10?
A. Well, there is a concern if you apply a fourfold criterion. Because in order to apply a fourfold criterion with a 10 cutoff, you need to be able to read down to 2.5 accurately. That may not be possible, technically not be possible.
Q. Well, that's a question of dilution, isn't it?
A. No, it's a question of the sensitivity of the assay. You can dilute as much as you want. As you dilute, you also dilute the antibody. You may get rid of some background, but you don't necessarily gain sensitivity.
Q. I see. So wouldn't that be an argument for increasing the cutoff?
A. As I said before, you can't see these things in isolation. Yes, if you wanted to use a fourfold criterion which I think would be inappropriate for this kind of an assay by today's standards, then it would




be an argument. But then you would get into the other problem that you misclassify people who are actually seropositive into being seronegative. So it's a decision that has to do with the classifications. And you would change whom you call positive and whom you call negative.
Q. I'm just trying to understand how you set a cutoff, serostatus cutoff. If it's not linked to whether or not it protects the kid, then what are you linking that cutoff at? It seems arbitrary.
MR. SANGIAMO: Object to -- what is your question?
BY MR. KELLER:
Q. Is that cutoff, is it arbitrary if it's not set to some ability to protect a kid, if you're going to use an assay that reports in seroconversion, and that seroconversion is based on a static cutoff, and that cutoff is not set to anything as to whether or not it's going to protect a kid from getting sick, I'm just trying to understand, how do you set the cutoff? What's




the basis for setting it?
MR. SANGIAMO: Object to the form.
THE WITNESS: I think I said that several times. The basis is a simple classification of positives and negatives. You can set it at different points and you will have different classifications. And they have -- they inherently have different errors relative to the assay and potentially relative to outcomes. But this particular assay and the outcomes are not linked in any meaningful manner. So I can't say that on protection rates because I don't know what they are. And besides, it's been observed in mumps that there isn't an absolute cutoff for protection, otherwise we probably would have cutoffs. In other words, there is not a titer that you're completely reliably protected.
BY MR. KELLER:

Q. So these errors that you're talking about, are these at all related to -- let me strike that.

What do you mean by "errors"? You just referred to the errors in the classifications.

A. Well, errors in classification would be if you had a crystal ball and you could tell the absolute truth of who has an antibody and who doesn't have an antibody even below the detection limit of an assay, which, of course, you can't, then you would falsely classify some by one cutoff and others by another cutoff. But you don't -- since you need a third, as they say in philosophy, tertium non datur, there is no third to compare it to. So you don't have an absolute measure and therefore, the -- there is always a degree of arbitrariness to setting a serostatus cutoff, to use your own words. However, it is based on some scientific principles which is you can reliably distinguish seronegatives and seropositives and you can reliably




distinguish those who will respond and those who will not respond. And that's good enough for this kind of an assay.

Q. I see. Here in this memo, they state, "the difference being within the variability of the assay." If the variability of the assay falls below -- if you set it at 10, the variability can run below 10, then you may have assays that have errors around that variability?

MR. SANGIAMO: Objection to form.

THE WITNESS: That would be true for any cutoff in any form of seroconversion rate you apply because there's always an error around any cutoff and any criterion and you will always have something that falls within the error. The art is to be reasonably outside of the error with the majority of your samples.

BY MR. KELLER:

Q. Later on in this document it says in the last paragraph, it says, If CBER




required a 4-fold rise in titers (defined as less than 10 to greater than equal to 40), the seroconversion rate for these studies would range from 80.9 percent to 85.2 percent.

Do you see that?

A. Yes.

Q. That range is based on the different potencies in the protocol for the wild-type ELISA. Correct?

A. Well, I assume that. I don't know that for sure. It could also be a different analysis that he performed. I mean, it's clear the more people you exclude from the analysis, the more you change the outcome.

Q. I see. So was that one of the concerns that they're talking about here, is that if CBER required this fourfold rise, that the seroconversion rate would, in fact, be lower than reported with the fixed 10 Ab cutoff?

MR. SANGIAMO: Objection.

THE WITNESS: I can't speculate as to that. That would have been a




consequence of what we thought at the time was not the right thing to do. I think CBER concurred in the end.

MR. KELLER: Let's mark this next exhibit as Exhibit 10.

- - -

(Exhibit Schodel-10, E-mail chain, Bates MRK-KRA00561361 - 00561365-00017, was marked for identification.)

- - -

BY MR. KELLER:

Q. For the record, Exhibit 10 is a document that bears Bates stamp number 561361 through 561365 which includes a PowerPoint presentation at 561365 through -- there's 17 pages of this presentation.

A. I have two different ones here.

Q. One is -- I'm sorry. Let's pull the one of them. The 19058 you can just get rid of. It's the same document. We previously marked 19085 in Morsy as Exhibit 20. I'm going to use this copy because it's attached to an e-mail that went to Dr. Schodel. So if that helps.

MR. SANGIAMO: Actually it doesn't. 19085 that's out of play right now.

MR. KELLER: That's out of play. I'm just -- for the record, that document was used in Schodel [sic] and it's the same presentation but this one was attached to an e-mail that went to Dr. Schodel.

BY MR. KELLER:

Q. So for the record, on January 18, 2002, there is a doc -- subject of this e-mail is CRRC Agenda - 22 January, 2002. And, Dr. Schodel, you received this and was sent by Dr. Chirgwin. Do you see that?

A. Yes.

Q. Can you take a minute and look at this presentation and tell me if you recall seeing this presentation? I'm not going to ask you about every page, but you're welcome to look at it.

A. Okay.

Q. If you look on the e-mails that attach this particular PowerPoint, there's an




e-mail from Jeffrey C-H-O-D-A-K-E-W-I-T-Z to you as well as a bunch of other folks including Emilio Emini and it's talking about the CRRC agenda. Here it says, Have you seen draft overheads for the mumps assay issue? Has the variability of the current status or contingency of extended commitment to 4.3 been discussed -- addressed by MMD --

A. Sorry, viability.

Q. Sorry. Viability. "Has the viability of the current status or contingency of extended commitment to 4.3 been addressed by MMD?"

And then you responded, "Dear Jeff, I asked Joye and Alan yesterday and they assured me that Keith would present. I have not seen any overheads yet?"

Then Chirgwin sent you the overheads. Does that refresh your memory, that you actually received these?

A. Yeah.

Q. Do you have any reason to believe that you didn't receive this document?

A. No.




Q. Let me direct your attention, do you recall -- the CRRC, that's the Clinical Regulatory Review Committee. Correct?

A. I don't know the exact acronym, but something like that, yes.

Q. Were you a member of that committee?

A. I don't think I was a member of that as a core member. I was probably called in on occasion.

Q. Why would you be brought in on occasion?

A. Well, if there were things discussed that were related to something I was responsible for. I mean, I was not responsible for all of clinical research or regulatory at Merck.

Q. Were you responsible for any aspect of Protocol 007?

A. No.

Q. So you don't know why you were called in?

A. Well, because I was -- I mean, it wasn't only Protocol 007. Some of the




people who were running Protocol 007 by that time probably reported to me and I was, as you have noted before, on the clinical assay subteam which is a subteam of the BPC.

Q. So you have expertise in the area of assays. Correct?

A. Yes.

Q. Let me direct your attention to slide 3 at 561365. And here talks of "Mumps Expiry Background Chronology of Events." Here it says, "1997 Clarification that labeled potencies must reflect end of shelf life claim (not minimal release)."

Do you see that?

A. Yes.

Q. Does that refresh your memory that in 1997 is when that clarification occurred for mumps --

A. Yeah. I mean, that's what it states here. I mentioned that several times, that I didn't know anymore when it occurred but that that particular clarification and the ensuing discussions ultimately led to the Protocol 007, not the modeling on stability

that you referred to later.

Q. So it's your understanding that as of 1997, CBER required that Merck's end of expiry shelf life have a minimum of what was identified in the label at that point, not just release. Correct?

A. I think that was the first time when CBER formally informed Merck that that was how their understanding of the labels had evolved. And then there was a discussion ensuing so that it wasn't a one-time event as far as I remember. But, yes, at that point in time CBER apparently shared its change of view.

Q. If you look on the next page, September 1999 "Chronology of Events Mumps Overfill." It says, Ongoing CBER concerns about misbranding result in general -- in agreement to increase the minimum release spec for mumps from 4.3 to 5.0. Do you see that?

A. Yes.

Q. If you look on the next page, "Concerns about Stability," in August of 2000 "Concerns raised regarding compliance with





stability monitoring during FDA inspection." Do you see that?

A. Yes.

Q. Do you recall the inspection that occurred in August of 2000 regarding mumps stability?

A. No. Only some of the discussions afterwards that you just shared with me again.

Q. Do you recall there being a concern that Merck's then current product was out of specification with its end expiry claims?

A. No, I don't recall that until the dates when you showed me the --

Q. If you see at the bottom it says December of 2000. The "Expiry trial sera began to be assayed; validations studies conducted in parallel." Do you see that?

A. Uh-huh.

Q. So while they were analyzing the Protocol 007 data, they were at the same time validating those same studies?

MR. SANGIAMO: Object to the





form.

THE WITNESS: I'm not sure what that exactly refers to, what was validated, whether it was the assay or something else. You have to see that this was obviously an ongoing discussion with CBER and there may have been very specific CBER requests that were honored by Merck. And that would supersede whatever normal procedure Merck had in place.

BY MR. KELLER:

Q. Is that typical for validating studies, to have them be validated concurrently with the running of the study?

A. It depends on -- it depends on the phase in which the study is done and what its purpose is. Very typical for Phase I and Phase 2 studies.

Q. This was Phase 3 study, though, correct, Protocol 007?

A. No, it's not. No, it's not. This was not. This was probably a Phase 4 study or a Phase 5 study. It was something





that was negotiated with CBER. CBER knew very well what assays were available and were not available and what had to be developed because they even influenced which assays had to be selected.

Q. So is it your testimony that you knew -- that CBER -- is it your testimony that CBER knew that Merck was validating the assay while it was conducting it?

A. That, I don't know. I simply wouldn't know. But it is my testimony that CBER had a major role in deciding on this IgG assay that you mentioned earlier.

Q. Why do you say that?

A. Because it came out of CBER. It was CBER who suggested that assay in the first place.

Q. How do you know they suggested it?

A. That was what I always heard.

Q. Who did you hear that from?

A. Probably from CBER as well as from Merck people. I don't remember who specifically told me. But this is an ongoing

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discussion. It was an ongoing discussion.

Q. What was the ongoing discussion?

A. I don't know the details anymore. Just what I remember is that this particular assay format was suggested by CBER.

Q. Do you know whether or not Merck had brought it up to CBER first and asked if they could use it?

A. No, I don't know that.

Q. Do you know whether or not CBER required that to use the rabbit anti-IgG, that it would have to properly validate that assay before it was used?

A. You'd have to ask Kathy Carbone since she would know that better than I. I don't know.

Q. Let me direct your attention to slide 6 which is the chronology of events for preliminary results of expiry trial. Do you see that?

A. Yes.

Q. Here it says February '01, "Subset analysis indicates that 4.0 log (but not 3.7...) dose will likely be acceptable."



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Do you see that?

A. Yes.

Q. Then in March it says, "Subset analysis results included in response to FDA warning letter regarding compliance with expiry potency claim."

Do you see that?

A. Yes.

Q. So is it fair to say that Merck was using the preliminary subset analysis as proof that the vaccine worked below 4.3 log at end expiry?

MR. SANGIAMO: Object to the form.

THE WITNESS: I think that's an over interpretation. I think in discussions with CBER at the time Merck agreed to provide whatever data were available, and CBER probably asked to provide any data that were available. So Merck provided the data.

BY MR. KELLER:

Q. Do you know that for a fact or



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are you just --

A. No.

Q. -- summarizing?

A. Well, I -- it was mentioned in some of the mails that you showed me.

Q. But you don't recall. Let me -- do you recall any discussion that Merck used the results of Protocol 007's PRN assay to prevent CBER from recalling the product that was out on the market below 4.3 end expiry?

A. I do not.

Q. You don't know. If you look on the last date in this chronology, December '01, "CBER indicates that compliance concerns may preclude using the mumps PRN data."

Do you see that?

A. Yes, I see that.

Q. Do you know what the compliance concerns were?

A. Vaguely. I remember that there was an FDA inspection of the lab that ran the assay as opposed to manufacturing. And then that in that particular -- I wasn't in the lab so I can't tell you all the details, but



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there seemed to be compliance concerns primary around documentation of the results, whether they were signed off and whether they had the right format and so on. Which is not atypical for a research laboratory. That may be what CBER says here, but I can't speak for CBER.

Q. Were you involved at all in responding to CBER with regard to those compliance issues?

A. No. Certainly not directly because I wasn't in the lab. I didn't even know what the exact compliance issues were.

Q. Do you recall there being any issues about Merck retesting samples without written justification?

A. Not specifically, no.

Q. Let me direct your attention to slide 10 of this presentation that was made to the clinical regulatory review committee on January 22, 2002.

MR. SANGIAMO: I'm going to object to the preamble.

BY MR. KELLER:

Q. It says, "Current Status."
A. Wait, wait, wait, wait. Wait a second. What's this here? This is -- this is -- okay. That's the presentation. Okay. So you're just referring to that presentation which was likely presented at the CRRC.
Q. Yes. Do you have any reason to believe that it wasn't presented at that meeting?
A. Well, no. I don't have any reason to believe that a presentation wasn't presented at that meeting, but this is the attachment of the e-mail that came with the invitation which you gave me. So is it exactly the same presentation that was given or not, I don't know, I would expect it to be.
Q. It's the one that you got, though. Correct?
A. It's the one I got. I'm just objecting to the additional premises that I know what was actually presented there and can reconstruct it out of my memory 15 years later.





Q. But you have no reason to believe that it wasn't provided?
A. No, I have no reason to believe anything.
Q. Sure. If you look at slide 10 under "Current Status," it says, Response to CBER comments on mumps PRN assay submitted January 21, 2002.
In the third bullet point it says, "Products still not compliant with labeled mumps potency 95% lower bound of potencies through end of shelf life is 4.0 log.
"However, subset analysis suggests that 4.0 log (but not 3.7 log) mumps dose will likely be acceptable."
Each time a log tests below 4.3, MMD must file a Biologic Product Deviation Report to CBER detailing results of investigation and medical impact (estimate around 6 to 10 a year).
Do you see that?
A. Yes.
Q. Were you involved at all in MMD





filing BPDR reports to CBER?
A. No. Unless they contained clinical data and they would have asked me for clinical data. But not in the filing at all.
Q. Do you know if Merck ever submitted a BPDR for those 106 lots?
A. No.
Q. You don't know, okay.
Can you see the last -- on page -- on slide 14, "Mumps Expiry Issue Path Forward?"
"Strategies for ensuring compliance if expiry trial data cannot be used."
Do you see that?
A. Yes.
Q. Do you recall any discussion at Merck regarding the failure of Protocol 007's PRN assay reaching the conclusions that were required as part of the end points?
MR. SANGIAMO: Object to the form.
THE WITNESS: The only thing I





remember was what is listed here on the slide that we looked at before where -- that CBER indicated that there might be compliance issues. I don't know what they are and I can't speculate what exactly they were. And then the fallback would have been to use the ELISA.
BY MR. KELLER:
Q. And so the path forward here, do you recall any discussion about the path forward -- let me strike that.
The term "path forward," is that a term used at Merck that you've seen in the past?
A. I've seen it used in many places, yes. Including Merck.
Q. What does that mean to you?
A. Something that goes in a direction in time probably. Instead of backward.
Q. So it's projecting the future, how to get to a future result. Correct?
A. Probably, yes.

Q. And here number 2 it says, "Reduce 90% lower bound for stability losses." Do you have any idea what they're talking about there?

A. No. That's a manufacturing issue. I wouldn't be involved in the discussions of how they ran their stability models.

Q. Do you recall any discussion about the next statement, "Reduce shelf-life to 13 months - not considered feasible"?

A. No.

Q. Do you recall any discussion at Merck that it's one log loss projections from its then current stability model projected that the shelf life would be below 12 months?

A. Not specifically, no. I remember what you showed me, that there was a model anyway that predicted potential one log losses, but I don't remember a discussion of a shorter shelf life.

Q. Do you recall any discussion about one log loss converted to a shelf life of 12 months or lower?





A. No.

Q. Do you --

MR. SANGIAMO: I think he answered, Jeff.

THE WITNESS: I said no.

BY MR. KELLER:

Q. I'm sorry.

A. Was too simple an answer. You don't take no?

Q. No, yeses are all fine.

Here it says, "Increase in release titer - safety concerns." Is there here a discussion -- do you recall a discussion about increasing the overfill in order to improve?

A. Where do you have that here?

Q. Number 2.

A. In a theoretical way I do not specifically, but I would certainly have been one who would have objected to doing that without data.

Q. I see. Why would you have objected to that without data?

A. Well, you can't just fill in





more mumps virus or any other live virus for that matter, if you don't have data to support that it's a --

Q. What kind of data would you look at?

A. Well, that's the difficulty. You would be particularly -- you would be particularly concerned about the very rare events like aseptic meningitis and that -- this particular mumps vaccine does not have associated with it, which is the reason it's used in the United States as opposed to the virology strains. But those events are so rare that they cannot be practically measured and that's where the feasibility comes in. I don't know whether they were -- I mean, you know, that's only on the safety side.

Q. Were you involved at all with the prior overfill where they increased the amount of mumps they put into every virus in 1999?

A. I don't really -- in 1991?

Q. 1999.

A. 1999.





Q. The overfill.

A. No, I don't remember that. Also 1999 I wasn't at Merck, so I wouldn't have been either informed or involved.

Q. Here it says, "Improvement in stabilizer (urea)." Do you see that?

A. Yes.

Q. Do you recall any discussion about actually changing the MMR II product by changing the stabilizer in it to help improve its stability over 24 months?

A. Well, I don't remember any discussions in this particular context. I remember them in very different context with the WHO but not necessarily even led by Merck. So I -- for this purpose, no, I don't remember it.

Q. Do you recall -- and the last one says, "Improvement in assay variability -- limited room for further improvement."

Do you see that?

A. Yes.

Q. That's talking about the stability model. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't know. You expect me to speculate, but I think it's probably, I think, to the stability model.

BY MR. KELLER:

Q. Do you recall any discussion about Merck trying to improve the assay variability of its stability model?

A. No, I don't, but I think that's a logical thing that one would consider.

Q. I'm sorry?

A. It's a logical thing to consider, but I don't remember any specific discussion. Mind you this is manufacturing so it wouldn't be my --

Q. Sure. Let me have you turn to the next page at 16, and it's "GMP Compliance Issues Recounting of Test Wells." What does GMP mean?

A. Good manufacturing practice.

Q. Under "Background" in the second bullet point says, Spreadsheet developed




during preliminary -- during testing and preliminary subset included flags for statistical and operational acceptance criteria triggered recounts and retests.

Do you see that?

A. Uh-huh.

Q. Do you recall any discussion -- you talked about generally that there was a compliance issue in the lab. This retesting, do you know whether or not Merck actually went back and retested vaccine failures?

A. No, I do not.

MR. SANGIAMO: Object to the form.

THE WITNESS: I do not. What I remember is what I told you, that there were documentation issues. But that was pretty general. I don't remember the details.

BY MR. KELLER:

Q. You don't know if they followed your suggestion of retesting the vaccine failures?

MR. SANGIAMO: Objection.




THE WITNESS: It wasn't actually a suggestion. It was I was expressing what kind of data I would like to see as a clinician.

BY MR. KELLER:

Q. I see. Here it says under "Concerns," "Recounts were made, dated, and signed, but not justified, on the raw data sheets."

Do you see that?

A. Yes.

Q. Do you recall any discussion at Merck regarding the justification for changing data without -- changing data without justification?

A. It doesn't say here that data were changed. All it says is that the recounts were made. That doesn't mean that any data was changed. It just means that the same plaques were counted again and it was probably dated and signed and recorded. So it doesn't change data. It just counts them again.

Q. You don't recall any discussion




about data being changed?

A. No.

Q. Here it says the "Rules developed/implemented after starting to assay the expiry trial sera."

Do you see that?

A. I see that.

Q. What do you understand that to mean?

A. Well, I don't know what rules it applies to. Maybe rules on recounts or rules on other things, documentations. So it doesn't really mean much if I tell you what I think of it because it depends on what it is.

Q. Sure. Let's go to the next page, "Impact of Recounts." Here it says on the first bullet point, "Majority of recounts involved pre-vaccination sero which were positive at one dilution only."

Do you see that?

A. Uh-huh.

Q. Do you understand what that means?

A. Well, I can read the sentence,

but I don't know whether that is just because of how the sera they recounted happened to be, whether it was a choice. I didn't even know that there was a recount, so leave alone whether the --

Q. Can you think of any clinical --

MR. SANGIAMO: Jeff.

THE WITNESS: Leave alone whether there was any deliberate selection.

BY MR. KELLER:

Q. I see. Can you think of any reason to recount only one data set that's one -- that's positive one dilution?

MR. SANGIAMO: Objection.

THE WITNESS: I can think of reasons to recount any data set. If you see a valid reason why it might have been counted wrongly, you recount it.

BY MR. KELLER:

Q. Would you recount all data or do you just recount a certain subset of data?

MR. SANGIAMO: Objection.




THE WITNESS: In general it depends on what the error is. So in principle I would probably recount all data if they were all the same. If, however, there are something -- there are something -- some specific characteristics, for example, that something is particularly hard to see or you're not worried about the ones that are in the middle of a distribution but you may be worried about the ones -- if you have a dish that's full of plaques, if you get too many points, they're hard to count. If you have too little, they're may be hard to recognize. So there may be reasons why something recounted because the error is higher. But I don't know what the case here is.

BY MR. KELLER:

Q. Here it says, "Recounts showed that plaques had been missed." So they added more plaques. Is that correct?

MR. SANGIAMO: Objection.




THE WITNESS: No, that's incorrect. If the statement says that they had been missed, it means that -- not that they were added, but that they hadn't been seen before. It means in the first count you see maybe ten plaques and you let somebody look again and they find 15 plaques.

BY MR. KELLER:

Q. So if they're only finding plaques that had been missed, that's one direction. Correct?

A. No. It's one direction on that specific plate, but it's not necessarily one direction in the assay, because it may move them in either direction depending on what the dilution is that you test. It's not unidirectional in terms of outcome, it's only unidirectional in terms of the physical measuring object that you have.

Q. But if it was unidirectional as to outcome, would that cause you concern?

MR. SANGIAMO: Objection.

THE WITNESS: Potentially. But




that's not what is described here. Obviously if you look at any -- if you look at a measure for which you have more likelihood of making an error, you would be more likely to repeat it because your measure is not as good.

BY MR. KELLER:

Q. In the next bullet point says, "Recounts resulted in pre-vaccination sero becoming negative and therefore valid for inclusion in pre-protocol analysis (subjects included in analysis increased from 449 to 514)."

Do you see that?

A. Yeah.

Q. So by changing -- recounting these specific results at one dilution, missed plaques were recounted and had the result of -- for just the pre-positives, converting pre-positives to pre-negatives 65 of these samples. Is that fair statement there?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, that's what

it seems to say here.
BY MR. KELLER:
Q. So if the results of recounting appear to occur in one direction and change results, would that cause you to have concern with how the assay was conducted?
A. Not necessarily. It depends on again what it's due to. I mean, something that's hard to see you would miss more often than something that's easy to see. If you have titers of several hundreds, you know that the blades are black, doesn't matter whether they're 449 or 451.
Q. I see. So in this case we're talking about --
A. Then you have to look -- when you talk about impact, you have to look at does that really change the result, not just the classification.
Q. Well, pre-positives mean that those kids are not included in the assay, correct, for the plaque reduction neutralization assay?
A. They're not included in --




they're included in the assay, but they're not counted as seroconverters. So you have to look at the end -- when you compare the end results with corrected and uncorrected results, whether there is any impact on this correction in terms of the outcome. Otherwise, you're talking about something which is not very useful.
Q. Do you recall any discussion at Merck regarding the impact of rabbit anti-IgG had on the plaque reduction neutralization assay in that it increased the pre-positives as well as increased the seroconvert --
A. No.
Q. -- for neutralize the pre --
strike that.
Do you recall any discussion at Merck regarding the use of rabbit anti-IgG in the plaque reduction neutralizing assay in Protocol 007 that had an impact on the pre-positives, that increased the number of pre-positives?
A. No, I don't. I mean, as I said before, I don't even specifically remember




discussing adding the rabbit IgG at all leave alone its impacts.
Now would be a really good time to take another break.
Q. Sure.
A. I'm sorry, but I'm getting older.
Q. That's fine.
VIDEOGRAPHER: Off the record 3:10. This will end disc number four.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: Back on the record at 3:17. Beginning of disc number five.
MR. KELLER: I'd like to mark as Exhibit 11.
- - -
(Exhibit Schodel-11, 10/19/01 Letter, Bates MRK-KRA01469018 - 01469020, was marked for identification.)
- - -
BY MR. KELLER:




Q. Exhibit 11 is a document that bears Bates stamp number 1469018 through 020. And it's a document dated October 19, 2001, from Manal Morsy to Henrietta Ukwu regarding CBER teleconference (October 16, 2001): Mumps -- Measles, Mumps and Rubella ELISAs. I'll say, Dr. Schodel, you are identified on the cc as well as identified as participating in this meeting with CBER on this date. Can you tell me -- if you can take a minute to look at this document and tell me if you recall participating in this teleconference, I mean this meeting on -- this teleconference on October 16, 2001?
A. Okay.
Q. Do you recall participating in this teleconference?
A. Honestly I don't, but I read -- I glanced over the meeting minutes.
Q. Do you have any reason to believe that you didn't attend this meeting?
A. No.
Q. Do you have any reason to believe that these meeting minutes are not

accurate?
A. No.
Q. Were these meeting minutes generated by Merck in its ordinary course of its business?
A. I suspect so.
Q. Do you know whether or not these meeting minutes would be provided to CBER?
A. They would be.
Q. If you look at this teleconference that occurred on October 16, 2001 --
A. 19. You've got 16.
Q. The date of this memo is three days later. It identifies the CBER participants as Kathy Carbone, Dr. Steven Rubin, Dr. Henry Hsu and Dr. -- I mean, and Ms. Luba Vujcic. Do you see that?
A. Uh-huh.
Q. Those were the folks that were typically working on the Protocol 007 assays at CBER, the primary contacts for Merck?
A. I don't know who else was working on that particular protocol, but certainly I've seen their names in





association with the protocol.
Q. Let me have you turn your attention to page 2, 1469019 under "Summary of discussion." Under the "Wild type mumps ELISA cutoff."
Do you see that?
A. Yes.
Q. That's the ELISA arm of Protocol 007. Correct?
A. Well, that's the assay used in Protocol 007, but it is also -- the discussion here is about not so much only Protocol 007 but whether the ELISA cutoff was set right apparently.
Q. Because that was going to be used with respect for gaining approval of ProQuad, too. Correct?
A. That's correct.
Q. So if you look in the second bullet point on 1469019 it says, "Assay variability and true seroconversion around the cutoff:"
CBER requested clarification on how we would be able to distinction between a





true difference of two samples measuring 9 and 10 Ab ELISA units and the inherent variability of the assay. CBER reminded Merck of their position regarding a threshold versus a 4 fold increase for Varicella gpELISA where a 4 fold rise is required for assignment of seroconversion (i.e. less than equal to 1.25 pre to greater than equal 5 post).
Do you see that?
A. I see that.
Q. So that exact or that very similar example that's being raised at this meeting had already been discussed internally at Merck --
MR. SANGIAMO: Objection.
BY MR. KELLER:
Q. -- in Exhibit 9. Do you remember that?
MR. SANGIAMO: Object to the form.
THE WITNESS: Well, it's -- you're making assumptions here. It's not the exact same issue. It's the same approach of requiring in addition





to a seroprotection cutoff, also a fourfold rise criterion. But it's not the same assay, it's not the same variability and it's not the same numbers.
BY MR. KELLER:
Q. So there's -- at this point CBER is still considering whether or not it was going to require Merck to do a fold increase to set the serostatus cutoff for its ELISA assay. Correct?
A. That is correct.
Q. If you look on the next page, in the middle -- one, two, three, four, five bullet points -- five paragraphs down it says, "It should be noted that if the question about justification and relevance of the mumps ELISA cutoff could be addressed (i.e. by correlating to PRN), then a 4 fold criterion would not be necessary. If, however there continues to be uncertainty about the biological/clinical relevance of the cutoff, it is expected that CBER would require a 4 fold...criterion, as that would be necessary to demonstrate

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significant response to the vaccine. This reasoning would parallel that which is used for measles and rubella ELISAs. CBER did not require a fold rise in these assays because measles and rubella ELISAs employ a recognized reference standard for seroprotection."

Do you see that?

A. Yes.

Q. So is it fair to say that if Merck did not correlate its PRN assay to its ELISA assay to justify its static cutoff, it was going to be required to do a fourfold criterion?

MR. SANGIAMO: Objection. Calls for speculation.

THE WITNESS: I think that's speculation. The -- that's the fear expressed by the person who wrote this, but that is not what CBER has stated.

BY MR. KELLER:

Q. Isn't this sent to CBER?

A. It is sent to CBER but it does not reflect only CBER's position. It





reflects a discussion.

Q. I see. So --

A. It was not sent to us by CBER saying this is what you have to do. This is what will happen if you don't do it. So this is a lot of speculation that you're asking me for.

Q. Sorry. This is a discussion that Merck had with CBER where CBER was communicating what it expected, though. Correct?

A. Yes, but the criteria are -- so CBER expected additional information which was provided. And it also recognized that there are constraints in the assay. It also recognized that in other assays like rubella and measles, this kind of a criterion was not applied.

Q. Because there there was some reference standard for seroprotection at that serostatus cutoff. Correct?

A. That is correct. But not the only reason because the same argument that you made before that if something is variable





right around that cutoff could be applied for these as well regardless of whether there is a correlation or not.

Q. Why would CBER -- what was the discussion in this meeting that CBER was requesting that Merck correlate that serostatus cutoff to the PRN?

A. I don't speculate on CBER's intent.

Q. You understood that's what CBER was asking for?

A. It was one of the issues they requested, and that was -- it was up to CBER to request it without justifying it.

Q. I see. Did Merck correlate its serostatus cutoff to the PRN assay?

A. Since CBER requested it, they would have probably done it.

Q. Did you ever see that data?

A. I don't remember it in detail, but I may have seen it.

Q. Do you know whether or not that was ever submitted? You don't know if it was ever submitted to CBER?





A. No, I don't know that.

Q. But you do know that the fourfold criteria was not required for purposes of the wild-type ELISA that was used and not just Protocol 007 but used for approval of ProQuad's BLA?

A. I do know that.

Q. They didn't require the fourfold criteria?

A. No, they did not. But the reason why they did not may be different. There are other -- if you read through the whole document, you find, for example, it is actually -- it turns out that the ELISA is more conservative in assigning seropositivity and seronegativity. So CBER may have had other reasons than simply the correlation for allowing the ELISA to go forward with a fourfold -- without a fourfold rise.

MR. KELLER: Can I get that answer back? I'm sorry.

- - -

(The court reporter read the pertinent part of the record.)

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- - -

BY MR. KELLER:

Q. What would those reasons have been?

A. They're listed in here somewhere.

MR. SANGIAMO: Object to that question as calling for speculation.

BY MR. KELLER:

Q. You can answer.

A. I can't speculate on what CBER wanted, but the assay -- let me see where it was. I just read something here. Actually it speaks directly to what CBER said, so I don't have to speculate. You can actually read what CBER said. It's the last paragraph on the second page. It says, "CBER pointed out that a correlation rate of 92% was low, particularly when related to the expected criteria for success in terms of seroconversion rate (5% delta, 90% floor), but noted that the ELISA seemed to be more conservative than the PRN in assignment of low sero-positives."

So that was CBER's opinion.





And that is obviously a major factor in making a decision. And they stated it here. So that's not a speculation, it's -- you have it in writing here.

Q. So your statement is that PRN assay was more variable at assigning low seropositives?

A. The PRN assay was probably more variable full stop as PRN assays are known to be.

Q. I see.

A. And it goes on also as stated by CBER, "It was pointed out to CBER that although this was true for pre-vaccination samples, results of this limited data set show that in case of post-vaccination sera, the ELISA was more sensitive than the PRN in assigning high titers," which also helps in the distinction.

Q. But taking all that together, CBER wanted to see some sort of correlation between the PRN assay and the serostatus cutoff because of the wild-type ELISA. Correct?





A. No. CBER wanted to see some type of correlation going into that meeting. Taking all that together, I don't want to speculate, but reading what CBER said, I'm not so sure that they were as interested anymore.

Q. I see. Let's find out.

A. And they still wanted it to be shown. Whether the data mattered, I don't want to speculate on that.

Q. I see. But they wanted to see that data?

A. Obviously.

MR. KELLER: Let me mark as Exhibit 12.

- - -

(Exhibit Schodel-12, 4/25/02 E-mail with attachment, Bates MRK-KRA00544512 - 00544538, 00544540 - 00544543, was marked for identification.)

- - -

BY MR. KELLER:

Q. For the record, Exhibit 12 is a document that bears Bates stamp number 544296





through --

MR. SANGIAMO: That's not what you gave us. Wrong one.

- - -

(A discussion off the record occurred.)

- - -

MR. KELLER: I'm sorry. Just mark this one the next one. Mark this one as 13.

- - -

(Exhibit Schodel-13, 5/7/02 E-mail with attachment, Bates MRK-KRA00544296 - 00544324, was marked for identification.)

- - -

THE WITNESS: Disregard 12 at this point.

BY MR. KELLER:

Q. Just set it aside for now. Start with 13. Let me mark Exhibit 13 Bates number 544296 through 331836. Wait. Whoa whoa, whoa. Sorry. It's hard to get good help these days. Let me strike that.

Let me mark Exhibit 13 Bates number 544296 through 544324. And for the record, Exhibit 13 is a document, an e-mail from Keith Chirgwin to Dr. Schodel regarding draft document mumps cutoff, and attaches a series of exhibits. This e-mail is dated May 7, 2002. And if you could take a look at this for a minute, Doctor, and tell me, if you recall receiving this e-mail.

A. I don't recall receiving this specific e-mail, but I mean, it's along the same lines.

Q. Do you have any reason to believe you didn't receive it?

A. No.

Q. Any reason to believe you didn't receive the attachments to it?

A. No.

Q. In this e-mail from Mr. -- from Dr. Chirgwin he writes, Florian, This is the latest version of the mumps cutoff CBER response from Joe. As per the previous e-mail message, it appears that things have gotten stuck with regard to the table that Joe




presented at the VAC several weeks ago showing the breakdown by ELISA strata of the discordant PRN negative/ELISA positive sera.

Do you see that?

A. Yes.

Q. That's the vaccine assay committee. Correct?

A. Uh-huh.

Q. That's the committee that you were either the co-chair or a member?

A. Yes.

Q. It goes on to say that the large majority of these discordants had ELISA titers less than 40 and one concern is that presenting the data in this fashion may prompt CBER to request that the ELISA cutoff be raised.

Do you see that?

A. Yes.

Q. Do you recall discussions regarding the removal of certain tables in response to CBER regarding the cutoff that there was a concern that that data would lead CBER to increase the cutoff?




A. No.

Q. If you look further, Chirgwin says, "I agree that CBER did not specifically indicate that we would be required to demonstrate concordance. However in reviewing the meeting minutes from last October (attached below), it is...clear that they are going to look closely at how sera with values around the cutoff are classified in the two assays."

Do you see that?

A. Yes.

Q. In this October, do you believe that's referring back to that October 16, 2001, meeting or teleconference where the serostatus cutoff was discussed?

A. I assume so.

Q. At least -- and he goes on to say, "At least based on October's discussion, if we are unable to provide sufficient reassurance about the clinical relevance of the ELISA cutoff (which in Kathy's mind means linking this to the PRN) then we may end up with some type of a fold-rise criterion which




I assume we would rather avoid if possible."

Do you see that?

A. Yes.

Q. So there was a concern that if Merck provided CBER certain data, that they would increase the ELISA cutoff. Is that what this document is saying?

A. That's what it seems to say here.

Q. So Joe, that's Joe Antonello, correct, he's a statistician?

A. I assume that if it's not Joe Heyse, it must be Joe Antonello.

Q. See below that there's a reference, it says, "Joe I removed tables 6 c and 6 d and information referring to them from the 007 ELISA and PRN comparison document (Attachment 2)...," and he says, "...too distracting." Do you see that?

A. Yes.

Q. Let me have you draw attention to Exhibit 12 that we had just marked previously. On the e-mail on 544512, there's a couple documents attached to it. And

Attachment 1 on 55 -- 544514 is a -- the Table 6c and 6d that the previous -- or the -- that was identified as being removed. Have you ever seen this table before?

MR. SANGIAMO: Object to your preamble. What is your question, whether he has seen the table at 544514?

MR. KELLER: Yes.

MR. SANGIAMO: Okay.

THE WITNESS: I would have probably seen it as an attachment of this e-mail provided -- I mean, provided I read the details of all these e-mails because I was not the primary person responsible anymore.

BY MR. KELLER:

Q. You see that you were cc'd on this e-mail.

A. Yeah. I was cc'd on a lot of e-mail, 200 or 300 a day.

Q. This was sent to Joseph Antonello. Do you see that?

A. Yes.





Q. And Jonathan Hartzel?

A. Yes, yes, yes.

Q. And David Krah?

A. Yeah.

Q. And Alan Shaw? Those were the folks that were working on Protocol 007. Correct?

A. Dave was working in Alan's lab, yes.

Q. And Alan reported to Emini?

A. Yes.

Q. And David Krah reported to Emini?

A. To Alan Shaw.

Q. And here Manal Morsy, she was the regulatory liaison at this time frame, wasn't she?

A. I believe so, yes.

Q. And here she writes Joe, Jon, Luwy, Alan and Dave:

"Please review the documents attached - two sections are needed (marked in red in the document).

"Joe: a table showing the





number of discrepant paired sera in ELISA and PRN relative to what is expected per assay variability in the STD range."

Do you see that?

A. Yes.

Q. STD, is that standard deviation? Do you understand that to be standard deviation?

A. I'm not exactly sure what STD stands for here.

Q. Do you have any reason to believe that you didn't receive this e-mail?

A. No. Just, you know, I'm copied as are others.

Q. Sure. It goes on to say, "I understand that at 1 STD and 2 STD discrepancies observed fall within expected % but at 3STD we have more discrepancies than what can be explained by just assay variability...."

Do you see that?

A. Yes.

Q. Do you understand why that would be important?





MR. SANGIAMO: Object to the form.

THE WITNESS: No.

BY MR. KELLER:

Q. It goes on to say, "Joe, also please confirm that the attachments enclosed are in fact the audited documents (I have deleted as you know tables 6c and 6d and their corresponding text from attachment 2 - I have attached the tables and text deleted for your reference - which I would like to replace as we discussed with a table showing discrepancies within std ranges instead of cutoffs)...."

Do you see that?

A. Uh-huh.

Q. So if you look on 544514, table 6c and 6d, is this a 4-by-4 table that you discussed earlier?

A. It's a little bit of a different format. But it's a classification of subsets by titer in another assay, I guess.

Q. Is this identifying the false

positives?

A. Quite frankly, I don't remember what HN stands for anymore.

Q. HN is the plaque reduction neutralization assay done in Protocol 007?

A. That's what I thought, but I just wanted to make sure. Yeah, it's a listing of numbers. I find these listings not very helpful because the cells, the individual cells become relatively small and so the inferences you can draw from them are very limited.

Q. So when Chirgwin said that we didn't want to give these tables to CBER because they may raise the serostatus cutoff in the wild-type ELISA, what about these tables would indicate that this would suggest that the serostatus cutoff that was proposed at ten should be raised?

MR. SANGIAMO: Again, I object to the preamble of your question.

THE WITNESS: I can't speculate on what Keith might have thought. I look at these tables differently as





indicating absolutely nothing.

BY MR. KELLER:

Q. So when it says --

A. That's why it shouldn't have been communicated, because they're meaningless and they're fine, they appear to say something but they don't really.

Q. I see. So when it says 60, when it's looking at titers between 10 and 20, 20 and 40 and 40 and 80 and identifying the numbers, the subset of negative samples in the PRN versus all samples, the number on percentage, that's identifying a -- discordant results that were positive. Correct?

A. Well, it seems to be identifying a percentage of titers that would be positive by ELISA or positive by neut and negative by the other assay. But it's always very small numbers.

Q. I see. Wasn't CBER concerned about the discordant results around the cutoff?

A. You have to ask CBER that.

Q. So you can't sit here today and





tell me how -- why this -- these two tables, if provided to CBER, may lead them to increase the cutoff as identified by Keith Chirgwin?

A. No, I personally don't think that that would be the case because if they interpret them the way I do, then they would say, okay, at a lower titer, the likelihood is that the standard deviation of the assay is higher and the likelihood for a discordance between two different assays is also higher. That doesn't mean that the assays are not concordant. It just means that you always see the discordance show up at the extremes.

Q. I see. Was there any discussion about any kind of standard that CBER was looking for with respect to what percentage of false positives it would deem acceptable in this concordance analysis?

A. You're assuming here two things. First of all, that there was a standard. The answer is no. Secondly, that these are false positives in one assay or the other. The concordance just means that





they're differently interpreted in the different assays. It doesn't mean that one is false and the other one is wrong. What CBER would also consider is what assay is more robust, more reliable, and in which direction does it classify the samples. And as you have seen from the CBER's -- from CBER's previous comment, they noted that actually the ELISA was more conservative.

Q. I see. But when you compared the two assays, which it appears that Kathy Carbone was asking about in terms of relying upon a serostatus cutoff versus requiring some fourfold increase, she wanted Merck to compare around the cutoff. And so if I'm reading this document correctly, a cutoff between 10 and 20 would result in 24 percent false positive rate, a cutoff between 20 and 40 would reduce that false positive rate to 11.8 percent. Is that correct?

A. No, that's an assumption based on a very small number. And, therefore, you cannot infer that as a general statement. You can just say that in this particular

classification, one assay classified a certain proportion into one direction and the other assay in the other direction. You can't make -- from such a small sample you can't make such a general statement.

May I just come back to your intro? Kathy Carbone is a person, I don't know what she was thinking and what she wanted. You are referring this to me through an e-mail from Keith Chirgwin who is specific as to what Kathy Carbone -- maybe he knows what Kathy Carbone wants. Neither is Kathy Carbone CBER nor am I, Keith Chirgwin, nor do I know what Kathy Carbone was thinking.

Q. You're talking -- you're stating that this is a small sample. This represents all the ELISA assays?

A. Still remains a small sample.

Q. I see. So these percentages, these are the discordant percentages. Correct?

A. Well, in this subset of available samples at the time.

Q. And so another way of saying that are false positive rate. Correct?





A. The false positive rate always assumes that one of them is the truth and the other one is not.

Q. So if you look at the top of this chart, "A further analysis of the post-vaccination titers is provided in Tables 6c and 6d. Table 6d shows the frequency distribution of AIGENT titers for (a) all AIGENT positive post-vaccination samples, and (b) the subset of ELISA negative in AIGENT positive post-vaccination samples." Then it goes to "...relative distribution of Table c indicate that" -- let me go back to this. Let me strike that.

Do you recall any discussion at Merck that CBER was concerned that the discordant false positive rate be below a certain percentage?

MR. SANGIAMO: Object to the form.

THE WITNESS: Beyond what I just read in this e-mail, no.

BY MR. KELLER:

Q. Is it fair to say that based on





the data that's on this chart, that a titer at 40 or above would have had a false positive rate of 3.4 percent based on this chart?

A. Yes, that would be wrong.

Q. Why is that wrong?

A. Because you're extrapolating from a small band 40 to 50 -- 40 to 80, sorry, to the whole behavior and you see that it actually changes and that the sample size gets larger, too.

Q. So when it says 20 -- titer 20 to 40 and it says percentage 11.8 percent, again, you're saying that's not a false positive rate for that range?

A. It's a rate of discordance between the two assays.

Q. I see.

A. At that particular very narrow bandwidth.

Q. I see.

A. In this particular sample which may not apply to any other sample.

Q. So your testimony is that this analysis has no relevance to whether or not





the serostatus cutoff is correct at 10?

A. It shows -- it shows how the two assays, so the answer is no. It shows that the two assays show a certain discordance and that the discordance is larger around the cutoff, as you would expect. But it does not necessarily imply that one cutoff is better than the other. In fact, the other part that CBER noted is that using the 10 cutoff in the ELISA moves you in a more conservative direction.

Q. So is it fair to say from this chart, that as you raise the cutoff, the discordant results go down?

A. That's fair. So you make a very reliable assay more concordant with a very unreliable assay.

Q. So is it fair to say that the discordant results, if you increase the titer from 10 to a range of 10 to 20, would go from 24 percent to a range of 20 to 40 down to 11.8 percent?

A. No, that's a -- that is -- you're extrapolating too much and generalizing

from a distribution in a small sample size.
Q. I see.
A. You would have to build a confidence interval around that. If you think of it in terms of a confidence interval, it could be much wider.
Q. So as you sit here today, Dr. Schodel, it's your testimony that you have no idea why Keith Chirgwin was concerned that by providing these tables to CBER, that they would increase the serostatus cutoff?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't know what Keith was thinking, but I don't share his concern.
BY MR. KELLER:
Q. I'm sorry, did you review the draft response that was going to go to CBER with respect to this justification for the serostatus cutoff?
A. I don't know. I mean, I had -- you know, I had Luwy in there who was a very good clinical monitor, and I generally relied





on my people doing work. So I don't know whether I reviewed it in detail.
Q. Who would be the one that was responsible for signing off on the response to CBER with respect to this issue of serostatus cutoff?
A. That's an interesting question that I can't answer, because probably -- again, I'm speculating. Probably Keith Chirgwin and the lab, but I'm not sure.
Q. It wasn't you?
A. Oh, certainly not.
Q. And it wasn't Dr. Musey?
A. Not directly. He's responsible for the clinical data in there.
Q. So if you look at 544515 which is this draft response to Merck regarding --
A. Which one is that, the next one or --
Q. It's Exhibit 544515.
MR. SANGIAMO: Still within 12.
BY MR. KELLER:
Q. Still in Exhibit 12.
A. Okay.





Q. Here's a draft, and I'll represent to you that this ultimately became 086 for the record. Under 1 on the first page it says, "CBER request that Merck provide additional justification for the cutoff chosen for the Mumps" --
A. Where are we now, I'm not following you?
Q. The first page.
MR. SANGIAMO: We're on this document. Jeff, do you intend to give him a chance to read this --
MR. KELLER: No, I'm just going to go through --
MR. SANGIAMO: -- two-page document?
MR. KELLER: The topics are very general.
MR. SANGIAMO: Are you going to ask him questions about it?
THE WITNESS: If you're going to ask me questions, let me read it, otherwise I'm not going to answer your question.





BY MR. KELLER:
Q. Take all the time you need to read it if that's what you need to do for me to ask you if you recall seeing this document?
MR. SANGIAMO: Is that the only question, whether he recalls seeing it?
MR. KELLER: I have some other questions.
MR. SANGIAMO: Well, then he needs to read it.
BY MR. KELLER:
Q. Go ahead, you can read it. It's a two-page document. Go ahead.
A. This document I have is much longer.
Q. The cover letter.
A. So you just want me to concentrate on the cover letter here, not on the -- not on where it --
Q. We'll get there in a minute. If you want to read the attached response, go ahead.
MR. SANGIAMO: Jeff, is it your

representation that this is the document that was submitted to CBER?

MR. KELLER: It's a draft.

MR. SANGIAMO: It's a draft, okay. I thought you said it was a document that was submitted.

MR. KELLER: I said for the record this draft is what was submitted as 086.

THE WITNESS: Excuse me, I didn't hear that last one. The ultimate one submitted was different from this one?

BY MR. KELLER:

Q. I'm asking if this is the one that was submitted to you, if you reviewed it? Let me know when you're ready, sir.

A. There's obviously -- there's still questions in there and so...

Q. It's a draft.

A. Okay.

Q. If you look on the cover letter, the draft cover letter to CBER under "With focus on the following issues," it says, CBER





requests that Merck provide additional justification for the cutoff chosen for the Mumps wild-type ELISA comparing the ELISA cutoff to the AIGENT assay cutoff and specifically to provide.

Do you see that?

A. Uh-huh.

Q. And so the attached -- the next page under B, "Identification of individual titers in relative range around cutoffs of both assays in order to confirm that both assay are characterizing sera in a comparable fashion."

Do you see that?

A. Yes.

Q. Then Merck attaches its response. Correct?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. This is a draft response?

A. I don't know whether this was sent to the agency, but this is a draft of what would have eventually been sent to the





agency.

Q. I just want to turn your attention just to the conclusion that's drawn in this draft at 544524. I understand it's a draft. Here it says, Conclusion: There is good agreement between the Mumps wild-type ELISA and the AIGENT assays in terms of serostatus classification when using a cutoff of 10 units in the Mumps wild-type ELISA and a cutoff of 1 to 32 in the AIGENT assay.

Do you see that?

A. Yes.

Q. What -- is there a scientific term for good agreement? What does good agreement mean? Let me strike that.

What does good agreement mean in the context of this analysis, if you know?

A. I don't know a specific number, but apparently they showed the degree of agreement, and it looked reasonably high, and so they called it a good agreement.

Q. And so the discordant results that were in charts 6c and 6d that had 24 percent discordant results for a serostatus





cutoff between 10 and 20, and that went down to 11.4 percent with a serostatus cutoff from 20 to 40, that was considered a good agreement?

A. You're extracting an inappropriate comparison that is based on small numbers and just a subfraction of the total results. If you look at Table 8 here, for example, you see the expected percentages of misclassified samples by the assays standard deviations from the cutoff, that gives you a better measure of what would be expected and what would be observed.

Q. So what standard deviation -- I mean, you have zero to three. Right?

A. Yes.

Q. And so in the previous e-mail, in the e-mail that attaches this document, there's a discussion here that at three standard deviations we have more discrepancies than that can be explained by just assay variability. That seemed to be a big issue to --

A. Joan Staub who was not --

MR. SANGIAMO: You have to let Mr. Keller finish his question.
MR. KELLER: Let him answer.
MR. SANGIAMO: No, no, no. That's a big issue, what's the rest? To and then what comes after that?
MR. KELLER: Can you read back my question?

- - -

(The court reporter read the pertinent part of the record.)

- - -

BY MR. KELLER:

Q. -- to Manal Morsy, the regulatory liaison.

So my question is, three standard deviation, is your testimony that that's not significant?

MR. SANGIAMO: Object to the form.

THE WITNESS: I didn't say that. But what I said is that she may not have looked at the complete analysis that is presented here in this draft





and that may be further enhanced in the ultimate -- what was ultimately sent because I'm not sure that the analyses were even complete here. So you're showing me something that at the time was not completed.

What I was starting to point out to you is that it's quite normal to see that as you get closer to the cutoff and no standard deviations, you would expect to see a higher mismatch. At no standard deviation it's 50/50, and then it goes up. And so I'm not clear to -- it's not clear to me that based on the analysis I see here in this draft Manal's concern is valid.

MR. KELLER: Let me mark as Exhibit 14.

- - -

(Exhibit Schodel-14, E-mail chain with attachments, Bates MRK-KRA00561199 - 00561209, was marked for identification.)

- - -





BY MR. KELLER:

Q. Exhibit 14 is a document that bears Bates stamp number 561199 through 561209. This is a series of e-mails and two attachments. And if you look at the first e-mail that's sent from Manal Morsy to Keith Chirgwin and you, Dr. Schodel, on May 31, 2002, can you tell me, do you recall seeing this e-mail?

A. I don't recall seeing this specific e-mail, but if I read it, I can probably figure out what it means.

Q. Sure.

A. Okay. I haven't read this attachment yet.

Q. We're not even going to look at the attachment. So let's just talk about the e-mails.

In here Dr. Manal -- I'm sorry. Dr. Morsy sent you and Dr. Chirgwin an e-mail and cc'd Joe Antonello, Dr. Antonello and Dr. Hartzel, Dr. Schofield. Is Schofield a doctor?

A. Schofield.





Q. Schofield. Is he a doctor?

A. Yes, he is. I think anyway.

Q. And here Manal Morsy is saying, "The attached is completed based on...," this is on 561200 which is her May 31, 2002, e-mail, "The attached is completed based on feedback and edits received and incorporated today (unless Keith, Florian...," that's you, Dr. Schodel, "...or Tim send in comments before noon tomorrow Friday)." It goes on, "I plan to finalize for submission early next week pending auditing sign off for attachments 2 and 3 (attachment 2 was I believe previously audited but is modified by deletion of Tables 6c, 6d and associated text)."

Do you see that?

A. Uh-huh.

Q. So that table that we went through earlier has been deleted from what was to be submitted to CBER?

A. Yeah, but read further down.

Q. I will.

A. The information is still --

Q. Yes. Joe - I removed Tables 6c

and 6d and associated text you re-inserted in attachment 2 to avoid confusions since Table 6d has different ELISA titer grouping used to show number of discrepancies between the AIGENT and the ELISA within each group than what we -- you have -- than which you have used in attachment 2 -- Table 2 of attachment 3, (titer groups in the deleted Table 6d are ELISA titers of 10 to 20, 20 to 40, and 40 to 60, et cetera, whereas they are based on sd from cutoff in table -- in attachment 3 and so are grouped differently: ELISA titer groups of 1sd (10 to 14), 2sd (14 to 20), 3sd (20 to 28) et cetera).

Do you see that?

A. Uh-huh.

MR. SANGIAMO: I just want to note for the record, there were a couple of points where you didn't read the right word but we can go back to the document as need be.

MR. KELLER: Sure.

BY MR. KELLER:

Q. So here Joe Antonello, the





biostatistician working on this analysis between the PRN assay and the wild-type ELISA assay who wanted to insert these two tables in the way that it was presented, it was removed by Manal Morsy, the liaison, FDA liaison because she thought it may encourage CBER to increase the cutoff, and so she had them replaced with a different way of identifying that data from using groups of cutoffs to using groups of standard deviations. Is that a fair statement?

MR. SANGIAMO: Object to the form.

THE WITNESS: There's too much speculation in there. She had removed the tables because, as I read it, the information is adequately captured in the alternative table and actually better understandable.

BY MR. KELLER:

Q. I see. And so why didn't they just put it in both tables?

MR. SANGIAMO: Object to form. Calls for speculation.





THE WITNESS: Why would you submit -- why would you submit redundant information to CBER and make it hard for them to interpret it?

BY MR. KELLER:

Q. Well, evidently is it fair to say that Mr. Antonello, this biostatistician, wanted that data in here?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: I don't know that for sure. He may not have noted that he's already provided the same information on another table as well.

BY MR. KELLER:

Q. He evidently re-inserted it after Manal Morsy took it out in the last draft.

A. I can't speculate.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. You can't speculate. I see. So Manal Morsy goes on to say, "I understand that





you have a desire to include them but you have very nicely captured all the discrepancy information and how it is distributed relative to the ELISA 10 cutoff in table 2 of attachment 3 so the information in the end is included, reflected accurately and completely to CBER and that's what's critical and important."

Do you see that?

A. Yes.

Q. But it's just included in the different format that the biostatistician didn't agree to. Correct?

A. No.

MR. SANGIAMO: Object to the form.

THE WITNESS: You're speculating.

BY MR. KELLER:

Q. I see.

A. We don't say that -- she doesn't say that he didn't agree to it. She just -- I mean, we often have people who provide a data dump. They generate all kinds of tables. And at the end, you have to make

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a call. It's her call because she's the regulatory liaison to figure out which ones are more useful.

Q. I see. So then she goes on, "Please review to insure that no statements were accidentally left behind in attachment 2 that are specific to these two tables."

So she's pretty adamant about removing his description of what was in those tables from what was provided to CBER. Is that a fair assessment?

A. No, not as far as the description goes. In fact, she makes extra sure that no statements are in there that would wrongly refer to the tables, not to the now attached whatever number two was. Just a matter of editing the document at the end to make sure that whatever statement is in there is accurate.

Q. I see. And so -- okay.

MR. KELLER: Let me mark as Exhibit 15.

THE WITNESS: May I just point out to you that actually the content





of these tables is in the document, here in this draft, 3a and 3b.

BY MR. KELLER:

Q. Where is the content of that information in these documents?

A. The tables that you were particularly asking about seem to be Tables 3a and 3b here.

Q. Do you know whether or not this was provided to CBER?

A. Do you know whether it was provided to CBER? I don't.

MR. SANGIAMO: Doctor, you just have to answer his question.

BY MR. KELLER:

Q. I do.

A. While you're looking, I'll take another short break. Is that okay?

Q. Sure.

VIDEOGRAPHER: Off the record at 4:15. This ends disc number five.

- - -

(A recess was taken.)

- - -





VIDEOGRAPHER: Back on the record at 4:21. The beginning of disc number five -- six.

MR. KELLER: Let me mark as the next exhibit, Exhibit 15 which had previously been marked with -- by Fisher Exhibit 17.

- - -

(Exhibit Schodel-15, E-mail chain, Bates MRK-KRA00791315 - 00791319, was marked for identification.)

- - -

BY MR. KELLER:

Q. Nor the record, Exhibit 15 is a document bearing Bates stamp number 791315 through 19 which is a series of e-mails.

Doctor, I'd like to direct your attention to the last e-mail on page 791319. This is an e-mail from Joe Antonello to Keith Chirgwin, and you're cc'd on this. The subject is Comparing Mumps wild-type ELISA and AIGENT Assay, June 29, 2004. If you want to take a minute to review that.

A. Okay.





Q. Here this is an e-mail -- and Keith -- Joe was saying, writing to Keith, "In response to your MVX...," that's a voicemail system that Merck had at the time. Correct?

A. Yes.

Q. So he got a -- this appears to be a voicemail from Keith Chirgwin who he's responding to. In the middle of the page it says, In that response, we contended that there was reasonably good agreement between the two assays in terms of serostatus classification when using a cutoff of 10 Ab units in Mumps wild-type and a cutoff of 1 to 32 in the AIGENT assay, so I am concerned when you say that the two assays are discordant around the cutoff. Concluding that the two assays agree reasonably well was important for the purpose of arguing that the ELISA was acceptable substitute for the neutralizing assay.

Do you see that?

A. Yes.

Q. Does that lead you to believe that Merck is arguing that they have

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correlated their plaque reduction neutralization assay to the ELISA assay?

A. No, it means exactly what it says, that a serostatus classification concordance testing was done and that the using the cutoffs of 1 of 10 and 1 to 32 there was reasonable concordance.

Q. And so Merck wanted to use that as a substitute, so to rely upon the ELISA as a substitute for the neutralization assay?

A. Those are Joe's words. I don't know what he means with a substitute.

Q. I see.

A. I mean, there were two assays used in 007. So ultimately the ELISA was important for that particular study and it was also used for the ProQuad filings. So obviously CBER accepted that the ELISA was a reasonable assay to measure mumps activity.

Q. I see. Here he says, "I do agree with your key points...," and he's responding to the Keith Chirgwin, "We don't really know what a clinically protective level is in either assay...."





Do you see that?

A. Yes.

Q. He's talking both about the wild-type ELISA and Merck's PRN assay as used in Protocol 0097. Correct?

A. Probably, yes.

Q. Do you agree with that statement?

A. Yes.

Q. So if you see on the next e-mail on 791318, dated June 29, 2004, later on that evening Chirgwin responds to Dr. Antonello, and you're cc'd on here, Dr. Schodel, "Thanks Joe. Just to clarify, I understand that the PRN and ELISA track fairly well and this is what I conveyed to Steve Rubin. The question is to what degree are these assays concordant."

Do you see that?

A. Yes.

Q. Do you understand what he meant by the term "concordant"?

A. No.

Q. He goes on and says, He was suggesting specific criteria for concordance





when I am not sure we could meet.

And so this is Steve Rubin saying that he wants specific criteria for concordance.

His suggestion was that we focus on sera with low antibody titers just above the ELISA cutoff, and that they would like to see no more than 10 percent of such ELISA low positive sera score negative to PRN assay.

Do you see that?

A. Yes.

Q. So isn't that what Table c and Table d identify?

MR. SANGIAMO: I'm going to object to your reading of that, not just because there were a couple of mistakes in there, but you also inserted something that was not from the document itself.

BY MR. KELLER:

Q. I'll rephrase it if you need to. "His suggestion was that we focus on sero with low antibody titers just above the ELISA cutoff, and that they would like to see no





more than 10% of such ELISA low positive sero score negative in the PRN."

Do you see that?

A. Yes, I see that.

Q. Isn't that exactly what Table c and Table d were identifying?

A. No. It overlaps with that statement, but it's not exactly the same.

Q. I see. How does it overlap?

A. Well, it overlaps by showing in a selected small sample how the low antibody titers just above the ELISA cutoff are scored in the PRN.

Q. Then he goes on and says, I do not recall whether we ever did such a subset analysis with low positives - this seems like a problematic approach as the low percentage of "false-positive" would depend on which specific sera are selected for inclusion in such an analysis.

Do you see that?

A. Yes.

Q. So this term "false-positive," what do you understand that to mean?

A. Well, I understand that to mean that they saw something -- a different result in one of the assays than in the other assay which does not -- doesn't speak to absolute truth or falseness. It just simply speaks to the level of discordance or concordance.

Q. Let's go to the first page of this e-mail. Here Michael Dekleva -- who is Michael Dekleva?

A. Mike at the time, he was at some point regulatory and clinical. And before that I think he was quality assurance and MMD. So I don't know what he was at that time.

Q. I see. So he sends you an e-mail on July 2, 2004, regarding comparing mumps wild-type ELISA or WT ELISA and AIGENT assay. You understand it to refer to the ELISA and PRN assays in Protocol 007?

A. Yes.

Q. Alison and I are pulling it together. In what we've been able to find so far, there doesn't seem to be any documentation that CBER actually concurred





with our recommendations regarding the WT ELISA and choice of less than 10 Ab unit cutoff. We requested their concurrence, but never received a response.

It goes on, in order -- In looking at the old documentation it's clear that CBER was very interested in the PRN assay for evaluating persistence. Afterwards we claimed that there was strong concordance between the PRN and wild-type ELISA, although around the cutoff (less than 10 Ab) there's a greater chance of seeing positive results with the PRN rather than the ELISA.

Do you see that?

A. Yes.

Q. And so this strong concordance, is that the analysis that you reviewed earlier where they were looking at whether or not the two assays --

A. Yes.

Q. It goes, Perhaps because of that there were slightly higher seroconversion rates reported with the wild -- WT ELISA versus PRN in the 007 study (something like 94





versus 92 percent). Then he writes is that significant with a question mark. Nonetheless, we opted for use of the wild -- WT ELISA for future studies.

Do you see that?

A. That's how he summarized the situation, yeah.

Q. And those future studies were the ones that were done for ProQuad?

MR. SANGIAMO: Objection. Calls for speculation.

BY MR. KELLER:

Q. Do you understand that's what he's talking about?

MR. SANGIAMO: Calls for speculation.

THE WITNESS: I don't know.

BY MR. KELLER:

Q. You don't know. And finally it goes, "So...we are pulling the information together, including all prior CBER communications. It may be that Steve Rubin is simply 'coming up to speed,' or it could be that he's trying to understand our rationale





for selecting an assay that while more precise and easier to perform, may overestimate seroconversion rates relative to their 'preferred' (?) PRN assay."

Do you see that?

A. Yes.

Q. So here -- is Mike Dekleva a doctor?

A. No.

Q. Here he's saying that the wild-type ELISA may overestimate seroconversion rates with -- compared to the PRN assay. Do you see that?

A. I think he's just speculating. We actually have just seen data to the converse.

Q. You don't agree with that?

A. No, I don't agree with that.

Q. It goes on to say, I spoke with Joe Antonello yesterday, and he re-emphasized that the decision with the PRN assay was very poor, and he felt that it was really hard to say whether the differences in the data sets were significant - influenced to a great

extent by the variability in the PRN assay -- PRN data.

Do you see that?

A. Yes.

Q. SO do you agree with Joe Antonello that the PRN assay was very poor with respect to precision?

A. It was certainly relatively worse than the ELISA which is one of the reasons why CBER also preferred the ELISA.

Q. I see.

A. It's generally harder to make a biological assay like a PRN assay as reliable as an ELISA. It's well known in the art.

Q. So do you agree that the PRN assay was very poor?

A. No, those were Joe's words or maybe they're Mike's interpretation of Joe's words. I don't think it was very poor, but the precision, it's a relative statement. If you compare it to the wild-type ELISA, it may appear very poor because the ELISA is much more reliable.

Q. Wasn't Merck comparing the





cutoffs of the wild-type ELISA with the PRN cutoffs in order to confirm that the cutoff used in the ELISA was accurate?

A. In order to satisfy a CBER desire. You cannot measure -- you cannot confirm that something is accurate with a lot of precision with something that in itself is imprecise.

Q. I see. That's what happened with Protocol 007. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's what happened not necessarily specifically for Protocol 007. That is what will happen every time you use a biological assay to try to measure concordance at the extremes.

BY MR. KELLER:

Q. And so here on July 3rd, the next day, 2004, Dr. Schodel, you responded to Michael Dekleva. And here you write, "Dear Mike, Thanks - I distinctly remember a conversation with Kathy Carbone in which we





closed out the issue - which allowed us to proceed with MMR and PQ studies..."

A. Where is that?

Q. The top of this?

A. Oh, here it is, yeah.

Q. "...at the time - hope this was captured."

MR. SANGIAMO: Let him read.

BY MR. KELLER:

Q. Sure. PQ there represents ProQuad. Correct?

A. Yes.

Q. You say, "Agree with Joe - could not overemphasize the weakness of the PRN (50% specifies!!!!!!)."

Do you see that?

A. Yes, I see that.

Q. So is it your opinion that the PRN assay was weak and only had 50 percent specificity?

A. I think it had its weaknesses. The 50 percent is a partial misquote. There was not -- as we pointed out earlier, there was not a formal specificity analysis





performed, so I couldn't know what the exact specificity was. What I was reacting to was that in a very, very small sample, in half of the samples some of the titers were reduced by unspecific reagents such as measles extracts, rubella extracts and Varicella extracts that summarized in the validation report does not necessarily mean that the overall specificity is only 50 percent because that wasn't formally analyzed. It just means exactly that, that there are other factors that contribute to the variability of the assay. And, again, didn't matter for 007 because it was a comparative study.

Q. Well, Doctor, you seem to be very well versed in the definition of specificity. So here you write 50 percent specificity with six exclamation points. So at this time that you wrote this, you agreed with Joe that the precision was very poor and that you could not overemphasize the weakness of the PRN assay. Is that a fair statement?

A. Yes, but I just explained to you that the specificity of 50 percent here

does not refer to a specific specificity analysis as could have been performed that wasn't performed.

Q. I see.

A. So I don't know what the real number was. I didn't know at the time.

Q. So the 50 percent specificity you're talking about is whether or not the neutralization that occurred in this PRN assay was the result of mumps -- I mean, measles or rubella?

A. Not at all. No. What I was reacting to was a data mentioned in the summary of the validation report which essentially states if you reread it, that in a number of sera, in half of them the titer could only be reduced by mumps so that half of them were completely specific. And the other half, some of the plaque reduction, I don't even know whether it's the titer, just the plaque reductions seemed to be reduced by unspecific reagents. That does not yet mean that the assay overall has a 50 percent specificity. I just interpreted that as





meaning that half is 50 percent. It is a sloppy expression which I should probably not have used, but it does not reflect on the overall specificity, nor does it matter.

Q. So it's your testimony today when you say specificity, you didn't really mean specificity?

MR. SANGIAMO: Object to the form. It's argumentative. He's already addressed this.

THE WITNESS: My testimony today is that I just translated four out of eight with something that doesn't translate into specificity as 50 percent.

BY MR. KELLER:

Q. So you're talking about with something in the clinical study report?

A. No, it's in the validation report for the mumps neutralizing assay.

Q. When did you review that?

A. I must have reviewed it around that time, but because that question arose again, I looked it up and that's what it was.





Q. When did you look it up?

A. I looked it up whenever it was, Monday.

Q. So you went back and looked up that on Monday?

A. Because I wanted to know what I had referred to at the time. I don't -- I'm sorry, maybe you're perfect, but I don't remember everything that I said in 2004.

Q. That was after you spoke to your lawyers. Correct?

A. No, not at all. It was after I saw this e-mail and they asked me what I meant.

MR. SANGIAMO: Hold on. Dr. Schodel, you can't discuss our conversations.

BY MR. KELLER:

Q. So the validation document that you reviewed, that was a validation document for the plaque reduction neutralization assay?

A. Yes.

Q. So it was looking at the specificity of other agents. What other





agents was it looking at?

A. It was not testing, formally testing specificity so I shouldn't have used that term. But it was using rubella, Varicella -- rubella, measles and cell extract, uninfected cell extract.

- - -

(Exhibit Schodel-16, Excerpted document of Clinical Study Report, Bates MRK-KRA00001270 - 00001466, was marked for identification.)

- - -

BY MR. KELLER:

Q. I'm going to mark as Exhibit 16 a document that bears Bates stamp numbers 1270 through 1466. This is an excerpted document of the entire clinical study report. It doesn't have all the attachments. But I ask you if you recognize this as the clinical study report that was used for Protocol 007 and was submitted to CBER?

A. It looks like it.

Q. Let me direct your attention to 1328 of the clinical study report. What is a

clinical study report?

A. A clinical study report is a report on the data generated in a clinical study.

Q. This is the backup data support, the label change for Protocol 007 to reduce the potency from 4.3 to 4.1?

A. That's certainly part of the information. I suspect it's not all the information.

Q. There's also a supplemental BLA that goes -- that this is attached to. Correct?

A. Yeah, probably.

Q. Did you ever review this CSR before it was submitted?

A. I don't remember. It depends on the time. I generally reviewed CSRs when I was responsible for them and didn't when I wasn't, so I don't remember. I mean, the direct responsible probably at the time would have been Luwy or another physician. And I would not always have reviewed all the details of a clinical study report. There were a lot of them.





MR. KELLER: Let me mark as Exhibit 17.

- - -

(Exhibit Schodel-17, 10/21/03 Memo, Bates MRK-KRA01638866 - 01639147, was marked for identification.)

- - -

BY MR. KELLER:

Q. Exhibit 17 is a document --

A. That's all you want to know on 16?

Q. We're going to go back to it. Just keep it in front of you.

A. You want me to read it?

Q. No, I'll show you what to look at.

So Exhibit 17 is a document that bears Bates stamp number 1638866 through 1639147. And it's a document dated October 21, 2003, from Mandie Lyon to Dr. Schodel and a bunch of other people, subject: "V205C Protocol 007 Clinical Study Report for Review 2." And there's handwritten documents -- handwritten notes on this and it





seems to appear to be signed by you, Dr. Schodel. Does this refresh your memory that you did review it and made comments?

A. It looks like my handwriting for sure.

Q. Let me direct your attention back to Exhibit 16 which is the formal CSR and I will represent to you that was submitted to CBER, according to Merck. If you go back to 1328 -- let me back up a little bit.

Let me go back to 1325 and start there. Here under 5.5.4.1.

A. Wait, wait, wait. On 1325 I have 5.7.3.3.

Q. I apologize, I'm looking --

A. Oh, oh, oh. Okay.

Q. It's the center number, not the one on the right. It's a different number. I apologize. Let me know when you're there.

A. I think I'm there.

Q. Here at 5.5.4.1 it says, "Anti-IgG Enhanced Mumps Plaque Reduction Neutralization Assay." Do you see that?

A. Yes.





Q. That's the PRN assay that was used in Protocol 007. Correct?

A. Yes.

Q. If you look on 1328 there's a topic of "Specificity." Is this a summary of the specificity analysis that Merck did on Protocol 007, the PRN assay?

A. Yes, I think it is. It is here.

Q. Is that what you're relying upon to say it was only 50 percent specific?

A. As I said, I -- this was a bit of an overstatement. But what I translated here was that in that "Absorption with the mock measles or rubella extract yielded similar results, whereas absorption with the mumps extract yielded a further reduction in...3 to 4...." I don't remember whether this is what I based it on. I think it was more the statement in the validation report.

Q. I see.

A. So I don't really remember, I don't remember, but I think that's a little different statement in the validation report. It's a little different than the statement

here.

Q. Fair enough. Let me direct your attention to page 12 -- to 1462. 1461 and 1462 under title 9 "Discussion."

A. Okay.

Q. Here -- actually let me do this: Let me direct your attention -- this is under section 9 "Discussion." What is typically the discussion section in the clinical study report, does that discuss the -- what is that -- the purpose of a discussion section?

A. Well, the purpose of the discussion section is to discuss any issues that need further discussion. It could be the endpoints, it could be the assays, it could be the selection of the population in which something was done. It's not a very narrow definition of that.

Q. Let me direct your attention to 1463 in the last paragraph. Let me know when you get there.

In this paragraph Merck is representing to CBER that, The mumps wild-type ELISA used in this study was shown to





correlate with the PRN assay, and previous studies have established a strong correlation between the development of mumps-specific neutralizing antibodies and vaccine efficacy. Therefore, the mumps PRN assay and ELISA results from this study support the effectiveness of M-M-R II containing a mumps virus potency of no more than 4.1 log TCID and the lowering of the mumps virus end expiry potency from the currently assigned potency of 4.3 to no less than 4.1 log TCID.

Do you see that?

A. Yes, I see that.

Q. So Merck submitted to CBER that it correlated its wild-type ELISA assay to its PRN. Does that surprise you?

A. No, as requested by CBER.

Q. So Merck is representing as part of the CSR that, in fact, it is correlating its wild-type ELISA assay to its PRN assay to support the effectiveness of MMR II?

A. Well, indirectly because the immunologic comparison between these different preparations of MMR with different





mumps potencies have relatively similar immune responses and, therefore, would expect -- be expected to protect in a similar way. The assay is just an adjunct. It's not -- since there is no correlative protection in the assay, it just shows that they're similar.

Q. Well, you testified there's a difference between the concordance, between a PRN assay and ELISA assay and a correlation between the two. Here Merck is representing that it correlated those two assays, isn't it?

A. I didn't say -- while the difference is -- the difference I pointed out was more in how you look at the comparison of two assays. It doesn't -- I didn't specifically say that one is worse or better than the other. It's just how you do things. But I never said that there was a correlation between any specific titer or any specific assay and the prevention of disease.

Q. Are you surprised to see Merck representing to CBER that it did correlate those two assays, the PRN and wild-type ELISA?





A. Well, you already know that CBER asked that that be done and so, of course, it was done. Because it was done it had to be summarized in a clinical study report.

Q. You understand that the use of these two assays was to show that the vaccine -- to support vaccine effectiveness?

A. Among other data, yes.

Q. So vaccine effectiveness means that the vaccine works in the real world, correct, based on your definition?

A. That's correct, but that's not based on the PRN assay result.

Q. So when you agreed with Joe that the PRN assay that's being used to correlate to the wild-type ELISA is very poor and could not overemphasize the weakness of the PRN assay, you think that's appropriate to submit to CBER that the wild-type assay was correlated to the PRN assay?

A. Yes. It's actually only very weak around this particular definition of a cutoff. It's not overall very poor. That's

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not what anybody said. And therefore, overall the correlation is pretty good. Most people are vaccinated at very high titers and then it would have an almost perfect correlation.

Q. So if Merck submitted this PRN assay as support and to be considered as a surrogate of vaccine effectiveness, would that cause you concern?

MR. SANGIAMO: Object to the form.

THE WITNESS: It's not what Merck has done as far as I can tell.

BY MR. KELLER:

Q. Let me show you the BSLA -- SBLA which I'd like to mark as Exhibit 32 -- I'm sorry, Exhibit 18.

- - -

(Exhibit Schodel-18, Supplemental Biologics License Application, Bates MRK-KRA00000032 - 00000139, was marked for identification.)

- - -

BY MR. KELLER:

Q. Exhibit 18 bears Bates stamp





number 32 through 139. Again, this is a excerpted document, doesn't have thousands of pages, it has the supplemental biologics license application.

Doctor, have you seen this document before?

A. Probably, but I don't remember.

Q. Let me direct your attention to Bates number 111.

A. 111?

Q. Yes. Under section 2.5.1.5.3, Study Endpoints, what is a study endpoint again, Doctor?

A. It's a measure taken in the study.

Q. Here it says, The Mumps neutralizing antibodies were measured immediately prior to vaccination and 6 weeks postvaccination using the plaque reduction neutralization assay. The PRN assay was used as a priority endpoint because it is a functional assay that can measure the ability of vaccine-induced immune response to inhibit viral replication in vitro, and can,





therefore, be considered a surrogate for vaccine effectiveness.

What do you understand surrogate of vaccine effectiveness to mean, Doctor?

A. I think that's a bit of a surrogate for vaccine. I mean, it's supportive data that the vaccine has not changed in that context of the comparison. You can use it as vaccine effectiveness because the vaccine has shown effectiveness. The immunogenicity to it has not changed and, therefore, you would expect the same effectiveness does not mean that it directly correlates with effective.

Q. I see. But isn't Merck representing --

A. The surrogate simply means that you can't measure the original, so it means it stands in for.

Q. Because you couldn't do an efficacy study today, that's unethical?

A. That's correct.

Q. So the best assay that you can use is a surrogate of vaccine effectiveness.





Correct?

A. Any assay that you can use you would try to use as a surrogate for vaccine effectiveness showing that the vaccine hasn't changed since it's been started to use and looking at the field effectiveness data that you constantly get. So it doesn't necessarily have to be the best. It is what the best effort that you can make. And in that regard both ELISA and both the PRN were used to support that the vaccine had not changed.

Q. I see. And so you're not concerned that any assay that you considered to be -- that you stated you cannot overemphasize the weakness of this assay, you agreed with Joe Antonello that it was very poor with regard to precision is being represented by Merck to CBER as a surrogate for vaccine effectiveness?

A. No, that doesn't concern me because you're taking my statements of its weakness out of context. It's not weak across the board. It's very precise in

estimating high titers, for example.
Q. It's just weak around the cutoff?
A. It's relatively weaker than the ELISA.
Q. I see. And Merck in the clinical study report stated that it correlated its wild-type ELISA to its PRN assay. Correct?
A. That's correct.
Q. Do you know that Merck was able to convince CBER to rely only on wild-type ELISA assays going forward based on this correlation analysis?
MR. SANGIAMO: Object to the form.
THE WITNESS: That is an assumption that -- you make too many assumptions in your question. Even in the document that you showed me, CBER itself provided other reasons why it would rely on the ELISA and which you have read and we talked about. So I would certainly not support the notion





that CBER accepted that solely on the correlation. That being said, the correlation wasn't all that bad.
MR. KELLER: I see. Let's take a break.
VIDEOGRAPHER: Off the record at 4:56.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: Back on the record at 5:08.
- - -
(Exhibit Schodel-19, Article draft, Bates MRK-KRA00032482 - 00032519, was marked for identification.)
- - -
EXAMINATION
- - -
BY MR. MACORETTA:
Q. All right. Good evening, Dr. Schodel. We met earlier. My name is John Macoretta. Mr. Keller had to leave so I'm going to finish up with a few additional





questions this evening.
A. Okay, John.
Q. I'm going to show you what we just marked as Exhibit 19, which I believe is a draft of an academic article for which you were one of the authors. Correct?
A. Yes.
Q. Do you remember working on this?
A. I saw it at some point and I made some comments on it, yes.
Q. So you were not the principal drafter, I take it?
A. No.
Q. Who was?
A. I suspect it was Tim Schofield, but I don't really know.
Q. Who is the first person -- the first author is C. Marchant. Who is that?
A. I don't know.
Q. Not a Merck employee I take it. Right?
A. I really don't know. I don't know. I don't know.
Q. Okay. Fair enough. I want to





talk to you towards the end, if you go towards the end, the Bates numbered page ending in 517.
A. 517. Okay.
Q. If you see at the top there's a sentence that's highlighted with a comment, it says, "Comment (FS12)." Take a look at that comment.
A. Yeah, I can't read this, it's too small print.
Q. I don't know how to help you with that. I mean, I can read what the comment says and then your lawyer can tell you if I got it wrong, is about the only other solution I have to that.
MR. SANGIAMO: That's fine.
BY MR. MACORETTA:
Q. I can read it. So can you read the sentence that's talking about -- that starts with "The mumps wild-type ELISA..."?
A. Yes, yes, yes. I can read part of it, but I'm not sure I read the whole thing right.
Q. Why don't I do the whole thing

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and then your lawyer will tell me if I got it wrong.

It says, "Comment (FS12): Did we really do a correlation study and if so, where is it. I don't think I have ever seen the data. If not, remove specific statement and only cite literature."

So you're asking about whether a correlation study was done between the wild-type ELISA assay and the PRN assay. Right?

A. I didn't remember that, yes.

Q. And the answer was you didn't do a study. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I'm not sure anymore whether I -- I mean there was this concordance analysis and a number of other analyses, so there was some sort of correlation established. They could have simply shown it to me at the time. So I -- that might have satisfied me actually.



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BY MR. MACORETTA:

Q. So let me show you -- well, let me show you the next draft where this is -- I can show you the next draft where this came out. We'll show you what we're going to mark as Exhibit 20.

- - -

(Exhibit Schodel-20, 10/28/11 E-mail with attachment, Bates MRK-KRA00046402 - 00046441, was marked for identification.)

- - -

BY MR. MACORETTA:

Q. If you go to Page Number 28 of the draft which ends in Bates number page 430, if you look one, two, three, four, five, six, seven lines from the bottom, you'll see at the end of the line is the last two words of the previous sentence "dose and controls," and then you'll see that the sentence you have was shown to correlate the PRN assay was changed in this draft. Do you see that?

A. Yes.

Q. The Footnotes 29 and 30, if we look to them, cite some other literature.



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They do not cite any correlation study by Merck. Right?

A. Yes.

Q. So does that indicate to you that there was no correlation study by Merck?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, not necessarily. That's one of the interpretations. The other interpretation was that it hadn't been published or wasn't included and, therefore, they preferred to follow my advice if they can't produce cite literature. You just wanted to have a reference for what was done. That was all I was asking for.

BY MR. MACORETTA:

Q. Whatever reference they used was not some study that was done by Merck?

A. That's irrelevant. I just wanted to have a reference as to whether they correlate or not.

Q. The correlations we're using,



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numbers 29 and 30, are papers done in 1984 and 1992. Right?

A. Well, this is when this was a hot topic. It's only become one with you again.

Q. I'm going to go back to the -- we'll use the later draft, Exhibit 20. At the bottom of -- the last line on the page we were looking at, there's a sentence that --

MR. SANGIAMO: I'm sorry, John, what page is that?

BY MR. MACORETTA:

Q. Page ending in 430, could you read for us the sentence that starts with the word "Although" on the last line there?

A. Sure. "Although being considered the 'gold standard' assay for the measurement of mumps-specific neutralizing antibodies...," gold standard in brackets, "...PRN assay is technically cumbersome and requires a large volume of serum which hampers its use in a large clinical study."

Q. Do you agree with that statement?

A. Yes, that's at least one of the limitations.

Q. Well, did you agree that the PRN was considered the gold standard assay for measurement of mumps specific neutralizing antibodies?

A. By some it is. And that's why this is in reference marks. I mean, it's not a -- that's not -- I wouldn't agree with that, but it is considered that by some people.

Q. I'm going to change topics now. I'm going to show you what has previously been marked as Fisher Exhibit 3. We're going to talk about the house standard for a little bit. Now we're marking it as 21, Schodel-21.

- - -

(Exhibit Schodel-21, E-mail chain, Bates MRK-KRA01481843 - 01481846 & 00566614 - 00566623, was marked for identification.)

- - -

BY MR. MACORETTA:

Q. So you can look at all of this





if you want, Dr. Schodel. The only e-mail from you is on the first page. I want to talk to you about that, but I am going to ask you about a couple other things in here. Let me know when you're ready to talk about it.

A. Okay.

Q. So let me start at the back. It talks about on the last page before the attendees, it says, "This is a BSEC assignment from the June 3 BPC meeting." So I'm going to ask you what those acronyms are, BPC and BSEC?

A. So BPC is the Biological Process Council. BSEC, I don't remember exactly anymore what that stood for.

Q. I believe somebody said it was the Biologic Standards Evaluation Committee or something like that?

A. Sounds very reasonable but what those acronyms are after many years, I don't remember it.

Q. Were you on either of these entities?

A. Yes, I was on BPC at times. And I think I was called into BSEC probably





on an ad hoc basis, not permanently. I don't remember that anymore, to tell you the truth.

Q. There's a discussion of house standard. What is the house standard as it relates to the mumps vaccine?

A. Well, the house standard for any vaccine is an internal lot of the vaccine that has been very carefully assigned a potency with more multiples of testing than would normally be used for release to assure relative accuracy. That is done repeatedly over the course of a longer period of time because assays tend to vary over time. And then it is -- this particular lot is assigned a potency out of this testing period. And that particular potency is used to compare the release titers when releasing a vaccine so that you have something that links it back to the manufacturing history.

Q. So the idea is that the lots in the house standard, we know what their potency is supposed to be. Right?

A. At a given point in time.

Q. And when we do an assay and we





test both the new lot and the house standard and we see how the -- what the assay says the house standard is. Right?

A. Uh-huh.

Q. And then we make some correction between what the assay says it is and what we think it's supposed to be?

A. The second one is a -- can be a use. And I don't know whether it is used that way. That would be introducing a factor. Or whether it's just simply a control to establish an expected range in which the new material should run without actually calibrating.

Q. So what does --

A. So I don't know how it was used in this particular case.

Q. Well, this -- the last page talks about "To reach consensus on the M-M-R® II House Standard which is required as part of the move to potency calibration." So what's potency calibration?

A. Well, that would be what I just mentioned. What you initially assumed, that

would be the use of a house standard, not just to control but also to adjust the measured potency because of changes over time so that they're always linked to something which is as much as that's possible for biologics kept constant.

Q. Around this time there's a discussion that the house standard for mumps is going to change, right, that it's going to go up by .1 log?

A. Yeah, and I don't remember the details of that, but remember as we said initially in the explanation for the house standard, was house standards do change from time to time because the material comes to an end. And then you have to have enough left to test it repeatedly to compare it to the new material and to assign a new potency. And in that process there can be changes.

Q. Does that mean that the number of virus particles in -- and I think Mr. Stannard who was here the other day said it's lot nine that is the house standard lot for mumps. I don't know if you know that.





A. No, I don't. I was not in manufacturing. This is way outside of my responsibilities.

Q. So when we talk about changing the house standard potency, does that mean that the number of virus particles in each vial in the house standard lot has change or the assay to measure them has changed?

A. It could be either/or. If the -- so the goal of the effort is always to keep the number in the product constant to the best of our knowledge. Now, in the standard, you have assay as in release, you have to deal with assay variability so the impression that you may have more or less material in there than really there is and you have to deal with the change in house standard which means moving from one manufactured lot that becomes the new house standard, from the old to the new house standard. And that may have a different assigned potency. In most cases it will because it's a different lot. So you have to do some careful analysis and to the best of your knowledge and bright procedure assign a new house standard potency.





Q. But over time the number of actual virus particles in those vials is not going to go up. Right?

MR. SANGIAMO: Objection to --

BY MR. MACORETTA:

Q. In the house standard lot?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, but the appearance of testing can suggest that it's going up which is a strange phenomenon because of assay variability. So just like over time the vaccine doesn't really change because you make it the same way, you dilute it the same way. But you measure it repeatedly. And when you measure something repeatedly, you're also prone to the variability of any assay over time.

BY MR. MACORETTA:

Q. Fair enough. On the first page of this is an e-mail from you to Roberta McKee and a bunch of other people. Right?





A. Uh-huh.

Q. And then it looks like somebody named Carl Burke sends your e-mail to Joye Bramble who then sends it to Keiko Simon. Do you see that right above it?

A. Yeah, that looks like it.

Q. So who are these -- who is Carl Burke?

A. Carl Burke is an engineer who was -- where was Carl at the time? I don't know whether he was manufacturing or in analytics, but he -- probably analytics, but he was an engineer. And I think they're all -- what these three people have in common is that they're -- that they were probably in some way associated with MMR, the MMR project team that would take care of MMR issues, whereas I was primarily taking care at that time of ProQuad issues. But because they both contain MMR, these things had to be aligned and so that's how this somewhat convoluted e-mail traffic is understandable.

Because one thing is done in MMR to be translated into ProQuad and vice versa.

Q. Because at least for mumps it was the same product in both?

A. Yes, for measles, mumps and rubella it is the same product in both.

Q. So who is Joye Bramble? What was her job at this time?

A. Joye Bramble is also an engineer. She was for -- she was reporting to me for quite a while. She was actually the person responsible for developing the CTT SOP for -- so basically the manufacturing piece of filings. She was in my department at the time. And then she was also at some point in time in project management. By that point in time it may be -- it's possible that she was back in the biologics pilot plant. She was an engineer who oversaw the biologics pilot plant for quite a while. And she did that after she -- after my department was reassigned and some structural changes. So I don't remember at that point in time where she was at, was she still working with me or





was she already in the pilot plant.

Q. So were you an MM -- you were in MRL. Right?

A. I was in MRL.

Q. Was Joye Bramble an MRL or an MMD person?

A. Joye Bramble was always an MRL person.

Q. When you said she's the project manager for a point in time --

A. At some point in time she also worked as a head of a group in project management. She was also a project manager.

Q. Okay. So what is --

A. But not at this time, not likely.

Q. So what I'm trying to understand is at this time was there some person who was responsible or in charge of MMR overall?

A. Well, you know, Merck is a highly collaborative company. I don't think that there is a single person that is responsible for any one single product. There are three different divisions that





collaborate in making product. And within that division a person would be responsible. And she may still have been the project team leader for MMR at the time. She was at that at some point in time. Maybe that's where this originates, but I don't remember that. I don't remember the time frames. I'm very bad with the exact time frames. It's a long time.

Q. That's fine. I'm trying to understand the overall structure. You said at this time you were involved with ProQuad?

A. Yes.

Q. What was your -- were you in charge of ProQuad or --

A. Well, in charge, I was -- I had different functions with ProQuad. I was -- for quite a while I was the project team co-leader of the Varicella-containing vaccines which encompassed, of course, ProQuad but also Zostavax and Varivax. We often invited MMR folks because we had this overlap of the common vaccine in ProQuad. Then I was responsible for the clinical team





that actually did the clinical development of ProQuad. It was Barb Kuter primarily who was reporting to me. And that was the extent of my involvement.

Q. So let me try it this way: At this time, June 2003 ProQuad wasn't on the market yet. Right?

A. No.

Q. It hadn't been approved?

A. No, it hadn't even been filed, I think.

Q. So who at Merck was in charge of overseeing the various aspects of getting the product, ProQuad approved?

A. Well, that would have been essentially the regulatory liaison.

Q. Well, when we -- was the regulatory liaison's job to say to the clinical people, I need these results from you, or to say -- or to make sure the regulatory filings were responded to on time or to do whatever else was necessary to get it approved?

MR. SANGIAMO: Object to form.

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THE WITNESS: In principle. I mean, that's one way of describing. Of course the whole project team knew what the expectations were, and so different jobs had to be done and different pieces were coming in and the regulatory person was ultimately responsible for collating and interacting with the agency, with the agencies, but wasn't solely responsible for the content. There were also two regulatory people, one who was on the clinical side and another one who was on the CMC side.

BY MR. MACORETTA:

Q. That's the manufacturing side?

A. The manufacturing side.

Q. So if -- let me try it this way: If the president of Merck in June 2003 wanted to know what the status of ProQuad was and where it was in getting approval, or be getting on the market, who would be the person that would have overall responsibility or would ask or would have overall responsibility





for that?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: I don't really know. I mean, as a project team co-leader, I would probably be involved in that. I mean, it depends on where the issues are.

BY MR. MACORETTA:

Q. So who coordinated the issues between manufacturing and regulatory -- and MRL regulatory?

A. Well --

MR. SANGIAMO: I'm sorry, John, are you saying between manufacturing regulatory and MRL regulatory?

MR. MACORETTA: I'll start with that, yeah.

MR. SANGIAMO: Go ahead.

THE WITNESS: That, I don't really know. I mean, they came up in the project team and ultimately each function was responsible to get their issues sorted out. So regulatory was





not my responsibility.

BY MR. MACORETTA:

Q. So when we say the project team, the projects team, the project was to get ProQuad on the market for the ProQuad project team?

A. The project for the ProQuad team was the development team, was to develop the product, get all the relevant clinical studies run, get all the relevant testing run, develop a manufacturing process and ultimately compile all the data and the information into a filing. Bring it on the market was not the -- it was not the responsibility of the project development team. That was the develop -- that is the responsibility of MMD just like manufacturing is the responsibility of the -- sorry, I have to shut down --

Q. Sure. But the project team would need help from manufacturing to get the product approved. Right?

A. Oh, yes, of course.

Q. So earlier there was a lot of





discussion about some of the exhibits we looked at. Should we say -- what do we say in response to the FDA when they ask the question should we include this information or not include that information? Who makes the ultimate decision about we're saying this, we're not saying this? Is that the person signing the letter?

MR. SANGIAMO: Object to the form.

THE WITNESS: This is not a question I can really answer. It depends on what the content is. I mean, obviously the person who signs the letter is responsible for what's written in the letter, but every department within Merck would be responsible for the veracity of its contribution to these filings. So, you know, in the CMC section you will have statements that come from manufacturing, in the clinical section you would have statements that come from clinical. And ultimately

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clinical would be responsible for the veracity of those statements. Then there is a layer of quality assurance and quality control where source documents are checked against the final document and the people who do that are responsible that everything is actually truthfully transcribed and transmitted. So they're responsible for that particular piece. If I give them wrong data, they're responsible for having them wrong in the filing, but I'm responsible if the data are wrong.

BY MR. MACORETTA:

Q. So the way you're describing it, then, there isn't one person who has overall responsibility?

A. Below the president of Merck or MRL for that matter, not really, no. I mean, the regulatory person takes a higher degree of responsibility than anybody else in that chain because they're the direct counterparts to the agencies. But ultimately if it's a





matter of data, they would have to concur, there would have to be concurrence.

Q. That's right. Okay. All right. Now I want to talk about your e-mail here that we looked at. You're talking about the points, I think, on Roberta McKee's e-mail right below yours which goes on to the following page. The end of the first paragraph, you have a sentence that says, "The responses should also be revised to explain the changed interpretation of the compendial spec that follows from house standard reassignment and why we think it is o.k. to do that." What does that mean?

A. It sounds very good, but I don't really remember exactly what that means.

Q. Well, okay.

A. I mean a compendial spec would be something that is written into a compendium such as, for example, the European pharmacopeia with 3.7 for mumps. I don't really remember why I thought at the time that a house standard reassignment might





change the compendial spec. I don't know. Maybe I'm talking about something else. It's out of context. I don't remember the details of these discussions. Remember this was manufacturing, I was just one voice sometimes as an outsider and sometimes as somebody who did not completely understand what they were talking about.

Q. So I guess I should ask then why do you get to have an opinion on this, why were you giving this opinion?

A. Well, because I was in between the different projects and there were not so many people that were. And also because I had a background in the assays. But, you know, there are pieces to that which I just simply don't know.

Q. So who would -- who is the expert on the house standard assignment?

A. At the time it would have been Roberta. I mean, Roberta was the regulatory person in MMD.

Q. And her equivalent at this time would have been Alison Fisher for MRL. Right?





A. No. No. Her equivalent would have been Keith Chirgwin probably.

Q. In the next sentence you talk about retaining the measles overfill. And then you say at the end of that line, "...you could as well use the 0.1 you gain on mumps now to claim a 24 months shelf-life."

Do you see that?

A. Yes.

Q. What does that refer to?

A. I don't even remember whether this refers to ProQuad or whether it refers to MMR. So I truthfully cannot tell you. But if -- so I have to speculate. I mean, if you have a .1 gain --

MR. SANGIAMO: Wait.

BY MR. MACORETTA:

Q. Go ahead, you can answer.

MR. SANGIAMO: I'm going to object. Jeff told him he's not supposed to speculate.

BY MR. MACORETTA:

Q. You can speculate. Go ahead.

MR. SANGIAMO: No, no. If this

is speculation --

MR. MACORETTA: Come on, you can't stop the guy in the middle of his answer because you don't like it.

MR. SANGIAMO: I don't know what his answer is.

MR. MACORETTA: Well, we're going to find out.

MR. SANGIAMO: Well, no. He just said he's going to be speculating. Jeff, your colleague, told him at the beginning don't speculate.

MR. MACORETTA: Unless he asked him to.

BY MR. MACORETTA:

Q. If you feel you can speculate to answer that question, please go ahead, Dr. Schodel.

MR. SANGIAMO: Do not speculate in your testimony, Dr. Schodel.

THE WITNESS: Okay.

BY MR. MACORETTA:

Q. Let me try -- we'll do it this





way: It says, "...to claim a 24 months shelf-life." Wasn't it always the case that every mumps vaccine Merck sold in the United States had a 24-month shelf life?

A. As I just said, I don't remember whether this applied to MMR or ProQuad. ProQuad hadn't been filed anywhere so it didn't have any shelf life.

Q. Let's look at the back. Do you know, what the -- the next page, the third bullet point in Ms. McKee's e-mail. "Quickly prepare and submit the mumps supplement to reduce expiry to 18 months...." Do you know what she's talking about there?

A. No, I don't remember that anymore.

Q. Well, is it -- you're in charge of ProQuad. Was there a discussion that there was going to be an 18 months as opposed to a 24-month shelf life?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't remember that.





BY MR. MACORETTA:

Q. Do you ever remember any discussion about having a shelf life less than 24 months for MMR?

A. With the exception of what we had discussed before, no.

Q. What was it we had discussed before?

A. The stability data e-mails that were just moved around.

Q. When you say, "...the 0.1 you gain on mumps now...," does that mean that because house standard potency has gone up by .1 log?

A. I don't know. I would -- it seemed to me, but, again, I'm extrapolating from my own sentences, that there is a gain in .1 through end expiry which may well mean that the .1 loss before was due to a different house standard calibration or it was due to an error in house standard calibration. So by doing it more properly, you actually gained one log. So you had less loss.





Q. So the house standard was recalibrated in a way that added .1 log?

A. I don't know that. It could have, as far as the house standard was concerned, gone down but the net result would be that you -- in the modeling you gain .1 in potency.

Q. If the house standard goes down, how does the potency go up?

A. Because you calibrate it to the house standard.

Q. But if it's calibrated before and after you change the house standard and the house standard goes down, how could the potency go up?

A. Well, because it's relative to the house standard. So if your assay point -- it goes in the other direction essentially. I mean, you calibrate it to the house standard. So if your -- if you do a calibration, you use the same measure over and over again and you calibrate it in the direction that the standard is going.

Q. So if the standard yesterday was

3.7 and it's 3.6 today, that means that a lot that we thought was 3.7 yesterday, we now think is 3.6. Right?

A. Not necessarily. You measure the same amount twice. Now it appears to be lower. So you put in more to get to the same number.

Q. You put in more product to get to the same number?

A. Well, your release number goes up. The same number appears to be higher. It's a bit counterintuitive, but it --

Q. It is. And that's what if the release spec for this -- let's assume --

A. That's at least -- I mean, I'm not the specialist on house standard for MMD. I was never in manufacturing. So that's a speculation that I would make. But I don't know how it was exactly used in calibration, so...

Q. I'm just asking you how you used it here?

A. Well, I just use -- I didn't -- that didn't -- it didn't -- for me, in this





particular statement, it was simply stating that if you have a better measure now, whatever that is, not opining on the house standard, that let's you show with credible data that you have .1 log more than you thought before in the product through end expiry, then that also means that actually the product will have a longer shelf life.

Q. Then the next paragraph you say, "I'm still not sure how the ProQuad filing will be handled as you go forward and change the mumps specs without changing the mumps maximum release spec in the ProQuad file which is supposed to reference the MMR license...."

Do you see that?

A. Uh-huh.

Q. The idea is that ProQuad is going to reference the MMR license for the specifications of the M, M and R parts of ProQuad. Right?

A. Yes.

Q. So it's going to be the same release spec for mumps in MMR as it is for ProQuad. Right?





A. Correct.

Q. The same end expiry potency. Right?

A. Correct.

Q. Because it's the same product, right, the mumps bulk is made -- it's the same mumps bulk for MMR as it is for ProQuad. Right?

A. Correct.

Q. Okay. So now you're asking here if you change -- when you say change the mumps specs, you're talking about changing something because the house standard changes. Right?

A. I'm not sure. This could be referring to house standard or it could be referring to the changes that we discussed previously with the introduction of a different view of CBER on what an end expiry means and, therefore, as a result and relative overfill that was done since '99 from what I saw in these documents. And I think that some of these changes in data for MMR had not made their way into the ProQuad manufacturing documentation yet. And,





therefore, I was just asking the question if we have agreement that they're the same, how are we going to introduce the changes that which you're currently working on at MMR for the agency, how are we going to introduce them into ProQuad to make sure that they remain the same.

Q. What's the ultimate answer to that question?

A. I don't know.

Q. Well, you were -- when did you stop working on ProQuad?

A. When did I stop working on ProQuad? I mean, I think I probably completely stopped working on ProQuad 2008 or 2009 or so. This was not the same level of attention anymore.

Q. Let me show you what we're going to mark as Schodel-22.

MR. MACORETTA: How much time do we have left?

VIDEOGRAPHER: About 21 minutes.

MR. MACORETTA: Thank you.

- - -

(Exhibit Schodel-22, 2/25/03 E-mail, Bates MRK-KRA00566606, was marked for identification.)

- - -

BY MR. MACORETTA:

Q. All right. Let me know when you've had a chance to look at this.

A. Yeah, I've looked at that. Not completely yet.

Q. The top e-mail is from you to Tim Schofield. Do you see that?

A. Uh-huh.

Q. And it says, "so...you can see the presentation in addition to my diatribe." What diatribe are you talking about?

A. I have no idea. Tim and I talked about stuff. I may have told him something about anything.

Q. Okay. And this says -- the e-mail below says the subject matter is "MMR House Standard assignment discussion," and it says, "Attached please find slides that were to be shown for tomorrow's Net Meeting...." Do you see that?





A. Uh-huh.

Q. What's a net meeting?

A. Probably a meeting over the Internet.

Q. Okay.

A. Or the intranet.

Q. Okay. Were you involved at all in creating any of these slides?

A. Nope. This is manufacturing stuff. This is not my direct responsibility at all.

Q. I got it. I understand that, but you looked at it and passed it on and had a diatribe about it apparently.

A. Or I had a diatribe unrelated to that.

Q. Maybe.

A. Much more likely actually.

Q. So -- well, let me start at the first page of the slide, the first one. It says -- there's a question from CBER, please give data concerning house standard potency values obtained. Then it says, "In preparation to answer question, recognized MuV





HS assigned value differs from historic performance."

Do you see that?

A. Yeah, I see that.

Q. What is MuV?

A. Mumps virus.

Q. What does it mean that its assigned value differs from historic performance?

A. That it's being given a value in -- when as we discussed before, in that crossover period when it was assigned a value, that is different from historic performance of that same house standard.

Q. So when you say assigned value, is that house standard?

MR. SANGIAMO: Object to the form.

THE WITNESS: Yeah.

BY MR. MACORETTA:

Q. So recognized mumps, MuV HS assigned value, that's the house standard value?

A. That's the house --





MR. SANGIAMO: Object to the form.

THE WITNESS: That's the house standard value that was assigned at a given period in time when that house standard was introduced.

BY MR. MACORETTA:

Q. Then it says, "...differs from historic performance." What does that mean, when you measure the potency of a lot -- what does that mean?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, it means -- look onto 616 and you can see what that means. So you'll see here historic performance of house standards, and you see that it measures as 4.2, 4.3, 4.1, up to 4. -- 4.4, down to 4.2. This is different data points from '95 to '02. And then it was assigned a value. And the problem is that it apparently fluctuated or differed from that

assigned value which is not too surprising in these things because assays do change, and they change unfortunately in sometimes long periodicities. You will sometimes have an assay that for unknown reasons runs a little different in the summer period or in a given year than in another year. Now, if you have a long-time assigned potency for a house standard, that has long-time consequences on manufacturing.

BY MR. MACORETTA:

Q. And it looks like -- I'm going to go back to page 615, the previous page under "How are potencies assigned," it seems to say for mumps that the house standard assigned was 4.2. Right?

A. Yeah, that's what it says here.

Q. But there's a -- when it says limits plus or minus .3, that's the variability. Right?

A. Those are controlled limits, not necessarily variability.





Q. Well, if we look back on 416, this would show us the variability. Right? We see some tasks as high as 4.8 and some down to 3.8. Right?

A. Now you're on 16?

Q. Yes.

A. On the lower half. Yeah, I mean, I see it going from 4.1 up to -- I mean, I was looking at the average line but if you look at the individual data points, yes, you can see anything from 3.9 up to 4.8 or so. Or 3. -- you were right, 3.8 even.

Q. So that's like a variability of .4. Right?

A. From 3.8 to 4.8, that's almost a log variability.

Q. That's almost a what?

A. That's almost a log.

Q. And a log is ten times. Right?

A. Yes.

Q. So when we -- so variability -- so when we change the log .1, that means that's 25 percent more or less product. Right?

A. You could see it that way,





yeah.

Q. Would you consider that a lot of variability for a house standard test, a one log?

A. The question is here more --

MR. SANGIAMO: The object to the form.

THE WITNESS: The question is here -- well, first of all, it's not really my field to opine on. I -- the question here is more does it behave differently in different periods of time.

BY MR. MACORETTA:

Q. Well, this is showing that it behaves, the period of time for these tests is over what, seven years, '95 to '02?

A. Yeah.

Q. If we look at 615, the top chart, it says, "What are the assigned potencies," and then for mumps it has "Assigned Potency* 4.2 (4.9)."

Now, is that the difference between a .1 mL and a per dose?





A. Yes.

Q. And if I'm reading Table 2 on page 615 right, they did 32 runs to come up with the house standard. Is that what that means?

A. You know, that's what it could mean, but I don't know that. These are obviously not data that I have generated or am that familiar with. So, for example, I can't tell you how many multiples are in there. So anyway.

Q. But if you were in charge of -- since you were in charge of ProQuad at this time, you had responsibility for ProQuad, how the house standard was calculated and applied was an issue for you, wasn't it?

MR. SANGIAMO: Object to the form.

THE WITNESS: In principle, no, as long as it remained stable. If it led to a change in the product or a change in how the product was made, then potentially yes.

BY MR. MACORETTA:

Q. But the application and calculation of the house standard was something that CBER had to know about. Right?

A. Yes, of course.

Q. If you could go to the next -- to the -- let's go to the last page, the "Summary" page. The second bullet point says, "...there is general agreement...with the exception of mumps."

Then the third bullet point says house standard increases from 4.2 to 4.3 is technically defensible.

A. This is the very last one, I see.

Q. Yes. I'm sorry. Do you know what that means, "is technically defensible"?

MR. SANGIAMO: Objection. Calls for speculation.

MR. MACORETTA: I just asked him if he knew what it meant.

MR. SANGIAMO: You're acting like he wrote the document.

MR. MACORETTA: That's fine.

BY MR. MACORETTA:





Q. You can answer the question.

A. I mean, the only thing I can see here and you can see that for yourself is on 618, if you look at all the data, you have a total number of 2,900 runs and you have an average of 4.28. So that is how the house standard has behaved. Then you have the qualification data that were done over a limited period of time with a limited number of runs and that resulted in an assignment of 4.2. That's different. And, therefore, the defense of that change would be the now available very large quantity of data that suggested that the house standard may have been assigned too low a potency and should be increased.

Q. So it goes from 4.2 to 4.3?

A. That is correct.

Q. But the release potency does not -- the minimum and maximum release potencies do not change. Right? It's still 5.0 or 5.5. Right?

A. They don't change.

Q. Well, but aren't you putting





more virus particles in the same product if you don't change the release potencies but the house standard recognizes there's more product in it?

A. No. No, you just call it a different number.

Q. So it's the same --

A. You do exactly the same thing.

Q. It's the number --

A. The manufacturing process remains stable. It remains exactly the same dilutions. Exactly what you've done before. The difficulty here is really one that is related to the accuracy of an assay of measuring whether or not it meets release specifications. You don't put in more or less. You just call it a different number.

Q. So what was 5 yesterday is 5.1 today?

A. In view of more data what you measured as 5 yesterday you now realize is in reality 5.1.

Q. But if my release spec is 5.0, isn't -- if I measured something at 4.9





yesterday, that's 5.0 today. Right?

A. Well, I'm not sure I follow.

Q. You know what, strike that. Let me -- I'll withdraw that question.

Let's look at the last bullet point. Mumps house standard assigned potency has important impact on - MMR II near-term manufacturability. What does that mean?

A. To tell you the truth, I don't exactly know, but -- I don't know.

Q. You just said that nothing changes, it's just a change in the number. If nothing changes, why would it impact manufacturability?

A. I mean, you -- I don't know. I mean, you may -- I really don't know.

Q. This would be something that you would want to know about, right, since you're in charge of ProQuad?

A. Yeah, absolutely.

MR. SANGIAMO: Object to the form.

BY MR. MACORETTA:

Q. Okay. And it also says, "MMR®II

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shelf-life, recon/store time," and "calibrated stability." Do you have an understanding of why changing the house standard potency would impact them?

A. Yeah. That -- we just discussed that, because the numbers that you assign to the potencies at given points in time change with a calibration to the house standard. The house standard is different, they go up or down.

Q. So does that mean that if my end expiry potency was 4.2 yesterday, it's 4.3 today when we increase the house standard?

A. No, it's still 4.3.

Q. No, it's if 4.2 yesterday. 4.0. Let's say if I --

A. You're not changing the end expiry potency, we're just changing what number we give the measurement.

Q. So the end expiry potency is the same but what measured 4.2 yesterday measures at 4.3 today?

A. It may still measure at 4.3, but it gets calibrated to a differently





assigned house standard and, therefore, it gets called a different number with more data.

Q. Okay.

A. I think we're coming to the end --

MR. MACORETTA: That's fine. We are. And I'm not going to start and do something else. I don't have any more questions today, Dr. Schodel.

THE WITNESS: Thank you.

MR. MACORETTA: Thank you.

MR. SANGIAMO: No questions here.

VIDEOGRAPHER: The time now is 5:57. This concludes the deposition. End of disc six of six.

- - -

(Witness excused.)

- - -

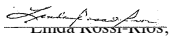
(Deposition concluded at 5:57 p.m.)



CERTIFICATE

I do hereby certify that I am a Notary Public in good standing, that the aforesaid testimony was taken before me, pursuant to notice, at the time and place indicated; that said deponent was by me duly sworn to tell the truth, the whole truth, and nothing but the truth; that the testimony of said deponent was correctly recorded in machine shorthand by me and thereafter transcribed under my supervision with computer-aided transcription; that the deposition is a true and correct record of the testimony given by the witness; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WITNESS my hand and official seal this 5th day of January, 2017.



Linda Rossi-Rios, RPR, CSR
Notary Public



INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

ACKNOWLEDGMENT OF DEPONENT

I have read the foregoing transcript of my deposition and except for any corrections or changes noted on the errata sheet, I hereby subscribe to the transcript as an accurate record of the statements made by me.

_____
FLORIAN SCHODEL, MD

SUBSCRIBED AND SWORN before and to me this ____ day of _____, 20___.

_____
NOTARY PUBLIC

My Commission expires:



E R R A T A S H E E T

IN RE: USA ex rel. vs. MERCK
DATE: 12/22/2016

| PAGE | LINE | CORRECTION AND REASON |
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(DATE) FLORIAN SCHODEL, MD

# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 117

**To:** 'Y. Kino'[kino-yo@kaketsuken.or.jp]; Morsy, Manal A.[manal_morsy@merck.com]
**Cc:** Chirgwin, Keith D.[keith_chirgwin@merck.com]; Bramble, Joye L.[joye_bramble@merck.com]; Matthews, Holly[holly_matthews@merck.com]; Heyse, Joseph F.[joseph_heyse@merck.com]; Schodel, Florian[florian_schodel@merck.com]; Simon, Keiko[keiko_simon@merck.com]; Musey, Luwy[luwy_musey@merck.com]; Schofield, Timothy L[timothy_schofield@merck.com]; Antonello, Joseph M[joseph_antonello@merck.com]; Galinski, Mark S.[mark_galinski@merck.com]; Abraham, Katalin G.[katalin_abraham@merck.com]; Shaw, Alan[alan_r_shaw@merck.com]; 'Shiosaki'[shiosaki@kaketsuken.or.jp]; 'Funatsu'[funatsu-ma@kaketsuken.or.jp]; 'Kanehara'[kanehara@kaketsuken.or.jp]; 'Timothy A. Corrigan'[corrigan@kaketsuken.or.jp]; 'Tochihara'[tochihara@kaketsuken.or.jp]; '????'[sakai-kaz@kaketsuken.or.jp]; '????'[mizuno@kaketsuken.or.jp]; '????'[tanaka@kaketsuken.or.jp]; '?? ??'[honda@kaketsuken.or.jp]; '?? ??'[mizokami@kaketsuken.or.jp]
**From:** Morsy, Manal A.
**Sent:** Fri 9/13/2002 9:59:17 AM
**Importance:** Normal
**Subject:** RE: Kaketsuken Questions regarding mumps end expiry potency

No trouble at all – in terms of the rHA history – I will have to get back to you on this one – for correction rHA is not a virus stabilizer – but rather like FBS, rHA is required for maintaining the mono-layer cell culture integrity.

in terms of the clinical trial – the study was designed to address a specific request made to us by the EU since rHA is a recombinant excipient to show that anti -HA antibodies are not generated.

in terms of why PRN and ELISA in the mumps end expiry and only ELISA in the MMRII/rHA – and this CBER's explanation because we asked the same question regarding the need for a PRN – CBER considers a neutralization assay essential for establishing efficacy were you need to define effectiveness for a product – the mumps end expiry trial is comparing release to expiry within the same product – however when you are comparing equivalence between two products – CBER considers ELISA sufficient.

Manal
-----Original Message-----
**From:** Y. Kino [mailto:kino-yo@kaketsuken.or.jp]
**Sent:** Friday, September 13, 2002 4:21 AM
**To:** 'Morsy, Manal A.'
**Cc:** 'Chirgwin, Keith D.'; 'Bramble, Joye L.'; 'Matthews, Holly'; 'Heyse, Joseph F.'; 'Schodel, Florian'; 'Simon, Keiko'; 'Musey, Luwy'; 'Schofield, Timothy L'; 'Antonello, Joseph M'; 'Galinski, Mark S.'; 'Abraham, Katalin G.'; 'Shaw, Alan'; 'Shiosaki'; 'Funatsu'; 'Kanehara'; 'Timothy A. Corrigan'; 'Tochihara'; '????'; '????'; '????'; '?? ??'; '?? ??'
**Subject:** RE: Kaketsuken Questions regarding mumps end expiry potency

Manal,

Thank you very much for your clarifications.

I understand that rHA is in a completely different category from FCS, because rHA is contained in the virus growth media and the stabilizer for the virus harvests, but FCS is not. However, I also understand that it is not appropriate to describe the M-M-R(TM)II with rHA as a "new formulation".

Because rHA is not a final excipient, a clinical study and even a partial change application would not be required upon replacement, as you previously expected. However, as a matter of fact, you are conducting a clinical study and are going to make a partial change application; therefore, the change of HSA from plasma-derived to recombinant is not supposed to be a mere replacement of one of the materials.

Because we also have to make a partial change application regarding rHA in Japan, I would appreciate it if you could summarize the history

of rHA replacement, especially the reason for the clinical trial and partial application. I am not in a hurry for this.

Finally, I do not understand the end of the last paragraph of your e-mail of September 12th. "....in both the primary and secondary endpoint...." I understand the protocol of the mumps dose justification study in that there are two endpoints, PRN and ELISA; however, in the clinical study with MMRII/rHA, you employ only ELISA. In that sense, the two studies are not the same. My question is, why only ELISA was accepted for MMRII/rHA whereas both PRN and ELISA were required for the mumps end expiry trial. I really need your explanation on this point. I am very sorry to trouble you, but I would like to clarify the situation before holding our internal meeting.

I would appreciate your response.

Regards,

Yoichiro

-----Original Message-----
**From:** Morsy, Manal A. [mailto:manal_morsy@merck.com]
**Sent:** Thursday, September 12, 2002 11:16 PM
**To:** 'Y. Kino'; Morsy, Manal A.
**Cc:** Chirgwin, Keith D.; Bramble, Joye L.; Matthews, Holly; Heyse, Joseph F.; Schodel, Florian; Simon, Keiko; Musey, Luwy; Schofield, Timothy L; Antonello, Joseph M; Galinski, Mark S.; Abraham, Katalin G.; Shaw, Alan; Shiosaki; Funatsu; Kanehara; Timothy A. Corrigan; Tochihara; ????; ????; ????; ?? ??; ?? ??
**Subject:** RE: Kaketsuken Questions regarding mumps end expiry potency

Dear Yoichiro,

In terms of the 20,000 CCID50 and rationale – I will have to defer answering until we review the papers you are referring to – also please keep in mind that we are still evaluating the shelf life and what we (Merck) can support – so please think of that as one of the potential options that may or may not be viable once we complete our sheif life evaluation.

Also please note that the rHA replacement in MMRII is NOT a "new formulation" rather this is a bulk culture media excipient like fetal bovine serum which is what it is actually replacing in the bulk process when the virus infection is initiated, not a "formulation" excipient in the final container for stability. We have to make sure that there is clarity on this issue other wise this can lead to great confusion especially in agency communications.

In terms of your question – if we were going to conduct another end expiry trial for the MMRII/rHA – the answer as previously stated is NO – MMRII/rHA is the same as the current MMRII except for the excipient replacement – therefore what ever the end expiry assignment becomes for the the current MMRII is what would translate to minimum potency for MMRII/rHA – ie what ever the results are for the ongoing mumps end expiry trial are will affect current label and will be transferred to revised label for MMRII/rHA.

The criteria in the MMRII/rHA study are the same except the assays used are exclusively ELISA – ie the PRN (plaque reduction neutralization) assay is not used to evaluate immune response for mumps in the MMRII/rHA study. Recall that the primary end point in the mumps end expiry is based on measuring immune response using the PRN assay while the secondary end point in the that study is based on using the mumps ELISA assay – in both the primary and secondary end point scenarios the criteria of success are the same and are the same as those set forth for the

MMRII/rHA.

Hope this helps.

Manal

**Manal Morsy, MD, PhD, MBA**
Director
Worldwide Regulatory Affairs
Vaccines/Biologics
morsy@merck.com
tel: 484-344-3785
fax: 484-344-2962

-----Original Message-----
**From:** Y. Kino [mailto:kino-yo@kaketsuken.or.jp]
**Sent:** Thursday, September 12, 2002 4:59 AM
**To:** 'Morsy, Manal A.'
**Cc:** 'Chirgwin, Keith D.'; 'Bramble, Joye L.'; 'Matthews, Holly'; 'Heyse, Joseph F.'; 'Schodel, Florian'; 'Simon, Keiko'; 'Musey, Luwy'; 'Schofield, Timothy L'; 'Antonello, Joseph M'; 'Galinski, Mark S.'; 'Abraham, Katalin G.'; 'Shaw, Alan'; Shiosaki; Funatsu; Kanehara; Timothy A. Corrigan; Tochihara; ????; ????; ????; ?? ??; ?? ??
**Subject:** RE: Kaketsuken Questions regarding mumps end expiry potency

Dear Manal,

Thank you very much for your quick response. The following are several additional questions I have for you:

Regarding Question #3, originally, we were going to use the results of your ongoing trial as a rationale for the end expiry potency of mumps; however, if we submit the JNDA with 20,000 CCID50, we will have to use another rationale. In such a situation, we will have to use the minimum immunizing titer reported in papers (J.A.M.A, 203:9-13, 1968 and The New England Journal of Medicine, 278(5), 227-232,1968). Is this OK for you, or could you suggest an alternative rationale?

For me, your reply to Question #4 is unclear. Are you going to conduct an additional clinical trial to determine the end expiry potency of the new formulation? Your explanation would be appreciated.

Finally, are the criteria for the endpoint of the ongoing clinical trial using M-M-R(TM)II with rHA the same as those of the mumps dose justification trial?

I am looking forward to your complete response. Thank you.

Regards,

Yoichiro

-----Original Message-----

**From:** Morsy, Manal A. [mailto:manal_morsy@merck.com]
**Sent:** Thursday, September 12, 2002 2:49 AM
**To:** 'Y. Kino'
**Cc:** Chirgwin, Keith D.; Bramble, Joye L.; Matthews, Holly; Heyse, Joseph F.; Schodel, Florian; Simon, Keiko; Musey, Luwy; Schofield, Timothy L; Antonello, Joseph M; Galinski, Mark S.; Abraham, Katalin G.; Shaw, Alan
**Subject:** RE: Kaketsuken Questions regarding mumps end expiry potency

Dear Yoichiro,

Please note comments to questions – I will get back to you with complete responses as soon as possible following internal discussions.

Regards

Manal
**Manal Morsy, MD, PhD, MBA**
Director
Worldwide Regulatory Affairs
Vaccines/Biologics
morsy@merck.com
tel: 484-344-3785
fax: 484-344-2962

-----Original Message-----
**From:** Y. Kino [mailto:kino-yo@kaketsuken.or.jp]
**Sent:** Wednesday, September 11, 2002 3:06 AM
**To:** Morsy Manal
**Cc:** Shiosaki; Kanehara; Funatsu; Tochihara; ????; ????; ?? ??; ????
**Subject:** Questions regarding mumps end expiry potency

Dear Manal,

As of the teleconference, we have been internally discussing possible options regarding the mumps end expiry potency. To make our discussions more concrete, I would like to confirm the following points:

1. Would it be possible to forward us the interim summary data of the study in which 265 samples were excluded? We are interested in the data for the subjects that were already fixed.
[Morsy, Manal A.] we will discuss internally and determine feasibility and timing

2. If 20,000CCID50 is adopted as the end expiry potency, do you recommend 1 year as the shelf life?
[Morsy, Manal A.] we are currently evaluating the shelf life recommendation

3. Is there any other basis regarding 20,000CCID50 as the end expiry potency other than the minimum required virus titer?
[Morsy, Manal A.] please clarify – I am not sure I understand your question.
As you recall we had previously forwarded to you the historical events that led to CBER's request that Merck conducts an end expiry trial if Merck wanted to change mumps potency in the label from 20,000. please see attached:

4. What is the mumps end expiry potency of the investigational vaccine with rHA which is being used in the clinical trial? Further, is the mumps sero-conversion rate one of the endpoints of the trial?[Morsy, Manal A.] yes
[Morsy, Manal A.] the investigational vaccine is tested at release – end expiry potency for mumps would follow what would be in the label post the end expiry trial conclusion.

5. When you change HSA to rHA, is an additional end expiry trial with the new formulation required?
[Morsy, Manal A.] No – see comment above

6. If the primary end point is not fulfilled and you negotiate with CBER, is there any possibility of going back to 5,000 CCID50?
[Morsy, Manal A.] unlikely the preliminary data from the mumps end expiry based on the criteria set forth by CBER would not support 5,000 – what we would negotiate if one of the two criteria is not met would be the 10,000 CCID50

We will hold an internal meeting next Wednesday to determine which option to pursue; therefore, I would appreciate it if you could forward your responses to the questions noted above by next Tuesday.
[Morsy, Manal A.] Additional comments will be provided as soon as internal discussion at our end are concluded to further address your questions.

Regards

Manal

As I explained previously, the timing of the JNDA submission is an extremely political issue both internally and externally. I would appreciate your cooperation.

=========

# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 118

**To:** Chodakewitz, Jeffrey A[jeffrey_chodakewitz@merck.com]; Chirgwin, Keith D.[keith_chirgwin@merck.com]; Heyse, Joseph F.[joseph_heyse@merck.com]; Schodel, Florian[florian_schodel@merck.com]; Matthews, Holly[holly_matthews@merck.com]; Willison, Barbara W[barbara_willison@merck.com]; Morsy, Manal A.[manal_morsy@merck.com]; Musey, Luwy[luwy_musey@merck.com]; Dietrich, Gary J[gary_dietrich@merck.com]; Hartzel, Jonathan[jonathan_hartzel@merck.com]; Karnik, Shaila[shaila_karnik@merck.com]; Kuter, Barbara J.[barbara_kuter@merck.com]
**Cc:** Schreader, Nancy T[nancy_schreader@merck.com]; Kriebel, Lonnie M[lonnie_kriebel@merck.com]; Daggett, Kathleen N[kathy_daggett@merck.com]; Shay, Charlotte[charlotte_shay@merck.com]
**From:** Simon, Keiko
**Sent:** Mon 10/27/2003 8:21:49 PM
**Importance:** Normal
**Subject:** VP Clinical planning meeting information
Final_October25_VP_PlanningMeeting_MumpsEndExpiry2004.ppt
oGOS versus GOS Comparison.ppt

Dear all,
Please find attached the presentation slides from Luwy and Jon for tomorrow's discussion. Apologies for the lateness of this distribution.

Outline of Clinical documentation

GOS vs. oGOS comparison

Thank you,
Keiko

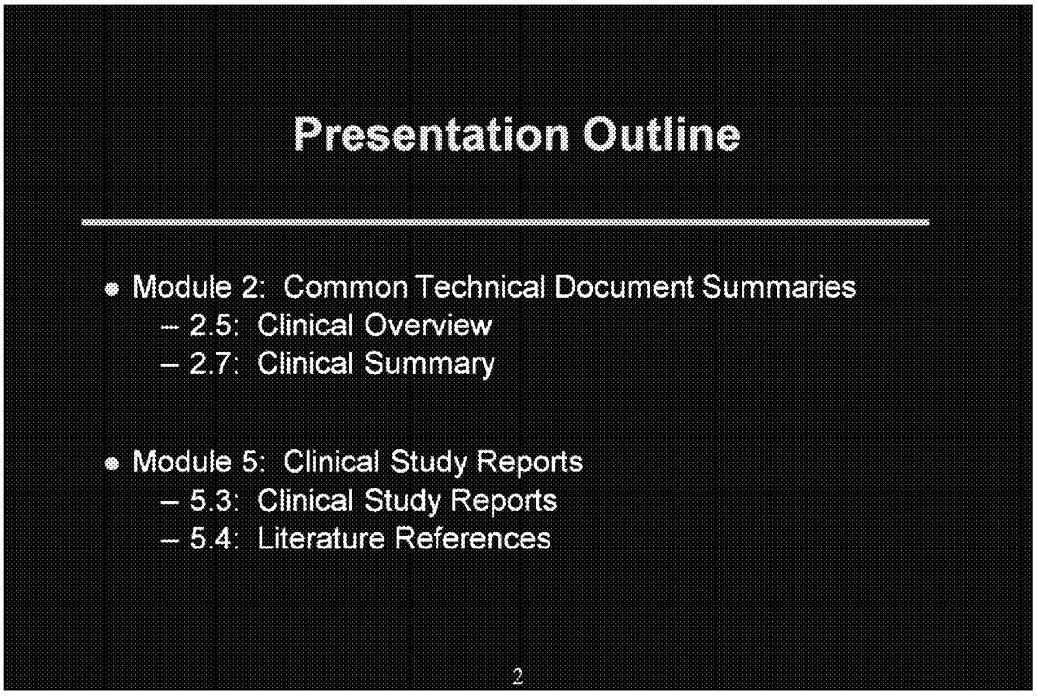
*Thank you,*
*Keiko O. Simon, PhD*
*Project Management*
*484-344-7590 (phone)*
*484-344-3659 (fax)*

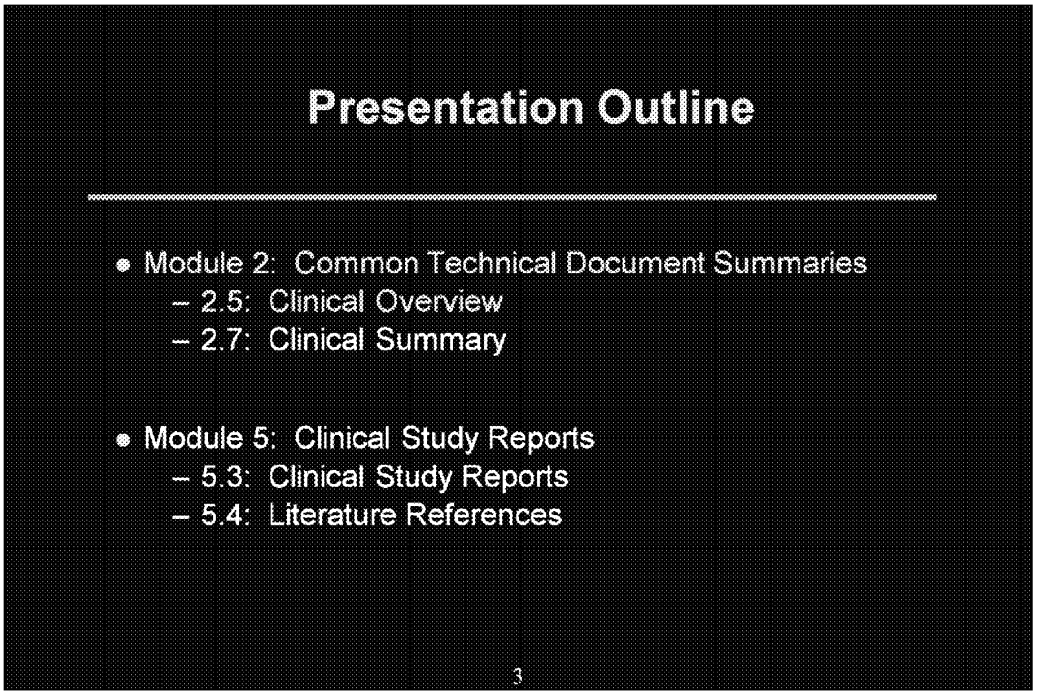
# M-M-R™II /Mumps End-Expiry U.S. sBLA Filing

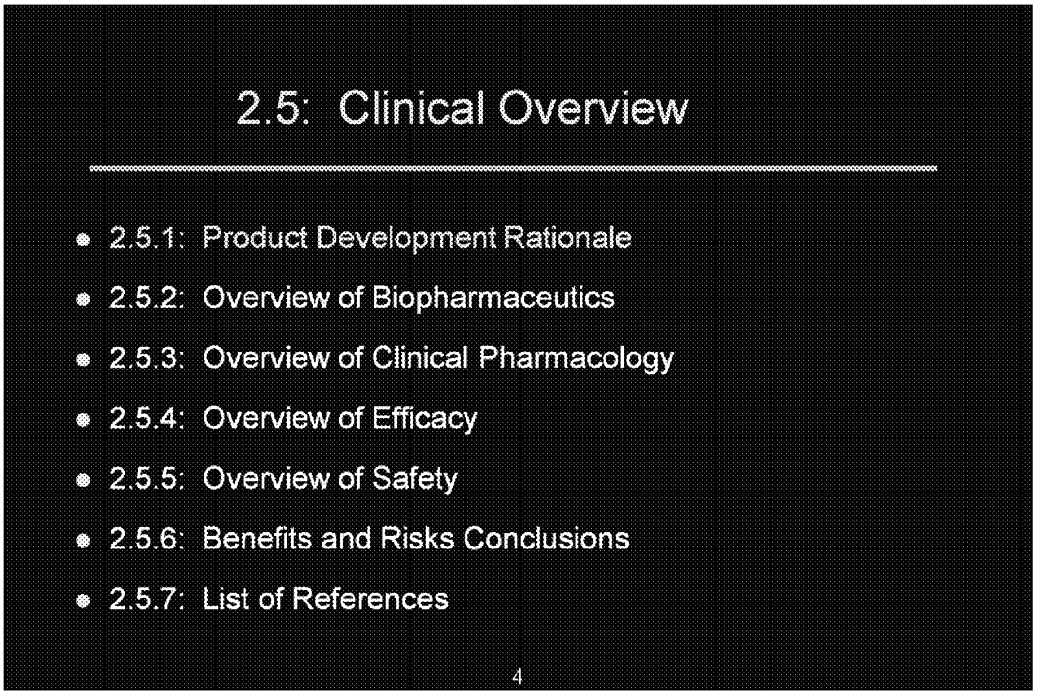
## Review of Clinical Section of CTD outline

VP Clinical Planning Meeting

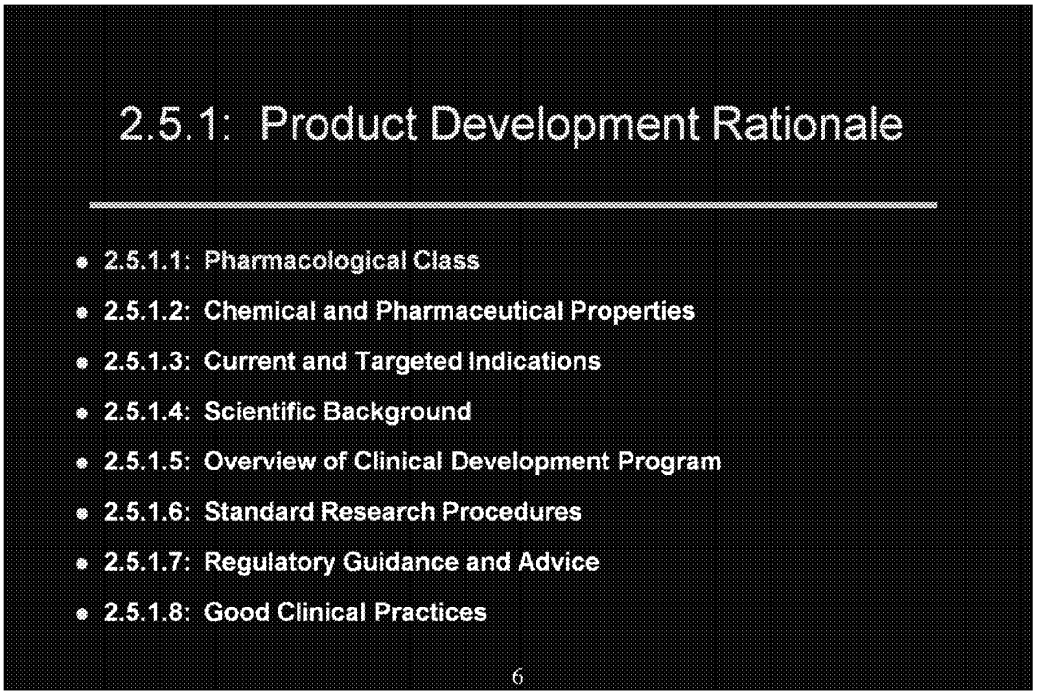
October 28, 2003






2.5: Clinical Overview
2.5.1: Product Development Rationale
2.5.2: Overview of Biopharmaceutics
2.5.3: Overview of Clinical Pharmacology
2.5.4: Overview of Efficacy
2.5.5: Overview of Safety
2.5.6: Benefits and Risks Conclusions
2.5.7: List of References
4


2.5.1: Product Development Rationale
2.5.1.1: Pharmacological Class
2.5.1.2: Chemical and Pharmaceutical Properties
2.5.1.3: Current and Targeted Indications
2.5.1.4: Scientific Background
2.5.1.5: Overview of Clinical Development Program
2.5.1.6: Standard Research Procedures
2.5.1.7: Regulatory Guidance and Advice
2.5.1.8: Good Clinical Practices
5


2.5.1: Product Development Rationale
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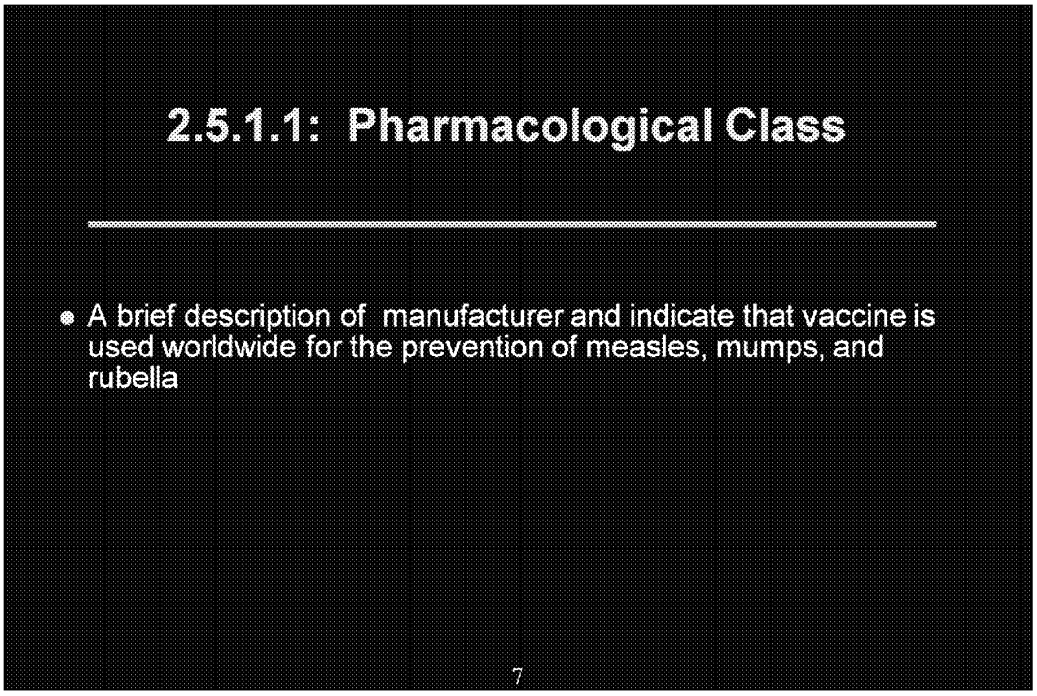
6




2.5.1: Product Development Rationale
2.5.1.1: Pharmacological Class
2.5.1.2: Chemical and Pharmaceutical Properties
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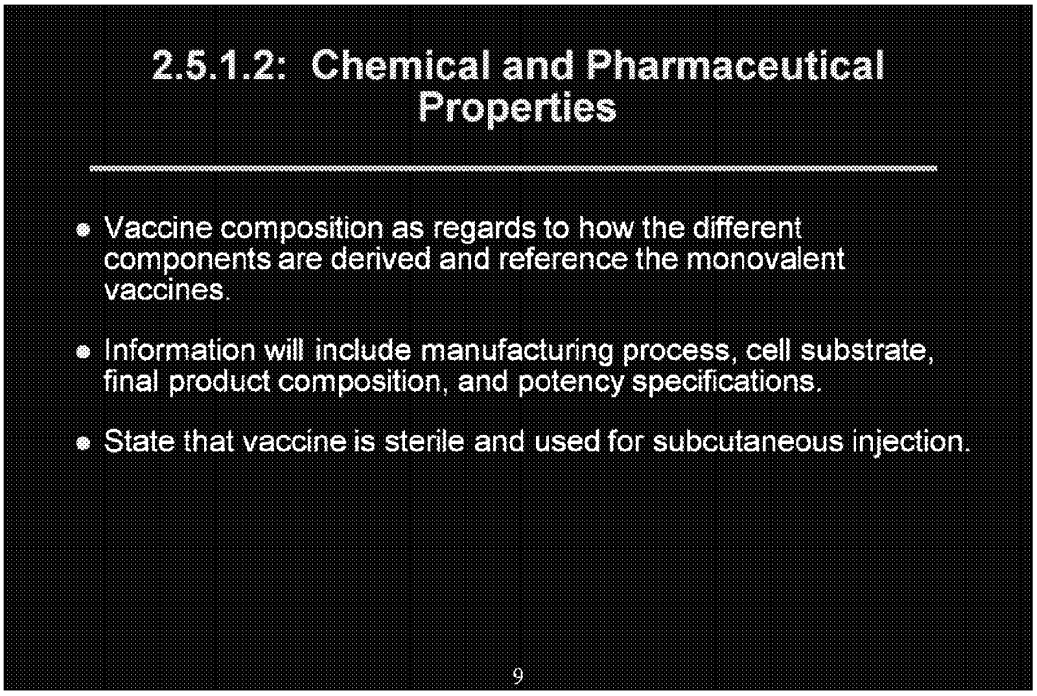
8


2.5.1.2: Chemical and Pharmaceutical Properties
Vaccine composition as regards to how the different components are derived and reference the monovalent vaccines.
Information will include manufacturing process, cell substrate, final product composition, and potency specifications.
State that vaccine is sterile and used for subcutaneous injection.
9


2.5.1: Product Development Rationale
2.5.1.1: Pharmacological Class
2.5.1.2: Chemical and Pharmaceutical Properties
2.5.1.3: Current and Targeted Indications
2.5.1.4: Scientific Background
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2.5.1.6: Standard Research Procedures
2.5.1.7: Regulatory Guidance and Advice
2.5.1.8: Good Clinical Practices
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## 2.5.1.3: Current and Targeted Indications

- State that present submission will not propose any change to the vaccine's indication, but rather sought to reduce the expiry potency for mumps component of M-M-R™II from 4.3 to 4.1 log10TCID50/dose
- Provide the current indication against the 3 diseases
- Recommended schedule in the United States and precautions for some subjects with history of anaphylactic reaction to any vaccine component
- State that marketed application never been rejected nor withdrawn for safety reasons
- Refer to appendix for the list of countries where the vaccine is currently licensed
- Refer to previous submission for additional information

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2.5.1: Product Development Rationale
2.5.1.1: Pharmacological Class
2.5.1.2: Chemical and Pharmaceutical Properties
2.5.1.3: Current and Targeted Indications
2.5.1.4: Scientific Background
2.5.1.5: Overview of Clinical Development Program
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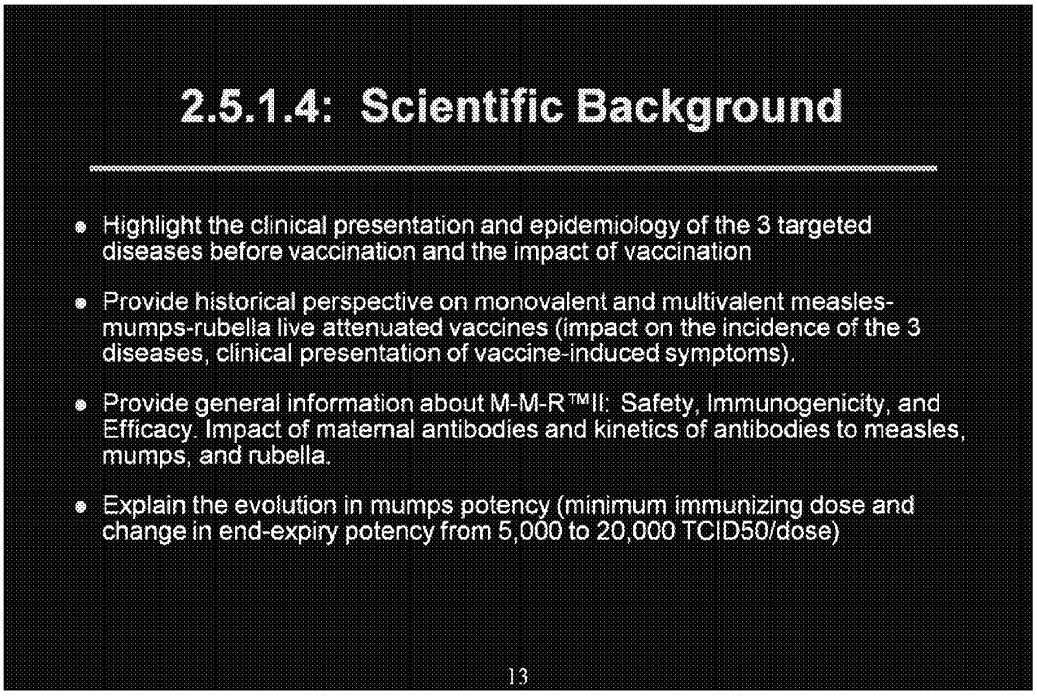
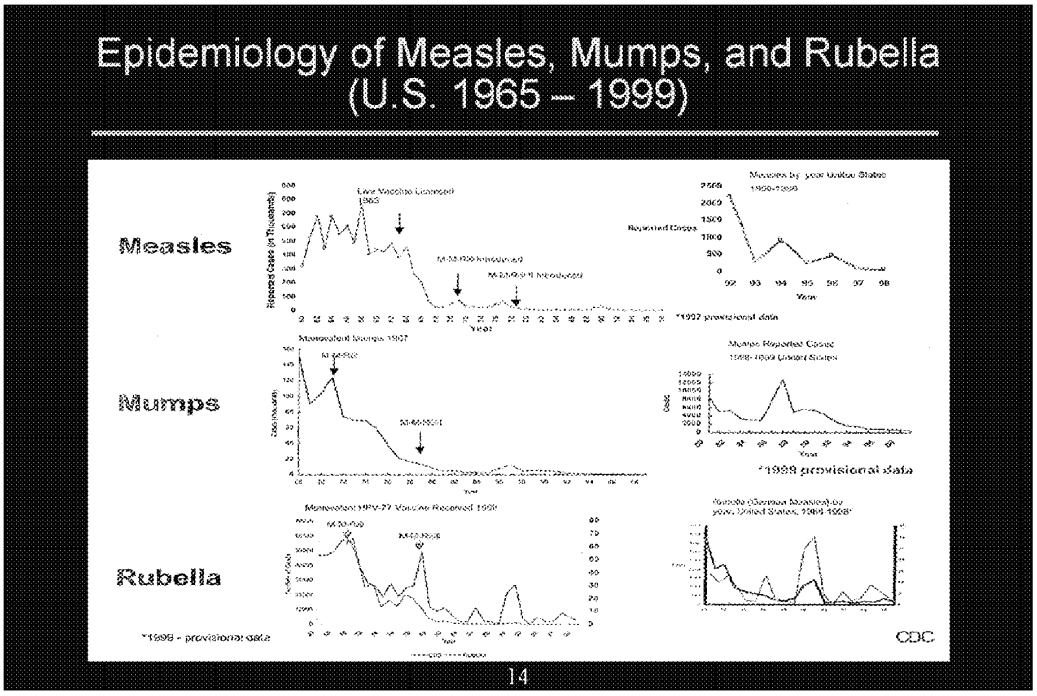
2.5.1.8: Good Clinical Practices
12





# Key Mumps Virus Potency Values

| Vaccine Component | Minimum Immunizing Dose ($TCID_{50}$/dose) | End-Expiry Potency ($TCID_{50}$/dose) | Minimum Release Potency ($TCID_{50}$/dose) |
|---|---|---|---|
| REDACTED – OMP | | | |
| **Mumps** | ~2.5 $log_{10}$ (~317)[§] | 3.7 $log_{10}$ (5,000)[¶] | 4.7 $log_{10}$ (50,000)[¶] |
| REDACTED – OMP | | | |

§ In 1972, potency value had to be adjusted (4-fold increase) due to a change in cell substrate (from BSC-1 to Vero cells).

¶ In 1999, minimum release was changed from 4.7 to 5.0 $log_{10}$ in agreement with CBER to support an end-expiry potency of 4.3 $log_{10}$ instead of 3.7 $log_{10}$ $TCID_{50}$

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## 2.5.1.5: Overview of Clinical Development Program

- State that application is to obtain approval to lower mumps end-expiry potency in M-M-R™II based on the clinical data; that lowering will reduce amount of unneeded virus given to children while preserving safety and efficacy profiles of the vaccine.
- Explain that lowering of mumps potency would more likely affect immunogenicity rather than safety
- Provide rationale for the conduct of this clinical trial (need to identify mumps end-expiry potency). What was the plan and How was it done?
- Vaccine aged at room temperature to mimic natural potency decay
- Briefly state that in agreement with CBER, study was done with oGOS as vaccine stabilizer; vaccine made with oGOS provides comparable immune responses to vaccine made with GOS (report provided in section 5.3.5) .
- Describe briefly protocol 007: study objective, Rationale for evaluating the kinetics of immune responses (1 year persistence).

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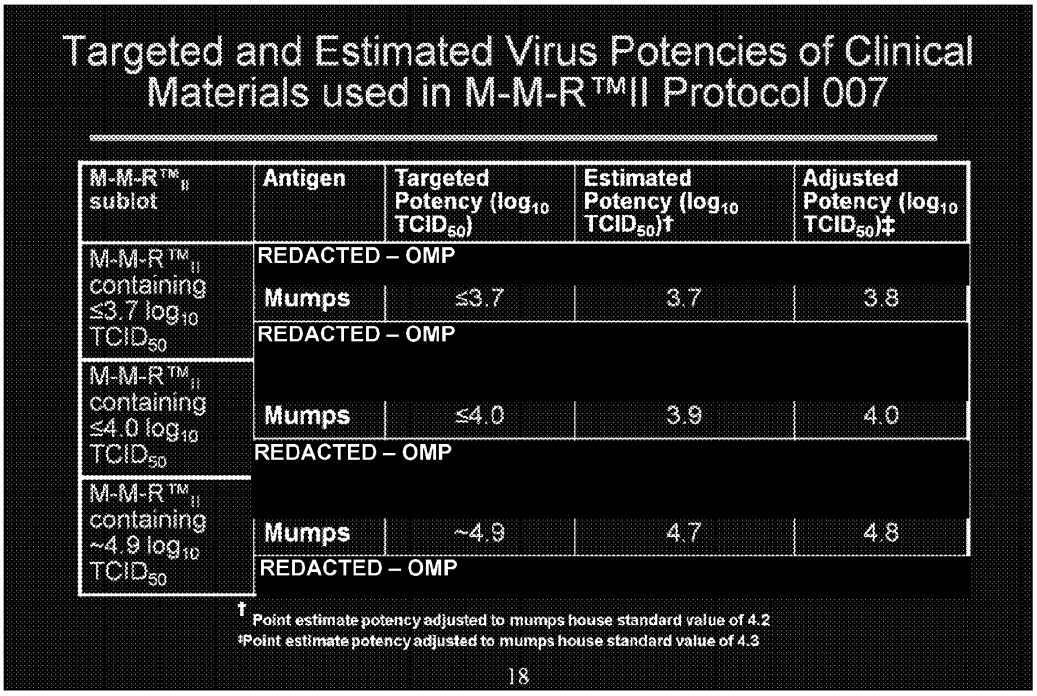


2.5.1: Product Development Rationale
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2.5.1.7: Regulatory Guidance and Advice
2.5.1.8: Good Clinical Practices
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## 2.5.1.6: Standard Research Procedures

- Conduct and Design of Study: Concordance with Standard Research Approaches (well-controlled, well powered, etc.)
- Vaccination Report Card (VRC)
- Similar to the one used in recent M-M-R™II studies
- Parameters prompted for on VRC and how often (Temperature, injection-site reaction, systemic AE)
- Statistical Analysis
- State that statistical analyses were pre-specified in the DAP
- Analyses performed according to standardized and validated methodology; refer section explaining methodology

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2.5.1: Product Development Rationale
2.5.1.1: Pharmacological Class
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2.5.1.3: Current and Targeted Indications
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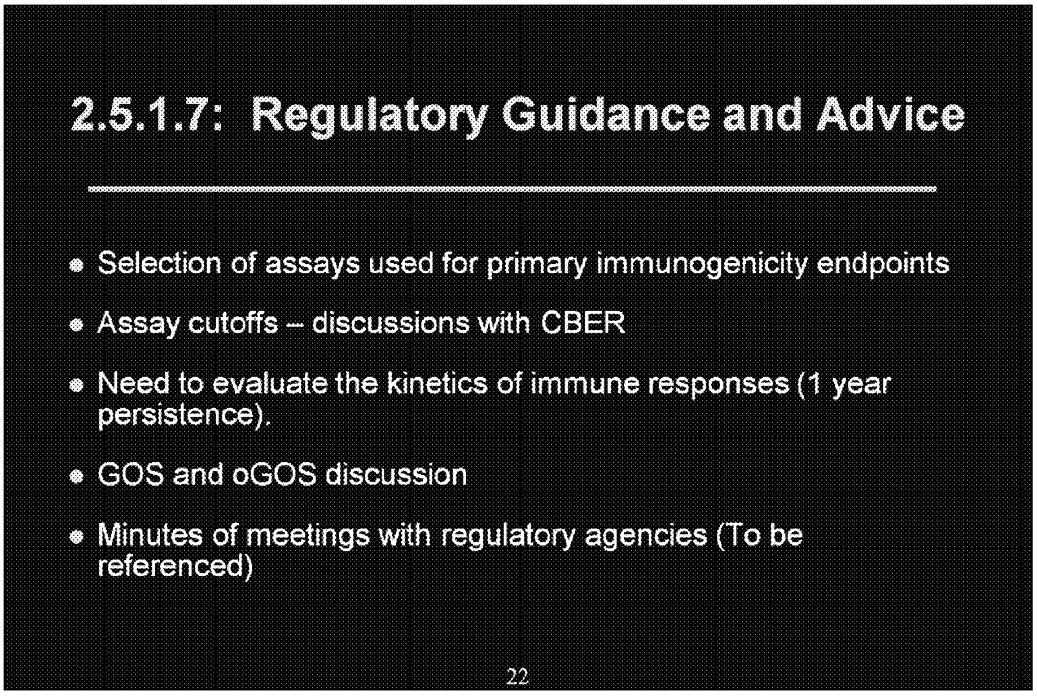
21




2.5.1: Product Development Rationale
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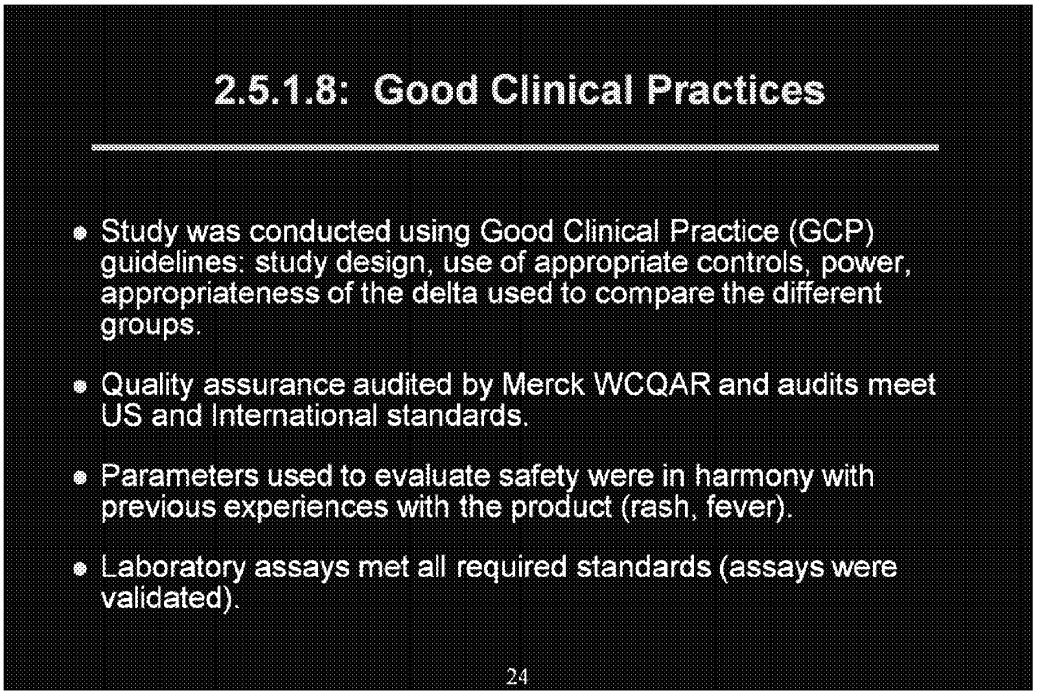
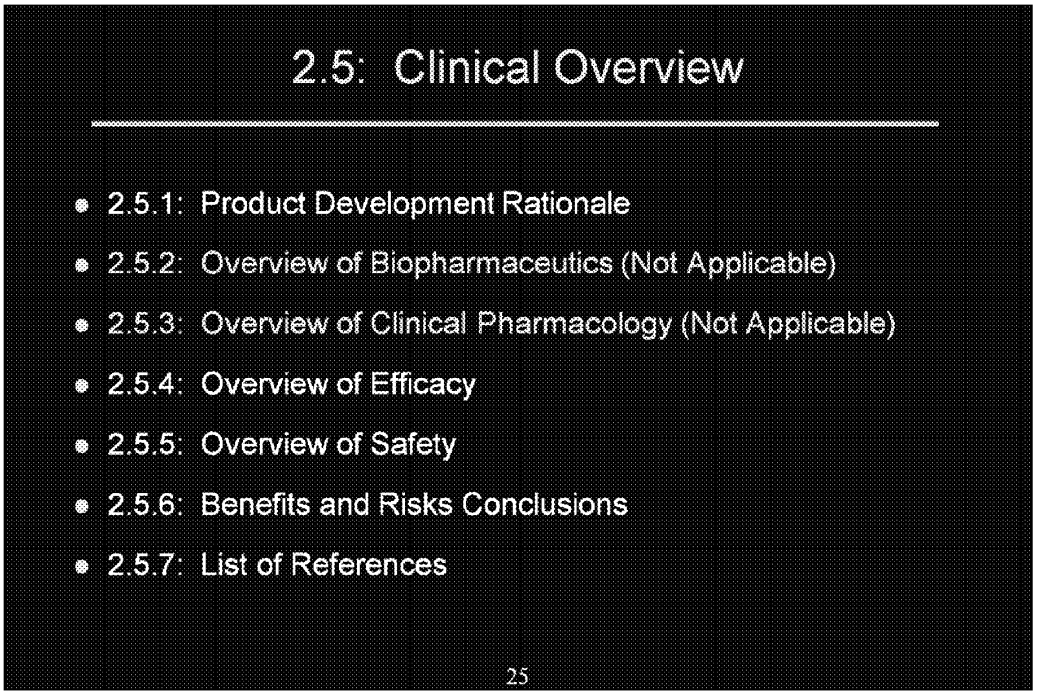
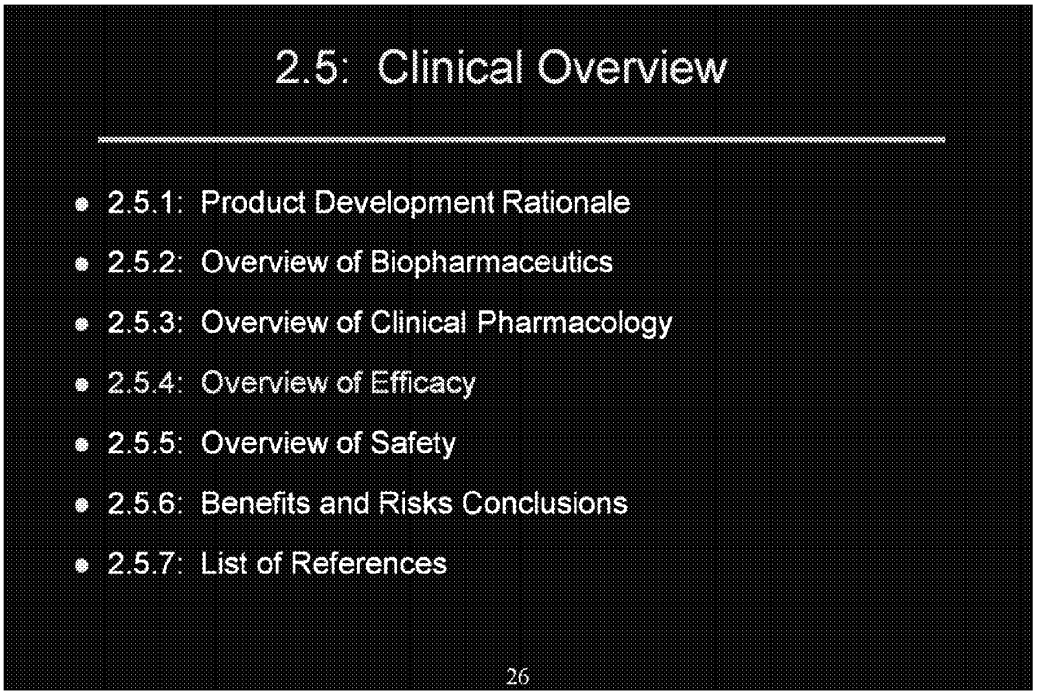
23




2.5: Clinical Overview
2.5.1: Product Development Rationale
2.5.2: Overview of Biopharmaceutics (Not Applicable)
2.5.3: Overview of Clinical Pharmacology (Not Applicable)
2.5.4: Overview of Efficacy
2.5.5: Overview of Safety
2.5.6: Benefits and Risks Conclusions
2.5.7: List of References
25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2.5.3: Overview of Clinical Pharmacology
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2.5.5: Overview of Safety
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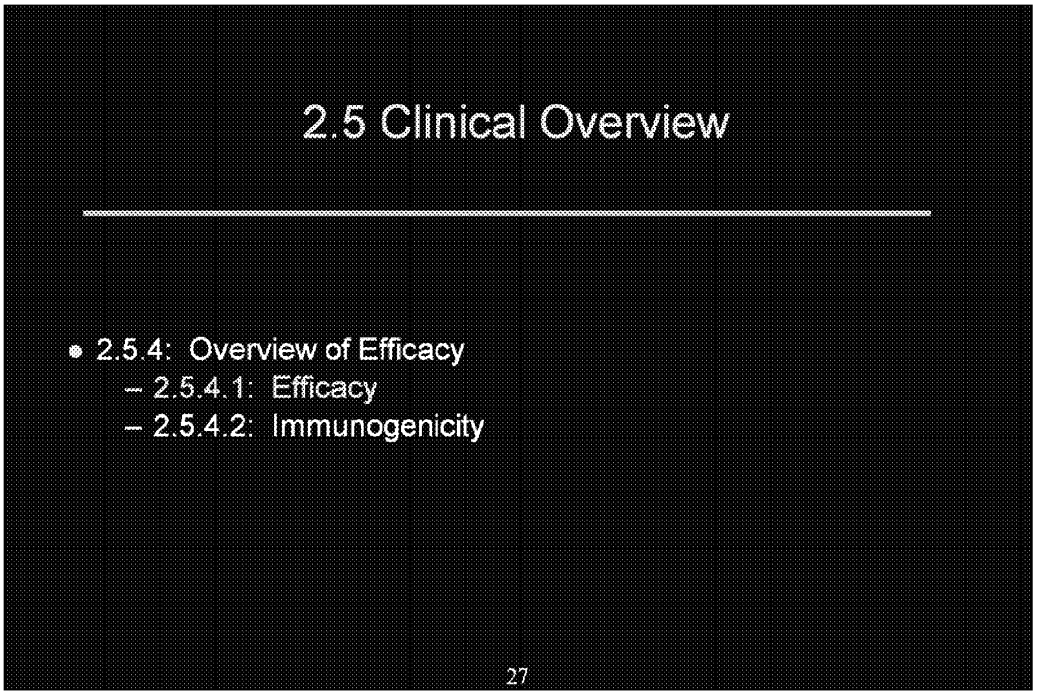
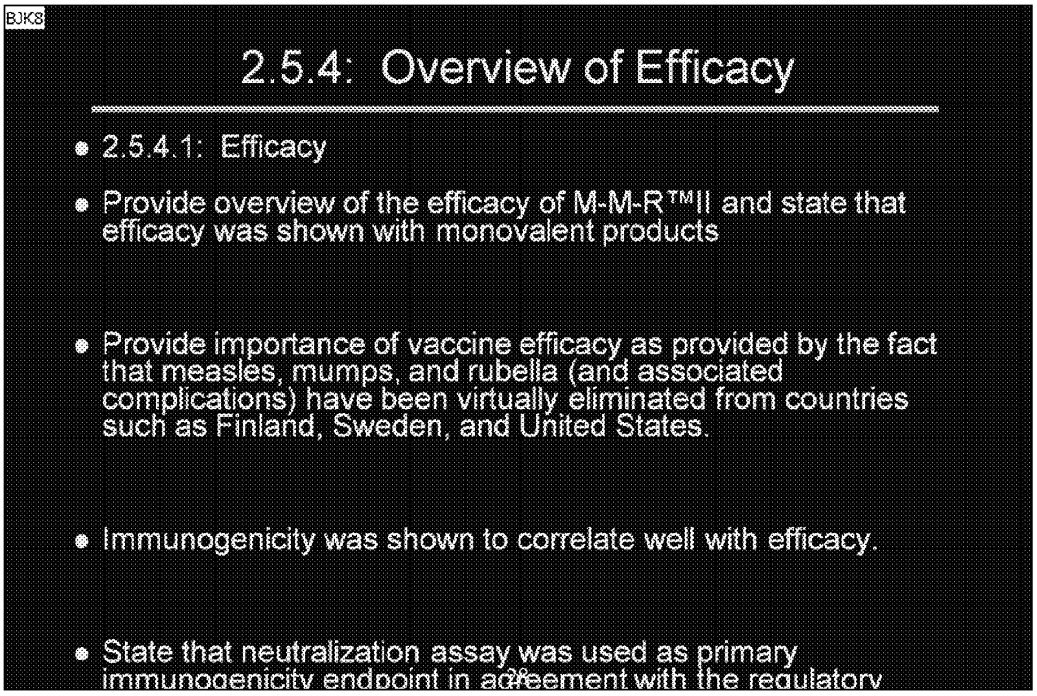
2.5.7: List of References
26

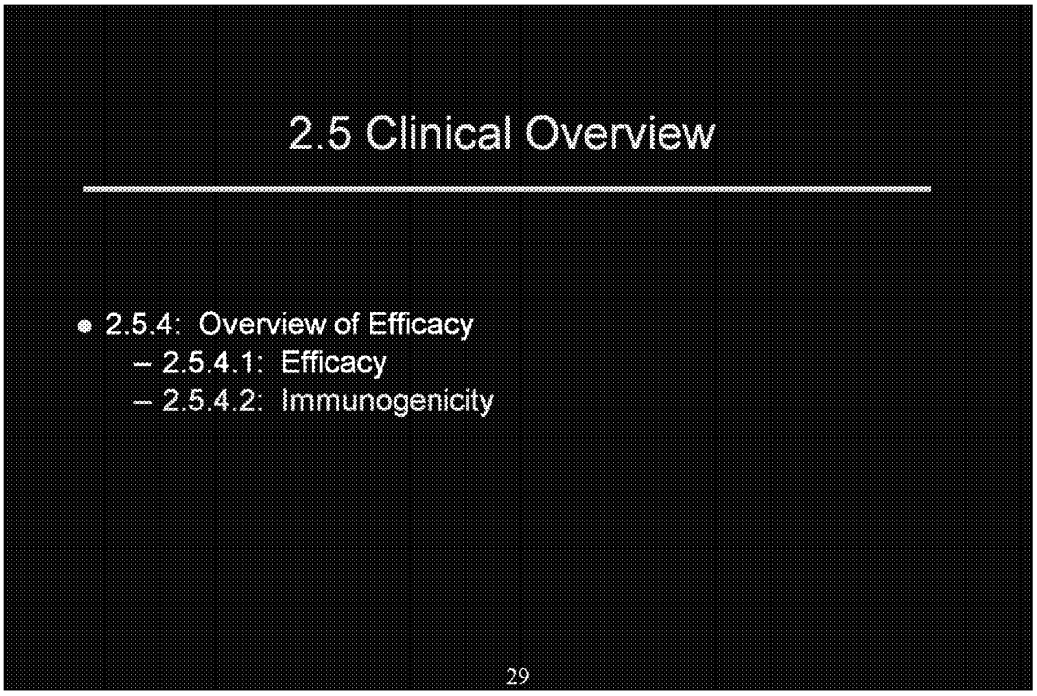


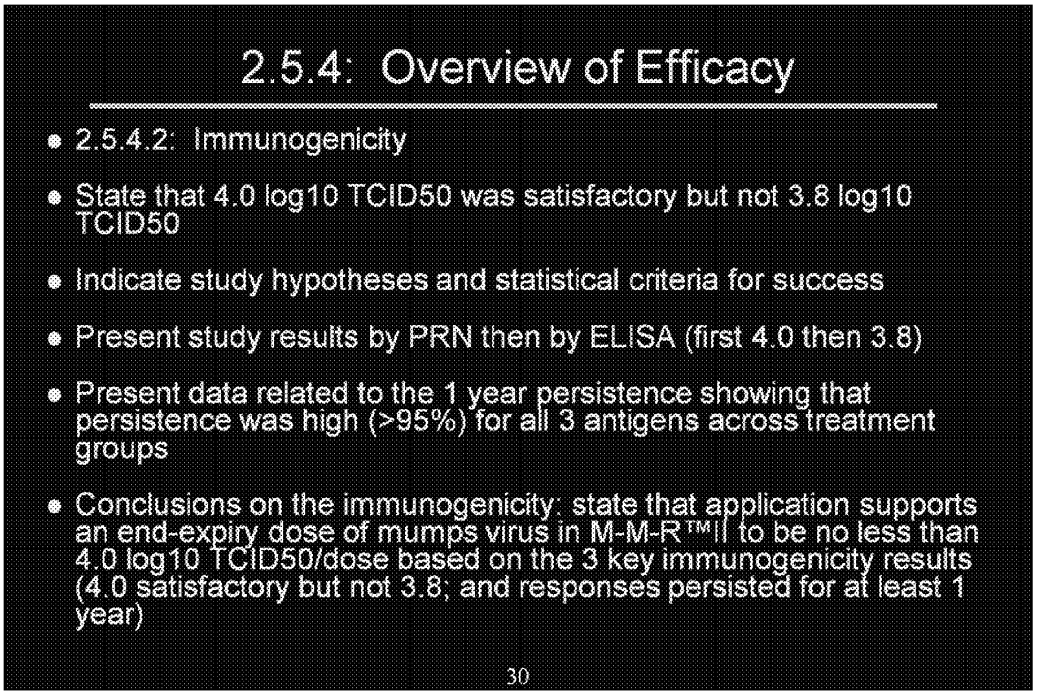

BJK8
2.5.4: Overview of Efficacy
2.5.4.1: Efficacy
Provide overview of the efficacy of M-M-R™II and state that efficacy was shown with monovalent products
Provide importance of vaccine efficacy as provided by the fact that measles, mumps, and rubella (and associated complications) have been virtually eliminated from countries such as Finland, Sweden, and United States.
Immunogenicity was shown to correlate well with efficacy.
State that neutralization assay was used as primary immunogenicity endpoint in agreement with the regulatory

**Slide 28**

**BJK8** Suggest first bullet say this is a "brief" summary

Change "bleeding" in last bullet to "blood specimen" - not sure how persistence fits under efficacy?
Barbara J. Kuter, 10/23/2003





# Analysis of Non-Inferiority and Acceptability of Mumps PRN Seroconversion Rates by Treatment Groups

| ≤4.0 $log_{10}$ $TCID_{50}$ Mumps Potency (N=662) | | | ~4.8 $log_{10}$ $TCID_{50}$ Mumps Potency (N=672) | | Estimated Difference (90% CI) | Acceptability | Similarity |
|---|---|---|---|---|---|---|---|
| n | Observed SCR (95% CI) | Estimated SCR | n | Estimated SCR | | | |
| 433 | 93.3% (90.5%, 95.5%) | 93.4% | 437 | 92.2% | 1.2 (-1.8,4.1) | Acceptable | Similar |

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# Analysis of Non-Inferiority and Acceptability of Mumps PRN Seroconversion Rates by Treatment Groups

| ≤3.8 $log_{10}$ $TCID_{50}$ Mumps Potency (N=663) | | | ~4.8 $log_{10}$ $TCID_{50}$ Mumps Potency (N=672) | | Estimated Difference (90% CI) | Acceptability | Similarity |
|---|---|---|---|---|---|---|---|
| n | Observed SCR (95% CI) | Estimated SCR | n | Estimated SCR | | | |
| 459 | 89.3% (86.1%, 92.0%) | 89.4% | 437 | 92.2% | -2.9 (-6.1 , 0.3) | Not Acceptable | Not Similar |

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# Comparison of Antibody Responses to Me, Mu, and Ru (ELISA) (1)

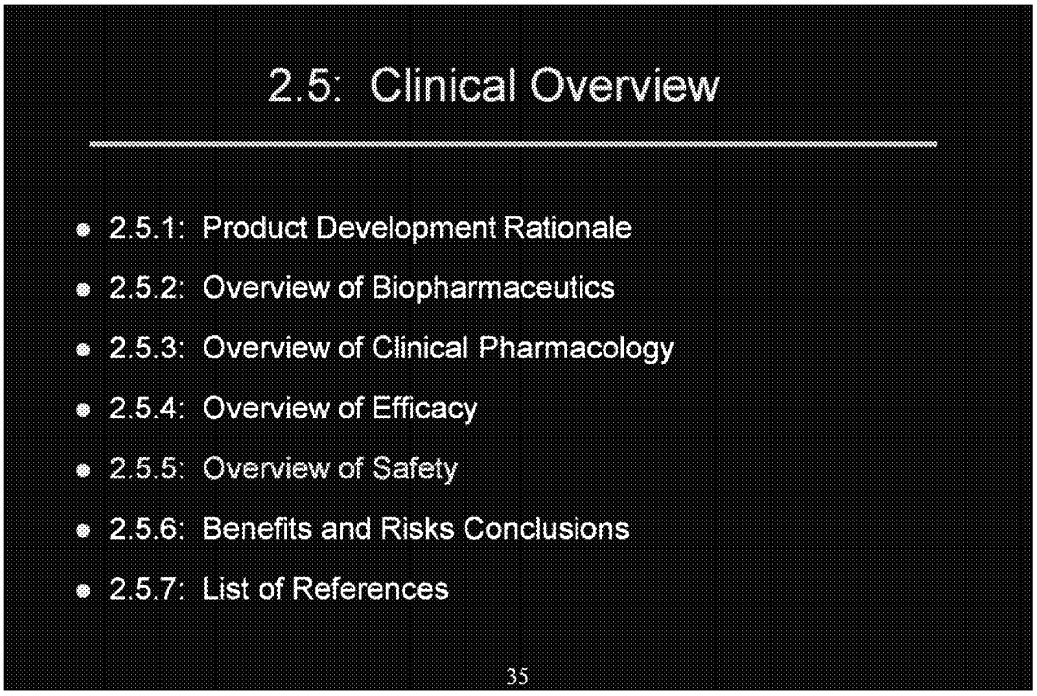
| Antigen | Mumps Potency ($log_{10}$ $TCID_{50}$/dose) | | | | Estimated Differences (90% CI) | Non-inferiority Conclusion |
|---|---|---|---|---|---|---|
| | ≤ 4.0 (N=662) | | ~4.8 (N=672) | | | |
| | n | Estimated SCR | n | Estimated SCR | | |
| REDACTED – OMP | | | | | | |
| Mumps | 583 | 97.4% | 588 | 98.0% | -0.6 (-2.1 , 0.9) | Similar |
| REDACTED – OMP | | | | | | |

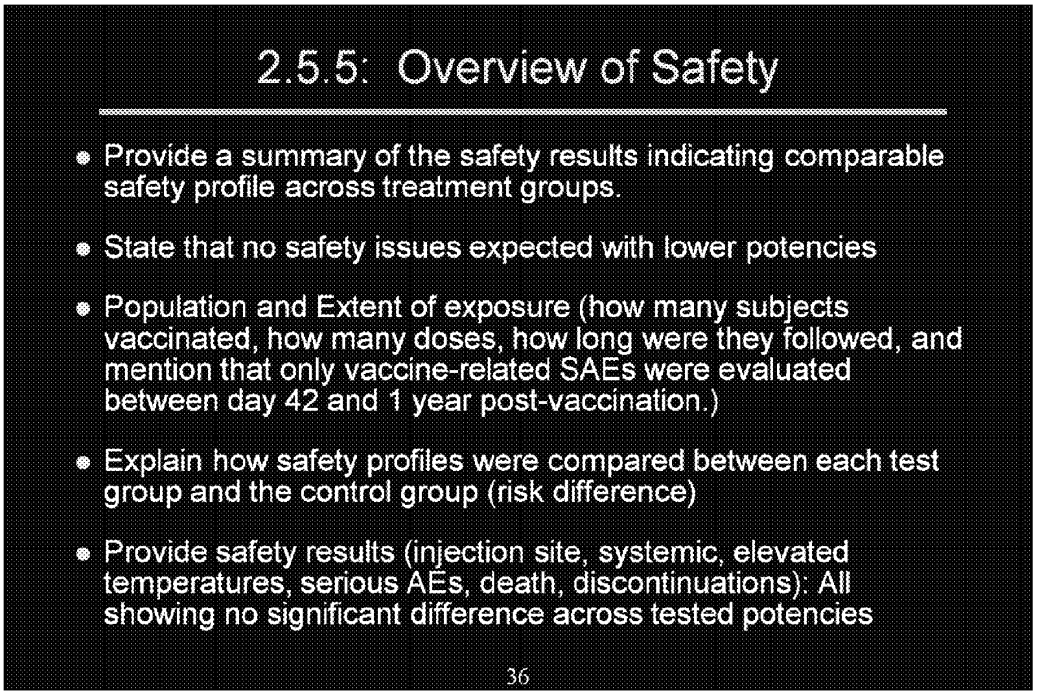
33

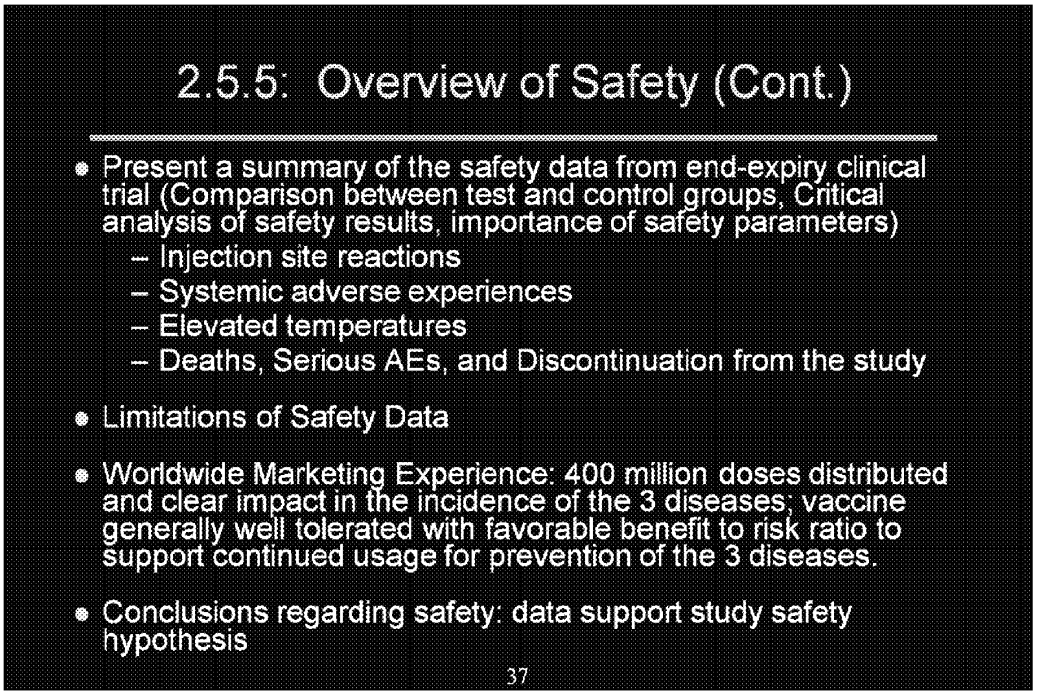
# Comparison of Antibody Responses to Me, Mu, and Ru (ELISA) (2)

| Antigen | Mumps Potency ($log_{10}$ $TCID_{50}$/dose) | | | | Estimated Differences (90% CI) | Non-inferiority Conclusion |
|---|---|---|---|---|---|---|
| | ≤ 3.8 (N=663) | | ~4.8 (N=672) | | | |
| | n | Estimated SCR | n | Estimated SCR | | |
| REDACTED – OMP | | | | | | |
| Mumps | 577 | 94.1% | 588 | 98.0% | -3.8 (-5.9 , -2.0) | Not Similar |
| REDACTED – OMP | | | | | | |

34


2.5: Clinical Overview
2.5.1: Product Development Rationale
2.5.2: Overview of Biopharmaceutics
2.5.3: Overview of Clinical Pharmacology
2.5.4: Overview of Efficacy
2.5.5: Overview of Safety
2.5.6: Benefits and Risks Conclusions
2.5.7: List of References
35


2.5.5: Overview of Safety
Provide a summary of the safety results indicating comparable safety profile across treatment groups.
State that no safety issues expected with lower potencies
Population and Extent of exposure (how many subjects vaccinated, how many doses, how long were they followed, and mention that only vaccine-related SAEs were evaluated between day 42 and 1 year post-vaccination.)
Explain how safety profiles were compared between each test group and the control group (risk difference)
Provide safety results (injection site, systemic, elevated temperatures, serious AEs, death, discontinuations): All showing no significant difference across tested potencies
36



# Clinical Adverse Experiences Observed During 42 days Follow-up* (1)

| | M-M-R ™ II with Mumps ≤ 3.8 $\log_{10}$ $TCID_{50}$/dose | | M-M-R ™ II with Mumps ≤4.0 $\log_{10}$ $TCID_{50}$/dose | | M-M-R ™ II with Mumps ≥4.8 $\log_{10}$ $TCID_{50}$/dose | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Total number of subjects | 663 | | 662 | | 672 | |
| Subjects with follow-up | 631 | | 636 | | 643 | |
| | | | | | | |
| Number (%) of subjects: | | | | | | |
| with no adverse experience | 91 | (14.4) | 105 | (16.5) | 92 | (14.3) |
| with one or more adverse experiences | 540 | (85.6) | 531 | (83.5) | 551 | (85.7) |
| MMR-related injection site reactions* | 213 | (33.8) | 220 | (34.6) | 219 | (34.1) |
| systemic adverse experiences | 489 | (77.5) | 488 | (76.7) | 497 | (77.3) |
| serious adverse experience | 10 | (1.6) | 6 | (0.9) | 9 | (1.4) |

*Adverse experiences include those related to both M-M-R™II and Varivax, with the exception of injection site reaction

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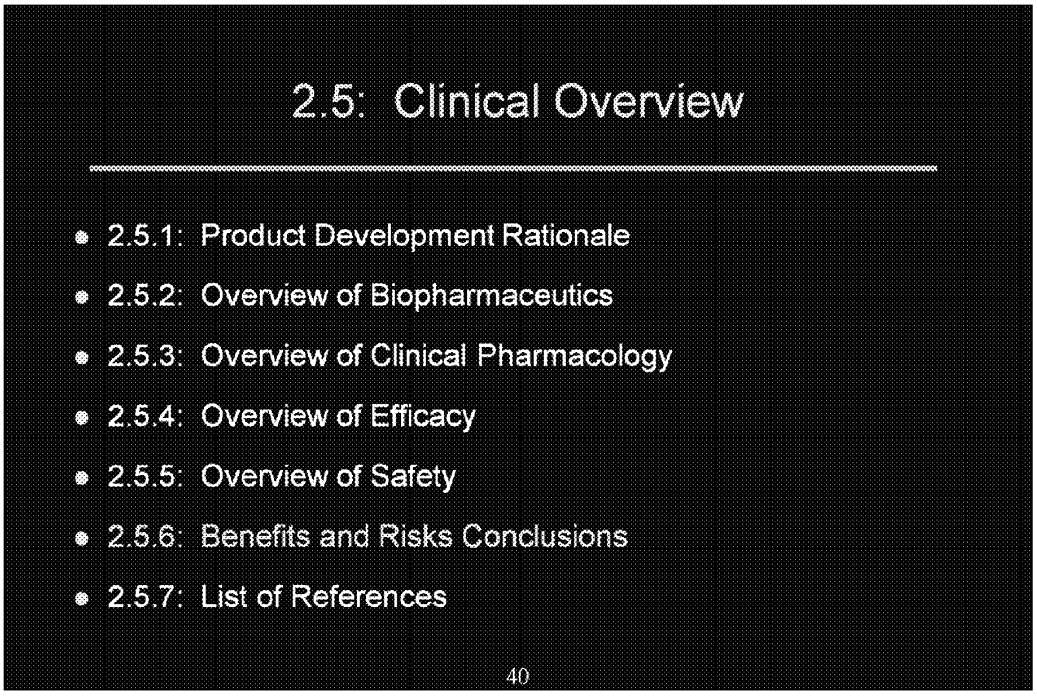
# Clinical Adverse Experiences Observed During 42 days Follow-up* (2)

| | M-M-R ™ II with Mumps ≤ 3.8 $\log_{10}$ $TCID_{50}$/dose N = 631 | | M-M-R ™ II with Mumps ≤4.0 $\log_{10}$ $TCID_{50}$/dose N = 636 | | M-M-R ™ II with Mumps ~4.8 $\log_{10}$ $TCID_{50}$ /dose N = 643 | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| With vaccine-related adverse experiences | 347 | (55.0) | 313 | (49.2) | 337 | (52.4) |
| MMR-related injection-site adverse experiences* | 213 | (33.8) | 220 | (34.6) | 219 | (34.1) |
| systemic adverse experiences | 181 | (28.7) | 148 | (23.3) | 150 | (23.3) |

*Adverse experiences include those related to both M-M-RII and Varivax, with the exception of injection site reaction

39


2.5: Clinical Overview
2.5.1: Product Development Rationale
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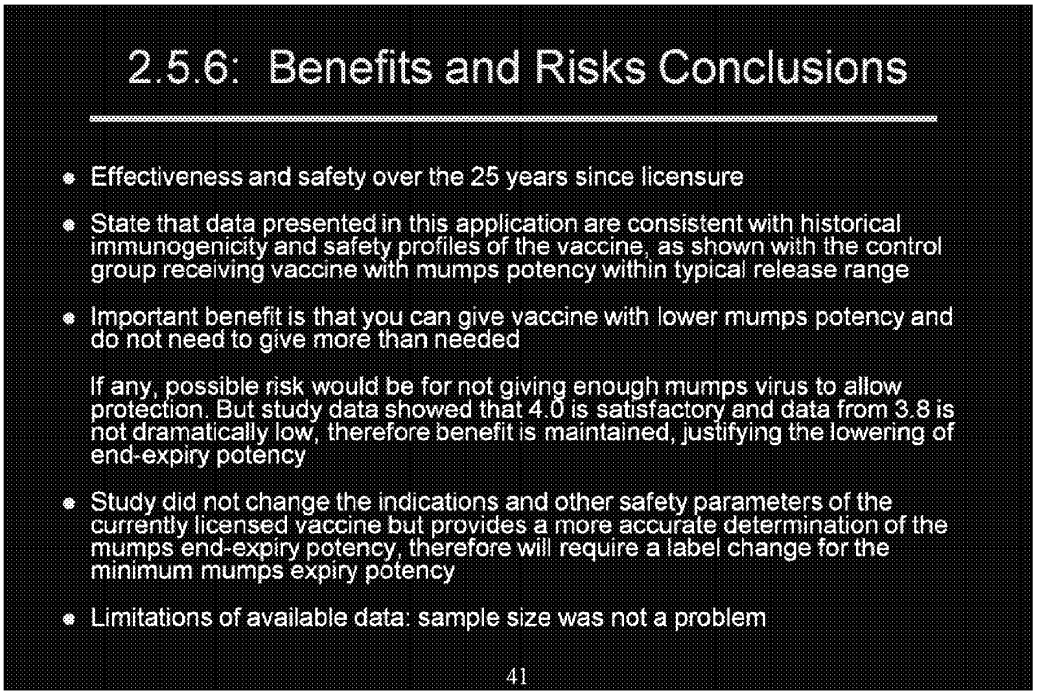
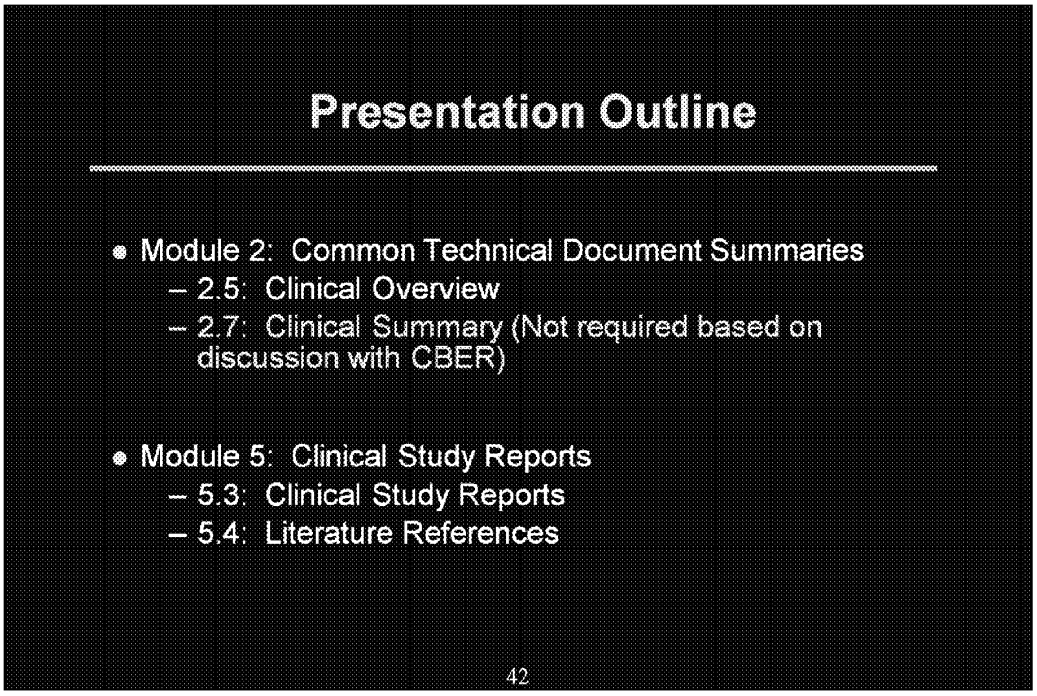
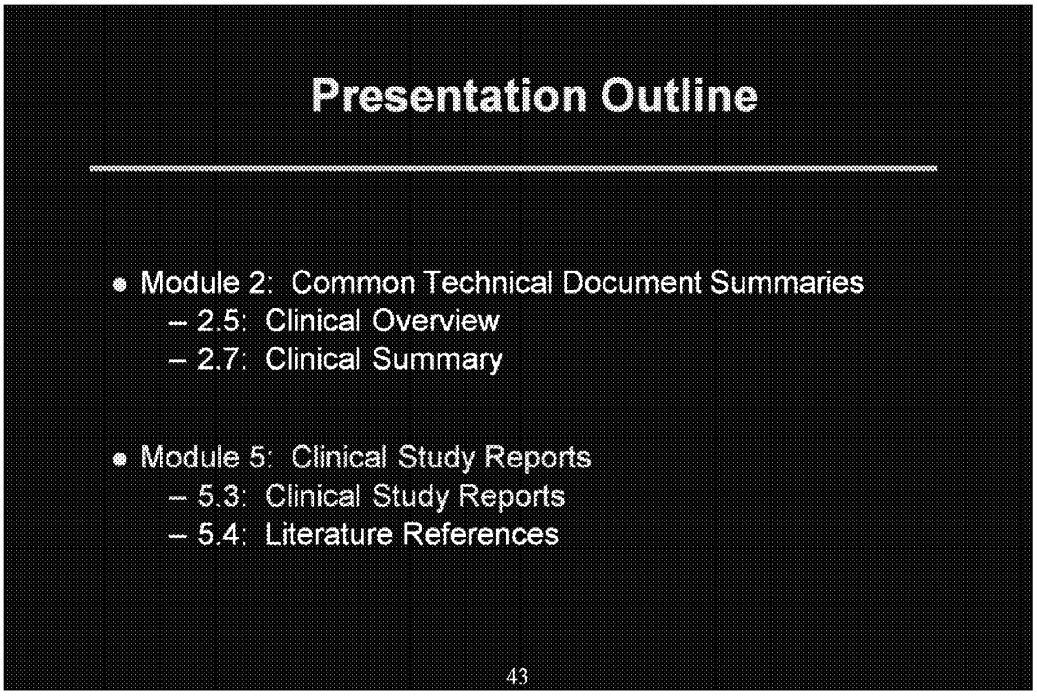
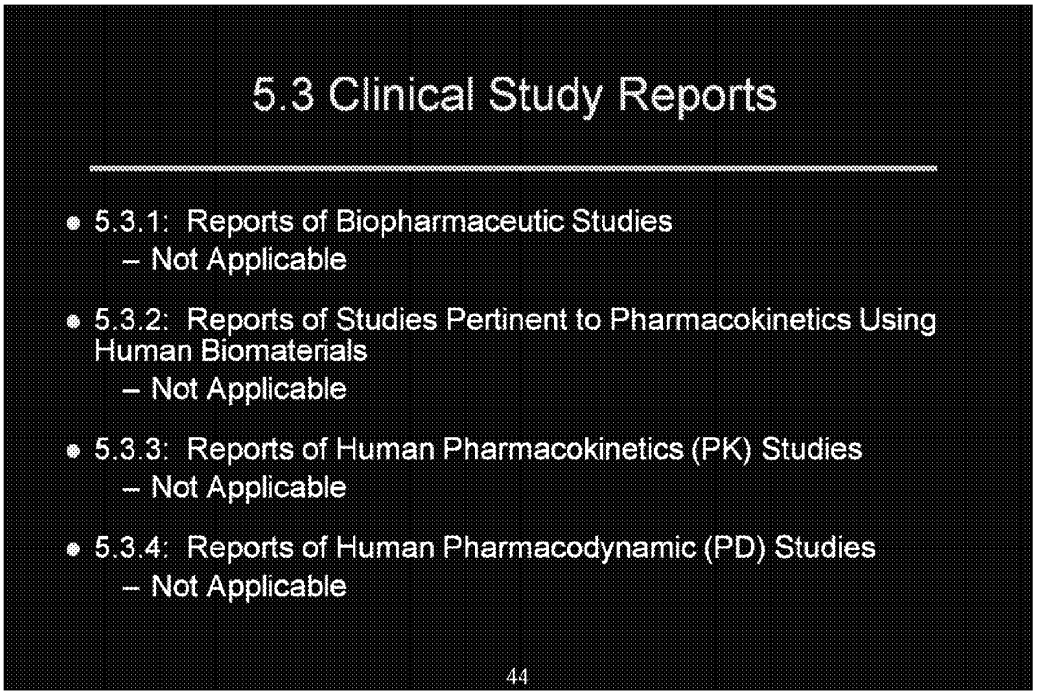
2.5.6: Benefits and Risks Conclusions
2.5.7: List of References
40





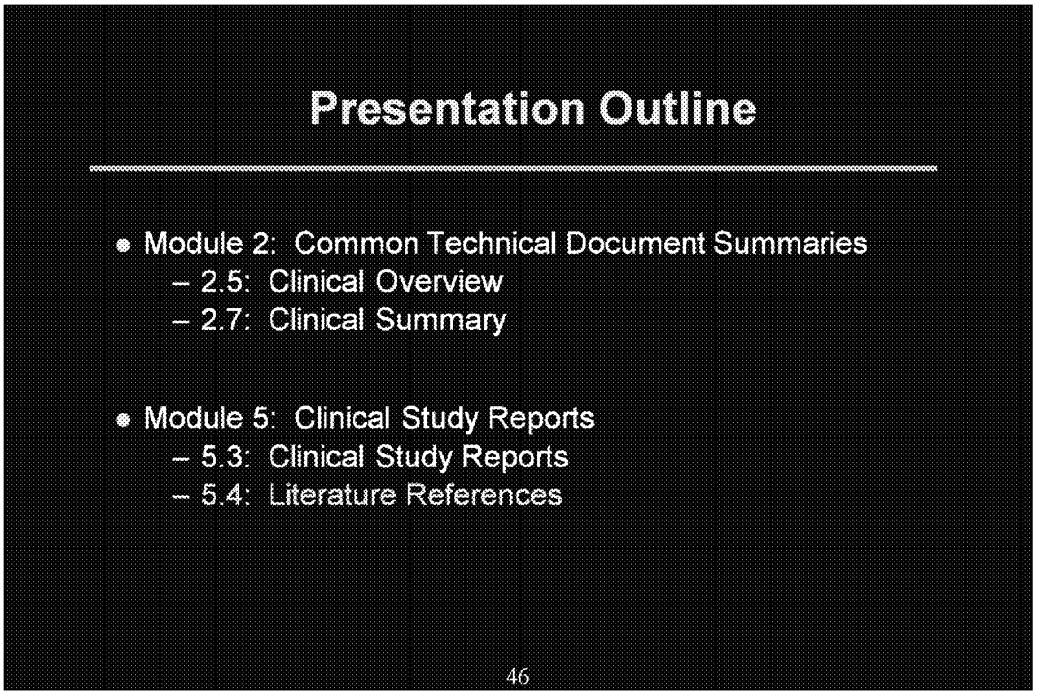


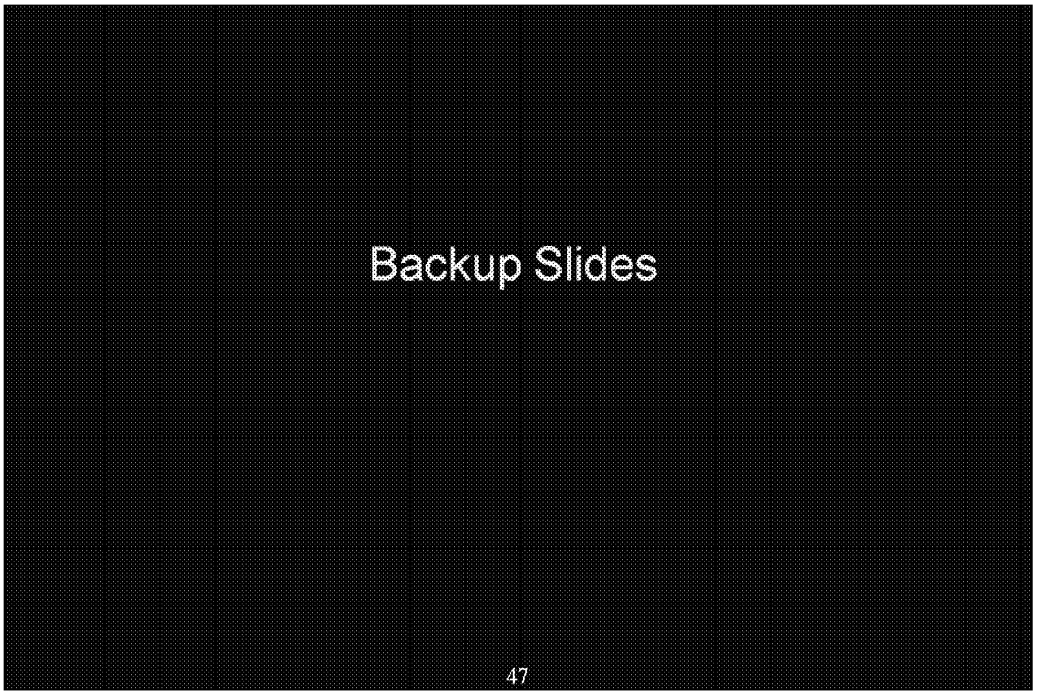

5.3 Clinical Study Reports
5.3.1: Reports of Biopharmaceutic Studies
– Not Applicable
5.3.2: Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials
– Not Applicable
5.3.3: Reports of Human Pharmacokinetics (PK) Studies
– Not Applicable
5.3.4: Reports of Human Pharmacodynamic (PD) Studies
– Not Applicable
44

## 5.3 Clinical Study Reports (Cont.)

- 5.3.5: Reports of Efficacy, Immunogenicity and Safety Studies
- Provide CSR for Protocol 007
- Provide report of the historical comparison of immunogenicity between M-M-R™II with oGOS and M-M-R™II with GOS
- 5.3.6: Reports of Post-marketing Experience
- Provide 5 year Post-marketing report (1996-2002)
- 5.3.7: Case Report Forms and Individual Subject Listings

45





# Methods Used To Achieve Expiry Potencies

| M-M-R™$_{II}$ Sublots | Experimental Conditions |
|---|---|
| M-M-R™$_{II}$ containing ≤3.7 $\log_{10}$ $TCID_{50}$ | Room Temperature for 12 weeks |
| M-M-R™$_{II}$ containing ≤4.0 $\log_{10}$ $TCID_{50}$ | Room Temperature for 7 weeks |
| M-M-R™$_{II}$ containing ~4.9 $\log_{10}$ $TCID_{50}$ | No Manipulation |

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# Targeted and Estimated Virus Potencies of Clinical Materials used in M-M-R™II Protocol 007

| M-M-R™II sublot | Antigen | Targeted Potency ($log_{10}$ $TCID_{50}$) | Estimated Potency (95% CI) ($log_{10}$ $TCID_{50}$)† | Adjusted Potency ($log_{10}$ $TCID_{50}$)‡ |
|---|---|---|---|---|
| M-M-R™II containing ≤3.7 $log_{10}$ $TCID_{50}$ | REDACTED – OMP | | | |
| | **Mumps** | ≤3.7 | 3.66 (3.69) | 3.8 |
| | REDACTED – OMP | | | |
| M-M-R™II containing ≤4.0 $log_{10}$ $TCID_{50}$ | **Mumps** | ≤4.0 | 3.94 (3.98) | 4.0 |
| | REDACTED – OMP | | | |
| M-M-R™II containing ~4.9 $log_{10}$ $TCID_{50}$ | **Mumps** | ~4.9 | 4.7 | 4.8 |
| | REDACTED – OMP | | | |

† Point estimate potency adjusted to mumps house standard value of 4.2

‡ Point estimate potency adjusted to mumps house standard value of 4.3

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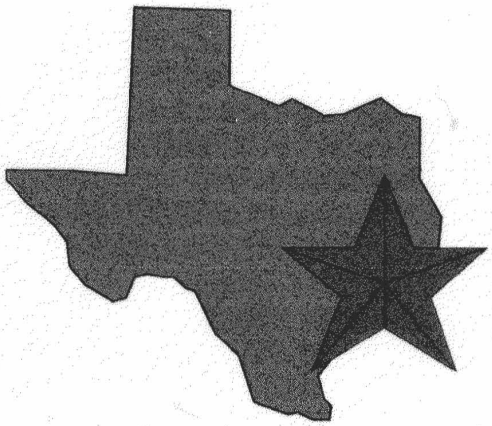
# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 119

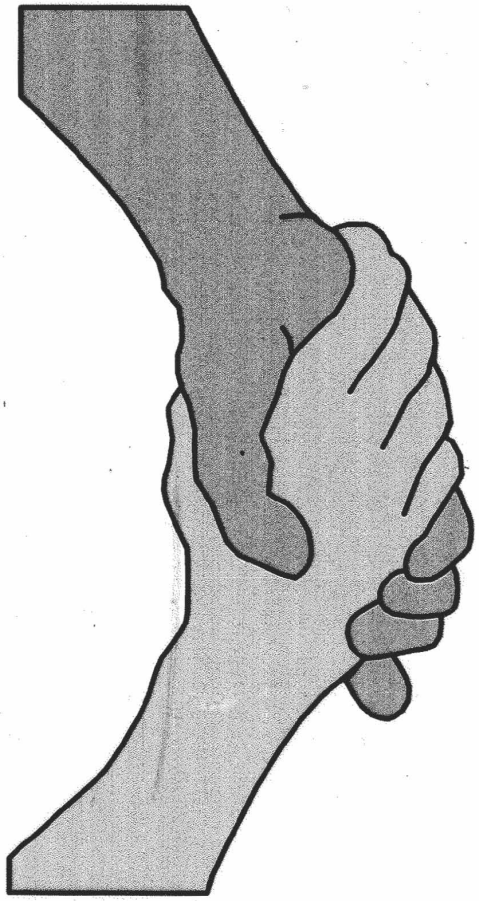
# M-M-R™II EXPIRY INVESTIGATORS MEETING



Irving, Texas

March 15-16, 1999

# INTRODUCTIONS



# MERCK PERSONNEL

- **Clinical**
  - Megan McBride
  - Kara Stockett
  - Colleen Taddeo
  - Dr. Scott Thaler
- **Statistics**
  - Dr. Stephanie Olsen
- **Data Coordination**
  - Leighann Graham
- **Quality Assurance**
  - Susan McNeill
- **Biometrics Research**
  - Timothy Schofield
- **Virus & Cell Biology**
  - Dr. David Krah
  - Mary Yagodich
- **Merck Vaccine Division**
  - Gina Esposito
  - Kim Haupt
  - Maureen Walter

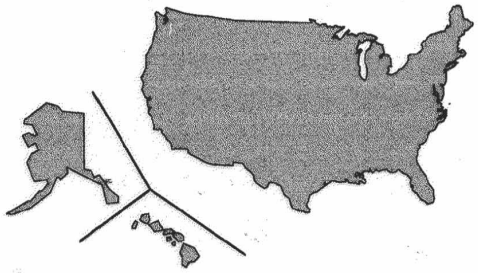
# MERCK PERSONNEL (cont'd)

## MRAs

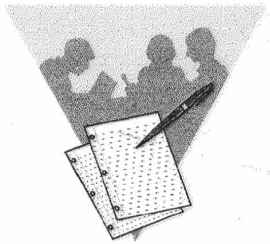
Medical Research Associates

- Yolie Amisola-Crume
- Cathy Anderson
- Joanne Bixler
- Jane Brunette
- Nicole Christison
- Michele Goldberg
- Madigan Harris
- Darrell Johnson
- Julie Kennedy
- Lee Lesneski
- John Loder
- Karen Martin
- Patricia Morgan
- Lawrence Peterson
- Nancy Reinhardt
- Jill Ryan
- John Smith
- Michelle Stallworth
- Eloise Watkins

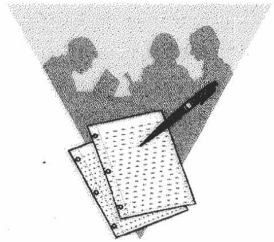
# STUDY SITES



- Boston
- Buffalo
- Chapel Hill
- Dallas
- Denver
- Honolulu
- Jackson
- Marshfield
- Nashville
- Norfolk
- North Canton
- Oakland
- Pittsburgh
- Rochester
- Salt Lake City
- San Diego



# AGENDA



| | | |
|---|---|---|
| Introduction | – | Dr. Scott Thaler |
| Protocol Background & Rationale | – | Dr. Scott Thaler |
| Protocol Overview & Administrative Issues | – | Megan McBride / Kara Stockett |
| Case Report Forms | – | Leighann Graham |
| Handling & Shipping of Sera | – | Megan McBride / Kara Stockett |
| Question & Answers | – | ALL |
| LUNCH | – | ALL |
| Adverse Event Review | – | Video |
| Study Monitoring | – | Darrell Johnson |
| Regulatory Aspects & Quality Assurance | – | Susan McNeill |
| Questions & Answers | – | ALL |
| Closing Remarks | – | Dr. Scott Thaler |

# A Study of M-M-R™II at Mumps Expiry Potency in Healthy Children 12-18 Months of Age

# BACKGROUND AND RATIONALE

- The components of M-M-R™II are live viruses and lose potency over time when stored at 2-8°C or higher.
- The FDA (CBER) has requested expiry potencies be placed on the label of M-M-R™II.
- No data exist for mumps at the expiry potency Merck has selected.
- A clinical immunogenicity trial is necessary to provide these data.

# M-M-R™II END EXPIRY POTENCIES SUGGESTED FOR THE LABEL

| Component | Potency/Dose ($log_{10}$ $TCID_{50}$) |
|---|---|
| REDACTED – OMP | |
| Mumps | 3.7 |
| REDACTED – OMP | |

# DETERMINATION OF VACCINE SHELF-LIFE

Target or Fill Potency

Vaccine Stability

Minimum Immunizing Dose

## TABLE 3: Marketing Stability Results for Measles Containing Vaccines

REDACTED – OMP

## TABLE 4: Marketing Stability Results for Mumps Containing Vaccines

| | | Total Loss: Release to 24 Mos. | | | Predicted Expiry Potency at 24 Mos. | | |
|---|---|---|---|---|---|---|---|
| Lot Subset | # of Lots | Average | 95% LCL | 95% UCL | Average | 95% LCL | 95% UCL |
| Single Dose | 65 | 0.52 | 0.36 | 0.68 | 4.45 | 4.29 | 4.61 |
| Multi-Dose | 10 | 0.37 | 0.21 | 0.52 | 4.53 | 4.37 | 4.68 |
| All | 75 | 0.50 | 0.37 | 0.64 | 4.45 | 4.32 | 4.59 |

# MEASLES AND MUMPS DATA ON MINIMUM IMMUNIZING DOSE

- Buynak EB et al. JAMA 1969; 207: 2259-62.
  - Includes data on MeMu, MeMuRu bi/trivalent
- Buynak EB et al. JAMA 1968; 203: 9-13.
  - Mu only
- Stokes J et al. Pediatrics 1967; 39: 363-71.
  - Mu only

# MINIMUM IMMUNIZING DOSE: MEASLES DATA

[redacted]

REDACTED – OMP

# MINIMUM IMMUNIZING DOSE: MUMPS DATA

| Vaccine | Dose | N | SCR | GMT (SNT) |
|---|---|---|---|---|
| Trivalent (HPV-77) | 4.4 | 28 | 93% | 8 |
| MeMu bivalent | 3.8 | 13 | 77% | 5 |
| Mu mono | 3.1 | 11 | 100% | 4.5 |
| Mu mono | 3.1 | 13 | 100% | 7.2 |
| Mu mono | 1.6 | 8 | 75% | 1.5 |

# DETERMINATION OF MEASLES AND MUMPS SHELF LIFE

## (all values in $log_{10}$ $TCID_{50}$)

| | Expiry Potency | 95% UL on 24 Month Loss | Target Fill | Buffer | Minimum Immunizing Dose |
|---|---|---|---|---|---|
| REDACTED – OMP | | | | | |
| Mumps | 4.3 | 0.64 | 4.9 | -0.04 | 3.1 |

# PRODUCTION OF M-M-R™II AT EXPIRY

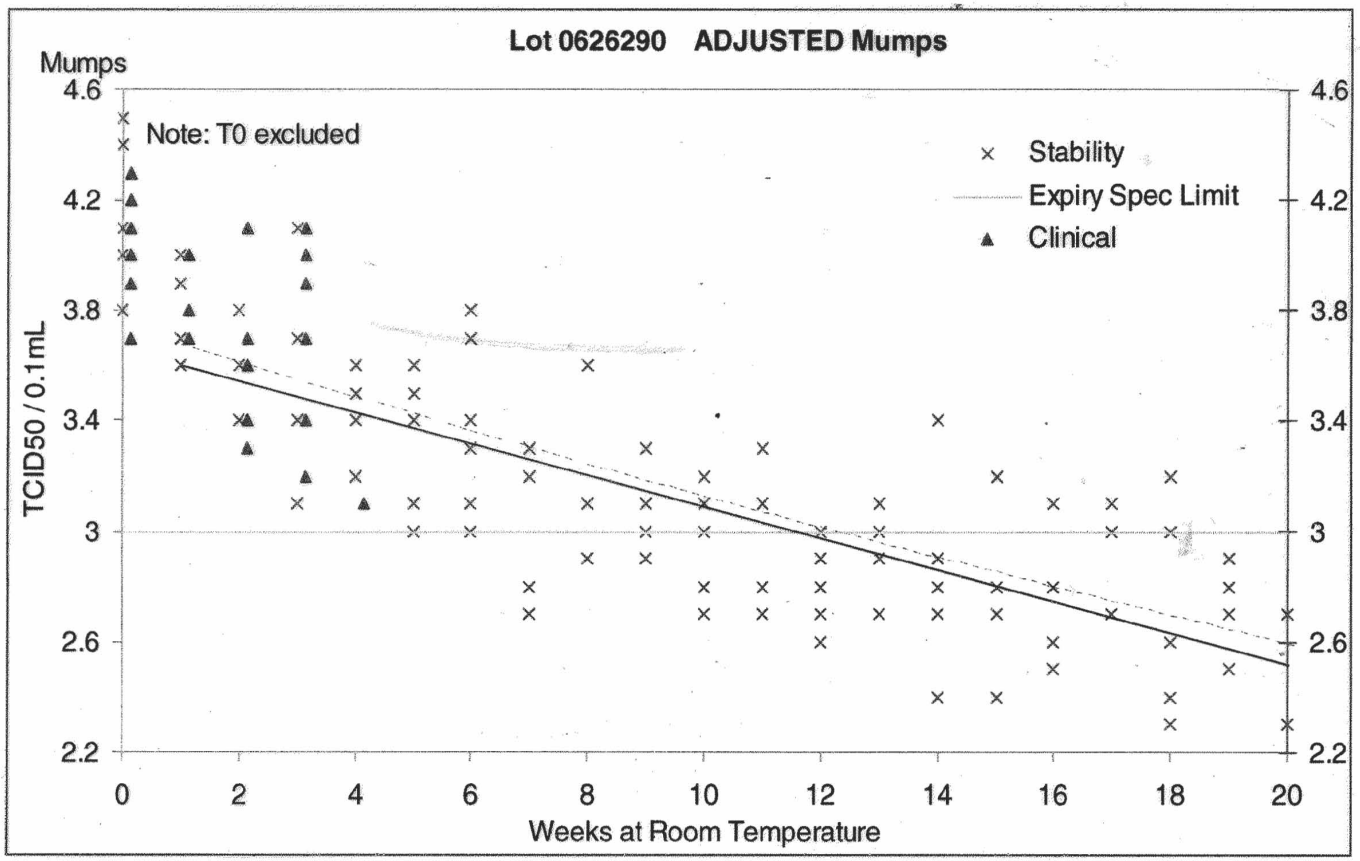
- Natural Aging (2-8°C).
- Accelerated Aging at RoomTemperature (20-25°C).
- Dilution of Components.

| Study Type | Advantages | Disadvantages |
|---|---|---|
| **Accelerated Aging at Room Temperature (20-25°C)** | • Material may be produced relatively quickly<br>• Change in live/inactive particle ratio similar to natural aging | • Heat-induced qualitative antigenic changes<br>• Effect on all 3 viruses in M-M-R™II not predictable<br>• Effect on more susceptible sub-populations |
| **Dilution** | • Material available relatively quickly<br>• No heat-induced change in antigenicity<br>• Enhance theoretical interference between components<br>• Similar effects on all sub-populations | • Least similar to natural aging process<br>• Alteration in protein concentration<br>• Ratio of live/inactive particles not maintained |
| **Natural Aging at 2-8°C** | • Measures real-time stability and decay | • Very slow process<br>• Effect on all 3 viruses in M-M-R™II not predictable |

# THE PRELIMINARY AGING EXPERIMENT

- **Goal:**
  - Reduce vaccine potency while minimizing the margin of error and ensure the true potency is no greater than the target.
- **Methods:**
  - Incubate 3 potential clinical lots at room temperature.
  - Use a 1x6 potency testing scheme for 27 weeks.
  - Generate best fit curves using all available data.
  - Begin aging clinical material once decay understood.

# Stability Data for Lot #0626290 Showing Results of Tests on Clinical Samples for Mumps.



# ESTIMATED POTENCIES OF STUDY SUBLOTS

| Group | N | Measles Titer ($log_{10}$ $TCID_{50}$) | Mumps Titer ($log_{10}$ $TCID_{50}$) | Rubella Titer ($log_{10}$ $TCID_{50}$) |
|---|---|---|---|---|
| Sublot #1 | 500 | REDACTED – OMP | ~4.9 | REDACTED – OMP |
| Sublot #2 | 500 | | ~3.98 | |
| Sublot #3 | 500 | | ~3.69 | |

# IMMUNOGENICITY MEASUREMENTS

REDACTED – OMP

- For Mumps, a functional (neutralization) assay has been developed.
  - Neutralization will be measured using a "bread and butter" plaque reduction neutralization (PRN) assay.
  - a wild type mumps strain will be used in the PRN assay to best assess protection from wild mumps infection.

# PLAQUE REDUCTION MUMPS NEUTRALIZATION ASSAY

- Serum dilutions are mixed with TN wt mumps for one hour, quenched, then added to Vero cell monolayers:
  - Presamples to be tested at 1:2 and 1:4.
  - Postsamples to be tested at 1:4 and 1:8.
  - A randomly selected subset (~20%) will be diluted out to titer to compute GMTs.
- Incubated 6 days with media supplemented with agarose.
- Stained with 0.2% Coomassie Blue R-250 in ETOH.
- Titer is the highest dilution that leads to at least 50% plaque reduction.

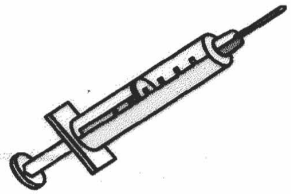
# PRELIMINARY GUIDELINES FOR THE PRN ASSAY

- **Negative (not protected)**
  - <1:2
- **Positive (protected)**
  - ≥1:4
- **Seroconversion by PRN**
  - ≥ 4 fold rise in antibody titer

# ADVANTAGES TO PARTICIPATION IN THIS TRIAL FOR SUBJECTS

- Avoid unnecessary exposure in the future to higher levels of mumps vaccine virus.
- A positive mumps neutralization titer almost certainly ensures protection from wild type infection.
- Lower doses of mumps may be associated with lower rates of side effects.

# PROTOCOL 007



## A Study of M-M-R™II at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age

# PRIMARY OBJECTIVES

- To demonstrate a similar immune response to mumps by neutralization among subjects receiving M-M-R™II containing an expiry dose of mumps compared to subjects receiving M-M-R™II containing a release dose of mumps.
- To demonstrate an adequate immune response to mumps among subjects receiving M-M-R™II with an expiry dose of mumps.

# SECONDARY OBJECTIVES

- To demonstrate similar immune responses (by ELISA) for measles, mumps and rubella among children who receive M-M-R™II containing an expiry dose of mumps and children receiving M-M-R™II containing a release dose of mumps.
- To summarize the GMTs to measles, mumps, rubella and varicella 42 days postvaccination in both the expiry and control groups.

# SECONDARY OBJECTIVES

(cont'd)


- To summarize the proportion of subjects with mumps PRN titers $\geq$ 1:8 in both expiry and control groups.

# SECONDARY OBJECTIVES

(cont'd)

- To summarize the PRN titers (GMTs) in a randomly selected subset of subjects in both the expiry and control groups 42 days postvaccination.
- To describe the safety and tolerability of M-M-R™II containing an expiry dose of mumps given concomitantly with VARIVAX™.

# STUDY DESIGN SUMMARY

- Randomized, Double-Blind, Multi-Center Study
- 3 Groups:
  - **Control** (~4.9 $\log_{10}$ $TCID_{50}$ mumps).
  - **Intermediate Expiry** (~4.0 $\log_{10}$ $TCID_{50}$ mumps).
  - **Expiry** (~3.7 $\log_{10}$ $TCID_{50}$ mumps).
- Each subject receives a single injection of M-M-R™II and VARIVAX™.
- 3 Visits: Day 0, day 42-56, and at one year.

# Study Flow Chart

| TEST/PROCEDURE | Sublot #1 M-M-R™$_{II}$A (Control Group) | | | Sublot #2 M-M-R™$_{II}$B (Mumps Expiry Group) | | | Sublot #3 M-M-R™$_{II}$C (Mumps Expiry Group) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Day 0 | Day 42 (42-56) | Day 365 (335-395) | Day 0 | Day 42 (42-56) | Day 365 (335-395) | Day 0 | Day 42 (42-56) | Day 365 (335-395) |
| VACCINATION<br>M-M-R™$_{II}$ | X | | | X | | | X | | |
| REDACTED – OMP | | | | | | | | | |
| OBTAIN BLOOD SAMPLE | X | X | X | X | X | X | X | X | X |
| LABORATORY TESTS<br>Mumps Neutralization Assay<br>ELISA | X<br>X | X<br>X | X<br>X | X<br>X | X<br>X | X<br>X | X<br>X | X<br>X | X<br>X |
| REDACTED – OMP | | | | | | | | | |
| CLINICAL FOLLOW-UP | | X | | | X | | | X | |

# INCLUSION CRITERIA

- Children 12-18 months of age.
- In good health based on medical history.
- Signed informed consent form.
- No clinical history of vaccination for measles, mumps, rubella, varicella or zoster.

# EXCLUSION CRITERIA

- Prior measles, mumps, rubella or varicella vaccine.
- Prior clinical history of measles, mumps, rubella, varicella or zoster.
- Any allergy to vaccine components including anaphylactoid allergy to eggs.
- Any exposure to measles, mumps, rubella, varicella or zoster in the past 4 weeks.

# STUDY FLOW CHART

- Day 0:
  - Review Eligibility
  - Obtain History/Consent
  - Obtain Blood Sample (~5-10 mLs)
  - Administer Vaccines:
    - M-M-R™II to the Arm
    - VARIVAX™ to the Thigh
  - Hand-out and Review VRC with Parent

# EXCLUSION CRITERIA
(cont'd)

- Receipt of immune globulin or blood products within 3 months of entry or 42 days thereafter.
- Febrile illness within 72 hours of vaccination.
- Any immune impairment including immunosuppressive chemotherapy.
- Vaccination with other live attenuated vaccines 30 days prior to entry or 42 days thereafter.
- Vaccination with any inactivated vaccine 14 days prior to entry or planned 42 days thereafter.

# CONCURRENT TREATMENTS

- No live virus vaccine for 30 days before and 42 days after each dose of vaccine administered in this study.
- No inactivated vaccines (Hib, DTP, etc.) for 14 days before and 42 days after receipt of each dose of the vaccine.

# STUDY FLOW CHART
(cont'd)

- Day 42 to 365:
  - Follow-up for vaccine-related SAEs
- Day 365 (335 to 395 days):
  - Obtain Blood Sample (~ 5-10 mLs)
  - Complete 1-year Persistence Bleed Workbook
  - Collect Exposure Information

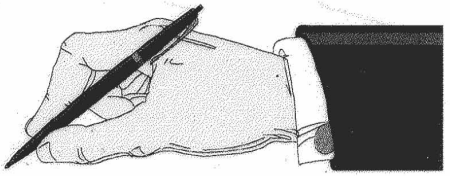
# STUDY FLOW CHART
(cont'd)

- Day 0 to 42:
  - Safety Follow-up
- Day 42 (42 to 56 days):
  - Obtain Blood Sample (~5-10 mLs)
  - Collect VRC and Review
  - Collect Exposure Information
- Day 279 (9 months Post-Vaccination):
  - Telephone Contact with Parent

# ALLOCATION NUMBERS

- Assign allocation number after subject is consented, inclusion/exclusion criteria are reviewed, and pre-vaccination blood draw is performed.
- A baseline number will only be assigned if the subject is consented but the vaccination does not occur. Contact MPC for assignment of baseline number.

# CONSENT



- Investigator must obtain written consent from each potential subject's parent/guardian prior to performing any clinical research procedures.

- Parent/guardian must sign two copies:
  - *One signed copy for study files.
  - *One signed copy for parent/guardian.

# CONCURRENT TREATMENTS

(cont'd)

- No administration of immune globulin or blood products for 3 months (90 days) before or 42 days after vaccination unless there is a medical emergency warranting their use.
- No salicylates during the 6 weeks after vaccination because the use of salicylates in children with varicella has been associated with Reye's syndrome.

# BLINDING (cont'd)

- Sites will unblind a subject only in the event of a **medical emergency.**
- Masked Schedules for unblinding subjects will be maintained with the SPONSOR and at the primary site.
- Masked Schedules should be maintained in a secure location.
- At the end of the study, all masked schedules should be returned to the SPONSOR either intact or with the unblinding log.

# BLINDING

- The following persons will be blinded until all subjects have completed the study and data is screened for completeness:
  - SPONSOR personnel directly involved in study.
  - Subject/Parent/Guardians.
  - Investigators.
- All vials of M-M-R™II will appear identical.
- Any vial of *supplied* VARIVAX™ may be used.

# SUGGESTED METHOD FOR BLOOD COLLECTION

- Blood should be drawn (~ 5-10 mLs).
- Blood should be allowed to clot in the collection tube for 30-60 minutes.
- Clotted blood should not sit at room temperature or refrigerated for more than 2 hours before centrifugation and separation.
- Do not refrigerate newly collected blood.
- After separation place the serum in a vial provided by Merck and place the correct label on the vial prior to freezing. Use only Merck provided vials and labels.

# SERUM VIAL LABELS

| Label Color | Bleed Interval |
|---|---|
| **Red** | **PRE** |
| **Blue** | **Day 42** |
| Yellow | 1-Year |

# REMINDER

- Megan or Kara: CRFs and Correspondence



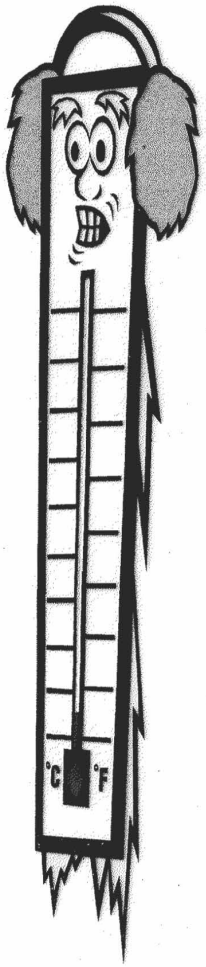


- Kyna: Serum Samples

# VACCINE SHIPPING AND STORAGE

- Because the M-M-R™II in this trial is artificially aged, all M-M-R™II vaccine will be shipped and stored frozen at -15°C.
- REDACTED – OMP
- For consistency, both M-M-R™II and VARIVAX™ should be used within 30 minutes of reconstitution.

# STORAGE OF VACCINE




- M-M-R™II / VARIVAX™
  - 15°C (+5°F) or colder, frost-free freezer.
- All vaccines supplied in 0.7 mL vials for a 0.5 mL injection.
- The vaccines must be administered within 30 minutes.
- Daily monitoring and documentation must be maintained for freezers and refrigerators.

# STORAGE OF DILUENT

- 2 to 8°C (36 to 46°F) or room temperature.
- Supplied in 0.7 mL vials.
- For use with M-M-R™II and VARIVAX™.

# RETENTION VIALS

- Use to monitor shipping, handling and storage of vaccines.
- 12 Vials of each vaccine (M-M-R™II, VARIVAX™) designated as retention vials.
- Must be stored with the study vaccine but not used during the trial.
- Must be returned to SPONSOR within 3 months of study completion or as requested.

# REPLACEMENT VIALS

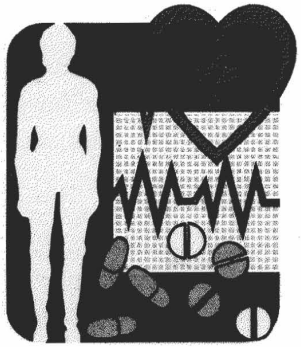
- Replacement vials will be available at each site to be used in the event of an error in reconstitution of vaccine or if not administered within 30 minutes.
- Contact MPC or Monitor (at home if needed) for replacement number.

# ADVERSE EXPERIENCE (AE)

"Any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with any use of a Merck product in humans."

***Whether or not*** *considered related to the use of the product*

# ADVERSE EXPERIENCES



| | **AE** |
|---|---|
| Pre-existing condition | NO |
| **RECURRENCE/WORSENING** of a pre-existing condition | YES |

# CLASSIFYING AEs BY INTENSITY

**Mild:**

– Awareness of symptom, but easily tolerated.

**Moderate:**

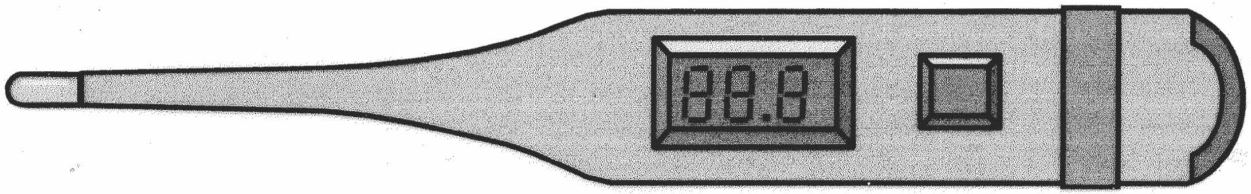
– Definitely acting like something is wrong.

**Severe:**

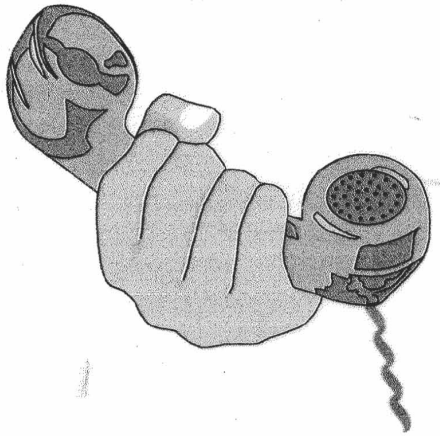
– Extremely distressed or unable to do usual activities.

# SAFETY MEASUREMENTS

- All AEs, whether systemic or injection-site occurring 42 days after each injection must be reported.
- Parent/guardian will record numerical temperatures for 42 days after each injection.



# SAFETY MONITORING



Report to Merck within 24 hours:

- All serious adverse experiences occurring 42 days after each injection.
- Only vaccine-related SAEs after Day 42 through Day 365.

# SERIOUS ADVERSE EVENTS

- Is life threatening.
- Results in a persistent or significant disability or incapacity.
- Results in or prolongs an existing in-patient hospitalization.
- Is a congenital anomaly or birth defect.
- Is cancer.
- Is the result of an overdose.
- Other important medical event .
  - (ex. Febrile seizures)

# AEs MUST BE REPORTED

- Serious AEs - within 24 hours to one of the individuals listed on the SPONSOR contact page of the protocol (usually via MPC):
  - Megan McBride ☎ (610) 397-2941
  - Kara Stockett ☎ (610) 397-2207
  - Scott Thaler, M.D. ☎ (610) 397-2625
- All AEs are to be recorded on case report forms.

# RASHES

- Measles or rubella-like and/or varicella-like rashes should be seen by study physician.
- Exposure to measles, mumps, rubella, varicella or zoster should be documented on the appropriate CRF.

# RASHES

## (cont'd)

- If a child is thought to have measles, rubella, measles or rubella-like rash, mumps, mumps-like symptoms, varicella, varicella-like rash or zoster:
- Collect exposure information and complete appropriate CRFs.

# STUDY DURATION

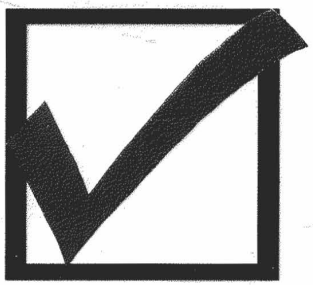
- Subject has completed study if:
- 42 days of safety follow-up after each vaccination.
- Received all scheduled vaccinations, and
- Pre- and Post-vaccination serum samples obtained.

# CONFIDENTIALITY

- By signing the protocol the investigator affirms that information furnished by MRL will be maintained in confidence.
- Information will be provided to the IRB; affiliated institution; and employees only under the understanding of confidentiality.
- Records must be maintained in a secure location.

# PUBLICATIONS

- We will establish a publications committee during the trial.
- MRL must review all publications 60 days prior to submission.
- Information identified by MRL as confidential must be deleted from any publication.



# IRB APPROVAL

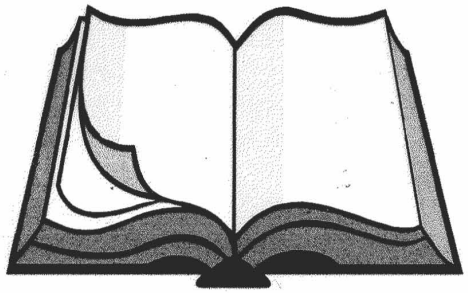
Written approval from the IRB must be forwarded to MRL before clinical supplies will be shipped. For continuing studies, written approval from the IRB must be sent to MRL at intervals not to exceed one year.

# STUDY REQUIREMENTS

- IRB approval of protocol/consents.
- FDA 1572 Form.
- Signed Protocol/Completed Title Page.
- Copy of approved consent forms.
- CVs for all personnel working on study.
- Pre-study site visit (Merck MRA).
- IRB Compliance Letter

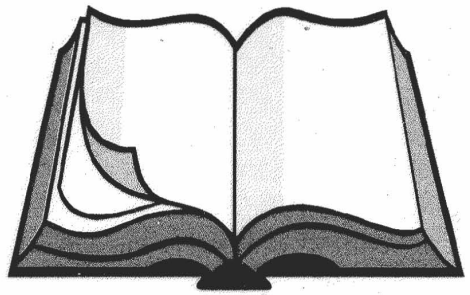
# ADMINISTRATIVE BINDER

- Merck Contacts.
- Protocol/Amendments.
- Consent Form.
- IRB Approval.
- Personnel Signature Page.
- Allocation Numbers/Study Enrollment Log.



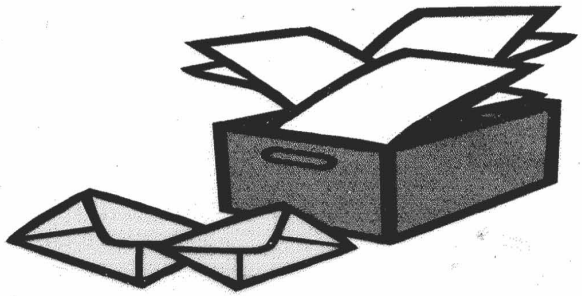
# ADMINISTRATIVE BINDER (cont'd)

- Data Collection Forms/Instructions.
- Vaccine Storage/Temperature Log.
- Vaccine Accountability/Returns.
- Good Clinical Practices.
- Serious AEs.
- Merck Monitoring Log.
- Correspondence.



# RECORDS RETENTION

Government agency regulations and directives require documentation pertaining to a clinical trial must be retained by the investigator for a minimum of 2-years after notification by MRL, or longer if requested by MRL.



# MEDICAL PROGRAM COORDINATOR

- Administrator for Merck Clinical Trials.
- Primary contact for study information.
  - *Serious Adverse Experiences*
- Responsible for study initiation, data collection and review.
- Summarization of study findings.

# MERCK CONTACTS

## *Clinical Monitor*

Scott Thaler, M.D.

☎ (610) 397-2625
FAX (610) 397-3371

## *Medical Program Coordinators*

Megan McBride ☎ (610) 397-2941
FAX (610) 397-3371

Kara Stockett ☎ (610) 397-2207
FAX (610) 834-7555

# HANDLING AND SHIPPING OF SERA

## Presenters:

## Megan McBride and Kara Stockett

# AGENDA

- Supplies received from Merck
- Checklist for shipping serum samples
- Packaging and shipping demonstration
- Federal Express Form
- Investigator memo

# SUPPLIES RECEIVED FROM MERCK (via MPC)

- Serum Vials
- Barcoded Labels for Vials
- Cell Boxes
- Shipping Boxes
- Shipping Labels (as needed)

# CHECKLIST FOR SHIPPING VACCINE SERA SAMPLES

## VIALS

- All samples MUST be in standard Merck-provided vials.
- Vials should not be overfilled (sera expands with freezing).
- Caps on vials must be tight to prevent leakage.
- All sera (not whole blood) must be frozen at the time of shipment
- Do not use parafilm or any other sealing device on Merck vials.

# LABELS

- Use only Merck-provided barcoded labels on the sample vials

** If the ***correct*** label for a specific sample is not available ***do not use any other barcoded label -- each barcode refers specifically to one sample.*** Print the following information on the vial with a non water-based writing utensil: **V# Study # Case # Bleed Date Patient Initials Bleed Interval**

- No other non-Merck labels should be affixed on top of the barcoded labels

# LABELS (contd.)

- Only initials and sample date are to be written on barcoded labels.
- Use indelible ink to write on labels.
- ***DO NOT use correction fluid***
- ***DO NOT*** write over or change any bar-coded information (Case #, Study #, etc.)
  Each barcode is unique in the database and specific to that particular sample.

# LABELS (contd.)

- Labels should be affixed so sample volumes may be seen and barcodes appear horizontally on vials.
- Date format on labels must match the date format on **IN** sheet (**MM/DD/YY or DD/MM/YY**).
- If the bar-coded labels do not adhere to the sample vial for any reason, affix with one strip of clear tape so that the barcode is clear and legible.

# INVENTORY LIST (IN Form)

- Include white & yellow copies of IN sheet in each shipment

  Retain pink copy of the IN form at the site.

  ***Samples will not be inventoried if they are not accompanied by a completed IN form.***

- List Case #, Bleed Interval, & Bleed Date on the IN form for each sample

  ***Samples will not be inventoried without being listed on the IN sheet along with the bleed interval and bleed date.***

# INVENTORY LIST (contd.)

- ***SAMPLES ARE TO BE PLACED IN THE CELL BOXES IN THE SAME ORDER AS THEY ARE LISTED ON THE IN FORM.***

  This is critical in order to expedite the movement of samples and ultimately to obtain assay results.

- All comments/error corrections on **IN** form must be initialed and dated.

# 54 CELL BOXES
# (for storage of serum vials)

- Order of samples in cell box must match order in which they are listed on the **IN** form.
- Vials must be upright in cell boxes.
- When full, cell box must be secured shut (rubber band or tape) so that all vials will remain in the cell box in transit

# SHIPPING BOXES

- Sufficient dry ice must be included to keep samples frozen & hold cell box securely.
  - Use 10 lbs (~4.5 kg) of dry ice
- On outside of shipping box, write:
  - Investigator name
  - Vaccine Name (M-M-R™II)
  - Study number (007-XXX)

# SHIPPING BOXES (contd.)

- Shipping container must be marked or labeled **"KEEP FROZEN at -20°C".**

- Place **Dry Ice stickers** on outside of shipping container. Dry Ice is a dangerous good but it does not require a *Dangerous Goods Shippers Declaration form*. Use a regular **FEDEX** shipping form and check the box that asks whether Dry Ice is contained in the shipment.

- IATA regulations require a **BIOHAZARD** label to be placed on the outside of any shipment which contains biological specimens. This does not signify that the samples are infectious.

# GENERAL

- Serum samples should be ***shipped only on Mondays or Tuesdays*** by overnight express mail (Federal Express).

- Notify the MPC ***prior to*** shipping out and give the following information:
  **V#, Study #, # of samples, and # of shipping containers/boxes**.

- Do not send any CRFs or other correspondence with the **IN** form and samples.

# ADDRESS FOR SHIPMENT OF SERA

Ms. Kyna De Horsey
Asst. Medical Program Coordinator
Merck Research Laboratories
Building 26 Research Stockroom
Sumneytown Pike
West Point, PA 19486 USA

Telephone: (215) 652-0925

Facsimile: (215) 652-6314

# PACKAGING & SHIPPING OF DIAGNOSTIC SAMPLES
## (Based on IATA Packing Instructions 650)

## INNER PACKAGING

- Leak-proof primary receptacle (Merck standard tubes) where the maximum quantity of substance does not exceed 100 mL.
- Compartmentalized containers for multiple primary receptacles (Merck standard cell boxes) to prevent contact and/or breakage.
- Absorbent material (durasorb pads) between primary and secondary packaging.
- Leak-proof secondary packaging (plastic bag) where the maximum quantity of substance does not exceed 500 mL.

# PACKAGING & SHIPPING OF DIAGNOSTIC SAMPLES

## OUTER PACKAGING

- Must be of adequate strength
- Mark "Diagnostic Specimen" or "Non-infectious Clinical Samples"
- Label with orange "Biohazard" sticker (OSHA standard)

# PACKAGING & SHIPPING OF DIAGNOSTIC SAMPLES

## DRY ICE

- Dry Ice is a dangerous good in and of itself, but it should **NOT** be marked as a dangerous good when used as a refrigerant in the transport of clinical samples.

- On Fedex Form, Check "Dry Ice"
(Shippers' Declaration not required)

- Place "Dry Ice" label on outside of shipping container

# SUMMARY

- Attention to detail prior to shipment of sera will result in less time spent resolving data issues later
- Sera cannot be delivered to assay lab at Merck until all data issues are resolved
- Make sure all personnel involved in handling sera are adequately trained

# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 120

**To:** Simon, Keiko[simonkei@NorthAmerica.msx.merck.com]
**Cc:** Krah, David[Krahda@NorthAmerica.msx.merck.com]; Byrnes, Vera D.[BYRNESV@NorthAmerica.msx.merck.com]; Staub, Joan M.[STAUBJ@NorthAmerica.msx.merck.com]; Arena, Deitra E.[loydei@NorthAmerica.msx.merck.com]; Yagodich, Mary[Yagodicm@NorthAmerica.msx.merck.com]; Shaw, Alan[Shawal@NorthAmerica.msx.merck.com]
**From:** Arena, Deitra E.
**Sent:** Fri 6/16/2000 12:46:37 PM
**Importance:** High
**Subject:** Backgrounder for CAS, 6/20/00
MPS Nt backgrounder for June 20 CAS.doc
June CAS Table 3.xls
June CAS Table 4.xls
June CAS Table 5.xls
June CAS, Table 6.doc
June CAS, Table 7.doc
Microsoft Word - MPS Nt backgrounder for June 20 CAS.pdf

Keiko,
Attached is the Background document for CAS in pdf format.
Deitra

---

**From:** Krah, David
**Sent:** Friday, June 16, 2000 8:06 AM
**To:** Staub, Joan M.; Arena, Deitra E.; Yagodich, Mary; Shaw, Alan
**Subject:** REvised MPS Nt backgrounder for CAS

All,
Attached is a re-revised backgrounder for the MPS Nt presentation to CAS. I had reversed some of the discussion on different viruses (tables 3 and 4)-These are now correct.

Thanks,
Dave

Pilot Study of Mumps Nt Titers for Pediatric Sera

TABLE 4

| Serum Sample | Nt Titer Against Indicator Mumps Vaccine | JL135 p8 | LO1 |
|---|---|---|---|
| 484 | 1024 | 1024 | 128 |
| 152 | 512 | 256 | 64 |
| 211 | 256 | 256 | 32 |
| 38 | 512 | 128 | 16 |
| 67 | 512 | 256 | 256 |
| 207 | 256 | 128 | 16 |
| 216 | 256 | 128 | 32 |
| 131 | 512 | 256 | 32 |
| 132 | 256 | 64 | 64 |
| 135 | 256 | 64 | 64 |
| 224 | 256 | 128 | 32 |
| 267 | 256 | 128 | 64 |
| 419 | 512 | 256 | 512 |
| 422 | 512 | <64 | 32 |
| 456 | 256 | <64 | 32 |
| 514 | 128 | 256 | 32 |
| 3 | 128 | 64 | 64 |
| 129 | 128 | 64 | 64 |
| 138 | 128 | 64 | 32 |
| 519 | 128 | 128 | 64 |
| 237 | 128 | 256 | 16 |
| 264 | 128 | 64 | 32 |
| 265 | 128 | 64 | 32 |

MKY/DK 5/5/00

Comparison of Mumps Nt Titers for Adult Sera Using different Indicator Viruses

TABLE 3

| | Neutralization titer against mumps indicator virus | | | | |
|---|---|---|---|---|---|
| Serum | Barnes | TN | Lo1 | JL-135 | JL-vaccine |
| MKY | <2, 8, 8 | nd, 8, 8 | nd, 8, 16 | 4, 16, 16 | 2, 8, 4 |
| DK | <2, nd, nd | nd, nd, nd | nd, nd, nd | 4, nd, nd | 2, nd, nd |
| AS | 32, 32, 64 | nd, 32, 64 | nd, 64, 64 | 64, 128, 64 | 64, 64, 128 |
| CM | <32, 32, 64 | nd, 64, 64 | nd, 32, 64 | 128, 128, 256 | 128, 256, 128 |
| PK | 32, 32, 32 | nd, 32, 32 | nd, 64, 64 | 128, 256, 256 | 128, 128, 128 |
| DW | 512, 256, 256 | nd, 512, 1024 | nd, 512, 512 | 1024, 1024, 1024 | 1024, 1024, 1024 |

ND = not tested

DK 8June 2000

Mumps Plaque-Reduction Neutralization Assay Development Update
Backgrounder

June 20, 2000 CAS presentation

## I. Executive Summary

A plaque-reduction neutralization assay using a low-passage Jeryl Lynn™ preparation is being optimized for use in evaluation of sera from the M-M-R®II Expiry Trial, with a goal of providing an assay that permits measurement of a ≥95% seroconversion rate. The low-passage Jeryl Lynn™ virus has provided neutralization titers closest to those obtained using the vaccine-passage Jeryl Lynn™, and plaques are visualized by immunostaining. Optimization of the concentration of anti-human IgG for enhancement of the neutralization is underway. The utility of the Spearman-Karber method to calculate titers is also being considered as a final refinement to maximize the capacity of the assay to detect seroconversions.

## II. Background and status of assay development

A need for a mumps neutralization (Nt) assay utilizing a wild-type indicator virus has been identified to support analysis of the immune responses to mumps in the ongoing M-M-R®II Expiry Trial (Protocol 007). Efforts to date have focused on evaluating conditions that affect assay sensitivity and in defining a suitable indicator virus in a multi-well plate plaque-reduction neutralization assay (PRN).

A summary of the mumps strains and some of the virus growth and assay parameters evaluated is presented in Table 1. Previous studies comparing neutralization titers to sera from adult lab volunteers (who had either wild-type infections or mumps vaccine-induced responses) and pediatric sera showed an effect of the virus strain on neutralization titers, with the highest seroconversion rates and titers observed for the vaccine-passage of Jeryl Lynn™ mumps. CBER has indicated that the vaccine passage Jeryl Lynn™ is not suitable for use in the PRN and has established a requirement to use a "wild-type" mumps strain to evaluate vaccine-induced immune responses. A range of wild-type isolates were therefore obtained and evaluated in the PRN to identify the optimum indicator strain. In early testing, the Tennessee (TN) isolate provided Nt titers close to those obtained using Jeryl Lynn™, but further evaluation of this strain was aborted due to difficulties in reliably detecting plaques. Several plaque staining methods were evaluated, including Coomassie Blue (general cell stain) and neutral red or tetrazolium salts (vital stains), without consistent success.

In addition to "mechanical" aspects of the assay (incubation times and temperatures, virus attachment times), two supplements were evaluated for their capacity to increase the Nt sensitivity. Complement supplementation provided modest titer increases for adult sera and was complicated by the anti-mumps activity of the complement sera. Further evaluation of this reagent was therefore not pursued. A second supplement, anti-human Ig, was evaluated to confirm its ability to increase Nt titers (approximately 100-fold titer increases), but was not immediately pursued.

Subsequent studies shifted to use the London 1 strain (Lo1) of mumps, which was also used in studies performed at CBER. This strain met the criterion of being a "wild-type" virus and became the "virus of choice" for development of

the PRN. Results of a series of pilot PRN assays of pediatric sera against Jeryl Lynn™, Lo1 and JL2 mumps strains showed respective seroconversion rates of 91% (63/69), 69% (43/62) and 56% (18/32). Testing of 169 paired sera from Protocol 006 (Competitive Trial) confirmed that the general assay format using Lo1 mumps would not provide the targeted ≥95% seroconversion rate.

In parallel with the studies of Lo1 mumps, a sample of SBL-1 mumps (reportedly antigenically similar to Jeryl Lynn™) was obtained and evaluated in the PRN assay. SBL-1 mumps did not provide increased Nt performance versus Lo1 using a panel of pediatric and adult sera (Table 2).

Through discussion with CBER staff, the following suggestions and comments were made for evaluation in increasing the sensitivity of the PRN:

- The use of "Low-passage" JL (between passages 7 and 12) would be acceptable
- Consider assay format used by Dr. Bagher Forghani (the State of California Department of Health Services) that reportedly provides >90% seronversion rates
  - Immunostaining (distinct "plaques" observed 3 days post- infection for all mumps strains tested in our hands).
  - Assay performed in 48-well plates
  - Evaluate the Barnes strain of mumps
- Consider using anti-human IgG to enhance Nt sensitivity
- Consider using the Spearman-Karber method to calculate Nt titers

In response to these suggestions, stocks of the Barnes and low-passage Jeryl Lynn™ (lot 135 [passage 7], used at passage 8 in PRN assays) were obtained and evaluated in the PRN. Due to the low-cytolytic activity of these viruses, immunostaining (polyclonal goat anti-mumps antibody, peroxidase-labeled anti-goat IgG and peroxidase substrate) was adopted for detection of plaques. The immunostaining method was found to be universally applicable to detect mumps plaques (for all available strains), and therefore also permitted re-evaluation of previous strains such as TN. The 48- and 24-well plate formats (as alternatives to the 12-well plate format used in our previous studies) proved to be technically inconvenient for sample inoculation and were not pursued further.

Results of preliminary Nt assays using vaccine-passage ("house standard") and low-passage (lot 135, passage 8) Jeryl Lynn™ mumps showed that Nt titers for adult lab volunteer sera using these indicator viruses were comparable Table 3). A series of assays was done using adult lab volunteer sera and Barnes, TN, Lo1, low-passage (lot 135, P8) Jeryl Lynn™ and vaccine passage Jeryl Lynn™ mumps as indicator viruses to determine the relative Nt for the different viruses (Table 4). Nt titers to the low-passage lot 135 Jeryl Lynn™ mumps were comparable to those obtained using the vaccine-passage virus, and greater by 2-4-fold than those to Lo1, TN or Barnes mumps. TN and Lo1 titers were comparable and approximately 2-fold higher than those to the Barnes strain of mumps. Screening of a panel of 23 pediatric sera (selected to have a titer ≥128 to permit assay using small serum volumes) showed that Nt titers to the vaccine-passage virus were approximately 2-fold higher than those to the low-passage

Jeryl Lynn™ and approximately 4-fold higher than those to Lo1. The low-passage Jeryl Lynn™ virus therefore provides Nt sensitivity most close to the vaccine-passage virus.

The use of the Spearman-Karber method to interpolate titers is expected to provide an increased number of seroconversions, but not to the targeted ≥95% value. It is therefore expected that further enhancement of Nt by addition of anti-human IgG will be required.Previous studies demonstrated that this enhancement boosted post-vaccination titers approximately 100-fold, but the effect on pre-vaccination titers was not measured. In pilot studies, undiluted anti-human IgG provided positive titers to 75% of the pre-vaccination sera (9/12: titers ranging from 32 to128) and 8-64-fold increases in post-vaccination titers, while lower amounts (1:2, 1:4 or 1:8 dilutions) of anti-IgG provided comparable enhancement of post-vaccination titers, but retained negative titers for 3/3 pre-vaccination sera (Table 5). The use of 1:4 or 1:8 dilutions of anti-IgG in a second study retained negative Nt responses for pre-vaccination sera (tested at an initial 1:32 dilution), and provided increases in titers for all three post-vaccination sera (Table 6). Results of a third experiment, using sera that previously provided titers of <2, 2 or 4, showed that a 1:2 dilution of anti-IgG permitted measurement of titer enhancements for all post-vaccination sera (Table 7). The amount of anti-IgG used in this study also resulted in positive Nt responses for several of the pre-vaccination sera. Current studies are focusing on determining the optimum concentration of anti-IgG to boost post-vaccination titers but not shift pre-vaccination sera to a positive Nt response.

III. **Path forward**

The proposed assay format will include:

- 12-well plate format
- Low-passage Jeryl Lynn™ indicator virus
- Enhancement of Nt with anti-human IgG
- Detection of plaques by immunostaining
- Calculation of Nt titers by 50% cutoff or Spearman-Karber method

Current studies (4-5 weeks) are designed to determine the optimum amount of anti-IgG for Nt enhancement while retaining negative titers for pre-vaccination sera. An evaluation can then be made of the effect of using the "50% Nt" cutoff (highest tested dilution tested that provides ≥50% Nt) versus the Spearman-Karber titer interpolation to finalize the assay format. It is proposed that the optimized assay format will then by applied to the sera from Protocol 006 (4 weeks after finalization of the assay format) to provide an estimate of the seroconversion rates detected.

Issues remaining to be addressed include:

- Serum dilutions to be tested
  - -the assay produces a "prozone" effect at dilutions approximately ≤32

-post-vaccination titers are expected to be increased approximately 100-fold
- Impact if a significant proportion of pre-vaccination sera register as Nt positive
- Impact if testing of "pre-evaluation" panel provides <95% seroconversion
- Transfer of the optimized assay

Table 1

Factors evaluated for effects on Mumps Nt sensitivity

- Indicator virus
  - Jeryl Lynn™
  - Swiss isolates
  - NY
  - TN
  - SA
  - Jones
  - Enders
  - Lo1
  - JL2
  - JL5
  - SBL-1
  - Barnes
  - Select viruses passaged in CEF vs Vero (Lo1, TN, Enders, Jones)
- Incubation time and temperature of virus and serum
- Virus concentration
- Virus harvest fractions and clarification methods
- Cell substrate for virus stock growth
- Staining method for plaque visualization
  - (Coomassie Blue, neutral red, tetrazolium salts, immunostaining)
- Virus attachment time
- Enhancements to Nt
  - Complement (≤8-fold enhancement)
  - anti-human IgG (~100-fold enhancement)

Table 2
Evaluation of PRN Titers Using Jeryl Lynn™, Lo1 and SBL-1 Mumps Strains

| Serum | | Nt titer using | | |
|---|---|---|---|---|
| | | Jeryl Lynn™ | Lo1 | SBL-1 |
| 1 | pre | <8 | <8 | <8 |
| | post | 16 | <8 | 8 |
| 2 | pre | <8 | 16 | <8 |
| | post | 16 | 8 | <8 |
| 3 | pre | not tested | | |
| | post | <8 | <8 | <8 |
| 4 | pre | not tested | | |
| | post | 8 | 8 | <8 |
| 5 | pre | not tested | | |
| | post | 16 | 8 | <8 |
| 6 | pre | <8 | <8 | <8 |
| | post | 16 | 32 | <8 |
| 7 | pre | <8 | <8 | <8 |
| | post | <8 | <8 | <8 |
| 8 | pre | <8 | <8 | <8 |
| | post | 16 | 16 | <8 |
| Adult control 1 | | ≥128 | 32 | 16 |
| Adult control 2 | | 16 | 16 | 4 |
| Adult control 3 | | 1024 | 512 | 256 |

# Comparison of Mumps Nt Titers for Adult Sera Using different Indicator Viruses

TABLE 3

| Serum | Neutralization titer against mumps indicator virus | | | | |
|---|---|---|---|---|---|
| | Barnes | TN | Lo1 | JL-135 | JL-vaccine |
| MKY | <2, 8, 8 | nd, 8, 8 | nd, 8, 16 | 4, 16, 16 | 2, 8, 4 |
| DK | <2, nd, nd | nd, nd, nd | nd, nd, nd | 4, nd, nd | 2, nd, nd |
| AS | 32, 32, 64 | nd, 32, 64 | nd, 64, 64 | 64, 128, 64 | 64, 64, 128 |
| CM | <32, 32, 64 | nd, 64, 64 | nd, 32, 64 | 128, 128, 256 | 128, 256, 128 |
| PK | 32, 32, 32 | nd, 32, 32 | nd, 64, 64 | 128, 256, 256 | 128, 128, 128 |
| DW | 512, 256, 256 | nd, 512, 1024 | nd, 512, 512 | 1024, 1024, 1024 | 1024, 1024, 1024 |

ND = not tested

DK 8June 2000

# Pilot Study of Mumps Nt Titers for Pediatric Sera

TABLE 4

| Serum | Nt Titer Against Indicator Mumps | | |
|---|---|---|---|
| Sample | Vaccine | JL135 p8 | LO1 |
| 484 | 1024 | 1024 | 128 |
| 152 | 512 | 256 | 64 |
| 211 | 256 | 256 | 32 |
| 38 | 512 | 128 | 16 |
| 67 | 512 | 256 | 256 |
| 207 | 256 | 128 | 16 |
| 216 | 256 | 128 | 32 |
| 131 | 512 | 256 | 32 |
| 132 | 256 | 64 | 64 |
| 135 | 256 | 64 | 64 |
| 224 | 256 | 128 | 32 |
| 267 | 256 | 128 | 64 |
| 419 | 512 | 256 | 512 |
| 422 | 512 | <64 | 32 |
| 456 | 256 | <64 | 32 |
| 514 | 128 | 256 | 32 |
| 3 | 128 | 64 | 64 |
| 129 | 128 | 64 | 64 |
| 138 | 128 | 64 | 32 |
| 519 | 128 | 128 | 64 |
| 237 | 128 | 256 | 16 |
| 264 | 128 | 64 | 32 |
| 265 | 128 | 64 | 32 |

MKY/DK 5/5/00

# Effect of Anti-Human IgG Treatment on Mumps Nt Titers

TABLE 5

| sample # | anti human IgG dil | Pre serum Nt titer | Post Seru Nt titer |
|---|---|---|---|
| **238** | undiluted | 128 | >=2048 |
| **238** | 1:2 | 128 | >=2048 |
| **238** | 1:4 | 256 | >=2048 |
| **238** | 1:8 | 256 | >=2048 |
| **238** | mock anti IgG | <32 | 32 |
| **321** | undiluted | 32 | >=2048 |
| **321** | 1:2 | <32 | >=2048 |
| **321** | 1:4 | <32 | >=2048 |
| **321** | 1:8 | <32 | >=2048 |
| **321** | mock anti IgG | <32 | 32 |
| **455** | undiluted | 32 | >=2048 |
| **455** | 1:2 | <32 | >=2048 |
| **455** | 1:4 | <32 | >=2048 |
| **455** | 1:8 | <32 | >=2048 |
| **455** | mock anti IgG | <32 | 32 |

Table 6
**Enhancement of Mumps Neutralization with Anti-Human IgG**

| Serum | Nt titer to Pre-serum at anti-IgG | | | | Nt titer to Post-serum at anti-IgG | | | |
|---|---|---|---|---|---|---|---|---|
| # | 1:4* | 1:8* | Mock* | Historical | 1:4 | 1:8 | Mock | Historical |
| 98 | <32 | <32 | <32 | <2 | ≥4096 | ≥4096 | <32 | 32 |
| 99 | <32 | <32 | <32 | <2 | 2048 | 2048 | <32 | 8 |
| 101 | <32 | <32 | <32 | <2 | 2048 | 2048 | 128 | 128 |

* = dilution of anti-human IgG
Nt titers with anti-IgG = using Low passage Jeryl Lynn™
Historical titer = using Jeryl Lynn™ vaccine passage without anti-IgG treatment

DK 15 June 2000

Table 7

## Enhancement of Mumps Neutralization Using Anti-Human IgG

| Serum[1] | Nt titer to low-passage Jeryl Lynn™ | | | | Nt titer[2] to Jeryl Lynn™ | |
|---|---|---|---|---|---|---|
| | Pre + anti-IgG[3] | Pre + PBS | Post + anti-IgG | Post + PBS | Pre | Post |
| 147 | 32 | <16 | ≥512 | <16 | <2 | <2 |
| 291 | <16 | <16 | 256 | <16 | <2 | <2 |
| 4 | ≥64 | <16 | ≥512 | <16 | <2 | 2 |
| 80 | <16 | <16 | 128 | <16 | <2 | 2 |
| 212 | ≥64 | <16 | 128 | <16 | <2 | 2 |
| 145 | <16 | <16 | ≥512 | <16 | <2 | 4 |
| 234 | <16 | <16 | ≥512 | <16 | <2 | 4 |
| 235 | ≥64 | <16 | 256 | <16 | <2 | 4 |
| 199 | not tested | | ≥4096 | 32 | <2 | 32 |

[1]Pediatric sera (protocol 006)
[2] Historical titers
[3]Anti-human IgG used at 1:2 dilution

Table 6
**Enhancement of Mumps Neutralization with Anti-Human IgG**

| Serum | Nt titer to Pre-serum at anti-IgG | | | | Nt titer to Post-serum at anti-IgG | | | |
|---|---|---|---|---|---|---|---|---|
| # | 1:4* | 1:8* | Mock* | Historical | 1:4 | 1:8 | Mock | Historical |
| 98 | <32 | <32 | <32 | <2 | ≥4096 | ≥4096 | <32 | 32 |
| 99 | <32 | <32 | <32 | <2 | 2048 | 2048 | <32 | 8 |
| 101 | <32 | <32 | <32 | <2 | 2048 | 2048 | 128 | 128 |

* = dilution of anti-human IgG
Nt titers with anti-IgG = using Low passage Jeryl Lynn™
Historical titer = using Jeryl Lynn™ vaccine passage without anti-IgG treatment

DK 15 June 2000

Effect of Anti-Human IgG Treatment on Mumps Nt Titers

TABLE 5

| | | Pre serum | Post Serum |
|---|---|---|---|
| sample # | anti human IgG dil | Nt titer | Nt titer |
| 238 | undiluted | 128 | >=2048 |
| 238 | 1:2 | 128 | >=2048 |
| 238 | 1:4 | 256 | >=2048 |
| 238 | 1:8 | 256 | >=2048 |
| 238 | mock anti IgG | <32 | 32 |
| 321 | undiluted | 32 | >=2048 |
| 321 | 1:2 | <32 | >=2048 |
| 321 | 1:4 | <32 | >=2048 |
| 321 | 1:8 | <32 | >=2048 |
| 321 | mock anti IgG | <32 | 32 |
| 455 | undiluted | 32 | >=2048 |
| 455 | 1:2 | <32 | >=2048 |
| 455 | 1:4 | <32 | >=2048 |
| 455 | 1:8 | <32 | >=2048 |
| 455 | mock anti IgG | <32 | 32 |

Effect of Anti-Human IgG Treatment on Mumps Nt Titers

DK, 8 June 2000

Table 7

## Enhancement of Mumps Neutralization Using Anti-Human IgG

| Serum[1] | Nt titer to low-passage Jeryl Lynn™ | | | | Nt titer[2] to Jeryl Lynn™ | |
|---|---|---|---|---|---|---|
| | Pre + anti-IgG[3] | Pre + PBS | Post + anti-IgG | Post + PBS | Pre | Post |
| 147 | 32 | <16 | ≥512 | <16 | <2 | <2 |
| 291 | <16 | <16 | 256 | <16 | <2 | <2 |
| 4 | ≥64 | <16 | ≥512 | <16 | <2 | 2 |
| 80 | <16 | <16 | 128 | <16 | <2 | 2 |
| 212 | ≥64 | <16 | 128 | <16 | <2 | 2 |
| 145 | <16 | <16 | ≥512 | <16 | <2 | 4 |
| 234 | <16 | <16 | ≥512 | <16 | <2 | 4 |
| 235 | ≥64 | <16 | 256 | <16 | <2 | 4 |
| 199 | not tested | | ≥4096 | 32 | <2 | 32 |

[1]Pediatric sera (protocol 006)
[2] Historical titers
[3]Anti-human IgG used at 1:2 dilution

Mumps Plaque-Reduction Neutralization Assay Development Update
Backgrounder

June 20, 2000 CAS presentation

I. **Executive Summary**

A plaque-reduction neutralization assay using a low-passage Jeryl Lynn™ preparation is being optimized for use in evaluation of sera from the M-M-R®II Expiry Trial, with a goal of providing an assay that permits measurement of a ≥95% seroconversion rate. The low-passage Jeryl Lynn™ virus has provided neutralization titers closest to those obtained using the vaccine-passage Jeryl Lynn™, and plaques are visualized by immunostaining. Optimization of the concentration of anti-human IgG for enhancement of the neutralization is underway. The utility of the Spearman-Karber method to calculate titers is also being considered as a final refinement to maximize the capacity of the assay to detect seroconversions.

II. **Background and status of assay development**

A need for a mumps neutralization (Nt) assay utilizing a wild-type indicator virus has been identified to support analysis of the immune responses to mumps in the ongoing M-M-R®II Expiry Trial (Protocol 007). Efforts to date have focused on evaluating conditions that affect assay sensitivity and in defining a suitable indicator virus in a multi-well plate plaque-reduction neutralization assay (PRN).

A summary of the mumps strains and some of the virus growth and assay parameters evaluated is presented in Table 1. Previous studies comparing neutralization titers to sera from adult lab volunteers (who had either wild-type infections or mumps vaccine-induced responses) and pediatric sera showed an effect of the virus strain on neutralization titers, with the highest seroconversion rates and titers observed for the vaccine-passage of Jeryl Lynn™ mumps. CBER has indicated that the vaccine passage Jeryl Lynn™ is not suitable for use in the PRN and has established a requirement to use a "wild-type" mumps strain to evaluate vaccine-induced immune responses. A range of wild-type isolates were therefore obtained and evaluated in the PRN to identify the optimum indicator strain. In early testing, the Tennessee (TN) isolate provided Nt titers close to those obtained using Jeryl Lynn™, but further evaluation of this strain was aborted due to difficulties in reliably detecting plaques. Several plaque staining methods were evaluated, including Coomassie Blue (general cell stain) and neutral red or tetrazolium salts (vital stains), without consistent success.

In addition to "mechanical" aspects of the assay (incubation times and temperatures, virus attachment times), two supplements were evaluated for their capacity to increase the Nt sensitivity. Complement supplementation provided modest titer increases for adult sera and was complicated by the anti-mumps activity of the complement sera. Further evaluation of this reagent was therefore not pursued. A second supplement, anti-human Ig, was evaluated to confirm its ability to increase Nt titers (approximately 100-fold titer increases), but was not immediately pursued.

Subsequent studies shifted to use the London 1 strain (Lo1) of mumps, which was also used in studies performed at CBER. This strain met the criterion of being a "wild-type" virus and became the "virus of choice" for development of the PRN. Results of a series of pilot PRN assays of pediatric sera against Jeryl Lynn™, Lo1 and JL2 mumps strains showed respective seroconversion rates of

91% (63/69), 69% (43/62) and 56% (18/32). Testing of 169 paired sera from Protocol 006 (Competitive Trial) confirmed that the general assay format using Lo1 mumps would not provide the targeted ≥95% seroconversion rate.

In parallel with the studies of Lo1 mumps, a sample of SBL-1 mumps (reportedly antigenically similar to Jeryl Lynn™) was obtained and evaluated in the PRN assay. SBL-1 mumps did not provide increased Nt performance versus Lo1 using a panel of pediatric and adult sera (Table 2).

Through discussion with CBER staff, the following suggestions and comments were made for evaluation in increasing the sensitivity of the PRN:

- The use of "Low-passage" JL (between passages 7 and 12) would be acceptable
- Consider assay format used by Dr. Bagher Forghani (The State of California Department of Health Services) that reportedly provides >90% seronversion rates
  - Immunostaining (distinct "plaques" observed 3 days post-infection for all mumps strains tested in our hands).
  - Assay performed in 48-well plates
  - Evaluate the Barnes strain of mumps
- Consider using anti-human IgG to enhance Nt sensitivity
- Consider using the Spearman-Karber method to calculate Nt titers

In response to these suggestions, stocks of the Barnes and low-passage Jeryl Lynn™ (lot 135 [passage 7], used at passage 8 in PRN assays) mumps viruses were obtained and evaluated in the PRN. Due to the low-cytolytic activity of these viruses, immunostaining (polyclonal goat anti-mumps antibody, peroxidase-labeled anti-goat IgG and peroxidase substrate) was adopted for detection of plaques. The immunostaining method was found to be universally applicable to detect mumps plaques (for all available strains), and therefore also permitted re-evaluation of previous strains such as TN. The 48- and 24-well plate formats (as alternatives to the 12-well plate format used in our previous studies) proved to be technically inconvenient for sample inoculation and were not pursued further.

A panel of adult lab volunteer sera was tested against Barnes, TN, Lo1, low-passage (lot 135, P8) Jeryl Lynn™ and vaccine passage Jeryl Lynn™ mumps indicator viruses to determine the relative Nt for the different viruses (Table 3). Nt titers to the low-passage lot 135 Jeryl Lynn™ mumps were comparable to those obtained using the vaccine-passage virus, and greater by 2-4-fold than those to Lo1, TN or Barnes mumps. TN and Lo1 titers were comparable and approximately 2-fold higher than those to the Barnes strain of mumps. Results of testing of a panel of 23 pediatric sera (selected to have a titer ≥128 from previous assays to permit further testing using small serum volumes) showed that Nt titers to the vaccine-passage virus were approximately 2-fold higher than those to the low-passage Jeryl Lynn™ and approximately 4-fold higher than those to Lo1 (Table 4). From the panel of wild-type mumps strains, the low-passage Jeryl Lynn™ virus therefore provides Nt sensitivity most close to the vaccine-passage virus.

The use of the Spearman-Karber method to interpolate titers is expected to provide an increased number of seroconversions, but not to the targeted ≥95%

value. It is therefore expected that further enhancement of Nt by addition of anti-human IgG will be required. Previous studies demonstrated that this enhancement boosted post-vaccination titers approximately 100-fold, but the effect on pre-vaccination titers was not measured. In pilot studies, undiluted anti-human IgG provided positive titers to 75% of the pre-vaccination sera (9/12: titers ranging from 32 to128) and 8-64-fold increases in post-vaccination titers, while lower amounts (1:2, 1:4 or 1:8 dilutions) of anti-IgG provided comparable enhancement of post-vaccination titers, but retained negative titers for 3/3 pre-vaccination sera (Table 5). The use of 1:4 or 1:8 dilutions of anti-IgG in a second study retained negative Nt responses for pre-vaccination sera (tested at an initial 1:32 dilution), and provided increases in titers for all three post-vaccination sera (Table 6). Results of a third experiment, using sera that previously provided titers of <2, 2 or 4, showed that a 1:2 dilution of anti-IgG permitted measurement of titer enhancements for all post-vaccination sera (Table 7). The amount of anti-IgG used in this study also resulted in positive Nt responses for several of the pre-vaccination sera. Current studies are focusing on determining the optimum concentration of anti-IgG to boost post-vaccination titers but not shift pre-vaccination sera to a positive Nt response.

III. **Path forward**

The proposed assay format will include:

- 12-well plate format
- Low-passage Jeryl Lynn™ indicator virus
- Enhancement of Nt with anti-human IgG
- Detection of plaques by immunostaining
- Calculation of Nt titers by 50% cutoff or Spearman-Karber method

Current studies (4-5 weeks) are designed to determine the optimum amount of anti-IgG for Nt enhancement while retaining negative titers for pre-vaccination sera. An evaluation can then be made of the effect of using the "50% Nt" cutoff (highest tested dilution tested that provides ≥50% Nt) versus the Spearman-Karber titer interpolation to finalize the assay format. It is proposed that the optimized assay format will then by applied to the sera from Protocol 006 (4 weeks after finalization of the assay format) to provide an estimate of the seroconversion rates detected.

Issues remaining to be addressed include:

- Serum dilutions to be tested
  - -the assay produces a "prozone" effect at dilutions approximately ≤32
  - -post-vaccination titers are expected to be increased approximately 100-fold
- Impact if a significant proportion of pre-vaccination sera register as Nt positive
- Impact if testing of "pre-evaluation" panel provides <95% seroconversion
- Transfer of the optimized assay

Table 1

Factors evaluated for effects on Mumps Nt sensitivity

- Indicator virus
  - Jeryl Lynn™
  - Swiss isolates
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  - TN
  - SA
  - Jones
  - Enders
  - Lo1
  - JL2
  - JL5
  - SBL-1
  - Barnes
  - Select viruses passaged in CEF vs Vero (Lo1, TN, Enders, Jones)
- Incubation time and temperature of virus and serum
- Virus concentration
- Virus harvest fractions and clarification methods
- Cell substrate for virus stock growth
- Staining method for plaque visualization
  (Coomassie Blue, neutral red, tetrazolium salts, immunostaining)
- Virus attachment time
- Enhancements to Nt
  - Complement (≤8-fold enhancement)
  - anti-human IgG (~100-fold enhancement)

Table 2
Evaluation of PRN Titers Using Jeryl Lynn™, Lo1 and SBL-1 Mumps Strains

| Serum | | Nt titer using | | |
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| | post | 16 | <8 | 8 |
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| | post | 16 | 8 | <8 |
| 3 | pre | not tested | | |
| | post | <8 | <8 | <8 |
| 4 | pre | not tested | | |
| | post | 8 | 8 | <8 |
| 5 | pre | not tested | | |
| | post | 16 | 8 | <8 |
| 6 | pre | <8 | <8 | <8 |
| | post | 16 | 32 | <8 |
| 7 | pre | <8 | <8 | <8 |
| | post | <8 | <8 | <8 |
| 8 | pre | <8 | <8 | <8 |
| | post | 16 | 16 | <8 |
| Adult control 1 | | ≥128 | 32 | 16 |
| Adult control 2 | | 16 | 16 | 4 |
| Adult control 3 | | 1024 | 512 | 256 |

# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 121

**Fechtenburg, Linda**

**From:** Morsy, Manal A.
**Sent:** Sunday, October 10, 1999 1:25 PM
**To:** Ukwu, Dr. Henrietta; Chirgwin, Keith D.
**Cc:** Fechtenburg, Linda
**Subject:** Re: highlights
**Importance:** High

Enclosed please find highlights I drafted for MMRII and MMRV. I left a copy this morning Sunday 10/10 in both of your offices for comments back.

Please note in the MMRII section I have stressed the need for obtaining total particle to infective particle count for all viruses used in the Neut. assay since I believe this is a critical piece of information needed for establishing technical feasibility or limitation of the currently used PRN and CPE assays.

With regards to the MMRV, I have modified slightly over what Keith and I had discussed previously.

I have not included highlights on OGOS, rHA and Japan, three area I have great discomfort with still.

If neither of you have comments back on the highlights I will distribute these out first thing Monday morning (10/11/99)

Thanks for your patients with me through this painful - challenging and exciting all at the same time - learning process


09-99.doc

Manal

MERCK
Research Laboratories

**M E M O**

**TO:** **Henrietta Ukwu** **DATE: October 8, 1999**

**CC:** **D. Blois, B. Buckland, C.Chan, H. Cohen, E. Emini, P. Kniskern, D. Krah, B. Kuter, L. Kuykens, S. Lenz, J. Lewis, W. Long, D. Margolskee, C. Russo, J. Sadoff, A. Shaw, R. Singhvi, E. Slater, J. Staub, S. Thaler, B. Thompson, R. Zeldin**

**FROM:** **Manal Morsy**

**SUBJECT:** **Monthly Highlights for September 1999 (M-M-R®II and MMRV)**

---

**M-M-R®II**

- End-expiry: The expiry trial has now enrolled ~50% of the subjects (Target 1500). The primary study hypothesis of a SCR ≥90% against WT mumps virus is unlikely to be met and therefore this should be revised either in terms of addressing the hypothesis or addressing the technical limitations of the assays used to date.

  The implications of the low neutralizing antibody seroconversion rate in terms of study design and sample size require discussion with CBER. The timing for this discussion is dependent on the timing of the results of the M-M-R®II to Priorix comparison (data will be available by last week of October to 1st week of November).

  Mumps neutralizing antibody assay: The results of the mumps plaque reduction neutralization (PRN) and cytopathic effect (CPE) assays were reviewed at the CAS. With JL as the test isolate, the SCR is ~90%, and with L01 as the test isolate, the SCR is ~70-75%. Prior to discussing the unanticipated low SCR for mumps with CBER, the sera from the head-to-head trial with M-M-R®II and Priorix will be assayed to confirm that this low SCR is observed with both products. The current timeline for this analysis is 4-6 weeks.
  An alternative assay that may overcome some of the potential technical limitations has been discussed. Preliminary data using a high through put QPA based Neut. Assay will be generated to determine if greater sensitivity can be attained (Time line 4Q99 – 1Q01).

  The key information requested and elements of the discussion with CBER about the mumps neutralizing antibody assay include:
  1) review of the arguments that the current WT neutralizing antibody assay may not capture all attributable protective efficacy;
  2) argue against the use of WT virus in the Neut. assays since SCR against JL is reproducible and confirms label claims using the current Neut. assays;
  3) review the total particle count to infective virus ratio for JL and the WT viruses (LO1, S. African and Swiss) used in the Neut. assay. If ratios of abortive to infective particle across the 4 viruses are not identical, and if abortive to infective particle ratio in the WT viruses is greater than that in the JL vaccine for which tissue culture growth conditions have been optimized, an argument against using WT viruses can be build supported by the technical

limitations of the PRN and CPE Neut. assays. Technically, both assays can not account for the percent of Neut. antibodies lost to abortive particle (unless the difference in ratios between total particle count and infective virus for each of the viruses is factored in).
4) review the extensive field experience in support of vaccine protective efficacy;
5) revision of the mumps expiry trial study hypotheses (if all viruses used in Neut. assays have similar total particle count to infective particles as found in JL, then we would review the mumps expiry trial study hypotheses and remove >90% SCR hypothesis; retain equivalence hypothesis with consideration of an increase in the equivalence margin to avoid an untenable increase in the sample size).

**MMRV**

- Filing strategy: The current strategy will be to accelerate MMRV licensure in the U.S. by pursuing a frozen product. The target date for submitting a frozen MMRV BLA is 3Q01. A refrigerated product will be licensed in the U.S. as a variation to the initial frozen quadrivalent. The current target date for submitting this sBLA is 3Q02.
  U.S launch dates approved at TPAC are: Frozen MMRV (3Q02) and 4°C MMRV (3Q03)
- Preparation for End-of-Phase II meeting with CBER: CBER concurrence with the CDP and registration package will be obtained at this meeting.
  Studies proposed for Phase III:
  1) Consistency lots : proposed FPI 1Q00.
  2) Concomitant use: proposed FPI 2Q00.
  3) Expanded safety: proposed FPI 2Q00.
- Outstanding issues requiring further discussion and closure with CBER include:
  1) Acceptable surrogate markers: for measles, mumps and rubella. The current serologic (EIA) assays lack an established correlation with protective efficacy and CBER has indicated that a functional antibody assay (e.g. WT Neut) will be required to establish equivalence. However, evidence of a correlation between the current assays and a WT Neut assay, or evidence of correlation with protective efficacy, would allow the current EIA-based assays to be used. This approach may be more feasible with measles and rubella than mumps. The proposed approach to surrogate markers for demonstrating equivalence between MMRV and M-M-R®II plus VARIVAX® will be finalized and confirmed with CBER
  2) Demonstration of equivalence: Approach to demonstrating equivalence with the licensed monovalent (VARIVAX®) and trivalent (MMR®II).
  3) Statistical criteria for success: The acceptable equivalence margins for each antigen.
  4) Expiry dose selection:(minimum acceptable immunogenicity). Preliminary data from the dose-ranging trial (25% accrual) was reviewed. These data will determine whether a feasible expiry dose (function of the maximum manufacturable release dose and estimated stability – 28,000 pfu PUVV is the release dose selected in the Consistency lot trial – protocol 013 ) provides adequate immunogenicity. Frozen MMRV must provide equivalent immunogenicity to the licensed monovalent.
  5) Consistency evaluation: (details of clinical consistency evaluation, lot selection) – protocol reviewed and approved at CDOC – Oct. 6
  6) Proposed product profile and label

Timing: An End-of-Phase II meeting is a Type B meeting under PDUFA, which means that the meeting should be scheduled to occur within 60 days of the FDA receiving the written

meeting request. The background document must be submitted no later than 30 days before the scheduled meeting date. Since the phase II dose-ranging data are an essential element of this background document, the timing for this CBER meeting is closely linked to the timing of availability of these data. At the present time the plan is to request a meeting for the 2-3 week in December.

MM
UN-B121

cc: file, chron

# 10/25/2019
# Declaration of G. Reilly
# EXHIBIT 122

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

| | | |
|---|---|---|
| UNITED STATES OF AMERICA ex rel., STEPHEN A. KRAHLING and JOAN A. WLOCHOWSKI, Plaintiffs, | : | CIVIL ACTION NO. 2:10-04374(CDJ) |
| vs. | : | |
| MERCK & CO., INC., Defendant. | : | |
| IN RE: MERCK MUMPS VACCINE ANTITRUST LITIGATION | : | Master File No. 2:12-cv-03555(CDJ) |
| THIS DOCUMENT RELATES TO: ALL ACTIONS | : | |

** HIGHLY CONFIDENTIAL - ATTORNEYS' EYES ONLY **

July 11, 2017

Videotaped deposition of DAVID KRAH, taken at the offices of Spector Roseman & Kodroff, 1818 Market Street, Suite 2500, Philadelphia, Pennsylvania 19103, beginning at 8:58 a.m., before LINDA ROSSI-RIOS, a Federally Approved RPR, CCR and Notary Public.

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JOAN A. WLOCHOWSKI

DANIEL GRBICH, Videographer

- - -



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EXHIBITS





EXHIBITS (cont'd.)

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(None)

STIPULATIONS
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(None)

QUESTIONS MARKED
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(None)



- - -

VIDEOGRAPHER: We are now on the record. Please note the microphones are sensitive and may pick up whispering and private conversations. Turn off all cell phones and place them away from microphones. They can interfere with the deposition audio.

My name is Dan Grbich representing Veritext.

The date today is July 11, 2017, and the time is approximately 8:58 a.m. This deposition is being held at Spector Roseman & Kodroff, located at 1818 Market Street, Philadelphia, Pennsylvania. The caption of this case is In Re: Merck's Mumps Vaccine Antitrust Litigation, United States of America, ex rel, Stephen A. Krahling and Joan Wlochowski versus Merck & Co., Inc. This is being held in the United States District Court for the Eastern District of Pennsylvania. The name of the witness is David Krah.

All attorneys will be marked

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present on the stenographic record.
At this time our court reporter, Linda Rossi of Veritext will swear in the witness and you may proceed.
- - -
DAVID KRAH, after having been first duly sworn, was examined and testified as follows:
- - -
EXAMINATION
- - -
BY MR. KELLER:
Q. Good morning, Dr. Krah. Can you state your full name for the record?
A. Yes. David L. Krah.
Q. And how old are you?
A. 61.
Q. 61. What is your current residence address?
A. 213 Brunswick Court, Lansdale, PA.
Q. You've lived there for quite a while?
A. Yeah, I think 28 or 29 years, I believe.

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Q. Have you ever had your deposition taken before?
A. Yes.
Q. How many times?
A. Once.
Q. When was that?
A. The late '90s.
Q. Is that with regard to your work or personal?
A. Work.
Q. Do you recall the nature of that lawsuit?
A. Yes.
Q. What was the nature of that lawsuit?
A. The nature was a claim, as best I can recall, that Merck and Beacon were making against GlaxoSmithKline for the varicella vaccine.
Q. And let me come back to that in a minute.
When you had your deposition taken in that case in the 1990s, I'm sure they went over the ground rules about how a deposition takes place. I'm sure your counsel

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has spent some time with you explaining the rules and sort of what to expect today, but it always helps for us to kind of do it again just to kind of go over it to make sure that we're all on the same page and you sort of understand what's going to happen and so that there's no confusion at the end of the day when the case -- the transcript in this case is written up.
As you can see, Linda is going to take down everything we say. Though she's amazing, it's very difficult for her to take down when we speak at the same time. She will be able to do it, but at the end of the day when they -- I'm sure when you were deposed before, you saw a thing called a transcript which had all the questions and answers. So we really want to have a complete question and a complete answer, not have them jumbled together, which is what happens when people speak over each other. So for purposes of today and tomorrow, please allow me to finish my question and you will see -- you'll get the hang of this pretty quickly, but you'll see that sometimes it may take me a second to

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formulate the second half of my question. Get the first part down, then I have to figure out the second part. Just give me a second to finish my question and then I will do my best to allow you to finish answering. Is that fair?
A. Yes.
Q. Perfect. And you're doing a great job with using words to answer. Though the court reporter can probably pick up uh-huhs and uh-uhs, for a clear record, we want a clear record, yeses or noes and using words instead of nonverbal communication. Is that fair?
A. Yes.
Q. You were interviewed by the Department of Justice. Do you recall that?
A. Yes.
Q. And how many days were you interviewed for?
A. One.
Q. One day. You understand in that interview you were under penalty of perjury when you answered their questions. Correct?
MR. SANGIAMO: Objection. You

can answer.
THE WITNESS: I don't recall giving the oath as I did at the beginning of this. I don't know.
BY MR. KELLER:
Q. You don't know.
Were you truthful when you spoke to the Department of Justice?
A. Yes.
Q. At the end of our two days here, Linda will prepare a transcript and you'll have a chance to review that transcript and make changes as you deem appropriate. Just be aware that any changes that you make we'll be able to make reference to that at trial. Okay? So if you change your testimony in the transcript, we will be able to use your prior -- the original testimony and your changes. Do you understand that?
MR. SANGIAMO: Let me just interpose, Jeff, the rules are what they are. We'll proceed according to the rules.
MR. KELLER: Fair enough, Dino.
BY MR. KELLER:



Q. One of the most important rules here is if you do not understand my question, and you don't say anything, we're all going to assume that you did. So if I ask a question you don't understand, please let me know; otherwise, we're all going to assume that the answer you gave was -- that you understood the question. Is that fair?
A. Yes.
Q. We are entitled to your best understanding. We don't want you to guess at anything, but we are entitled to your best understanding. So if you need to -- you know, if you don't know specifically an answer but you know generally of an answer, you still need to answer, though you can identify that to the extent that you have your knowledge. I remember something, I don't remember everything. But you can't say I don't remember when you remember something. Is that fair?
A. Yes.
Q. Is there any reason today why you can't have your deposition taken? Are you on any sort of medication? Have you any



medical conditions that would affect your ability to tell the truth today? Just yes or no.
A. No.
Q. Who is representing you today?
A. Pardon me?
Q. Who is representing you today? Are these Merck's lawyers or your personal lawyers?
MR. SANGIAMO: I'm serving as both Merck's counsel and Dr. Krah's counsel.
BY MR. KELLER:
Q. Is that true?
A. Yes.
Q. When did you -- let me back up to the 1990s when you had the case with varicella.
Who sued who with regard to the varicella vaccine?
A. I recall that Merck and Beacon were involved. I don't recall specifically who the actual entity was that was suing GSK, GlaxoSmithKline.
Q. And GSK was trying to develop



their own varicella vaccine?
A. They were trying to develop a varicella vaccine, yes.
Q. With a different virus strain?
A. No.
Q. Same virus strain?
A. Yes.
Q. Do you know -- do you recall whether or not -- where that case was venued? Was it in federal court or state court?
A. I recall it was in Delaware, but I don't recall whether it was federal or state.
Q. Why were you deposed in that matter?
A. I had -- it was my understanding why I was deposed is that I had a detailed understanding of the varicella manufacturing process and had -- including information that we gained from Beacon.
Q. Did Beacon, was that the entity that developed the varicella vaccine and did Merck purchase it from them?
MR. SANGIAMO: Object to the form.

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BY MR. KELLER:
Q. Let me rephrase that. Who developed the varicella vaccine that was at issue in this lawsuit?
MR. SANGIAMO: Objection. You can answer.
THE WITNESS: There are parts of the process that were developed by Beacon and then parts of the process that were extended, from my understanding, at the different, either Merck or GSK.
In this case it was GSK.
BY MR. KELLER:
Q. You stated earlier that you were familiar with the manufacturing practice of the varicella vaccine. How did you become knowledgeable about that topic?
A. I didn't say practice. Process. The process.
Q. Sorry, I misheard you.
A. I became familiar with that through two -- two -- actually at least one is interacting with our manufacturing group at Merck to understand the manufacturing process that Merck was using. Also I was requested to

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and made a trip to the -- to Beacon. It's -- when I refer to Beacon, it's -- I'm trying to remember the name. It's -- Osaka University is, I think, like the parent organization. Beacon, as best I recall, is the manufacturing part of that. So at any point I made a visit to both Beacon and Osaka University, talked to one of the people that began the development of the vaccine to ask questions, understand details about their manufacturing process.
Q. Were you -- I don't want you to disclose any communications with counsel, but do you know whether or not you were testifying as a person most knowledgeable or based on your -- let me -- let me just start with that. Were you testifying as a person most knowledgeable for the company?
MR. SANGIAMO: Object to the form.
THE WITNESS: I wouldn't say I was most knowledgeable. I would say that it's my understanding that I -- since I had direct experience interacting with Beacon, that that was -- there were others on the trip

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along with me, but I was able to get firsthand information about the discussions with Beacon.
BY MR. KELLER:
Q. Was that in preparation to take -- to sit for a deposition or was that information you had before you were being called as a witness?
MR. SANGIAMO: Objection.
THE WITNESS: That was information that was before I was deposed.
BY MR. KELLER:
Q. So that's information you had as part of your normal job duties at Merck in working on that particular vaccine?
A. Yes.
MR. SANGIAMO: Objection.
BY MR. KELLER:
Q. When did you first learn that you were going to be deposed in this case?
A. I can't remember a specific date. I would say sometime last year there was a suggestion that I would be deposed.
Q. What did you do in -- did you do

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anything to prepare for your deposition today since last year when you first learned about it?
MR. SANGIAMO: Object to the form.
THE WITNESS: Can you clarify as far as specific examples?
BY MR. KELLER:
Q. What did you do personally? Did you do anything personally to help prepare yourself for today's deposition?
A. I didn't do anything. The only thing I did do was meet with counsel for the preparation sessions.
Q. How many sessions did you have?
A. I believe five.
Q. And were those full-day sessions?
A. I believe. As best I can recall, yes.
Q. And when was the first full-day session?
A. I don't recall.
Q. When was the last time you met?
A. Yesterday.
Q. And did you meet for a full day

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yesterday?
A. It was the majority of the day.
Q. And before yesterday, when did you meet before that?
A. Friday, last Friday.
Q. And that was, again, a full day?
A. The majority of the day.
Q. What about before that?
A. I think -- as best I recall, Thursday of last week.
Q. And before that?
A. I don't recall.
Q. So you met yesterday and two days last week. Correct?
A. As best I can recall, yes.
Q. And then the other two meetings, do you recall when those occurred?
A. They were within the last few weeks, but I don't recall specific dates.
Q. Prior to the last few weeks, have you spoken to Merck's counsel regarding this case?
MR. SANGIAMO: That's a yes or no, Dave.
THE WITNESS: Yes.

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BY MR. KELLER:
Q. And how many conversations have you had?
MR. SANGIAMO: I'm going to object to that.
THE WITNESS: I don't recall.
BY MR. KELLER:
Q. Was it more than one?
A. It's more than one.
Q. Was it less than ten?
MR. SANGIAMO: That's invading the attorney-client privilege.
MR. KELLER: The number of conversations?
MR. SANGIAMO: Yeah. I'm going to instruct him not to answer that.
BY MR. KELLER:
Q. You're going to follow your counsel's instruction?
A. Yes.
Q. In preparation -- let me ask you, when did you first learn about this lawsuit?
A. I don't recall a specific date.
Q. Was it -- do you recall, was it several years ago?
A. It was several years ago, but I don't recall the date.
Q. Did you read the Amended Complaint?
A. I recall seeing parts of it. I didn't read every part of it.
Q. What part do you recall seeing?
A. I don't recall.
Q. Do you recall discussing the Complaint? Do you recall reviewing with anybody at Merck, excluding any attorneys?
A. I did not discuss it with anyone else.
Q. Have you -- so you did not discuss this case with anybody other than Merck's lawyers?
A. That's correct.
Q. Are you married?
A. No.
Q. Do you have a girlfriend?
A. Not currently.
Q. And during the time that you first learned about this lawsuit, did you have a girlfriend between then and now?

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A. Not that I recall.
Q. In preparation for your deposition today, over those five full-day meetings that you had with your counsel, did you look at documents?
A. Yes.
Q. Do you recall how many documents you looked at?
A. That, I don't recall.
Q. More than one?
A. Yes.
Q. Less than 100?
A. I can't say with any --
Q. Can you give me your best recollection of how many documents?
A. There were at least -- they're running together in my head, so I can't really give a...
Q. It could have been two or it could have been 500?
A. I can't recall the specific number. It's more than two, I would say. I don't recall.
Q. So it could have been three? Sir, I'm trying to get fair testimony from

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you. If you -- how big of a stack of documents can you recall looking at?

MR. SANGIAMO: You know, Jeff, the documents that are reviewed in preparation for a deposition are work product. So you're certainly not allowed to ask him what those documents were. I'd have to think about whether you're allowed to ask him how many he looked at, but I don't see where that's going since you're not going to be able to ask him what he looked at. He's given you his best recollection.

BY MR. KELLER:

Q. Sir, did you look at a Bankers Box worth of documents?

A. I can't -- there were -- as best I can recall, there were documents one at a time, and I -- there was no pile or assembly that would remind me of how many there were.

Q. Can you recall how many documents you looked at in an hour?

MR. SANGIAMO: Objection.

THE WITNESS: Some documents -- all I can offer for that is that some

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documents took -- were reviewed more quickly than others. So I can't exclude that some took an hour to review and others were less than an hour.

BY MR. KELLER:

Q. I'm asking how many documents do you recall looking at in an hour on average?

A. That, I don't recall.

Q. You can't tell. Okay. How many documents did you look at yesterday?

A. That, I don't recall.

Q. Have you looked at any deposition transcripts in this case? Did you review any deposition transcripts in this case?

A. For this case?

Q. Yes.

A. No.

Q. Did you look at any deposition summaries in this case?

A. No.

Q. Sir, over the course of your professional life at Merck, did you maintain a journal?

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A. Yes.

Q. How many journals did you maintain? Let me rephrase that question.

The journal that you maintained, was that kept on a computer program?

A. Yes.

Q. What was the -- did that computer program change over the years?

A. As best I can recall, it was Microsoft Word. I don't recall how that changed over time.

Q. And did you keep more than one journal?

A. There -- the -- I'll say yes in that there was one general format for the journal but over multiple years, and they were saved as separate -- by different years. So they exist as separate documents but are -- one could view them as a continuation.

Q. So other than segregating them out by year in separate files, did you keep any separate personal journals?

MR. SANGIAMO: Object to the form.

THE WITNESS: Not --

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BY MR. KELLER:

Q. Let me rephrase the question.

Did you keep a journal at home?

A. No.

Q. Did you maintain any documents at home from Merck?

A. No.

Q. Do you have a personal computer at home?

A. I have my work computer.

Q. That's a laptop?

A. Currently it's a laptop, yes.

Q. And back in -- let me just sort of back up.

Back in the late '90s, did you have a laptop?

A. I don't recall -- I don't recall when the Merck laptop was issued. I don't recall in the late '90s if we had a laptop or -- I didn't have a personal laptop.

Q. Did you have a personal computer at home?

MR. SANGIAMO: In the late '90s?

MR. KELLER: Yes.

THE WITNESS: Not that I recall.

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BY MR. KELLER:
Q. Did you have a desktop computer?
A. At work?
Q. At home.
A. At home, no.
Q. Do you have a personal computer at home currently?
A. No.
Q. During -- so from the late '90s to today you've never had a personal computer at home?
A. Not that I recall.
Q. Back to your journals that you maintained on Word, did you ever have separate journals for work stuff and another journal for personal stuff?
A. I did not have a separate journal, but I did, on occasion, excerpt information from the one journal into a separate compilation, but it was the same information that was in the primary journal.
Q. So your journal kept all the information that you -- let me strike that. When I say "strike," it means I'm just going to do it over again and forget that question.

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So did you ever delete information from your journal?
A. Not that I recall other than a typographical error.
Q. But you would copy things from your journal and move them into a different file for other purposes. Correct?
A. There are occasions where that was done.
Q. And under what occasions would that occur, if you can recall, between the late '90s and current?
A. If there was a -- one example perhaps is if we had -- if there was a topic where I wanted to compile information over the course of time into one document so that it was all that topic rather than sorting through the original journal, then I would do that compilation.
Q. So for personnel issues you would compile information about somebody's -- if they were late multiple times, you would copy that out of your journal into a compilation?
MR. SANGIAMO: Object to the

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form. You can answer.
THE WITNESS: Not -- I think that specific example I do not recall doing.
BY MR. KELLER:
Q. What specific example do you recall?
A. If there were personnel issues or personnel discussions that I thought were -- that were continuing that I wanted to compile, I would excerpt the information from the journal into a separate summary on that personnel topic.
Q. Well, in the case of a personnel issue, why would you be excerpting different references from different days into a compilation?
A. One application for that would be to compile, if there was a trend of behavior or trend of events. And then include efforts I was making to try to understand or address the questions.
Q. What did you do with that information once you compiled it?
MR. SANGIAMO: Object to the

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form. You can answer.
THE WITNESS: For the most part, as best I can recall, I would just have it available for reminding me of the summaries. I can't exclude that on some cases that was forwarded to management for review.
BY MR. KELLER:
Q. Did you ever recommend that somebody get fired from your lab?
A. Yes.
Q. How many times did that happen?
A. Twice.
Q. And do you recall when that happened?
A. I don't recall the dates, but I remember the occasions.
Q. Can you describe those occasions?
A. One was -- they were both contract employees in the lab. One was someone who had come to us, as best I can recall, in her resume claiming extensive lab experience on a particular topic. When she came to the lab, she showed none of those skills and, in fact, was missing many

rudimentary skills. I had her work with multiple people in the lab throughout the course of a week to see if everyone would have the same observation. They confirmed that this person wasn't -- appeared that they had basic lab skills. We recommended to the contract agency that she be terminated.

Q. The second occasion?

A. The second occasion was another contract employee who, as best I can recall, was, I would say, technically competent but not -- from my recollection, not very interested -- not interested in the work that he was doing, was not completing assignments on time. And after several weeks, we recommended that he be terminated.

Q. Did you ever recommend any Merck employees be terminated?

A. No.

Q. Did you ever recommend any Merck employees be demoted?

A. No.

Q. Let me ask you, in response to this litigation, did you do anything to search for any of your -- any documents that you kept



in your files?

A. No.

Q. And your -- when did you start Merck?

A. 1988.

Q. And since 1988, have you ever brought any documents home from work?

A. Yes.

Q. And what kind of documents did you bring home?

A. I believe, as best I can recall, minutes of meeting or -- meeting minutes or agendas.

Q. Why did you bring those home?

A. To review, or if I didn't have time to review them at work, to be able to review them before the next day or whatever the -- whatever I needed to review them.

Q. Was that an acceptable policy at Merck?

MR. SANGIAMO: Objection. Answer if you know.

BY MR. KELLER:

Q. To your understanding.

A. To my understanding, yes.



Q. Do you currently have your own office?

A. I have an office where there's no other person in the office.

Q. Do you maintain files in your office?

A. Yes.

Q. Did you ever go through those files to see if there's any documents that are related to this lawsuit?

A. Yes.

Q. Did you provide those documents to your counsel?

A. Yes.

Q. Did anybody else search those files other than you?

MR. SANGIAMO: Answer if you know.

THE WITNESS: A group came to retrieve the files. I don't know if that counts as counsel or not. But I don't recall who they were.

BY MR. KELLER:

Q. So just so I understand, the procedure that you followed in order to



produce documents in this case from the files that you maintained in your office is that you went through those files, segregated them and then somebody came by and picked them up?

MR. SANGIAMO: Object to the form.

Dr. Krah, you should not disclose the content of communications with counsel on this topic.

BY MR. KELLER:

Q. You can answer, though. Do you need the question back?

A. There was no -- I did not segregate any documents.

Q. So you just opened your office files to somebody to come look or did you -- strike that.

You testified a minute ago that you went through your files and provided them to somebody to come pick up. Did somebody go -- did you provide them all of your files or a subset of the files?

MR. SANGIAMO: Object to the form.

THE WITNESS: I provided all the

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files that were -- that had any relationship to the litigation.
BY MR. KELLER:
Q. And you made that decision yourself?
A. Yes.
Q. And so -- did that include files outside of your physical office?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Do you understand my question?
A. I don't.
Q. Yes or no?
A. No, I don't understand.
Q. If you don't understand it, just say I don't understand. That's fine. That wasn't a great question, I'll try to rephrase it.
Did you also look for documents responsive, that related to this case outside of the files that are kept in your physical office?
MR. SANGIAMO: Object to the form.

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THE WITNESS: There were documents that were kept in our laboratory, and those were provided.
BY MR. KELLER:
Q. Did you do the same -- go through the same procedure of going through those files that were in your lab identifying those that you believe related to the case and then provided those to counsel?
MR. SANGIAMO: Object to the form.
THE WITNESS: As best I recall, I provided an index of the experiments and provided those to counsel, and counsel determined which files were relevant.
BY MR. KELLER:
Q. So you only provided an index of the experiments. Did you provide an index of all the different documents that you had? You had more than just -- more than -- strike that.
Is there a centralized filing system that you have in your lab?
MR. SANGIAMO: Object to the

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form.
THE WITNESS: Can you clarify as far as what are --
BY MR. KELLER:
Q. How do you maintain your files in your lab? Let me back up and get some more foundation here.
The lab that you currently work in, how long have you been in that lab?
A. Perhaps 14 years.
Q. 14 years. So around 2003, where did you -- did you work in a different lab?
A. Yes.
Q. Where -- from 2003 to today, what's the -- does the lab have a location identifier?
A. Yes, there are room numbers.
Q. And what was the room number for the lab that you've worked in since 2003 to current?
A. There's -- if I maybe qualify this in that there's the lab, there's an office area by the lab, so the labs themselves are 309 and -- building 16, room 309 and 327.
Q. And then there's an office that

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you maintain near that lab. Correct?
A. Yes.
Q. That's from 2003 to current. Correct?
A. Yes, as best I recall.
Q. Now, from the time before 2003, before you worked -- had a lab in room 309 and 327, you worked in a different lab. Correct?
A. We had two other labs -- two other labs, we were using those, the 309 and 327 labs periodically but not exclusively.
Q. What other lab did you work in more often?
A. The other labs were same building 16, room 203, 213 and periodically 212.
Q. And so did you maintain the same office -- they're in the same building. Correct?
A. Yes.
Q. And those labs are organized -- did you maintain the same office during that time frame?
A. I moved my office, I believe, twice during that time.

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Q. In the same building?
A. In the same building.
Q. On the same floor?
A. No.
Q. So that when you -- they're on different floors. Prior to 2003 you were on the second floor, after 2003 you moved to the third floor. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: The labs that we were using were on the third floor 2003 and beyond. So the labs that we were -- primary labs that we were using were on the second floor approximately 2003 and then third floor after 2003.
BY MR. KELLER:
Q. So you moved your offices in 2003 from the second floor to the third floor?
MR. SANGIAMO: Object to the form.
THE WITNESS: If I could clarify. What I was referring to were the laboratories. Laboratories in my view are separate from the offices.

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BY MR. KELLER:
Q. Is it fair to say that the office, there's offices on each floor. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not all the time.
BY MR. KELLER:
Q. On the second and third floor of building 16, there's offices on each floor?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Let me just sort of cut through this if you can. Can you describe, when you were working -- when you had labs on the second floor, 203 and 213 and sometimes 212, how long were you in those labs? Just to get some more foundation.
A. I was using those labs since I started in 1988.
Q. 1988, okay. Why did you move to the third floor?
A. As best I recall, the second floor was being renovated.

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Q. As part of your move in 2003, did you move your office?
A. My office did move, but I don't recall that it was part of that renovation move or not.
Q. When the office moved, did it move from the second floor to the third floor?
A. My office did not --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Your office stayed on the second floor?
A. No.
Q. Where did it move to?
A. The first floor.
Q. The first floor, okay. And so -- and that was in 2003, do you recall?
A. I don't recall the date of that.
Q. When you moved your offices, you don't recall the date, did you -- did somebody come in and move all your file cabinets? Let me back up a second.
How did you keep your documents prior to 2003, your files that you maintain in

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your office?
MR. SANGIAMO: Object to the form.
THE WITNESS: Can you clarify what you mean by how I kept them?
BY MR. KELLER:
Q. Did you have files in your office?
A. Yes.
Q. Were they kept in file cabinets?
A. Yes.
Q. Were they kept anywhere else?
A. There were some experiments that were kept on shelves.
Q. And so what experiments would you keep on shelves?
A. They were experiments that were in notebook binders that were -- lab experiments that were in binders.
Q. And those binders, are those called workbooks?
A. No. They're like -- I view them as like three-ring binders. Like, I don't know, there must be other names for them. I wouldn't call them a workbook.

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Q. So those were your experimental -- experiments that you were running, you kept those in binders in your office?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not all experiments were kept in binders, but I did have experiments in binders.
BY MR. KELLER:
Q. What did you keep in your file cabinets?
MR. SANGIAMO: Object to the form. You can answer.
BY MR. KELLER:
Q. In this 2003 through -- 1998 through 2003 period.
A. A variety of documents and some of the lab experiments.
Q. When you moved your offices, did somebody come in and move all the binders on the shelves and all the file cabinets?
A. Someone did move them. I packed them up and somebody moved them.
Q. When you packed them up, did you go through them and discard anything?

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A. No.
Q. So those documents that were in your office from 1998 through 2003, those were moved when you moved your offices. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: All of the documents that I had at the time of the move were moved.
BY MR. KELLER:
Q. You said you moved again twice. And the same, did you go through the documents when you moved the next time to see -- to sort through and get rid of anything or did you just move everything to the next office?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't exclude that in the next move that I didn't sort through -- I think examples are like old journal articles that I didn't feel were relevant anymore. But as best I can recall, all other documents were moved wholesale into the, I'll say a temporary office and then eventually

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moved back to the, what was the previous office on the first floor.
BY MR. KELLER:
Q. So these moves were -- you moved to a temporary office when they were renovating and you moved back to your original office?
A. There were two renovations involved. So one move was related to renovation of the second floor, I don't recall that they're exactly the same time, but then when I moved to the first floor, there was a renovation that was happening there as well and I had to move to a temporary spot.
Q. So the files that were maintained in the labs in 203, 213 and 212, when you moved to the labs at 309 and 327, did those file cabinets -- did those files get moved as well?
A. Some of the documents from it were moved to my office and some were moved -- and I don't recall what percentage of them were moved to the new file cabinets in the third floor space.
Q. Were any documents destroyed, do

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you recall?
A. No.
Q. When you -- in response to this case when you were looking -- when you were going through the documents to identify documents that were relevant to this case, you also searched the files in the labs in rooms 309 and 327 in building 16. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: There were -- as best I recall, there were no files in those laboratories.
BY MR. KELLER:
Q. So the only files that you recall searching that were relevant were in your office. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's not fully correct. The third floor, not in the laboratory space, we had an office space, a shared office space by the laboratories, and there were files there.

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BY MR. KELLER:
Q. You searched those files?
A. Yes.
Q. You determined what was relevant and you gave those to your lawyers. Correct?
A. In that case --
MR. SANGIAMO: Object to the form. You can answer.
THE WITNESS: In that case, at least as best I can recall, we provided the indexes of the lab experiments to counsel and counsel reviewed them and decided what was relevant.
BY MR. KELLER:
Q. Was there anything other than lab experiments in those file cabinets?
A. Not that I recall.
Q. Were there -- did you maintain any notes that were not in lab experiments as part of the ordinary course of running your labs? In the files that you maintained in your office after 2003, or in a shared office, were those just experiments?
A. I'm sorry, the first half of that, did you say in my office were the only

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experiments?
Q. Let me ask -- I'll break it up. In your office, did you maintain just lab experiments?
A. No.
Q. What else did you maintain?
A. Reports, minutes of meetings, journal articles, safety information, manuals, equipment manuals.
Q. And so you went through those to determine what was relevant to provide your counsel?
MR. SANGIAMO: Object to the form.
THE WITNESS: I reviewed it to identify what was relevant to provide them.
BY MR. KELLER:
Q. Did anybody else review them other than you?
A. Not that I recall.
Q. Did you -- you said that you would bring documents home periodically as part of the ordinary course of your job at Merck to review. Did you ever keep those

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documents at your house in a file?
A. No.
MR. SANGIAMO: Object to the preamble of your question. If you want to ask what they were kept in, that's fine.
THE WITNESS: I never retained anything. They were returned to Merck.
- - -
(Exhibits Krah-1, Curriculum vitae, 00000695 - 00000702, was marked for identification.)
- - -
BY MR. KELLER:
Q. Let me mark as Exhibit 1 a document that bears Bates stamp number 695 through 702, which is an older CV of yours, sir. Can you tell me if you recognize this document?
A. I can't say that I recall the specific date on it, but the general content looks familiar to me.
Q. When is the last time you saw this document?
A. The one dated January 1998?

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Q. Yes.
A. That, I don't recall.
Q. Do you have a current CV?
A. Yes.
Q. Did you provide that to counsel?
A. I don't recall.
Q. Can you take a second and tell me if there's anything in this CV that you believe to be -- is this -- to be accurate as of the date of January 1998?
MR. SANGIAMO: I'm sorry, what was your question, Jeff?
BY MR. KELLER:
Q. Can you take a look at this and tell me if you think it to be correct as of January 1998? Let me strike that.
Did you prepare this CV?
A. I don't recall if I prepared it or one of our administrative associates prepared it.
Q. Do you have any reason to believe that the information in here is incorrect?
MR. SANGIAMO: Take your time and look through it if you need to.

MR. KELLER: In fairness I will identify for the record that page 7 of this CV is missing from the production that was given to us.

THE WITNESS: I don't have any reason to expect that anything is not correct.

BY MR. KELLER:

Q. So the education and employment history, that's accurate. Correct?

A. To the best of my understanding, yes.

Q. So after 1998 -- I'm sorry, after 1995, it says you are the "Senior Research Fellow Department of Virus and Cell Biology." Do you see that? Can you tell me what your positions were from 1998 through current? I don't have a current CV, so we have to fill in the gap. So if you can identify what your employment history is at Merck after 1995 to fill in the gaps in the CV.

A. The title names have changed over the years. As best I can recall, 1998 I was promoted to senior investigator.



Q. That is the department of virus and cell biology?

A. Our department name changed many times so I think that -- like we were virus and cell biology and cellular/microbiology and then -- I can't -- I don't recall how many -- it's in the same theme of virus and cell biology. The department number changed and the name changed, but the same entity, basically. The same group. It was still in the same group.

Q. The same management group?

A. Yes.

Q. Your job duties were the same even though the department may have changed names?

A. Within a given -- within a given job title, yes.

Q. So in 1998 you were promoted to a senior investigator. Correct?

A. The best I can recall is 1998.

Q. Can you tell me your next promotion or next position?

A. That's been -- still the same level. Now, the name has changed to senior



principal scientist or something of that sort.

Q. It's the same level?

A. Yes.

Q. So from 1998 to 2017 you've had the same job?

A. Yes.

Q. What is -- so if I say senior investigator, is that a fair way to describe your title? How would you like me to describe your title between 1998 and 2017?

A. Senior investigator is as good as any. It's just a set of words.

Q. Fair enough. And did your job duties change from 1998 to 2017?

A. So projects changed. I don't know if one could infer from that responsibilities changed. There's a broad -- so there's not a -- it's my understanding a formal change of -- range of job responsibilities between 1998 and present.

Q. Sorry, I didn't mean to interrupt you.

MR. SANGIAMO: Are you done with your answer?

THE WITNESS: I guess getting to



the point that the -- there are core job responsibilities for a given position, but the project responsibilities can vary between projects even with the same title.

BY MR. KELLER:

Q. You're researching different -- you may be researching different viruses. Correct?

A. Yes, as an example.

Q. Can you just give me a description of what you do as a senior investigator during this time frame? I understand you worked on different projects, but is there a way to describe what your job responsibilities were in a very general way?

MR. SANGIAMO: You said this time frame, that being?

BY MR. KELLER:

Q. 1998 to 2017 you've had the same job title, and my question is, were you generally doing the same work?

A. There were some -- I would break it up into two time periods.

Q. Sure.

A. From 1998 through 2013 I was in some version of virus and cell biology. Again, I don't recall the name of the department at the time. With the responsibility of, as best I can recall, applying cell biology and virology to answer questions for projects that the project -- that the department was supporting. That ranged from looking at alternate cell substrates for virus growth, increasing productivity, evaluating different virus strains, looking into animal models for infection. So a range of applications. My responsibility was to lead a group who contributed to that area.

Q. These are basically research projects. Correct?

A. Yes.

Q. So you were a research lab. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: We were a lab in a research department.

BY MR. KELLER:



Q. Did you do any manufacturing testing?

MR. SANGIAMO: Object to the form.

MR. KELLER: Strike that.

BY MR. KELLER:

Q. Did you work with Merck manufacturing on any of the products that were on the market for purposes of -- let me strike that.

So you said that you were doing research under virus and cell biology. Those projects were changed based on whatever the department was interested in pursuing. Correct? Is that fair?

MR. SANGIAMO: Object to the form.

THE WITNESS: Our -- the department had objectives, the research labs had objectives, and our department had objectives that were a subset of that. And then our lab contributed to whatever the objectives were for the area.

BY MR. KELLER:



Q. What do you mean by -- can you describe what you mean by an objective?

A. Objective meaning work on a specific program or in our case largely vaccines. In my personal experience, largely vaccines.

Q. Do you consider yourself to be an expert in vaccine research?

A. I consider myself --

MR. SANGIAMO: Object to the form.

THE WITNESS: -- to be an expert in cell biology and virology. Perhaps less so in the cell biology, more so in the virology part. Not specifically in vaccine research.

BY MR. KELLER:

Q. And so -- and that's your educational training, is in virology. Correct?

A. Yes.

Q. Can you tell me during this time frame -- let me sort of narrow this down a little bit.

Between 1998 and 2002, how many people were in your lab that you had



responsibility for?

A. I don't recall specific number. I would estimate between four and something more than four. I don't remember the upper number.

Q. Were there people that reported to you that other people reported to in your lab --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- during this time frame 1998 to 2002?

A. There -- as far as formal reporting structure, everyone reported to me. There were some informal, I don't know if they called it reporting structure, but someone who might oversee other -- another group's activities in the lab.

Q. During this time frame, from 1988 to 2002, I'm going to talk about that for a while. Unless I say otherwise, that's the time frame I'm talking about for purposes of this series of questions. This informal reporting structure, who was -- was there a

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second in command in your lab at this time frame?
MR. SANGIAMO: Object to the form.
THE WITNESS: There were people -- or there were people, some people with more seniority than others. I wouldn't characterize them as second in command.
BY MR. KELLER:
Q. Ever hear that term used at Merck before?
A. I've heard it used in general before. I don't -- can't say that specifically specific to Merck or that I heard it at Merck.
Q. So in terms of the more seniority, who had the highest seniority in your lab during this time frame?
A. Mary Yagodich.
Q. Did you depend on Ms. Yagodich --
MR. SANGIAMO: Object.
BY MR. KELLER:
Q. -- to oversee certain aspects of the lab?

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MR. SANGIAMO: Object to the form. You can answer.
THE WITNESS: I looked to Mary to be the most highly trained, experienced person in the lab who I would go to to ask questions or have her -- if other people needed help, help her go to them.
As far as -- I forget what your original --
BY MR. KELLER:
Q. I'm trying to get this formal --
MR. SANGIAMO: I'm sorry, what is it?
BY MR. KELLER:
Q. Let me just -- we just stepped on each other. Let me ask the question again if you're done answering. Are you done answering?
A. Yes.
Q. Other than Mary Yagodich, was there anybody else in this informal hierarchy that you thought of as having seniority in terms of overseeing other people?
MR. SANGIAMO: Object to the form.
THE WITNESS: There is one other person who -- I don't know if it fits into the seniority part, but another person, DeeMarie Watson who --and this actually may precede 1998, the dates. Had her oversee largely a group of contract employees while another group of the lab was busy with other activities.
BY MR. KELLER:
Q. So Ms. Yagodich, she's a virologist as well?
MR. SANGIAMO: Object to the form.
THE WITNESS: Her undergraduate education, I -- actually, I don't recall what her undergraduate degree is in. Her undergraduate education would not be focused on virology, but from her experience in the lab, I would consider her a virologist.
BY MR. KELLER:
Q. You believe her to be competent?
A. Yes.

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Q. Honest?
A. Yes.
Q. Do you recall that she had a good memory?
MR. SANGIAMO: Object to the form.
THE WITNESS: I recall that she was fluid in the work she that was doing. Whether that constitutes a good memory, I can't say.
BY MR. KELLER:
Q. Do you recall her -- let me back up.
Did you have a romantic relationship with her?
A. No.
Q. Were you in love with her?
A. No.
Q. Did you ever date anybody's family members in the lab?
A. Yes.
Q. And who was that?
A. Sister of Mary Yagodich.
Q. So you were close to Mary?
MR. SANGIAMO: Object to the

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form.
THE WITNESS: Not -- I was close to her being a long time member of the laboratory, not because of any other factor.
BY MR. KELLER:
Q. Did you ever socialize with her outside the office?
A. I remember one occasion, at a Christmas party when she first moved into her house. That's the only event I recall.
Q. Did you ever socialize with anybody in the lab outside of the office?
A. Periodically the group would go to a restaurant or bar like Friday's after work. I remember going once, so not on a -- I do recall doing it occasionally, but not on a regular basis.
Q. Did you ever take any of your employees to lunch? Let me strike that.
Did you ever take anybody in your lab that you had supervisory responsibilities over to lunch?
A. I did take lab members to Christmas lunches. There were other lunches

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that I attended, I don't know if that qualifies as taking them. I was with them at lunch.
Q. Would that include the entire lab or just a subset of the lab --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- during this time frame 1998 to 2002?
MR. SANGIAMO: Same objection.
THE WITNESS: I recall at least on one occasion it was a subset of the lab. The majority of the cases were the full lab or whoever was either interested or available to come.
BY MR. KELLER:
Q. If you turn back to Exhibit 1, under "TRAINING," it appears that there's -- in the first reference it says, "Good Manufacturing Practices for Biologics and Vaccines" in 1989.
Do you see that?
A. Yes.
Q. And then you've got below that starting in 1992, "GMP Training," '93, '94,

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'95. Do you see that?
A. Yes.
Q. Was that required to take GMP training yearly at Merck --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- through this 1998 through 2002 period? Let me back up.
Did you take GMP -- let me strike that.
What does GMP -- what's your understanding of GMP?
A. It's a changing target of technically CGMP, current good manufacturing practices, reflecting whatever the expectations are or requirements at the time for manufacturing things like clinical supplies or indoor manufactured product or product for human use.
Q. Do you know what the difference between CGMP is and Good Clinical Practices?
A. No.
Q. You never were trained in that?
A. I don't recall being trained in

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Good Clinical Practices.
Q. Your lab was not certified as a GCP lab. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. At any time during the 1998 to 2002 period?
A. That, I can't say with certainty. I know we were inspected by Merck quality assurance, but I don't recall what the -- we passed the certification, but I don't recall what that certification included.
Q. Was your lab GMP compliant?
MR. SANGIAMO: Object to the form.
THE WITNESS: As far as I can recall, we were not evaluated for -- there was a period of time where we were evaluated in the early '90s in the -- from the 1998 to 2002 period, we weren't operating as a GMP laboratory, to the best of my understanding.
BY MR. KELLER:
Q. So you weren't operating as a

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GMP lab from 1998 to 2002. Is that correct?
A. I cannot exclude that there was a -- again, with the inspection that our internal quality assurance group did, what that -- what the outcome of that was, if that said that we were behaving as GMP or not. I don't recall.
Q. You weren't trained in GMP compliance to run your lab. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: I did receive GMP training. As far as what GMP training would be needed to run the lab, I can't say that I know that there is specific training for that.
BY MR. KELLER:
Q. Was your lab ever certified as a GMP lab during this 1998 through 2002 time frame?
A. Come back to the inspection that our quality assurance group did. We passed -- I don't recall if that constitutes a certification.
Q. That was just one inspection.

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Correct?
A. Yes, that's the only one I recall.
Q. And that came, that inspection occurred after the FDA inspected your lab. Correct?
A. Yes.
Q. And other than that one inspection, you don't recall ever being inspected by the CGMP folks at Merck?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not during the 1998 to 2002 period.
BY MR. KELLER:
Q. What about after?
A. There was a -- we were doing some work, and this actually may fall into the 2002 period, where we were working on an emergency vaccine program where our CGMP group did a review of our lab just to assess whether we were -- could make material under conditions appropriate for using it as an emergency vaccine.
Q. Do you recall when that was?

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A. My first thought was it was after 2002, but it may have been -- it may have been in the late 2001 to 2002 period. I don't recall the date.
Q. So there may have been another inspection with respect to that?
A. Internal inspection by Merck to see if we would -- if our lab would be capable of making, basically, clinical supplies.
Q. Do you recall the results of that inspection?
A. I have a general recollection. They had recommendations and we complied with. I don't recall that they had major reservations.
Q. Did you have any procedures in place to ensure compliance with GMP requirements?
MR. SANGIAMO: Object to the form.
THE WITNESS: We had SOPs, as best I can recall, that we obtained from the manufacturing division that we were using as a guide. Then we generated additional documents,

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additional SOPs within our department to try to be compliant with the GMP expectations.
BY MR. KELLER:
Q. That was after the FDA inspection in August of 2001. Correct?
A. Yes.
Q. But before that, you didn't have any SOPs?
MR. SANGIAMO: Object to the form.
THE WITNESS: There were -- documents existed, but I don't recall that we had any that were applying to the work that we were doing.
MR. SANGIAMO: Jeff, we've been going about -- probably about an hour and ten, so when you get to a good stopping point.
MR. KELLER: Take a break, that's fine.
VIDEOGRAPHER: The time is now 10:07. Going off the video record.
- - -
(A recess was taken.)

- - -

VIDEOGRAPHER: The time is now 10:26. This begins disc two. You may proceed.

BY MR. KELLER:

Q. Sir, I'm going to show you what has been -- we're going to mark as Exhibits 2 through 19 which have been produced to us as your journals from 1999 through 2015. You testified earlier that you kept a journal in Microsoft Word. Correct?

A. Yes.

- - -

(Exhibits Krah-2, 1998 Journal, 488056 - 488404, Krah-3, 1999 Journal, 455405 - 488932, Krah-4, 2000 Journal, 490081 - 490591, Krah-5, 2001 Journal, 490592 - 491038, Krah-6, 2002 Journal, 491039 - 491419, Krah-7, 2003 Journal, 491420 - 491835, Krah-8, 2004 Journal, 489194 - 489500, Krah-9, 2005 Journal, 488933 - 489193, Krah-10, 2006 Journal, 489501 - 4897111, Krah-11, 2007 Journal, 489903 - 490080, Krah-12, 2008 Journal, 489712 - 489902, Krah-13, 2009



Journal, 491836 - 492024, Krah-14, 2010 Journal, 492025 - 492278, Krah-15, 2011 Journal, 492279 - 492511, Krah-16, 2012 Journal, 492516 - 4925738, Krah-17, 2013 Journal, 486274 - 486490, Krah-18, 2014 Journal, 486593 - 486830, Krah-19, 2015 Journal, 486491 - 486592, were marked for identification.)

- - -

BY MR. KELLER:

Q. Let me show you Exhibit 2 which I put in front you, sorry, which is the 1998 journal. Take a look at Exhibit 2, starts at Bates stamp number 488056, and tell me if you recognize this document as a journal from starting in 1998 through -- from January through the end of December for 1998?

MR. SANGIAMO: Object to the form.

THE WITNESS: Just to clarify, you're asking if this looks like one of my -- a journal that I had that spanned those periods that you mentioned?

BY MR. KELLER:

Q. Yes. Do you recognize the



format?

A. I recognize the format, yes.

Q. Do you have any reason to believe that this is not a printout of your journal that you maintained in Microsoft Word?

A. Yeah, I can't -- just to look to see if -- can't immediately verify completeness that there's not a day missing or something. But it looks like the format that I would use. And the dates look like they're covering the period that you mentioned.

Q. Do you have any reason to believe that this is not a full and complete set of the journals that you maintained?

MR. SANGIAMO: Object to the form.

THE WITNESS: I have no reason to suspect or -- anticipate or expect that this is not a complete version.

BY MR. KELLER:

Q. And the journal that you created from at least 1998 through 2015 that was produced to us, those journals were created in the ordinary course of your job duties at Merck. Correct?



MR. SANGIAMO: Object to the form.

THE WITNESS: Are -- sorry. Just to clarify, are you asking if having a journal was part of my job duties or --

BY MR. KELLER:

Q. Yes, was it part of your job duties?

A. It's not -- at least my understanding, it's not a requirement for my job.

Q. Did you do it as part of your -- though it wasn't a requirement, was it something that you did to help you perform your job at Merck?

A. I did it to help increase my efficiency, for example, be able to recall or -- recall old information.

Q. So you -- as part of your job duties, you used these journals that we've marked Exhibit 2 through 19 from 1998 through 2015 as part of your -- to help you do your job at Merck. Correct?

MR. SANGIAMO: Object to the

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form.
THE WITNESS: I did it to help me be more efficient in my job at Merck.
BY MR. KELLER:
Q. Did anybody know -- did your superiors know that you were using a journal at Merck?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say that they did or didn't, no.
BY MR. KELLER:
Q. Was it your practice during your time that you worked at Merck, at least from 1998, you maintained a daily journal of your -- what you were -- strike that.
What was the purpose of you maintaining a journal on a daily basis?
A. The original intent, as best I can recall, is to keep track of experiments, both progress and experiments, in some cases experiment numbers, in some cases results of those experiments. And then additionally over time began to include summaries of meetings or

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points that I thought were relevant to being a more easily retrievable form for my personal efficiency.
Q. You didn't use this journal for your personal life. Correct?
A. I can't exclude that there were no -- in fact, I expect there are entries, have a car service done today or something like that. So it was a journal to keep track primarily of work-related things, but there are some work -- life-related events that I would have -- like reminders, for example.
Q. Did it act as your calendar as well?
A. It was a reminder for certain items that would be part of a calendar.
Q. I noticed in your journals that some things had checks on it and some things just had bullet points.
A. Yes.
Q. What do the checks mean?
A. The check typically means that that comment was completed or addressed.
Q. And did you also capture communications with other Merck employees?

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A. There are occasions where that was included.
Q. Why would you capture a communication between another -- for example, a superior?
MR. SANGIAMO: Object to the form.
MR. KELLER: Let me strike that.
BY MR. KELLER:
Q. Did you ever capture communications with your superiors?
A. Yes.
Q. Who were your superiors, who did you report to from this 1998 to 2002 time frame?
A. Alan Shaw.
Q. Who did Alan Shaw report to?
A. Emilio Emini.
Q. Who did Mr. Emini report to?
A. That, I don't recall.
Q. During this time frame, did you ever have any communications with Emilio Emini?
A. Yes.
Q. Did you ever capture those in your journals?

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A. As best I can recall, yes.
Q. Did you have any communications with Alan Shaw?
A. Yes.
Q. Did you capture those in your journals?
MR. SANGIAMO: Object to the form.
THE WITNESS: Yes.
BY MR. KELLER:
Q. Did you have communications with individuals in the lab that you captured in the journals during this 1998 to 2002 time frame?
A. I don't recall specific examples, but I would anticipate so.
Q. Do you have any reason to believe that the entries that you entered into your journals were inaccurate?
MR. SANGIAMO: Object to the form.
THE WITNESS: The entries that I made are, to the best of my understanding, my impression or -- so as far as whether they're accurate, I would say they

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reflect my impression, my understanding. Whether that constitutes accuracy I guess one could debate, but there were -- it was -- represented my understanding.
BY MR. KELLER:
Q. And you would enter things in the journal contemporaneous when those things were happening. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: The objectives was to enter them as -- or ideally on the same day, but I can't guarantee that in all cases it was done on the same day.
BY MR. KELLER:
Q. Was part of the use of the journal to track the flow of the running of the experiments?
A. In the context of -- so I'll say yes in the context of, for example, I recall cases where I would have a list of experiments that were in progress and then as they were completed, confirmation that they were completed so we can basically have a reminder

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of what is still to be completed.
Q. Did you ever capture results in your journal of certain experiments?
A. Yes.
Q. Did you ever discuss issues within the lab in your journals, for example, problems with equipment?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. During this 1998 to 2002 time period?
MR. SANGIAMO: Same objection.
THE WITNESS: I don't recall. I don't recall examples of that.
BY MR. KELLER:
Q. Let me do this: Let me give you -- take a look at Exhibit 4 and Exhibit 5 which are the 2000 and 2002 journals and tell me if you -- I'm sorry, 2000 and 2000 -- strike that.
Let me show you Exhibits 4 and Exhibit 5 which are the 2000 and 2001 journals. Can you tell me if you recognize those journals as journals that you prepared

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as part of your duties as you described in your testimony?
MR. SANGIAMO: Object to the form.
THE WITNESS: The 2001, at least the format looks consistent with the format that I had used previously. There is -- this may have been an error in the date entry. The back end of it, the dates, the year kind of jumps from 2001 back to 2000.
BY MR. KELLER:
Q. Did you understand that the journal, the Word -- the Microsoft Word -- were there -- strike that.
As part of you using Microsoft Word to do your daily journal entry, did you ever edit an entry?
MR. SANGIAMO: Object to the form.
THE WITNESS: Edit in what? Can you give an example?
BY MR. KELLER:
Q. Did you ever copy sections from one day and move it to the next day?

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A. Yes.
Q. Do you understand what metadata is? Metadata?
A. I've heard the term before, but I can't say that I know what it means.
Q. So you don't know whether or not the information that's at the back of these journals were captured in Microsoft Word and when the lawyers produced these documents, produced all the data that was in Microsoft Word but not viewable as your daily journal?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's not a situation I'm aware of. The dates that I had questioned looked like the right dates. For example, on page 478, it's 1/14/01, 1/15/01, 1/16/01, 1/17/01, 1/18/01, 1/19/01, and then goes to 1/21/00. So I -- I just point out it's a date discrepancy, but that it could have just as easily be that when I was putting the dates in, I entered for the balance from 1/22 -- I'm sorry, 1/21/2001 on I put in 2000 as the year

instead of 2001.
BY MR. KELLER:
Q. Or you could have been -- do you recall ever using the same file folder for your journal and then moving that data into the next year in a different file or do you recall just every January 1st starting a new file?
A. I at least -- the best of my recollection, the practice I was using typically was to, for the next year, include -- this one that comes to mind, one going back to December 1st of the previous year and carry that over to the next year. So it wasn't a January 1st to January 31st -- January 1st to December 31st.
Q. That explains why the beginning of every journal may have dates from December the prior year?
A. Yes. Yes.
Q. Fair enough. Let me have you look on the -- you're looking in the 2000 journal. Right?
A. Yes.
Q. Can you turn to page 428 of that



journal? There's a page number at the top of the journal.
A. Okay.
Q. Do you see that?
A. Okay. Yes.
Q. And here you have Wednesday, December 6, 2000. Correct? Do you see that?
A. Yes.
Q. What is the first entry there?
A. What it says is "Start mumps AIGENT assays for Protocol 007."
Q. Is that when you started running the sera for Protocol 007?
A. I can't tell from this if that's what that means.
Q. You understand what Protocol 007 is?
A. Yes, I'm familiar with it.
Q. What was Protocol 007?
A. My understanding of Protocol 007 was a study to compare the immunogenicity of the mumps component of MMR at three different doses.
Q. Was there any -- when you say -- is that -- do you understand what an objective



is of a protocol?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Let me back up.
Do you know what a protocol is?
A. I've heard of them and seen them, but I can't say that I understand all the components that are in there.
Q. And so did you ever see the protocol for Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall seeing the full protocol. I can't exclude that I saw some part of the protocol.
BY MR. KELLER:
Q. What does the protocol, based on your understanding, describe? What is the purpose -- strike that.
What is the purpose of a protocol?
A. It's an area outside of my expertise. I've read them, I've seen them,



but I can't speak with confidence about what their -- the purpose is or what it includes.
Q. When you said that your understanding of the Protocol 007 was to compare the immunogenicity between three doses, is that a fair statement of what you just testified to?
A. That's my recollection of my understanding.
Q. Did you understand that to be the objective of Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say that that is -- I don't know what the objective -- the formal objective was. That was in a practical way my interpretation of what I thought the purpose of the study was for.
BY MR. KELLER:
Q. Nobody disclosed to you what the purpose of the study was for?
A. As best I can recall, but it's a comparison between the immunogenicity between two different vaccine doses, as best I can

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recall, my understanding.
Q. Do you recall what those three doses were?
A. No.
Q. Do you recall what the purpose was behind those three doses were?
MR. SANGIAMO: Object to the form.
THE WITNESS: All I recall is that they were comparing the immunogenicity of those three doses. I don't recall further details.
BY MR. KELLER:
Q. So you don't know how that data was going to be used?
A. I recall that there was going to be a comparison of immunogenicity between doses, but I don't recall details of how that was going to be used.
Q. Did that comparison have any clinical relevance to whether or not the vaccine would protect a kid from getting sick from mumps?
A. I don't -- I'm not -- it's outside of my area of expertise. I don't know

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what the clinical -- connection for clinical relevance was intended.
Q. Did you develop the assay for Protocol 007?
MR. SANGIAMO: Objection. Form.
THE WITNESS: Other members of the lab and I did development work to develop the assay. It wasn't a -- multiple people in the lab were involved in the development of the assay.
BY MR. KELLER:
Q. When you say "people in the lab," people that worked for you, under you?
A. Everyone in the lab reported to me, so yes.
Q. So when -- you say they helped you run the experiments. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: In some cases, helped design experiments and run experiments.
BY MR. KELLER:
Q. At any time, did you understand

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that -- did you have any understanding that the purpose of this assay was to identify an end expiry potency for Merck's marketed MMR product for the mumps component?
A. I recall that the title of the study was an end expiry study. So that would imply that an expiry was part of the study. But I don't know, I don't recall how the data factored into that calculation.
Q. When you say that you did development work, can you describe for me what you mean by development work?
MR. SANGIAMO: Object to the form.
THE WITNESS: Just to clarify, you're looking for, like, variables that we are -- looked at in developing the assay?
BY MR. KELLER:
Q. Sure.
A. So initial work was largely based on any discussion with the FDA where we ran options for the assay format, meaning different virus strains, different supplements to the media, different means of calculating

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an endpoint, different means of visualizing plaques. So in discussion with the FDA, we presented data that we had from preliminary experiments that we had conducted. Received feedback from the FDA over their suggestions of how to proceed in the assay development. And then communicated results as we were giving them to the FDA -- maybe not exactly the day, but in a timely way from our perspective to the FDA. And then identified an assay format to move ahead for Protocol 007.
Q. When you say you got feedback from the FDA, what do you mean by "feedback"?
A. Feedback meaning we presented data, the FDA made suggestions, recommendations of how to proceed.
Q. Did you understand those suggestions and recommendations were binding on the FDA? Did you understand that the FDA was -- let me back up a second. We'll come back to that in a moment.
So as you sit here today, you -- strike that.
Is it fair to say that your

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testimony is you don't know why Protocol 007 was being conducted?
A. As best I can recall, my recollection and understanding was to compare the immunogenicity of the three vaccine doses.
Q. Do you recall there being any requirement by CBER -- you understand what CBER is, right?
A. Yes.
Q. What's CBER?
A. Center for Biologics Evaluation and Research.
Q. And they're a division of the FDA. Correct?
A. Yes.
Q. And they specialize, for the purposes of this case, in vaccine, correct, biologics?
A. Biologics of vaccines, yes.
Q. So do you recall any communications with the FDA or CBER where they required for Protocol 007 that the assay be linked to protection from disease?
MR. SANGIAMO: Object to the form.

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THE WITNESS: I do not recall any connection to protection.
BY MR. KELLER:
Q. If the assay was required to be linked to protection from disease, would you have developed a different assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: No.
BY MR. KELLER:
Q. You would have ran the same assay?
A. My personal opinion is that the protection from disease and antibody assay are independent events. I would not have automatically or wouldn't automatically consider a different assay as more predictive of protection versus another.
Q. So is it your belief that -- I'm trying to understand that answer. You don't believe that any assay that can be developed is any more predictive of protection from disease than any other? Is that your testimony?
MR. SANGIAMO: Object to the form.

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THE WITNESS: My opinion is that the -- my understanding and opinion is that the -- an antibody assay is an imperfect model, imperfect measure of an immune response to a vaccine. It's not a given correlate of protection. The assay itself is not -- does not provide an automatic correlate of protection.
BY MR. KELLER:
Q. Do you understand what a surrogate of protection is?
A. I've heard of correlates of protection. Surrogate I'm not sure about.
Q. You don't know what a surrogate of protection is?
A. I've heard of correlate of protection. Surrogate of protection, it's not a familiar term to me.
Q. You said that antibody assays are imperfect. Are any antibody assays more relevant to a clinical link to protection than others?
A. I can't -- I'm not an expert in

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the area of the -- of clinical as far as making a comment on protection from disease. My personal opinion is that none of -- at least from my knowledge and experience, none of the assays are an exact mimic of the immune response that people would have.
Q. Right. But some assays are better than others at predicting whether or not a result from that assay is linked to a clinical -- clinically relevant connection to protection from disease?
A. I do not -- I don't agree with that because I think it depends on the assay format. For example, there may be some assays that -- it would depend on the virus and the disease.
Q. Let's talk about mumps.
A. Okay.
Q. Do you believe that -- you understand what an ELISA assay is. Right?
A. I'm familiar with the format.
Q. You've never run an ELISA assay?
A. I have run ELISAs.
Q. Do you understand that an ELISA assay is just a binding assay?

A. There are some versions of ELISA that have functional activity, but the majority of them are binding assays.
Q. Do you know what -- are you familiar with the ELISA assay that was run in Protocol 007? Let me strike that.
Do you understand that an ELISA assay was run in Protocol 007?
A. I recall that an ELISA was run as part of the Protocol 007 study.
Q. And did you ever review the protocol for that ELISA assay?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Let me strike that.
Do you recall whether or not a protocol was developed for that ELISA assay using Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't know.
BY MR. KELLER:
Q. You don't know. Do you recall ever reviewing a protocol for the ELISA



assay --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- that was run -- used for Protocol 007?
A. I don't recall reviewing the protocol.
Q. Are you aware of whether or not Merck has ever correlated its ELISA assay to protection from disease?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's -- I don't have experience in that area. So I don't know.
BY MR. KELLER:
Q. Do you recall ever -- any discussions about Merck's inability to correlate its ELISA assay to a plaque reduction neutralization assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not recall any discussion of the inability to



correlate.
BY MR. KELLER:
Q. Do you know whether or not Merck ever correlated its plaque reduction neutralization assay to an ELISA assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: I am aware of a correlation that was done as part of -- as best I can recall, Protocol 007, the ELISA and the AIGENT assay.
BY MR. KELLER:
Q. Do you recall -- what do you mean -- what's your understanding of the correlation that was conducted as part of the Protocol 007?
A. I don't have any details on how the comparison was done.
Q. Were you involved in that at all?
A. I can't exclude that I might have received some e-mails about it, but I was not involved in the planning of it or, as far as I can recall, the exclusion other than the neutralization part.



Q. When did you first learn about Protocol 007?
A. I don't recall a specific date. Late '90s. I don't remember a specific date.
Q. Who told you about Protocol 007?
A. As best I can recall, at least the person who comes to mind was Emilio Emini. I can't say with certainty that he was the first one who mentioned it, but he's the first one that I recall.
Q. There was two SOPs for Protocol 007, wasn't there?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Do you know what an SOP is?
A. I've seen SOPs, familiar with the general format.
Q. Standard operation procedure?
A. Yes.
Q. Do you understand what an SOP is with respect to an assay?
A. I'm familiar -- I understand what its purpose is and what it includes for the most part.

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Q. What is the purpose?
A. The purpose is described the method of material, reagents, equipment that are needed, and in some cases the interpretation of the results.
Q. You say interpretation of the results, how to calculate a result?
A. What I'm thinking of there, for example, defining a negative result versus a positive result.
Q. Seroclassification cutoff? Let's talk in particular about --
MR. SANGIAMO: Wait a minute. You're withdrawing the last question?
MR. KELLER: I'll withdraw the question.
BY MR. KELLER:
Q. When you learned about Protocol 007, did you learn that you would be -- did anybody ask you to develop an assay for Protocol 007?
A. Yes.
Q. At that point, had an assay already been developed and you were asked to fine tune that assay or were you starting from

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fresh?
MR. SANGIAMO: Object to the form.
THE WITNESS: There was a request to implement an assay that met a requirement that CBER imposed on the assay, and then as part of that implement was evaluation whether an existing assay was capable of providing that result, or assay, further assay development was required.
BY MR. KELLER:
Q. So was your -- what was that requirement?
A. The requirement -- my understanding of the requirement was that CBER required a 95 percent seroconversion rate.
Q. So you designed an assay to get a 95 percent seroconversion rate?
A. Not to get a 95 percent seroconversion rate, but one that was capable of measuring a 95 percent seroconversion rate.
Q. So was the purpose to define an assay that would get you that result?
MR. SANGIAMO: Object to the

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form.
THE WITNESS: The purpose was to evaluate assay variables and see if any of them would allow us to have the capability of entering 95 percent seroconversion.
BY MR. KELLER:
Q. That's what you did, isn't it? You developed that assay, didn't you?
A. We developed in collaboration and discussion with the FDA.
Q. You disclosed everything about that assay to the FDA. Is that your testimony?
A. Yes.
Q. Yes?
A. Yes.
Q. And so the FDA knew -- let me -- we'll get to that.
I just want to make sure, because you're under oath, you understand that. Correct?
A. Yes.
Q. So it's your testimony under oath that you disclosed every aspect of the assay to the FDA?

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MR. SANGIAMO: Object to the form.
THE WITNESS: My testimony is that I -- we provided available data on the effects of the variables, meaning different virus strains, supplements to the media, plaque utilization options. I can't exclude that there was some other factor aspect that we looked at that we didn't think was relevant or important to the key part of the discussion. So I can't exclude that some detail that I -- at least that I -- the best of my knowledge was not relevant was not disclosed to them. I can't say that it was not disclosed, but I can't exclude that there might not have been -- there might have been some aspect that we did not disclose.
BY MR. KELLER:
Q. Do you recall when you learned about the Protocol 007, what type of an assay CBER was looking for?
A. The requirement, as best I understand it, I was at the meeting, one of

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the meetings with Cathy Carbone, is a CBER representative, one of the CBER representatives, she wanted a plaque reduction neutralization assay.

Q. Are you sure that they didn't just ask for a functional neutralizing assay? They specifically said a plaque reduction neutralizing assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: The best of my recollection, it was a plaque reduction neutralization assay. I can't exclude that they might have used a different term, but my recollection, it was a plaque reduction neutralization assay.

BY MR. KELLER:

Q. Do you recall, in any of those communications with CBER, why CBER wanted a plaque reduction neutralization assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: I do not recall them, at least in my presence, giving an explanation of why.

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BY MR. KELLER:

Q. Do you recall -- you don't -- as you sit here today right now, you don't recall ever hearing from CBER that they wanted a plaque reduction neutralization assay that could be clinically linked to protection from disease?

A. I do not recall that -- a comment about a link to protection from disease.

Q. Do you believe that an ELISA assay is just as good as a plaque reduction neutralization assay in terms of identifying whether or not a result from those assays is linked to protection from disease, from mumps?

A. I would say -- I'm not familiar with the ELISA results either at Merck or outside of Merck to be able to comment on how well it correlates with protection from disease.

Q. And that's not what you used to develop the assay, is trying to find an assay that would correlate to protection from disease. Correct?

MR. SANGIAMO: Object to the form.

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THE WITNESS: For which assay?

BY MR. KELLER:

Q. The plaque reduction neutralization assay.

A. The objective for the plaque reduction neutralization assay was to provide an assay that was capable of providing 95 percent seroconversion. Whether that -- beyond that, I don't have any understanding.

Q. The plaque reduction neutralization assay -- let me strike that.

We talked about SOPs. Did you draft an SOP for the plaque reduction neutralization assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall if I did or someone else, another -- I don't recall if I was the author of the SOP or not.

BY MR. KELLER:

Q. Did you approve that SOP for the original plaque reduction neutralization assay -- strike that.

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When I say "plaque reduction neutralization assay," if I use PRN, you understand that to be the same?

A. I'm sorry, PRN meaning the one used for Protocol 007? There are other plaque reduction neutralization assays that we've had in place.

Q. Let's start with the one -- you start -- there was -- do you recall there being multiple SOPs for the neutralization assay that was used for Protocol 007? Correct?

A. I recall two versions of it, yes.

Q. And the first version, can you describe that assay to me? That was -- was that a PRN assay?

A. Yes. Yes.

Q. So when we say PRN throughout the rest of the deposition, we understand that to be a plaque reduction neutralization assay. Is that fair?

A. Okay. Yeah. Well --

Q. I know it changed.

A. It's a plaque reduction

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neutralization assay.
Q. You said there was two versions -- another version. Did you prepare that SOP?
A. Again, I don't recall if I was the author of it. I just recall that there was another version prepared.
Q. And that second version modified the SOP from the first version. Correct?
A. The procedure did not -- it's my understanding did not change -- the assay procedure did not change. To the best of my recollection, the changes in the revised procedure were additional criteria for specific, like, retests of samples or assays, responses to flags from a workbook that was in place.
Q. The first version, did the first version that you worked on include antihuman IgG?
A. For protocol -- the assay that we used to start the testing of Protocol 007 included anti-IgG.
Q. Was there an assay before -- an SOP before that?

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MR. SANGIAMO: Object to the form.
THE WITNESS: An assay for?
BY MR. KELLER:
Q. Strike that.
Was there an SOP for a PRN assay that was run in the development of Protocol 007 before the AIGENT SOP?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm sorry, I don't understand.
BY MR. KELLER:
Q. Sure. You testified that you understand that there's two different SOPs written for Protocol 007, the PRN assay that was used for Protocol 007. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: There were two versions of the SOP for the AIGENT assay used in Protocol 007.
BY MR. KELLER:
Q. Prior to the AIGENT assay, was that developed from another SOP?

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MR. SANGIAMO: Object to the form.
THE WITNESS: There were -- there was a previous plaque reduction neutralization assay not using anti-IgG that had some common, some common steps. So I -- my expectation is that that was used as a template since some of the steps were common -- I mean, common cells, medium, overlay it, a couple, various steps. So that would have been used as a template for the Protocol 007 development.
BY MR. KELLER:
Q. I see.
Who drafted that, I mean, that other PRN that was used before the use of anti-IgG step?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall who the author.
BY MR. KELLER:
Q. Did you run any experiments off of that original PRN SOP?

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MR. SANGIAMO: Object to the form.
THE WITNESS: We ran plaque reduction assays with an assay without anti-IgG. What I'm not remembering with clarity is whether there was only one plaque reduction neutralization assay without anti-IgG. So there was a plaque reduction neutralization assay without anti-IgG that was used to test in some testings.
BY MR. KELLER:
Q. When you were brought into the project to work on Protocol 007, had development work already been started --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- for Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: That, I don't know.
BY MR. KELLER:
Q. But you don't recall preparing

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the SOP that used without the IgG step. Correct?
A. I don't recall who the author. There's an equal chance I wasn't the author, I don't remember.
Q. Do you recall whether or not the original PRN SOP before the anti-IgG step was added, was that a -- considered a standard bread and butter PRN assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: It's -- I don't know the term "bread and butter," I guess I would -- not clear on how to respond to that. But it's an assay format that others had or other labs had used.
BY MR. KELLER:
Q. Had that assay -- do you know what validation means of an assay?
A. I'm familiar with some aspects to it.
Q. Have you ever -- do you know what a validation protocol is?
A. I've seen validation protocols

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for assays. I don't know if there's validation for assays for other things. But for protocols of assays, I have seen them.
Q. Have you ever validated an assay yourself?
A. I've been involved in assay validation.
Q. Have you ever validated a plaque reduction neutralization assay before?
MR. SANGIAMO: Object to the form.
THE WITNESS: I was -- or did part of the work for validation of a plaque reduction neutralization assay.
BY MR. KELLER:
Q. And that was part of Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: There was a validation protocol done, assay protocol done for Protocol 007 which I did contribute to.
BY MR. KELLER:
Q. Did you draft that protocol?

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MR. SANGIAMO: Object to the form.
MR. KELLER: Let me strike that.
BY MR. KELLER:
Q. Did you draft the validation protocol for the AIGENT SOP that was used for Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't -- I do recall drafting a document that included aspects of the validation. I don't consider that to be the protocol itself, but -- and I don't recall drafting the formal protocol.
BY MR. KELLER:
Q. Do you know who did?
A. I know who issued the report on it. I don't know who -- I don't recall who drafted it.
Q. Do you understand the difference between a validation report and a validation protocol?
A. I can't say -- I don't have confidence of what -- how they relate.

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Q. Have you ever been trained in any way on validating an assay in terms of the steps that are required?
A. I have consulted with our, for example, our biometrics group on what is required for the validation study. Whether that constitutes training, I can't comment.
Q. Who did you -- and that's for Protocol 007? Strike that.
Did you confer with -- the person that you conferred with for -- from biometrics research for validating an assay, was that for Protocol 007?
A. That's an example where a biometrics person was consulted.
Q. The biometrics person, is that a statistician?
A. That's my genericized view of them. I don't -- I can't say with certainty what their full background is.
Q. So have you ever drafted a validation protocol prior to Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: Again, I don't

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recall if -- I remember preparing a document, whether it was a protocol or not, but there was a series of them before Protocol 007.
BY MR. KELLER:
Q. Let's start before Protocol 007. Have you ever validated an assay where you were required to draft the validation protocol for that assay?
A. Again, with the reservation of the term validation protocol. I'm not sure if whatever I drafted was a protocol, but --
Q. Let's start from the beginning.
MR. SANGIAMO: Wait a minute. You have to let him finish the question --
MR. KELLER: Sure.
MR. SANGIAMO: -- finish the answer.
THE WITNESS: So there are other assays for which I have contributed to a validation study. Whether the document that I -- document or documents I prepared were a formal validation protocol or just an outline

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of what was being done, I can't say. I don't recall.
BY MR. KELLER:
Q. Was Protocol 007 a clinical study?
A. That was a clinical study.
Q. Was it a Phase III study?
A. I don't recall what the phase is. I have an expectation just based on just general exposure to clinical studies, but it would be a guess.
Q. Do you know whether or not Protocol 007 was a pivotal study? Let me strike that.
Do you know what a pivotal study is?
A. No.
Q. Had you ever run clinical samples with human sera in your lab prior to Protocol 007?
MR. SANGIAMO: Objection. Form.
THE WITNESS: Yes.
BY MR. KELLER:
Q. Were those used for a marketed product?

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MR. SANGIAMO: Object to the form.
THE WITNESS: Yes.
BY MR. KELLER:
Q. Were those used to -- do you recall what that product was?
A. It was a comparison between MMR and Priorix.
Q. Other than that -- that was Protocol 006, do you recall that?
A. Yes.
Q. Other than Protocol 006, had you ever run any clinical samples?
A. Yes.
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. When would that happen?
A. That was in -- I don't remember the exact date, but it was a mid -- in the 1990s. I was going to say mid-1990s, but I don't recall specifically.
Q. When you ran those clinical studies in the 1990s, do you recall whether or not you ran those studies in accordance with

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the rules of current GMP?
MR. SANGIAMO: Object to the form.
THE WITNESS: Well, they were not clinical studies, they were clinical samples. They were -- as best as I understand, they were not run under GMP requirements, nor did we expect that they needed to be run under GMP.
BY MR. KELLER:
Q. Protocol 006, did you understand that had to be run under GMP?
A. My understanding was that it did not.
Q. Did you understand that Protocol 007 had to be?
A. No.
Q. Where did you gain that understanding from, that it didn't have to be run under GMP?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Strike that.

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Where did you learn that Protocol 007 did not have to be run under GMP studies?

A. Management had -- no one had made any indication in the assay development discussions that it was required to be run under GMP conditions. I'm sorry, qualify that up and to the point of the FDA inspection.

Q. After the FDA inspected in August of 2001, is that the first time that you learned that Protocol 007, the assays that you ran were supposed to be run under GMP conditions?

MR. SANGIAMO: Object to the form.

THE WITNESS: That was the first I heard of the expectation that the assays were run under GMP conditions.

MR. KELLER: Let me do this. Let me mark as Exhibit 20.

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(Exhibit Krah-20, 3/15&16/1999 MMR II Mumps Expiry Study Investigators Meeting Agenda, 17644 - 17666, was marked for identification.)

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MR. KELLER: For the record, Exhibit 20 is a document that bears Bates stamp number 17644 through 66, and it's an agenda for a March 15 and 16, 1999 investigator's meeting, MMR II mumps expiry study.

BY MR. KELLER:

Q. Sir, can you tell me, if you recall, seeing this document before? And I will direct your attention to 17646 where it identifies the Merck attendees, and you are identified as one of the attendees of this particular meeting.

A. I don't recall this. I do see my name there as a Merck attendee, but I don't recall it.

Q. Do you have any reason to believe you didn't attend?

A. If they have me listed as an attendee, I would take that to mean that I did attend.

Q. This MMR mumps expiry study, do you understand it to be Protocol 007?

A. That's my understanding of what

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that refers to.

Q. Under -- in the first page of the agenda it identifies Dr. Scott Thaler. Do you see that?

A. Yes.

Q. It identifies him as a clinical monitor. Do you see that?

A. Yes.

Q. Do you understand what a clinical monitor is in a clinical study?

A. I have a very general understanding of it, but not -- I don't have any details or a full understanding of what that person's responsibilities are.

Q. What's your understanding?

A. For one to -- perhaps adding a little -- someone who monitors the clinical -- the progress -- the design and actually -- and progress of the clinical study. That's just my personal, the way I frame what the responsibility is. But, again, what that really means -- what the roles are, what they actually do, I don't know.

Q. Fair enough. If you look under the attendees, it has Ms. Yagodich was also an

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attendee. Do you see that?

A. Yes.

Q. This is an investigator's meeting. Do you understand what investigators -- do you understand what the purpose of this meeting was?

A. I don't recall, no.

Q. Do you know what an investigator is?

A. I know what an investigator is.

Q. What is an investigator?

A. And investigator is someone who is going to be taking part in a clinical study.

Q. Were you an investigator for Protocol 007?

A. No, my understanding -- maybe qualify the investigator, that my understanding is it's an external person who is involved in the clinical study execution in the field. I don't consider myself an investigator in the context of the investigator's meeting.

Q. I see.

For purposes of running clinical

studies that you ran in your lab, do you consider yourself an investigator for that function?

MR. SANGIAMO: Object to the form.

THE WITNESS: I was a research scientist supporting the studies. Whether one calls that an investigator, I wouldn't specifically term or phrase it as an investigator.

BY MR. KELLER:

Q. Do you know what a sponsor is in a clinical study?

A. I don't have a full understanding of it. It would be a guess of what that means.

Q. You don't know?

A. No.

Q. Here Mary Yagodich was also an attendee. Do you know why she would have attended an investigator's meeting for Protocol 007?

A. I can't say with certainty.

Q. Who is Timothy Schofield?

A. Timothy Schofield was listed here as someone in the biometrics research.



So my generic description is that he's a statistician. I don't recall what his role was in the overall statistics evaluation.

Q. You testified earlier that you conferred with somebody in biometric research regarding the validation of the AIGENT?

A. Yes.

Q. Is that who you conferred with?

A. I can't say with certainty that he wasn't the person. The person I was thinking of was someone else.

Q. And Dr. Thaler was at this meeting as well. Correct?

A. He's listed here as being one of the attendees.

Q. There's three people from MPC. Do you know what that represents?

A. I don't recall what that stands for.

Q. There's also a Susan McNeill from clinical quality assurance. Do you know what her job responsibilities were?

A. I don't.

MR. KELLER: Let me mark this next exhibit as Exhibit 21.



- - -

(Exhibit Krah-21, PowerPoint presentation, 17605 - 17612, was marked for identification.)

- - -

BY MR. KELLER:

Q. I'll represent to you that these documents all came from a single file. Exhibit 21 is a document that bears Bates stamp number 17605 through 17612.

Sir, can you tell me if you recall seeing this document before, and if you recognize any of the handwriting on this document?

MR. SANGIAMO: Dr. Krah, make sure you're clear on your answer, what you're saying yes or no to.

MR. KELLER: Strike that question.

BY MR. KELLER:

Q. Sir, can you tell me if you recognize the handwriting on 17611?

A. I do not.

Q. Do not. That's not your handwriting?



A. No, it's not my handwriting.

Q. If you look on the -- do you recall seeing this document before?

A. It doesn't -- I don't -- it doesn't look familiar to me. I don't recall seeing it before.

Q. Under the third -- this is a PowerPoint presentation document. Do you recognize the format?

A. It looks like a PowerPoint presentation.

Q. And the third -- the third slide on the first page, it identifies Merck personnel, and you're identified there along with Ms. Yagodich. Do you see that?

A. Yes.

Q. Do you -- are you familiar with Ms. Yagodich's handwriting?

A. Yes.

Q. Do you recognize that to be the handwriting of Ms. Yagodich's at 17611?

A. That does not -- at least it's my recollection, does not look like her handwriting.

Q. Do you have any reason to

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believe that you didn't receive this document as part of your -- the meeting that happened on March 15th and 16th --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- regarding the Protocol 007 investigator's meeting?

MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: I don't have any recollection of seeing it. I can't -- I don't recall that this was handed out at the meeting. I have no recollection of it.

BY MR. KELLER:

Q. You don't recall?

A. No.

Q. You don't recall going to a meeting where Protocol 007 was discussed to the investigators of the clinical study?

A. I don't -- yeah, I don't recall that.

Q. Let me turn your attention to 17607 in the second slide. It says the

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"BACKGROUND AND RATIONALE."

Do you see that?

A. Yes.

Q. The first bullet point, it says, The components of the MMR II are live viruses and lose potency over time when stored at 2 to 8 degrees Celsius or higher.

Do you see that?

A. Yes.

Q. Do you recall ever -- do you have any reason to believe that statement was untrue?

A. All I can say is a generic statement that live viruses lose potency over time. So the statement about live vaccines that lose potency over time are stored at 2 to 8 or higher. I have no reason to question that statement.

Q. Do you recall learning that as part of your development -- strike that.

Do you recall learning that statement as part of your work on Protocol 007?

A. No.

Q. No. The second bullet point it

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says, "The FDA (CBER) has requested expiry potencies be placed on the label of MMR II."

Do you see that?

A. Yes.

Q. Is this the first time you're learning that --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- today?

MR. SANGIAMO: Object to the form.

MR. KELLER: Let me strike that.

BY MR. KELLER:

Q. Did you have that understanding of -- of this statement?

MR. SANGIAMO: Wait until he finishes. I'm sorry, what's your question?

MR. KELLER: I'll rephrase it.

BY MR. KELLER:

Q. Do you recall ever hearing that statement before?

A. I can't -- I don't recall.

Q. You don't recall. So you don't

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recall participating in this meeting, but you have no reason to believe you didn't participate. Correct?

A. My name is listed as an attendee. Just I don't have any memory of the meeting.

Q. You don't recall traveling to Texas; Irving, Texas?

A. I don't.

Q. Have you ever been to Irving, Texas?

A. I've been in Texas. I don't recall what the meeting --

Q. Have you ever been to the Omni Mandalay Hotel? It's a nice hotel.

A. I recall being at the Omni in Atlanta. I don't recall the Omni in Irving.

Q. So you don't recall ever learning that CBER required that end expiry potencies be placed on the label?

A. I'm sorry, did I ever? I didn't -- I'd say, yes. I don't -- I'm not that familiar with the label or what goes in the label to be able to say that that is expected.

Q. So you don't know?
A. I don't know.
Q. The next bullet point says, "No data exist for mumps at the expiry potency Merck has selected."
Do you see that?
A. Yes.
Q. In the next slide, it identifies "MMR II END EXPIRY POTENCIES SUGGESTED FOR THE LABEL Mumps 3.7."
Do you see that?
A. I'm sorry.
Q. The third slide on this page.
A. Oh, okay.
Q. Is that a fair representation of that statement?
MR. SANGIAMO: Object to the form.
MR. KELLER: Strike that.
BY MR. KELLER:
Q. Is that a fair representation of that slide?
A. It says that the end expiry potency suggests that the label for mumps is 3.7 TCID50 per dose.



Q. So are you aware that Merck had no data for mumps at end expiry of 3.7 --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- at this time frame?
MR. SANGIAMO: Objection. Form.
THE WITNESS: I don't recall that lack of data.
BY MR. KELLER:
Q. Sir, I'm going to show you what is marked as Exhibit 3, Bates page 488502, page 98, dated Tuesday, March 16, 1999. Can you tell me if that -- if your journal references you participating in this investigator's meeting on March 15 and 16, 1999?
A. Let's see. So it lists the mumps expiry file clinical investigator's meeting in Dallas, Texas and has a check mark next to it which implies -- the check mark implies that that happened.
Q. Does that lead you to believe that you actually went and participated at this particular meeting?



A. So I can't say with certainty that that check mark means I attended. The PowerPoint presentation has me listed -- not the PowerPoint. The slides have me listed as an attendee, but the check mark, and the only reason I'm saying that is, I may not necessarily mean that, because I don't -- there are some meetings for which I might have called in or taken part in part of the meeting but not physically been there and I might have still put a check mark.
Q. That would mean that you had participated, you may not have been there physical present, you may have done it on the phone?
A. Yes. It may have been on the phone, may have been -- included a subset of the presentation.
Q. So if you go back to Exhibit 21, in the second slide, the last bullet point says, "A clinical immunogenicity trial is necessary to provide these data."
Do you see that?
MR. SANGIAMO: I'm sorry. You said second slide?



BY MR. KELLER:
Q. 17607, the second slide, the last bullet point, do you see that?
A. The fourth bullet point on the second slide --
Q. Yes.
A. -- you have "clinical immunogenicity trial is necessary to provide the data." Yes.
Q. Does that refresh your memory that the purpose of Protocol 007 was to try to establish that a potency of 3.7 would be used as the end expiry on the label for the mumps component of MMR II?
A. It does not. Again, my recollection is that this was comparing three different vaccine doses. I don't have a recollection of which was -- what those three were or what the implications were.
Q. Was 3.7 one of the doses that you were testing?
A. I don't recall. I recall there were three doses, but I don't remember what the doses were.
Q. Let me direct your attention to

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17611, in particular to the last slide.
MR. SANGIAMO: You're asking a lot of questions about this document. I don't think he's had a chance to review the whole document yet. Dr. Krah, certainly feel free to read the document.
MR. KELLER: Could we off the record?
MR. SANGIAMO: It's not going to take long. Stay on the record.
BY MR. KELLER:
Q. Let me know when you're done.
A. Okay.
MR. KELLER: Back on the record.
MR. SANGIAMO: Yes. Never went off.
BY MR. KELLER:
Q. Sir, you've had a chance to review every slide on Exhibit 21. Do any of these slides refresh your recollection that you've seen these slides before or this presentation?
A. No. Nothing --
MR. SANGIAMO: Object to the

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form.
THE WITNESS: Nothing looks familiar.
BY MR. KELLER:
Q. Let me direct your attention to 17611, see if I can't refresh your memory of this time frame. Under "IMMUNOGENICITY MEASUREMENTS," do you see that?
A. Yes.
Q. In the second bullet point it says, "For Mumps, a functional (neutralization) assay has been developed."
Do you see that?
A. Yes.
Q. What do you understand functional to mean?
A. To me it means a plaque reduction neutralization assay. That's my personal interpretation of that. That it's showing a reduction in infectivity.
Q. When you say "reduction in infectivity," you're -- can you describe that a little bit for me? What are you testing to show reduction infectivity?
A. Phrase this so it's not

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circular. So the purpose of the plaque reduction neutralization assay would be to -- or a plaque reduction assay would be to show that antibodies are capable of binding to the virus and causing it to be less capable of forming -- of infecting and replicating in cell culture.
Q. And so the antibodies that you -- strike that.
Are there any other functional neutralization assays other than a plaque reduction neutralization assay?
A. There may be. Plaque reduction is the one I'm most familiar with. Yes, there are.
Q. The one you're most familiar with is the PRN. Correct?
A. Yes.
Q. Do you know what a CPE assay is?
A. I'm familiar with the term.
Q. Ever run one?
A. Yes.
Q. Is that a functional assay as well?
A. It's a -- when I said ran CPE

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assays, I ran assays to monitor cytopathic effects in the titer virus, not in a neutralization format. But it -- I would say an assay such as a CPE reduction would be a measure of the capacity of an antibody to reduce infectivity so that -- I guess, one could also call it a functional assay.
Q. When you're talking about an antibody, let's talk about it in -- let's pick one antibody. Let's talk about mumps. In a mumps plaque reduction neutralizing assay, are you looking for any antibody that's capable of binding to a mumps virus or are you looking for something else?
MR. SANGIAMO: Object to the form.
MR. KELLER: Let me strike that.
BY MR. KELLER:
Q. In the plaque reduction neutralization assay using a mumps vaccine, can you describe for me how that's run?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. You take serum. Correct?

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A. Yes.
Q. From a kid before they're vaccinated. Correct?
A. Typically.
MR. SANGIAMO: Object to this line of questioning. Keep going.
BY MR. KELLER:
Q. Let me -- for Protocol 007, did the plaque reduction neutralizing assay you ran in that assay, you understood that you took kids before they were vaccinated, correct, you took their blood?
A. There was a serum before vaccination.
Q. And then you wait a certain number of days and then you took -- the kid is vaccinated and you wait a certain number of days after vaccination and you take the kid's blood after vaccination. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: The serum is drawn before vaccination and then some interval after vaccination.
BY MR. KELLER:

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Q. And in the plaque reduction neutralization assay you're comparing those two blood samples. Correct?
A. That's part of the evaluation.
Q. So in -- just so I understand how this process works, you take -- you're looking for, in the pre-vaccination sample to see whether or not the kid has mumps neutralizing antibodies. Correct?
A. Yes.
Q. Are you looking to see whether or not the kid has any antibodies that will neutralize the mumps virus?
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding is that we're looking for antibodies that are capable of binding to a neutralizing virus.
BY MR. KELLER:
Q. That could be any antibodies, whether it's mumps antibodies or any other antibodies. Correct?
A. It would have to be mumps specific.

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Q. It has to be mumps specific?
A. Yes.
Q. If it's not mumps specific, would that be a problem?
MR. SANGIAMO: Object to the form.
THE WITNESS: If it's not mumps specific, that difference in specificity would need to be considered.
BY MR. KELLER:
Q. Why would it need to be considered?
A. It depends on how to interpret what it means.
Q. So if -- what does specificity mean? Can you describe that for me?
A. My interpretation of specificity is uniqueness of the -- in the case of an antibody, its ability to bind or neutralize a virus, meaning that an antibody to one virus won't neutralize another virus.
Q. So if a virus other than mumps would bind -- strike that.
If an antibody other than a mumps antibody were to bind to the virus and

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neutralize it, that would be part of an analysis of specificity. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: From my understanding, an evaluation of specificity could include or amongst other options looking for ability or capacity of antibodies unrelated to mumps to bind and neutralize.
BY MR. KELLER:
Q. Why would that be important in a plaque reduction neutralization assay that was run for Protocol 007 -- strike that.
Was that important for -- to determine the specificity of nonspecific binding in the Protocol 007 assay?
A. I'm not sure I understand your question.
Q. Let me rephrase it if you don't understand it. As part of Protocol 007 validation, did you investigate whether or not -- what the specificity of that assay was?
A. Yes.
Q. And you looked at -- what did

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you look at to determine the specificity of that assay?
A. As best I recall, we had lab volunteer sera, meaning sera from adult lab volunteers, that then were absorbed with measles, mumps, or rubella antigens or just diluted in culture medium. And then the residual neutralizing capacity of that -- those sera were tested.
Q. And do you recall the results of that?
A. I don't recall all the specific results, but as a general recollection --
Q. What's your general recollection?
A. General recollection was that the antibody titers were reduced more by mumps absorption than by measles or rubella absorption.
Q. And so did you ever come to a conclusion as to what the specificity of that assay was based on those experiments you ran?
A. So I have a personal conclusion that I reached --
Q. Sure.
A. -- which was that the assay was

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specific. Those data were shared with others at Merck and with the FDA and with -- I never received any feedback to the contrary.
Q. Did you understand that the rubella virus was also neutralizing, the mumps virus in the PRN assay?
A. I'm sorry, your question is --
Q. Sure. Did you understand that the rubella had neutralizing impact on the PRN assay?
MR. SANGIAMO: Object to the form.
MR. KELLER: Let me strike that.
BY MR. KELLER:
Q. Do you recall that the rubella antibodies were having a neutralizing effect on the PRN assay that was tested by your lab?
MR. SANGIAMO: Object to the form.
THE WITNESS: That is not my interpretation of the data.
BY MR. KELLER:
Q. What about the measles?
A. No.
MR. SANGIAMO: Object to the

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form.
THE WITNESS: That's not my interpretation.
BY MR. KELLER:
Q. Did you ever come up with a percentage of specificity?
A. No.
Q. Did anybody ever discuss the percentage of specificity?
A. No, and I never actually heard that.
Q. Did you ever test -- you never heard that the assay was only 50 percent specific to mumps specific antibodies?
A. What I recall seeing was that for half of the sera tested, there was absorption of some of the sera with other antigens other than mumps.
Q. That was measles and rubella. Correct?
A. I don't know that it was both of them. I do recall rubella giving some -- absorbing with rubella reduced the neutralizing titers for some of the sera. But for some of the -- some number of the sera, the absorption

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was much greater for mumps antigen.
Q. Do you recall that --
MR. SANGIAMO: Jeff, we've been going about an hour and 20 minutes.
MR. KELLER: Why don't I finish this line of question.
BY MR. KELLER:
Q. Do you recall that the control medium was also neutralizing the mumps virus as part of the specificity assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: It was not neutralizing.
BY MR. KELLER:
Q. Did you ever consider testing whether or not the use of the rabbit anti-IgG was, in fact, causing neutralization in and of itself?
A. Yes.
Q. How did you do that?
A. By incubating the virus with the anti-IgG in the absence of serum.
Q. Did you try it with serum?
A. Yes, I --

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Q. Was there interaction --
MR. SANGIAMO: Whoa, whoa, whoa. Hold on.
BY MR. KELLER:
Q. Finish your answer.
MR. SANGIAMO: The question is did you try it with serum?
THE WITNESS: Yes.
BY MR. KELLER:
Q. And did you -- you ran experiments with serum and anti-IgG and virus without mumps antibodies --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- to see whether or not there was any neutralization?
MR. SANGIAMO: Object to the form.
THE WITNESS: That is almost an undoable experiment. That would require you showing that the serum is absent of antibodies.
BY MR. KELLER:
Q. That's an undoable experiment?

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It's not standard to look at a serum sample, a negative serum sample that's been -- that has no antibodies in it to see whether or not --
A. Well, you can have a negative serum sample, a sample that is negative in the an assay, but the challenge is how to prove that that serum is really devoid of an antibody.
Q. Do you know what a boost analysis is in a specificity test?
A. No.
Q. You never discussed that with anybody?
A. Not that I recall.
Q. Nobody recommended doing a boost analysis specificity test?
A. Not that I recall.
Q. So you never looked at what would happen if you took blood, virus, and anti-IgG without mumps antibodies to see whether or not there would be neutralization of that virus?
MR. SANGIAMO: Object to the form.
MR. KELLER: Let me strike that.

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BY MR. KELLER:
Q. Did you ever conduct a single experiment, sir, taking a negative serum sample that has no antibodies in it, adding the IgG and adding the virus to see whether or not there would be neutralization caused by the anti-IgG?
MR. SANGIAMO: Object to the form.
THE WITNESS: The prevaccination sera were included -- were part of the testing with the anti-IgG but, again, you can't certify that those sera are truly devoid of antibody. They could have maternal antibody. What I don't recall is how -- if that or how that neutralization compared with the serum sample versus a sample -- in each assay, the serum anti-IgG is present along with the virus and no antibody. There are pre-vaccination sera that are present, some of which are, majority of which are negative. So, I guess, I'm having trouble understanding your compare -- what you're trying to

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compare it to.
BY MR. KELLER:
Q. My question is, did you run any experiments that took negative serum, rabbit anti-IgG and virus and test that --
MR. SANGIAMO: Objection.
BY MR. KELLER:
Q. -- to see whether or not there was any neutralization --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- at any time in your career at Merck?
MR. SANGIAMO: Object to the form.
THE WITNESS: Again, what I'm struggling with is a negative serum. We had pre-vaccination sera that were tested.
BY MR. KELLER:
Q. For antibodies?
A. For antibodies, yes.
Q. Explain that to me.
A. The pre-vaccination sera as well

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as post-vaccination sera are added to the virus and the anti-IgG in a plaque reduction neutralization assay. And results are calculated as a percentage of plaques relative to a control that didn't have any serum.

Q. I understand that. My question is, did you run that assay, that experiment? At any time in your career at Merck, did you ever look and ran an experiment with -- whether it's development of the assay, validation of the assay, or any time before, during or after, in your career at Merck, did you ever run an experiment that took a negative medium sera, negative sera, rabbit anti-IgG and virus to see whether or not there would be a neutralization occurring?

MR. SANGIAMO: Object to the form. Asked and answered.

THE WITNESS: Again, I'm struggling with the "negative serum" part.

BY MR. KELLER:

Q. Let me rephrase it. Did you ever -- let me just -- I'll make it more simple.

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Did you ever run an experiment to count the number of plaques that occurred in a experiment that had negative non-immune serum, rabbit anti-IgG and virus?

MR. SANGIAMO: Object to the form. Asked and answered multiple times. And we've been going an hour and a half, but go ahead and answer the question, Doctor.

THE WITNESS: Negative or pre-immune sera were tested.

BY MR. KELLER:

Q. Yes or no, sir. Did you do that analysis? Did you do that, did you ever run that experiment, yes or no?

A. Well, the negative serum part is what I'm struggling with because we don't have a serum that's a proven absolute negative.

Q. The FDA does, doesn't it? Didn't you actually ask for a sample of that at some point?

MR. SANGIAMO: Object to the form. Jeff, take one or two more questions and we're taking a break.

THE WITNESS: I don't know.

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MR. SANGIAMO: This is going in circles.

BY MR. KELLER:

Q. Let me ask you a question. Was there any analysis of a -- you're saying that there's no serum that you can identify that has negative -- that's negative for antibodies?

MR. SANGIAMO: Object to the form.

THE WITNESS: In theory one could -- there could be a potential to show that it was absent of antibodies, but it depends on the assay that you're using.

BY MR. KELLER:

Q. Is there an industry standard for negative serum?

A. I don't -- I'm not aware if there's an industry standard.

Q. Can you buy that from other companies, negative sera?

A. One could buy negative -- serum that's identified as negative by an assay, whether that's truly negative, an absolute

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negative I can't say.

Q. Can you --

MR. KELLER: I'm not done.

MR. SANGIAMO: Well, Jeff, you didn't --

MR. KELLER: Let me finish. I'm not done with this line of questions.

MR. SANGIAMO: Well, it's going on forever. So we'll do one more and then we're taking a break.

MR. KELLER: If you want to pull your client out of here, you can.

BY MR. KELLER:

Q. Was there any analysis done with an off-the-shelf negative serum that tested with anti-IgG and without anti-IgG in virus in each sample? Did you ever do that analysis?

MR. SANGIAMO: Object to the form.

THE WITNESS: The only samples that I recall testing were pediatric samples where you would have a pre-vaccination, post-vaccination sample. I don't recall that we took an off-the-shelf ever serum that was

identified as negative by some other assay and run that analysis.

MR. KELLER: Take a break.

VIDEOGRAPHER: The time is now 11:55. This ends disc two.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is now 12:11. This begins disc three. You may proceed.

BY MR. KELLER:

Q. Sir, can I turn your attention to the last page of Exhibit 21 which is 17612.

A. Okay.

Q. In the first slide there it says, "PLAQUE REDUCTION MUMPS NEUTRALIZATION ASSAY."

Do you see that?

A. Yes.

Q. Do you understand it to be the standard PRN assay that you're familiar with?

MR. SANGIAMO: Object to the form.

THE WITNESS: I recognize it to



be -- the serum dilutions I can't confirm, but a neutralization format that we had run previously in our laboratory.

BY MR. KELLER:

Q. Is that the Protocol 006 format or methodology?

A. There are steps there that are common to mumps plaque assays. I can't say with certainty that is the same one that's used in -- was used in Protocol 006.

Q. Did you design this assay that's identified in the first slide?

MR. SANGIAMO: Let him finish.

THE WITNESS: I don't recall if I did or someone else in the lab did.

BY MR. KELLER:

Q. The reference there to TN wt mumps, that's Tennessee wild type mumps?

A. Yes.

Q. And Tennessee wild -- is that a strain of mumps virus that was circulating in the United States in this time frame?

A. It was a strain of virus mumps circulating in the US. I don't recall the



time frame, but it was circulating.

Q. That's considered a wild type Tennessee?

A. WT indicates wild type.

Q. What does wild type mean to you?

A. Wild type to me means minimal passage, at least my personal interpretation, minimal passage from a clinical isolate.

Q. What do you mean by "a clinical isolate"?

A. Clinical isolate meaning a sample that's collected from an infected individual.

Q. And do you understand that viruses change over time?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Do viruses -- do mumps viruses evolve over time?

MR. SANGIAMO: Object to the form.

THE WITNESS: There are different genotypes of mumps that have appeared over time. Whether -- so the frequency



of which I'm not familiar with. But there are occasions where -- whether it's an evolution or a change, I can't speak to, but there are changes in the virus that have been detected across years.

BY MR. KELLER:

Q. Is Merck's vaccine strain a wild type under your definition?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. The virus chain used to make Merck's mumps vaccine, is that -- do you consider that to be a wild type?

A. It's the Jeryl Lynn strain. The passage level that it's at is not considered wild type.

Q. If I were to get that passage strain, experience that in the wild, I wouldn't get sick?

A. That would be the expectation.

Q. At what point of passaging do you believe that a kid would likely be infected with the mumps disease if they're

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exposed to a Jeryl Lynn with a lower passage?
A. I don't recall the specific passage level, but I recall that Maurice Hilleman did a study with what he was calling an A level and B level of Jeryl Lynn. I don't recall the passage levels but there was -- the lower passage level that he evaluated, there was evidence of parotitis, as best I recall, in some percentage of the children.
Q. You just don't recall what those levels were?
A. Offhand I don't remember the numbers.
Q. You don't recall what passage level would be considered wild type for Jeryl Lynn?
MR. SANGIAMO: Object to the form.
THE WITNESS: I have -- so I don't have a personal opinion on it, but I recall CBER making a statement of what passage level they consider to be wild type.
BY MR. KELLER:
Q. Do you recall what that was?

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A. I believe it was 12, as best I recall.
Q. So anything lower than 12 would be considered wild type?
A. That was my understanding of their comment.
Q. Do you recall there being any discussion in any of the meetings you had where there was a dispute about whether or not the Jeryl Lynn strain at any passage should be used in Protocol 007 PRN assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: I recall a comment from Steven Rubin in response to a publication that he submitted for review where he made a comment about the choice of Jeryl Lynn.
BY MR. KELLER:
Q. What was his comment?
A. I don't recall the specifics of it. My general recollection is that he -- I don't remember the specific wording of it, but the understanding I had from it was that he didn't necessarily agree with Cathy Carbone

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and others' position.
Q. That using Jeryl Lynn in Protocol 007 was proper. Correct?
A. That was his, the view that he -- that was the implication from the comment he made, but others at CBER at the time we were doing Protocol 007 had approved its low passage virus use.
Q. Was Steven Rubin considered the preeminent expert on mumps virus testing at CBER, based on your experience?
A. My -- at the time of our discussions with the FDA and CBER, at the time my understanding was that Cathy Carbone was the expert. I think, as I understand it, Cathy Carbone has since moved on to either -- I don't know if she's retired, but moved on to other assignments, and Steve Rubin has been publishing a lot in the area.
Q. So he's -- you believe he stepped in to be the CBER expert on mumps virus now?
MR. SANGIAMO: Objection.
THE WITNESS: Whether he's CBER's expert, I don't know who else at

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CBER who would be contributing.
BY MR. KELLER:
Q. Let me direct your attention back to Exhibit 21 on 17612. In the third PowerPoint presentation, in the second bullet point it says, "A positive mumps neutralization titer almost certainly ensures protection from wild type infection."
Do you see that?
A. Yes.
Q. This is based on -- do you understand that to be based on the PRN assay identified in this assay?
A. In which -- I'm sorry, in which assay?
Q. Identified in the first slide.
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding is that the assay that we described, that's described with the Tennessee mumps, that there was no protection aspect to that study.
BY MR. KELLER:
Q. So do you understand what --

under this slide it says, "ADVANTAGES TO PARTICIPANTS IN THIS TRIAL FOR SUBJECTS."
Do you see that?
A. Yes.
Q. You understand that they're talking about the assay that's going to be run in this Protocol 007, correct, the purposes behind this protocol?
A. I can't say with certainty that they are talking about this particular assay or mumps neutralization in general.
Q. Let me ask you more directly. A positive mumps neutralization titer in your assay, the AIGENT, do you believe that ensures protection from wild type infection?
A. I have no experience in that area. I don't have any direct experience with --
Q. Were you ever -- go ahead.
A. -- with clinical relevance.
Q. Were you ever -- did you ever discuss the development of Protocol 007 with anybody at Merck?
A. I'm sorry?
Q. Strike that. That's a bad



question.
Did you ever discuss the clinical relevance of the assay you were developing for Protocol 007 with anybody at Merck?
A. Not that I recall.
Q. In the second bullet point, the second slide it says primary -- sorry, strike that.
In the second slide of this investigator meeting presentation it says, "PRELIMINARY GUIDELINES FOR THE PRN ASSAY."
Do you see that?
A. Yes.
Q. It says, Negative (not protected) less than 1 to 2.
Do you have an understanding of what's meant by that?
A. The only understanding I have is what the words say, that if the titer is less than 1 to 2, it's considered negative and I'll say assume not protected.
Q. So in a sample that's greater than equal 1 to 4 is protected. Correct?
MR. SANGIAMO: Object to the



form.
THE WITNESS: That's what it says.
BY MR. KELLER:
Q. In that greater than 1 to 4, that -- is that the same serostatus cutoff that was used in your PRN --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- for definition of seroconverter?
A. I don't recall what dilutions we used.
MR. KELLER: Fair enough. Let me mark this next exhibit as Exhibit 22.
- - -
(Exhibit Krah-22, PowerPoint presentation, 17647 - 17762, was marked for identification.)
- - -
BY MR. KELLER:
Q. For the record, Exhibit 22 is also part of the same packet, the file regarding the March 15 and 16, 1999, investigator meeting relating to the mumps



expiry study. And it bears Bates stamp number 17647 through 17762.
Sir, I'll ask you if you recall seeing -- there's two documents in this packet. One is a PowerPoint presentation and then the second one starting at 17654 is a Protocol 007-00 product V205C. I'll ask you, if you recall, seeing either of these two documents before today?
A. They don't look familiar to me.
Q. Do you recall -- again, you don't recall participating in this presentation or seeing any of the presentations that were given to it. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: All I can say is they don't look familiar to me.
BY MR. KELLER:
Q. Again, you don't have any reason to believe you didn't see them, you just don't recall seeing them. Correct?
A. If this was -- if this is the same meeting or is this the same meeting from Texas?

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Q. Yes.
MR. SANGIAMO: You don't have to accept that representation, but he's premising his question on the supposition that it is. It's possible.
THE WITNESS: If it was that meeting and that meeting said I was an attendee, then I would have been there, but I don't have a recollection of seeing -- I don't recall seeing these or have a memory of them.
BY MR. KELLER:
Q. That's fine. Let me direct your attention, then, to 17654, the protocol. Take whatever time you want to look at this protocol, it's very long. We can go off the record if you want to read it cover to cover because I may have some questions for you on it.
Do you recall ever seeing the protocol for Protocol 007?
A. I don't remember.
Q. And so do you recall -- let me direct your attention to -- have you ever seen a protocol before?

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A. I've seen sections of protocols. It doesn't mean I read it and understood it, but I remember seeing documents that were part of protocols before. I don't remember how much I understood it.
Q. Fair enough. Let's look at a couple pages here and see if that refreshes your memory if you've seen parts of this protocol as part of your job developing and running the experiments for Protocol 007's AIGENT assay.
MR. SANGIAMO: What I propose we do here, if you're going to --
MR. KELLER: Why don't we go off the record.
MR. SANGIAMO: Why don't you start your questions, if you're just asking if he's seen certain things, then that's fine. If you're going to start getting into asking him to interpret the language, that might require a different level of his review. So why don't you just --
MR. KELLER: Why don't we just go off the record and take whatever

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time you want to to look at this protocol.
MR. SANGIAMO: No, I don't agreed that you get to soak up his day by handing him really long documents and then having it be off the record. So let's just see if we can avoid a fight, see if it works. And if there might just be sections that he can read depending on what your questions are, that might solve the problem.
MR. KELLER: This is the protocol for Protocol 007, and the fact that he says he doesn't recall ever seeing it again, you want him to spend the next 30 minutes on the record reviewing it the first time to answer questions about it, I don't think that's fair, and we would likely go back to the court for more time if that's the position you want to take. Because there are a lot of documents and unfortunately some of these documents are longer and we have limited time with him. If you are

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going to require us to take that time for him to review a document on the record, then we're going to go back and seek additional time with this court. You decide.
MR. SANGIAMO: I suggest we see where it goes.
MR. KELLER: Sure.
MR. SANGIAMO: Start your questions, if it looks like he needs to read, he will read as much of it as he needs to read and maybe we won't have any kind of problem.
MR. KELLER: Sure.
BY MR. KELLER:
Q. Let me direct your attention, you've -- sir, you've reviewed protocols in the past. Are you familiar with the format of them?
A. I wouldn't say reviewed. I have seen them. I wouldn't call it a -- I wouldn't constitute -- qualify it as a review.
Q. Let's turn to your attention to the table of contents on 17655. It's broken up into a couple of different sections. I is

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"CLINICAL SECTIONS," "ADMINISTRATIVE AND REGULATORY SECTIONS." Do you see that? And "SIGNATURES." Do you see that on 17655 and --

A. The second one I don't.

Q. On 17657. Roman numeral I, Roman numeral II, Roman numeral III. Do you see that?

A. Yes.

Q. On the "CLINICAL SECTIONS" under III [sic] it says, "OBJECTIVES." Do you see that on 17655?

MR. SANGIAMO: Number III?

BY MR. KELLER:

Q. Roman numeral I(C), "OBJECTIVES." Do you see that?

A. Yes.

Q. Do you understand what objectives are in a protocol?

A. No.

Q. Let me direct your attention to 17665 -- strike that.

Let me direct your attention to 17693 under F, "EFFICACY/PHARMACOKINETICS /IMMUNOGENICITY, ETC., MEASUREMENTS." In the second paragraph it says, "Serologic testing

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will be performed by Merck Research Laboratories..., West Point, PA."

Do you see that?

A. Yes.

Q. What do you understand serologic testing to mean generally outside of this protocol?

A. It could be a variety of things. It would depend on what this -- the document indicates is the specific assay.

Q. Let me ask you, for Protocol 007, did you do serologic testing in your lab?

A. Yes.

Q. And what serologic testing did you do?

A. For Protocol 007?

Q. Yes.

A. The mumps AIGENT assay.

Q. So you ran the kid's serum in that assay. Correct?

A. Yes.

Q. Let me direct your attention to 17706, under "DATA ANALYSIS." In the first sentence it says -- let me know when you're there. The first sentence says, On the

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subjects enrolled in each of the treatment groups, 5 percent are expected to be initially seropositive.

Do you see that? The first sentence.

A. Yes.

Q. The treatment groups, did you understand that to be the three doses that were run in the AIGENT?

MR. SANGIAMO: Object to the -- you said did he understand?

MR. KELLER: Yes.

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall that specific part of the document, seeing that before in this document.

BY MR. KELLER:

Q. Did you ever learn that there is an expectation that only -- what do you understand initially seropositive to mean in a plaque reduction neutralization assay?

A. My general understanding of that would be that the pre-vaccination, 5 percent of the pre-vaccination sera would be expected

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to be positive.

Q. What does that mean to you, what does seropositive mean?

A. It means that there's a positive neutral -- the serum is neutralizing in the -- it's giving a positive neutralization result.

Q. For mumps specific antibodies?

A. Yes.

Q. So is it the understanding that those kids are immune from the disease because they've already got mumps neutralizing antibodies in their bloodstream?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't know that -- the clinical conclusion from that result.

BY MR. KELLER:

Q. You don't. This expectation of 5 percent being pre-positive, have you ever heard that expectation before?

A. I've heard of estimates of initially seropositive. I can't say that the 5 percent is familiar.

Q. Have you done any research to

determine what would be expected for kids to be immune from mumps prior to being vaccinated?
A. Personally, no.
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Has anybody, are you aware of anybody -- strike that.
Are you aware of anybody connected with Protocol 007 doing any research to determine what the expectation was for kids before they're vaccinated to be immune from mumps disease?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not aware, I'm not familiar with whether such studies were done.
BY MR. KELLER:
Q. You made projections for pre-positive rates, didn't you, when you ran the AIGENT?
A. There were estimates of the expected pre-positive rates based on the results of our development studies.



Q. Other than running your development studies to get a pre-positive rate, are you aware of any other control to identify whether or not these kids are, in fact, immune from disease, from mumps?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not aware of other -- are you asking if there is another independent test of antibody in those sera?
BY MR. KELLER:
Q. Did you do any other independent testing to determine seropositive rates for kids that would expect in this study of the this nature PRN study?
MR. SANGIAMO: Object to the form.
THE WITNESS: I didn't personally do it.
BY MR. KELLER:
Q. Did you ever compare it against ELISA results for pre-positivity?
A. I did not.
Q. Are you aware of what the



pre-positive results were for the ELISA testing?
A. No.
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Nobody ever told you?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall.
BY MR. KELLER:
Q. Would that have been relevant for you to understand a kid identified as having no mumps antibodies in an ELISA, to use that as a comparison to what was being seen in the AIGENT?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm sorry, that doesn't make sense.
BY MR. KELLER:
Q. It doesn't make sense to you? An ELISA identifies mumps antibodies. Correct? Isn't that the whole purpose of an ELISA, a mumps ELISA assay, to identify mumps



antibodies?
A. Yes.
Q. So if a kid is pre-positive for an ELISA mumps antibody test, that would presume that the kid has mumps antibodies. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: It would indicate that that serum has detectible antibodies.
BY MR. KELLER:
Q. You don't think that information to be at all relevant in determining the pre-positive rate for your plaque reduction neutralization assay?
A. From my view, no.
Q. Why?
A. They're independent assays. I wouldn't -- at least in other assays that are -- other neutralization assays I've run, I'm not aware of any suggestion of -- a suggestion of using the ELISA as a guide for what to expect in that assay.
Q. Have you ever -- are you aware

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of anybody who has correlated an ELISA assay to a plaque reduction neutralization assay for mumps?
A. Yes.
Q. Who?
A. Steve Rubin is one of them, one person.
Q. For determining whether or not the assay is -- when did that happen?
A. I don't recall specific years, but he's published on those studies.
Q. Has there been a correlation between an ELISA assay and protection from disease?
MR. SANGIAMO: Object to the form.
THE WITNESS: From my understanding, there is no correlate of protection from -- protection from disease for mumps.
BY MR. KELLER:
Q. Do you understand what the term "efficacy" means?
A. I have a general understanding of that.

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Q. What's your understanding?
A. That that's the -- in a controlled clinical setting, the protection from -- the protection from disease achieved during a controlled clinical study.
Q. Did your -- the AIGENT you developed, did that show efficacy?
MR. SANGIAMO: Object to the form.
THE WITNESS: There -- my understanding, there was no protection in the study. This was an immunogenicity study. So efficacy, from my understanding, would require evaluating protection from disease in the vaccinees.
BY MR. KELLER:
Q. Did you ever -- do you know what effectiveness means?
A. I have a general understanding of that.
Q. What's your understanding, sir?
A. My general understanding of that is protection from disease in a global world setting versus a controlled clinical setting

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protection in the broader population.
Q. Do you recall ever representing in a document that the assay that you ran is linked to efficacy?
A. Not that I recall.
Q. Would that surprise you if you saw a document linked to your name, that you represented that this assay, the assay that you ran was linked to efficacy?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall. I'm not aware of one study that I might link to.
BY MR. KELLER:
Q. Would that surprise you if somebody represented that the assay that you developed, the AIGENT, was linked -- represented as being linked to efficacy?
MR. SANGIAMO: Object to the form.
THE WITNESS: Well, the statement of the link to efficacy would be a statement that would be beyond my expertise, require clinical and

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regulatory input. So if a document did exist, my input would not have been beyond the assay description.
BY MR. KELLER:
Q. When you were developing the AIGENT that ultimately got used in Protocol 007 -- strike that.
Let me direct your attention back to Exhibit 22, in particular at 17720, under "COMPLIANCE WITH LAW, AUDIT, AND DEPARTMENT."
You testified that you may have seen pieces of protocols. Do you ever recall seeing pieces of protocols that discussed how the clinical studies would be conducted?
A. I do not.
Q. In this protocol for Protocol 007, it's dated February 2, 1999. Do you see that in the bottom right-hand corner?
A. Yes.
Q. You were working on that -- on Protocol 007 at this time frame, weren't you?
A. I don't recall the date.
Q. You don't recall. Here it says, "COMPLIANCE WITH LAW, AUDIT, AND DEPARTMENT,"

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the first paragraph, can you read the first sentence on 17720?
A. The first, "By signing this protocol...," that one?
Q. Yes.
A. "By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study."
Q. It's your testimony that you didn't have an understanding that the samples that you ran for Protocol 007 would be required to be run under the Good Clinical Practices because you didn't even know what that was, did you?
A. I was not familiar with what that term referred to nor that we were -- that it applying to the testing laboratory.
MR. SANGIAMO: Jeff, if you're going to ask him questions about the substance, why don't you just go ahead

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and read that very short section.
BY MR. KELLER:
Q. Sure. Why don't you read this section, it's only three pages, take your time.
A. Okay.
MR. SANGIAMO: Also read the final paragraph.
BY MR. KELLER:
Q. Just those two pages.
A. Okay.
Q. Having read these three sections, does that refresh your memory whether or not you've seen this language in Protocol 007?
MR. SANGIAMO: I'm sorry, the which three section? I thought he read two sections.
MR. KELLER: Section H and I.
BY MR. KELLER:
Q. Those two pages.
A. That does not change my -- I don't recall.
Q. So in the section I under "QUALITY CONTROL AND QUALITY ASSURANCE," do

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you understand what quality control and quality assurance is?
A. I've heard the terms before. How it applies in this particular case I am not familiar with.
Q. Is it a department at Merck that handles quality control and quality assurance?
A. There are people at Merck whose job includes that. I don't recall whether there is a specific department that covers those particular items alone or if they include other responsibilities.
Q. Do you recall -- do you understand what the difference is between quality control and quality assurance?
A. Not offhand.
Q. Here it says, "By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local

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laws, rules and regulations relating to the conduct of the clinical study."
Do you see that?
A. Yes.
Q. That's reference to Protocol 007. Correct? Is that a fair statement, the clinical study referenced there is Protocol 007?
A. That's what it appears to be, yes.
Q. Did you understand -- and you ran the serum for Protocol 007, correct, in your lab?
A. Yes.
Q. Does that lead you to believe that your lab should have been complying with the accepted standard for Good Clinical Practices?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't have experience whether that -- the description as written here applies to the testing laboratory.
BY MR. KELLER:

Q. The reference here to sponsor, that's Merck, right? Merck was the sponsor for this protocol?
A. That's my -- I can't say for certain, but that's my understanding of the wording.
Q. During the time that you ran the samples for Protocol 007, were there any SOPs in place for quality control that related to those clinical samples?
A. I don't recall.
Q. Were there any quality assurance SOPs that were in place with respect to the running of the clinical samples in Protocol 007 that you recall?
A. I don't recall.
MR. KELLER: Let me mark this next exhibit as Exhibit 23.
- - -
(Exhibit Krah-23, E-mail string, 337141 - 337157 & 121082, was marked for identification.)
- - -
BY MR. KELLER:
Q. For the record, Exhibit 23 is a



document that bears Bates stamp number 337141 through 157. And there's a separate document attached to this that bears Bates number 121082. I'll keep these together as Exhibit 23.
Sir, can you tell me if you recognize the attachments? The attachment says "Study of MMR II at Mumps Expiry Potency," and, sir, you're identified as one of the writers of this document. And the last page at 121082 is actually a poster. Correct?
MR. SANGIAMO: Hang on a second. What's the question?
MR. KELLER: I'll start again.
BY MR. KELLER:
Q. Sir, if you look on the first page, 337141, there's an e-mail from a Mande Lyon to you. Do you see that, August 17, 2004?
A. August -- I'm sorry. The initial one, the August 17, 2004, yes.
Q. Typically the way e-mails work when they're printed up is they start with --
A. The more recent.
Q. Yeah. So the top of it is the more recent. The bottom is later in time. So



who is Mande Lyon?
A. I don't recall.
Q. The subject here is "MMR II Protocol 007 IDSA Poster Draft."
Do you see that?
A. Yes.
Q. What's the IDSA?
A. It's, as best I recall, an organization. I don't recall what it stands for.
Q. Do you recall ever giving a presentation at that organization regarding Protocol 007?
A. Clarification, me personally or --
Q. You personally.
A. I don't recall personally giving a presentation.
Q. Do you recall, has anybody ever presented on the results of Protocol 007 to anybody outside of Merck other than the FDA or CBER?
MR. SANGIAMO: Answer if you know obviously.
THE WITNESS: I don't know.



This document suggested that this was -- is the planned presentation, but I don't know what's presented.
BY MR. KELLER:
Q. Did you ever publish your findings in Protocol 007? Let me strike that.
Did you ever prepare a paper for publication from your findings in Protocol 007?
A. Did I or did Merck?
Q. Were you involved in that?
A. I was -- yes, there was a publication put together in which I was a co-author.
Q. Was that ever published?
A. Not to my knowledge.
Q. Do you know why?
MR. SANGIAMO: Dr. Krah, you should exclude from any answer anything that involves communications from counsel. So do you know of reasons other than anything that would have been communicated to you by counsel?
THE WITNESS: No.
BY MR. KELLER:

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Q. This is a 2004 poster. Correct?
A. The date is from 2004. I don't know when the actual --
Q. Did you draft --
MR. SANGIAMO: You don't know when the actual what?
THE WITNESS: Presentation was.
BY MR. KELLER:
Q. Did you draft this?
A. That is not typical -- no, I did not draft it.
Q. Your name is on it, though. Correct?
A. Yes.
Q. So who would typically draft these types of documents at Merck?
MR. SANGIAMO: Object to the form.
THE WITNESS: It varies. I was looking -- typically the first author is the one who prepared it. But the first author is not a -- doesn't look like is a Merck person. So I can't say with certainty who was the lead in drafting it.

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BY MR. KELLER:
Q. Mande Lyon is from Merck, according to this poster. Do you see that?
A. Yes.
Q. You don't know who that is?
A. Other than like on the page before it says she's associate medical program clinical specialist, I know her, the name is familiar to me, but I don't have any other specific recollection.
Q. If you didn't draft it, why is your name on it?
MR. SANGIAMO: Objection. Answer if you know.
THE WITNESS: I can't say with certainty. There's a general scientific rationale for it, but I can't say with certainty for this particular one why I'm on it.
BY MR. KELLER:
Q. Do you recall commenting on this draft?
A. The e-mail indicates that I had some comments to the poster, so yes.
Q. So you reviewed it?

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A. This suggests, yeah, the e-mail suggests that I reviewed it.
Q. When you reviewed it, did you see anything that was incorrectly stated in this poster?
A. Not that I was aware of.
Q. And if there was something incorrect here, would you have -- you would have raised that, wouldn't you have?
MR. SANGIAMO: Dr. Krah, why don't you take a look at the document since he's asking the substance of it.
BY MR. KELLER:
Q. I'm asking generally without looking at the document. If there was something incorrect in a poster like this, you would have raised that objection, wouldn't you have?
MR. SANGIAMO: You said a poster like this. So that means he needs to look at the document to find out what the document is about.
BY MR. KELLER:
Q. You can't answer that question without looking at the document?

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MR. SANGIAMO: What's your question? Rephrase your question.
BY MR. KELLER:
Q. If you would have seen a statement that was incorrect in a poster that was being published with your name on it, sir, would you have raised that objection before it was published?
A. If I was aware of a mistake, I would have raised it.
Q. Fair enough. Take a second to look at this poster and tell me -- it's multiple pages. I really only have one question. Actually two questions.
On page 337144 --
MR. SANGIAMO: He's still looking at the document, Jeff.
THE WITNESS: Okay.
BY MR. KELLER:
Q. Do you see anything incorrectly stated in this poster?
A. In my review, my focus would be limited to my experience with the neutralization assay. So I did not see anything that was incorrect regarding those --

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the neutralization assay details.
Q. The numbers?
A. Either the numbers or the format of the assay.
Q. So under this poster that has your name on it, sir, it says, "Study Rationale." Do you see that on the first page of it?
A. Okay.
Q. What do you understand the study rationale to mean?
A. All I can say literally what the words are written here. I don't have any understanding beyond that.
Q. Your name is on this thing so why don't you tell me what your understanding is?
MR. SANGIAMO: He just answered your question, Jeff.
BY MR. KELLER:
Q. Tell me what you understand it to be.
A. Literally what the words say here.
Q. Is it the rationale for Protocol

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007? Is that a fair assessment?
A. If there is --
Q. Look at the -- on the next page, on the third bullet point from the bottom, do you see that? It says, "To determine the minimum mumps virus potency at expiry in MMR II, a clinical trial was conducted among children 12 to 18 months of age"?
Do you see that?
A. Yes.
Q. That's talking about the AIGENT that you ran. Correct? That's the clinical trial?
MR. SANGIAMO: Object to the form.
THE WITNESS: There was an antibody assay that was part of the clinical trial. The clinical trial also included the actual preparation, administration of the vaccine.
BY MR. KELLER:
Q. Fair enough. In the next bullet point says -- can you read the next bullet point for the record, please?
A. "Antibody response measured by

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mumps-virus specific plaque reduction neutralization (PRN) assay was used as a surrogate of vaccine efficacy; ELISA assays for mumps antibodies were also performed."
Q. So the statement here that the mumps virus specific plaque reduction neutralization (PRN) assay was used as a surrogate for vaccine efficacy, that was Protocol 007, wasn't it?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. The AIGENT that you worked on?
MR. SANGIAMO: Object to the form.
THE WITNESS: The Protocol 007 -- the AIGENT assay was used in Protocol 007.
BY MR. KELLER:
Q. Correct. So what they're referencing here, was there any other mumps virus specific plaque reduction neutralization assays as part of Protocol 007 other than the AIGENT?
A. Not that I'm aware of.

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Q. Here it represents that that assay was used as a surrogate of vaccine efficacy. Do you see that?
A. Yes.
Q. Is that the first time you've ever seen that your -- the analysis that you ran, the studies that you ran, the results that you ran were going to be used as a surrogate of vaccine efficacy?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say with certainty it's the first I saw it, but I don't recall seeing that.
BY MR. KELLER:
Q. What do you understand that to mean, a surrogate of vaccine efficacy?
A. That's an area beyond my expertise.
Q. You don't understand after working in research, vaccine research since 1988 what a surrogate of vaccine efficacy means?
A. That's correct.
MR. SANGIAMO: Jeff, we've been

going about 45 minutes.
MR. KELLER: Let's go for lunch.
VIDEOGRAPHER: The time is now 12:57. This concludes disc three.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is now 2:08. This begins disc four. You may proceed.
MR. KELLER: I'm going to mark as Exhibit 24 a document that bears Bates-stamped number 625837 through 839, and it's an e-mail, and there's an attached document to the e-mail.
- - -
(Exhibit Krah-24, 10/6/98 E-mail with attachment, 625837 - 625839, was marked for identification.)
- - -
BY MR. KELLER:
Q. In the e-mail dated at the top of the page October 6, 1998, from Henrietta Ukwu to a series of individuals, and, sir, you are one of the cc's on this e-mail entitled:



Mumps expiry; summary of prep meeting on September 30 for CBER telecon.
Do you see that?
A. Yes.
Q. Do you recall receiving this e-mail?
MR. SANGIAMO: Obviously take a minute to look at it, Dr. Krah, read it to your satisfaction.
THE WITNESS: I don't have a recollection. I see my name on the cc list, but I don't recall -- it doesn't provide a memory.
BY MR. KELLER:
Q. Do you have any reason to believe you didn't receive it?
A. If I'm on the cc list, it would imply that it was sent to me. So I don't have any reason to believe it was not sent to me.
Q. Was it your practice to review e-mails that you received?
A. My practice, as best I recall, was to read the -- or look at who it's from and read the subject, the subject line. I can't say that every -- I can't say I then



read the content of everything.
Q. So it's fair to say if somebody of importance e-mailed you something, you would read that e-mail. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: I would say it would -- perhaps it would depend on the subject and who the person was. A person of importance would be relative to me. It may be an important person in the organization but not necessarily in my reporting structure.
BY MR. KELLER:
Q. Gotcha. Who is Henrietta Ukwu?
A. I don't recall her title. I'd be guessing at what her -- even what group she was in.
Q. She was senior management at Merck, wasn't she, at this time frame?
A. I don't know -- I don't know what constitutes -- well, I don't recall her position and title and whether that constituted senior management or not.
Q. And here under subject, it says,



Mumps expiry; summary of prep meeting 600 for CBER telecon. Would that have been of interest to you during this time frame?
A. I don't -- I don't -- it's not obvious to me that it would have been of interest, but I -- so I can't say one way or the other whether it would be of interest.
Q. In the first sentence it says, "Please note the summary, from Dr. Chirgwin...." Who is Dr. Chirgwin?
A. The Dr. Chirgwin I know is Keith Chirgwin. I don't know his position at the time.
Q. Do you recall, is he -- do you recall when he left Merck?
A. No.
Q. Do you recall him working in regulatory affairs?
A. I recall him working, as best I can recall, in regulatory affairs at some point in his career at Merck.
Q. Do you recall him reporting to Henrietta Ukwu in regulatory affairs?
A. That, I don't recall.
Q. This topic of mumps expiry, you

don't recall if you were working on the development of the PRN assay during this time frame?
A. I don't recall.
Q. Let me direct your attention to the last sentence. It says, "The key members of the team are copied on this memo...."
Do you see that?
A. Yes.
Q. And under the cc, you understand that's carbon copy. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Do you understand what copy means?
A. cc -- yeah, cc just means it's someone who is copied, whether it's -- in the olden days my understanding was carbon copy. I don't know if that still applies.
Q. Fair enough. You're identified as -- in the cc's. Do you see that?
A. Yes.
Q. As of this date, did you consider yourself to be one of the key members



of the team for running the mumps expiry studies?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say one way or the other at that time what preparations we had been making to run the assay.
BY MR. KELLER:
Q. So you have no recollection as to -- let me strike that.
You were on the team that ultimately worked on running the clinical assays for Protocol 007. Correct?
MR. SANGIAMO: Object to the form.
MR. KELLER: Let me strike that.
BY MR. KELLER:
Q. You were ultimately on the team that ran the clinical serum as part of Protocol 007. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: In the AIGENT, the mumps AIGENT assay, yes.



BY MR. KELLER:
Q. Did you understand that to be the mumps expiry studies?
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding was that that was a component of the mumps expiry study.
BY MR. KELLER:
Q. So at some point you became part of that team. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: I would say presumably because I'm copied on this.
BY MR. KELLER:
Q. So when it says the key members of the team are copied, you just don't know whether or not you were a key member as of this date?
A. That's correct. Yes.
Q. But you became a key member at some point. Correct?
MR. SANGIAMO: Object to the form.



THE WITNESS: I became a member of the team. Whether -- a key member would be a subjective assignment.
BY MR. KELLER:
Q. So you can't -- you can't -- okay.
Who else is cc'd on here? You have Dr. Ukwu. Who is Kati Abraham, do you know?
A. I know Kati Abraham or Kati Abraham, but I don't recall her position at the time. She has had multiple positions at Merck.
Q. What was the position that she had the last time you remember her position?
A. She -- last I recall, she was overseeing -- I have a general sense of what she was doing. I don't know what her official title was or overall responsibilities.
Q. What's your general sense?
A. General sense is something along the lines of quality control or quality assurance. And I'm not sure which, within our -- I don't recall if she was in our -- whatever our department was called at the time

or if she was -- I know she was supporting our department. Whether she was actually part of the department, I don't recall.

Q. Did she ever support Protocol 007?

MR. SANGIAMO: Object to the form.

THE WITNESS: She was at Merck and involved in a quality control/quality assurance role during Protocol 007 to the best of my recollection.

BY MR. KELLER:

Q. Did you ever interact with her regarding quality control and quality assurance regarding the serum that you ran in Protocol 007?

A. I interacted with people in her group. Whether I interacted with her directly, I don't recall.

Q. Who did you interact within her group?

A. The person, I think it was Leah Gottlieb.

Q. What was her position, do you recall?



A. I don't -- to be honest, I don't recall.

Q. How did you interact with her, for what purpose?

A. Leah, as best I can recall, helped in the SOP review and approval and also served a function in monitoring and reviewing data from the Protocol 007 study.

Q. How was she monitoring the data and reviewing the data? For what purpose? Strike that.

For what purpose was Leah Gottlieb monitoring the serum in Protocol 007?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. The data from the serum -- strike that. You're right.

Can I get his answer read -- sorry.

What -- how was she monitoring and reviewing data for Protocol 007?

A. As best I can recall, she was looking through the results spreadsheets identifying sera that were -- in the case



where we had a workbook that were flagged -- for criteria that the workbook was flagging, for example, extravariability is one example, and then helping to identify sera then for a retest.

Q. Was that something that you asked her to help with?

A. No.

Q. Was she -- were you providing results of the clinical studies to her in Protocol 007? Strike that.

Were you providing results of experiments to her during the running of Protocol 007?

A. Workbooks from Protocol 007 were being provided to her during the running of Protocol 007.

Q. And do you know why she was reviewing them?

A. I have an, I'll say an understanding of it. I don't know if it's the only reason.

Q. What's your understanding?

A. Emilio Emini asked how -- I'm sorry. Emilio Emini and Alan Shaw were



looking for someone who could identify sera for -- this is the best of my understanding, for retest, and having Leah look through them allowed more expedited identification of sera for retest.

Q. Was that after all the serum was run for Protocol 007 through the experiments?

A. It was --

MR. SANGIAMO: Object to the form.

THE WITNESS: It was -- the reviews were done, as best I can recall, whenever the data were available from a particular experiment or set of experiments. So it was not at the end of a study but at the end of an experiment.

BY MR. KELLER:

Q. You also testified that she reviewed the SOP. Correct?

A. I don't believe I used the term reviewed, but one of her roles was to help in generating and having SOPs approved.

Q. How were they -- who approved them?

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A. I don't recall who all the approvers were. I don't recall the procedure for review and approval at the time.
Q. Do you know why they were approved, why somebody was approving the SOPs?
MR. SANGIAMO: Objection. Objection to the form. Calls for speculation.
THE WITNESS: I would say that any approval of an SOP was done in order to have the SOP available in an approved form for use.
BY MR. KELLER:
Q. You don't know what the criteria upon which it was reviewed for and approved?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall. I'm not familiar with that.
BY MR. KELLER:
Q. In Dr. Ukwu's e-mail she writes in the second paragraph, "I would like us to have a firm plan for our assay development and validation prior to their use in any clinical studies to support registration/claim."

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Do you see that?
A. Yes.
Q. And so the assay development, that was something that you did as well for Protocol 007, you did assay development, you developed the AIGENT. Correct?
A. I was part of the team that developed the AIGENT assay.
Q. And validation, what do you understand validation to mean?
A. My understanding of that as written here is that validation would be designing and performing the -- whatever studies were appropriate for a validation plan.
Q. So is it fair to say that Dr. Ukwu is saying that she wanted to have a plan for having the validation completed prior to running of any clinical sera in Protocol 007? Is that a fair statement here?
MR. SANGIAMO: Objection.
THE WITNESS: That's what the words say in her e-mail, appear to be saying.
BY MR. KELLER:

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Q. Did you ever talk to Dr. Ukwu about validating Protocol 007?
A. I don't recall talking to her about that.
Q. Do you recall talking to anybody about the criteria for validating the AIGENT SOP?
MR. SANGIAMO: Object to the form.
THE WITNESS: Yes.
BY MR. KELLER:
Q. Who did you speak to?
A. I don't recall. It was someone in biometrics. I don't recall. I'm trying to remember. I'd be guessing, but it was someone in the biometrics group.
Q. Do you recall when that happened?
A. That, I don't recall.
Q. You testified earlier to that person, you just didn't recall.
Did you -- and just to go back, did you design the experiments that were going to be used in the validation protocol?
A. I contributed to the design of the experiments that were going to be used in

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the validation protocol.
Q. What did you contribute?
A. I don't recall the specifics.
Q. Who else worked on -- was that the person from biometric research who helped identify what experiments would be run as part of the validation protocol?
A. As best I can recall, they provided, the biometrics representative or representatives provided guidance as to what sorts of experiments. And, again, I don't remember with certainty but my expectation would be they would give an indication of how many samples, how many runs of the assay, for example.
Q. Did you follow their recommendations?
A. As best I can recall, yes.
Q. Did you run all the experiments that they recommended?
A. I'm not aware of any that were recommended that we didn't run, so yes.
MR. KELLER: Let me mark this next exhibit as Exhibit 25.
- - -

(Exhibit Krah-25, Agenda - revision 1, 1614153, was marked for identification.)

- - -

MR. KELLER: For the record, Exhibit 25 is a single-page document bearing Bates stamp number 1614153, entitled, "AGENDA - Revision 1 Vaccine Tactical PAC June 21, 1999."

BY MR. KELLER:

Q. What is a -- what is the PAC, do you recall?

A. I don't recall.

Q. You don't know. Do you recall participating in this meeting on June 21, 1999, regarding vaccine tactical PAC? You see at 9:30 there's a discussion of the competitive update for MMR. Do you see that?

A. Yes, I see it.

Q. You're identified as one of the invitees. Do you see that?

A. Yes.

Q. Do you recall participating in this meeting?

A. I don't recall.



Q. If you could find on -- I've already marked the location of June 21, 1999, in your journals. Can you tell me if you can identify the page that's marked there, the bottom right-hand corner?

A. 8615. Page 211 at the top of the report.

Q. 0 -- I'm sorry, 48615. Okay. And at 48615, is there a reference for a meeting on June 21, 1999?

A. Yes.

Q. And what's -- can you tell me what's written there?

A. MMR II TPAC presentation 9:00 a.m. to 1:00 p.m. Hilleman Conference Room.

Q. Can you tell from your journal on that day that you attended this meeting?

A. The check mark may suggest that I attended it.

Q. If you look on the agenda -- do you have any reason to believe that you didn't attend it?

A. I don't have a recollection. I don't have a reason to believe I didn't. But



I don't have a recollection that I did.

Q. Fair enough. There is a reference on the agenda to Nick Spring. Do you know who Nick Spring is?

A. I'm sorry?

Q. On Exhibit 25.

A. I'm sorry, the name Nick Spring?

Q. Nick Spring, do you know who Nick Spring is?

A. That name is not familiar to me.

Q. You don't recall receiving a marketing update at this meeting?

A. I don't recall -- I don't recall one.

Q. Do you recall receiving a backgrounder in preparation for this meeting?

A. I don't recall.

Q. Would you be surprised if you -- strike that.

MR. KELLER: Let me mark this next exhibit as Exhibit 26.

- - -

(Exhibit Krah-26, 6/16/99 E-mail with attachments, 285267 - 285296, was marked for identification.)



- - -

MR. KELLER: Steve and Joanie, can you step out for a minute?

For the record, Exhibit 26 is a document that bears Bates stamp number 285267 through 285296. There's an e-mail and an attachment, two attachments. The e-mail is dated June 16, 1999, from Joan Staub to a laundry list of people including you, Dr. Krah.

BY MR. KELLER:

Q. Can you tell me if you recall receiving this backgrounder for the June 21st TPAC meeting?

A. I would say it doesn't look familiar to me.

Q. If you go to the first page of the e-mail, there's a reference that says, "Attached please find the backgrounder and appendix document for the MMR II Competitive Defense Presentation to the TPAC on June 21."

Do you see that?

A. Yes.

Q. You were a member of the

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Competitive Defense Task Force, weren't you?
A. That I -- I was invited to this meeting. Whether I was a member of that, I don't know.
Q. Your counsel has represented that you were a member during this time frame. Does that refresh your memory that you were a member of this particular committee?
A. I don't recall.
Q. Have you ever heard of the Competitive Defense Task Force before seeing this document?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm sorry, which document?
BY MR. KELLER:
Q. Let me direct your attention to 285276, entitled: MMR II Defense Action Plan TPAC Background document, prepared by The Competitive Defense Task Force for MMR II June 1999.
Do you see that?
A. Yes.
Q. Sir, my question for you is, did

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you ever -- you don't -- is it your testimony you don't recall being a member of that particular task force?
A. I remember attending or being invited to meetings of it, but I don't recall if I was -- that I was a member.
Q. Why would a research scientist be invited to -- let me back up a second. Strike that.
Let me direct your attention to the third page of the defense action plan at 285278, under "EXECUTIVE SUMMARY."
A. Okay.
Q. The first sentence, it says, "The cross-functional defense of MMR II was created in 1996 when the Competitive Defense Task Force was chartered by TPAC."
Do you see that?
A. Yes.
Q. You don't recall what TPAC stands for, do you?
A. Not at this time. At the time I may have known, but I don't recall what it stands for.
Q. You don't recall whether or not

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you were a member of the TPAC. Correct?
A. I do not recall that.
Q. You don't remember -- you don't recall if you were a member of the Competitive Defense Task Force either, do you?
A. No.
Q. But you recall being invited to meetings where the Competitive Defense Task Force gave presentations. Correct?
A. At least this one example that you had I was on the invitee list.
Q. Let me ask you, sir, why would a research scientist be invited to a meeting to discuss competitive defense of the MMR II vaccine?
MR. SANGIAMO: Objection. Answer if you know.
THE WITNESS: I don't know.
BY MR. KELLER:
Q. And so did you learn about Merck's marketing plans for its MMR II products at these meetings?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't -- there

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may have been information presented on that, but I don't recall meaning anything to me.
BY MR. KELLER:
Q. In the third paragraph it says, "Initiatives continue in MRL and MMD to ultimately provide a product line which will be competitive and satisfy all regulatory requirements. Those programs will be updated in this background document include:" In number 3 is "the defense of Mumps expiry titers."
Do you see that?
A. Yes.
Q. Do you recall whether or not Protocol 007 was part of this defense of the mumps expiry titers?
A. I don't know whatever the date is for this, I don't recall what the status of -- whether Protocol 007 existed at that time.
Q. This is June of 1999.
MR. SANGIAMO: Dr. Krah, you should be sure to familiarize yourself with the document to the extent you

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need to respond to Mr. Keller's questions.
BY MR. KELLER:
Q. Let me direct your attention to -- you don't know is what you're saying?
A. I don't recall the dates.
MR. SANGIAMO: You don't recall the dates.
BY MR. KELLER:
Q. Do you recall any discussion, irrespective of dates, regarding the use of Protocol 007 results in defending mumps expiry titers?
MR. SANGIAMO: Moving away from the document?
MR. KELLER: I'm talking generally about the document.
MR. SANGIAMO: Then, Dr. Krah, take your time to familiarize yourself with the content --
BY MR. KELLER:
Q. I'm talking about one paragraph. You want to read the paragraph. If you want to go off the record, you can read every single page of this document.

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MR. SANGIAMO: No, we're not going off the record.
Dr. Krah, read the document to the extent necessary to familiarize yourself with it.
MR. KELLER: Let's go off the record. I think we should call the magistrate at this point. This is getting ridiculous.
MR. SANGIAMO: You're telling him he's only allowed to read one paragraph of this document?
MR. KELLER: Sure. He can do it off the record. He's going to take three hours to read a document, by the time --
MR. SANGIAMO: What makes you think it's going to take him three hours to read a document?
BY MR. KELLER:
Q. Go back on the record.
Sir, tell me when you're done familiarizing yourself with the paragraph that I just referenced you.
A. The initiatives continue

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paragraph?
Q. Yes. Under "EXECUTIVE SUMMARY."
MR. SANGIAMO: Dr. Krah, I would suggest that you read the executive summary in its entirety and look over the rest of the document and that will be sufficient to answer Mr. Keller's question, but we'll see.
THE WITNESS: Okay.
BY MR. KELLER:
Q. My question is, again, do you recall ever learning that Protocol 007 was to be used as part of the defense of the mumps expiry titers as part of Merck's competitive defense?
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding was that Protocol 007 was being used to support and characterize MMR whether -- I'm not -- I don't recall that it was part of a -- like a competitive defense strategy.
BY MR. KELLER:
Q. Fair enough. Look on page 285279

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under "Marketing Response to SB Competition."
Do you see that?
A. Okay. Yes.
Q. "RESPONSE TO COMPETITION." Do you see that at the top of this page?
A. Yes.
Q. SB, do you understand that to be Smith Barney? I'm sorry, Smith Beecham. Sorry, strike that.
What do you recall SB to stand for?
A. Two paragraphs down it has SmithKline Beecham as SB. I don't have a recollection of it, but the paragraph just before -- or just under the graphs defines that SB as SmithKline Beecham.
Q. Gotcha. Did you understand that SmithKline Beecham had its own MMR product that it was selling outside the United States called Priorix?
MR. SANGIAMO: Object to the form.
THE WITNESS: I was aware that they had one or more vaccines that contained measles, mumps and rubella.

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I don't recall having familiarity with -- it wasn't being sold in the US. It was being sold outside the US.

BY MR. KELLER:

Q. Do you recall as part of this presentation in June of 1999 a discussion about Priorix and its threat of Priorix coming to the US market?

MR. SANGIAMO: Object to the form.

THE WITNESS: In reading through the document, at the beginning of the discussion I recall seeing sections that comment on that aspect of the GSK -- I'm sorry, the SmithKline Beecham vaccine being a competitive threat to the MMR vaccine.

BY MR. KELLER:

Q. Do you recall -- other than reading this document today, do you recall any discussions about it back in 1999?

A. At least one aspect to it, yes.

Q. What is that?

A. When we did -- conducted the Protocol 006 study which was a head-to-head

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study of MMR with Priorix, that was, from my understanding, a competitive trial to compare immunogenicity of the mumps component of MMR with Priorix.

Q. They may have used a plaque reduction neutralization assay in that study. Correct?

A. Yes.

Q. That study, that was Protocol 006. Correct?

A. Yes.

Q. That study didn't use any anti-IgG steps, did it?

A. That's correct.

Q. Which assay do you think is a better assay for showing immunogenicity, the AIGENT or the assay used in Protocol 006?

A. Let me tell you, it depends on the goals of the study. I would say both are equally relevant and important. So at 1.1 is better than the other.

Q. When you say the goals of the study, you testified that you didn't know what the goals were for the Protocol 007. Correct?

A. I knew from discussions with

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CBER that -- so I don't -- it's correct I don't know the overall study goals, but I do know from discussion with CBER that a 95 percent seroconversion was a requirement.

Q. And that requirement of 95 percent, do you understand that that was what was represented in the then current label of MMR II for mumps?

A. I don't recall.

Q. Just that they wanted 95 percent seroconversion in a neutralizing assay. Correct?

A. Yes.

Q. What were the goals of Protocol 007? I mean, sorry. What were the -- strike that.

What were the goals of Protocol 006?

A. I have a -- my perspective or my understanding of the goals in the same context of Protocol 007, there may have been other study goals than are beyond what I was thinking, the goals that I was aware of were comparing the immunogenicity of the mumps component of MMR and Priorix against different

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wild type mumps strains to see if there's a difference in the breadth of neutralization induced by MMR versus Priorix.

Q. What do you mean by "immunogenicity"?

A. Neutralization results, meaning there are two, at least as best I can recall, two sets -- two forms of data that were provided in Protocol 006. One is a seroconversion rate. The other is a geometric mean titer. So from a immunogenicity standpoint I put those both in as immunogenicity measures that were part of Protocol 006.

Q. Was Protocol 006 designed to determine whether or not kids would be protected from mumps?

A. Not -- not to my understanding, but I wasn't -- it's beyond my scope of responsibility. I had no awareness that it was designed to show protection.

Q. If you go back to Exhibit 26. In the second paragraph it says, MMR is currently an exclusive license in the United States.

Do you see that?
A. I'm sorry, what page?
Q. 285279, the same page we were on.
A. Okay.
Q. Do you recall a discussion at this --
A. Could you repeat that?
Q. Sure. In the first sentence it says, MMR II is currently the exclusive vaccine in the United States...
Do you see that?
A. Yes.
Q. Do you recall any discussion about that statement in June of 1999 at this meeting?
A. I don't -- yeah, I don't recall?
Q. Do you recall whether or not there are any other mumps, measles and rubella vaccines being sold in the United States as of 1999?
A. I would say I wasn't aware of any others, but I'm not an expert in the area.
Q. Are you aware of any other MMR vaccines that are being sold in the US today?



A. I am not aware of any.
Q. Are you aware of any MMR vaccines being sold in the US between 1999 and today?
A. I'm not aware of any.
Q. Have you ever used the term "exclusive license" in any of your communications with anybody?
A. Yes.
Q. Can you -- when have you used that term?
A. Early -- one example is if we're -- for example, a scientist outside Merck has a method or reagent that we're interested in, we might consider engaging in an exclusive license so Merck would be the only organization to which they would license the product, or the method or reagent.
Q. Do you recall ever discussing with anybody that Merck's MMR product, that they had -- that Merck had an exclusive license for MMR II in the US?
A. I do not recall discussing that with anyone.
Q. In the next paragraph it says,



The objectives of the Marketing element of MMR II Competitive Defenses are to, in 1, "Pursue a proactive tactical plan including initiatives to delay and disrupt the launch of Priorix into the market."
Do you see that?
A. Yes.
Q. Do you recall any discussion at this meeting regarding that tactical plan to prevent Priorix from entering the market?
A. I do not.
Q. Have you ever discussed that with anybody at Merck outside of this presentation?
A. As part of the Protocol 006 study I would say yes, because my understanding of the study was a potential first step in trying to show whether MMR was superior to Priorix in protecting from a range of different viruses.
Q. I thought you just testified that Protocol 006 had nothing to do with determining whether or not it was protective against disease. I'm confused.
MR. SANGIAMO: Hold on a second.



What's your question?
BY MR. KELLER:
Q. So my question is, can you explain yourself, what you mean?
MR. SANGIAMO: What he means by what, I'm sorry?
BY MR. KELLER:
Q. The differences between protection in discussion of Protocol 006 and your discussion testimony earlier that Protocol 006, as you understand it, was not linked to protection from disease?
MR. SANGIAMO: Object to the form.
THE WITNESS: It was not -- the study Protocol 006 was not, to my understanding, designed to evaluate protection. But from a scientific standpoint, the concept of one vaccine giving higher seroconversion rate and geometric mean titer to a wider range of viruses would be suggestive or indicated in vitro at least one vaccine versus the other would be able to produce a more broadly neutralizing set

of antibodies. It's not a direct indicator or measure of protection but suggestive of a broader in vitro capacity of sera from the one -- generated by one vaccine to induce a different quality antibody.

BY MR. KELLER:

Q. Do you recall how many different wild type viruses you tested?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall specifically. I know at least two. I don't remember the exact number.

BY MR. KELLER:

Q. You say -- my question is, how many you actually tested, not how many you reported. Did you only test two wild type viruses or did you test more than two wild type viruses and only report two?

MR. SANGIAMO: Object to the form.

THE WITNESS: We reported results for all the viruses that we tested in Protocol 006.



BY MR. KELLER:

Q. Was there ever discussion about testing more than those two wild type viruses?

MR. SANGIAMO: Object to the form.

THE WITNESS: As best I can recall, there was both discussion and an initial plan, at least on my part, to look at additional viruses.

BY MR. KELLER:

Q. Why didn't you look at additional viruses? Who made the decision not to look at additional viruses?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can't say for certainty. My understanding was -- my recollection is it was a team decision.

BY MR. KELLER:

Q. What were the pros and cons in looking at more wild types versus the ones you decided upon?

MR. SANGIAMO: Object to the form.

THE WITNESS: The interest in



looking at additional wild type viruses would be to gather more information about comparisons between the MMR vaccine and Priorix. I wouldn't count this as a con, but the negative aspect, which is my understanding of why we didn't proceed, was that there wasn't sufficient vials of sera to test additional viruses. We had a limited volume of sera from the pediatric samples. For each virus that you test, there's more of a serum volume that you need to use.

BY MR. KELLER:

Q. Didn't you use sera from Protocol 006 to test, to develop the protocol for Protocol 007?

A. I don't recall if -- that we did.

Q. You could have, you just don't remember?

A. I don't remember. If we did, I would offer if we did use it, the Protocol 007 study required a much smaller volume of sera than Protocol 006. So I would expect cases



where there's insufficient volume to do more testing in Protocol 006 but would be sufficient volume to use in an assay that used less volume.

MR. KELLER: Mark this next exhibit.

- - -

(Exhibit Krah-27, Handwritten note, 448146, was marked for identification.)

- - -

BY MR. KELLER:

Q. Exhibit 27 which is a document that bears Bates number 448 -- 448146, 448146. Sir, can you tell me what this document is?

A. It's a page indicated purpose of a study involving a mumps neutralization assay.

Q. And there is a book and page number on this. What does that mean to you? Can you describe what that means?

A. Yes. The book would be a combination of numbered pages.

Q. Is this part of a -- would this go into a -- why would the pages be -- why

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would this be written into a book on a page? Explain that to me.

MR. SANGIAMO: Objection.

BY MR. KELLER:

Q. Strike that. Let me start over.

What was the purpose of having a book and page?

A. This was part of our general notebook policy of having a uniquely numbered book and page for documenting the experiments.

Q. Here it says, Project Number V205C. That's a reference to MMR II. Correct?

A. That is a project code that has been used previously for MMR II.

Q. Under "Project Page" it says, "MMR/V 80-99."

Do you see that?

A. Yes.

Q. That identifies the experiment. Correct?

A. That -- it's a unique a combination of letters and numbers and year that identify -- it's a shorthand that was used to identify the experiment.

Q. And MMR/V, I've noticed

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throughout all the experiments that I've reviewed from the record, they all have MMR/V and not MMR for Protocol 007. Can you explain to me why that is?

A. Yes. The basis for this, when I started the lab, we had and continued to work on different viruses, so we had different codes for different sets of viruses. For example, hepatitis A might be HAV and then a number. Many experiments we were doing included measles, mumps, rubella or varicella so we needed a catchall MMR/V. So it could include something that's measles, something that's mumps, something that's rubella, something that's varicella.

Q. So that's just a grouping within that sort of -- for that product line. Correct? Is that fair?

A. It's more -- I would characterize it as a grouping, a convenience grouping for in the lab, for example, if we were doing work with rotavirus, we might have a rota 1-1-99 or MMR/V-1-99. So it's a -- it's a convenient grouping, I don't know if you call it by product because some of the projects weren't

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products, but it's a way of grouping experiments by family of viruses or group of viruses.

Q. Fair enough. In the first number, did you number all of the experimental -- experiments you did in developing Protocol 007? Did you start from one and went through whatever the end number is?

MR. SANGIAMO: Object to the form.

THE WITNESS: The numbering system, as best I recall, for all experiments that are being done in the lab, they're not unique to one particular like Protocol 006 or any other protocol.

BY MR. KELLER:

Q. And then the last two numbers are just the year that it's running?

A. Yes.

Q. Here it says, "Investigator," what does that mean?

A. That means that that's the person who was involved in running the experiment, writing up the experiment.

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Q. So that's the person that actually wrote up this page, was you?

A. Yes.

Q. And that's your handwriting?

A. Yes.

Q. And then it says, "Subject." What is the purpose of the subject line?

A. The subject -- purpose of the subject line is to give a descriptive summary of the experiment that then can be put in an index and someone looking through the index could identify what the -- what that experiment referred -- relates to.

Q. Is it just sort of a general statement of what is followed in the details?

A. Yes, descriptive, the attempt is the goal is to be a descriptive general statement about what follows.

Q. Gotcha. And then under "Filed in Book Number/Title," what is the purpose of that field?

A. The notebooks, which were paper notebooks, we would put in three-ring binders typically. The three-ring binders were labeled by year and then letter, for example,

1999, if we had four binders, we would have an A, B, C, D.

Q. It just helped you find the actual experiment in the binder?

A. Yes. It tells you what binder it's in.

Q. This particular experiment, you ran this -- it says date February 6, 1999?

A. Yes.

Q. So, if you recall, the Protocol 007 -- in Protocol 007 I showed you earlier in Exhibit 22, that was done on February 2, 1999. So this was done a couple of days after that protocol was finalized?

MR. SANGIAMO: Exhibit 22.

BY MR. KELLER:

Q. Strike that. So the protocol that is in Exhibit 22 I recall you testified you don't recall seeing this one. This one was dated February 2, 1999. Do you see that at the bottom? It's on every page, so you can't miss it.

A. Okay.

Q. Do you see that?

A. Yes.



Q. So this experiment that you ran in Exhibit 27 was done a couple of days after that protocol was drafted. Correct?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: The dates say that the experiment was done a couple of days after that protocol was approved.

BY MR. KELLER:

Q. And so is it fair to say was this experiment, this experiment related to Protocol 007 in Exhibit 27?

A. I can't say with certainty. My expectation is that it would because it included anti-IgG. I don't recall other experiments that we were doing at the time.

Q. Do you recall preparing for a meeting with CBER to discuss the methodology for running the neutralization assay in this time frame?

A. I don't recall the time -- I recall preparing for a meeting with CBER, but I don't recall the time frame.

Q. Could you read your handwriting for the purpose of this particular lab



experiment?

A. Yes. It says purpose to "determine the capacity of antihuman IgG antibody to enhance mumps neutralizing activity of a human serum. A low-positive (by nonenhanced neutralization assay) serum is being tested in this pilot experiment."

Q. When you say "pilot experiment," what do you mean by pilot?

A. Pilot means it's an initial early probe experiment to look for a phenomenon to try to answer a general question without going into our yet defining multiple variables that could be considered. But just to see like, in this case, if there's a question of does the anti-human IgG antibody enhance mumps neutralization activity, yes or no. And if it's yes, then design additional experiments to do further development. If no, consider why it might not have worked if it was expected to work or just say it didn't work, end of story.

Q. Why were you looking at antihuman IgG at this time frame, do you recall?



A. At this time I don't -- I can't say with certainty why it was being looked at at that time.

Q. Were you considering using it as part of Protocol 007 at this time?

A. It was being considered after discussion with the FDA or CBER on including it in Protocol 007. Whether that at this time matches that, I don't recall.

Q. Why were you focusing here on -- in my review of your files, this is the first experiment that I could find where you were investigating antihuman IgG. Do you recall doing any experiments prior to this date?

A. I don't recall.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Do you recall -- when do you recall the first time you considered using an antihuman IgG in a plaque reduction neutralization assay?

A. For mumps?

Q. For any purposes.

A. Early to mid-1990s.

Q. And you used that in a different vaccine?
A. Yes.
Q. That was used in varicella. Correct?
A. Yes.
Q. And so in varicella you used anti-IgG with complement. Correct?
A. Yes.
Q. Why?
A. The two -- in evaluation of the anti-IgG and complement, it was found that both had enhancing effect to neutralization but the two together had an -- the two together had an increased enhancement versus either alone.
Q. Did you try that with the mumps virus -- strike that.
Did you try that with the PRN assay for mumps using both the complement and the anti-IgG step?
A. We evaluated complement. I don't recall that we evaluated complement and anti-IgG together.
Q. Why were you focused on low



positives in this experiment?
A. I don't recall.
Q. So it appears as a low positive by non-enhanced neutralization assay. Did you test that same sample in a standard neutralization assay and compare it to a -- the assay using the anti-IgG still?
A. I can't say for certain what's written here. The wording implies that it was -- there was a result from using the non-enhanced neutralization assay.
Q. When you say "neutralization assay," what do you mean by that?
A. What I mean by that --
MR. SANGIAMO: Object to the form. You can answer.
THE WITNESS: -- reduction, percent reduction in plaque relative to those serum control.
BY MR. KELLER:
Q. What's the serum control?
A. Typically a sample with virus and no antibody. Incubated in the same conditions as the antibody-containing samples.
Q. So a mock control?



A. It's like often referred to as a no serum control. One could call it a mock control, but I'd call it a no serum control typically.
Q. So you would take the medium antihuman IgG and virus and see what happens?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. I'm trying to understand what you mean.
A. So it would be -- it's a sequential -- kind of a small technical detail. It's a sequential addition, meaning the virus and antibody is incubated first and then anti-IgG is added later.
The incubation is a sequential incubation of virus plus antibody or in this case no anti -- serum or culture medium alone, no sera. And then anti-IgG is added. So the no serum control would be the virus, culture medium, which is the diluent, and the assay and then anti-IgG.
Q. Did you ever discuss with anybody what an appropriate control would be



for using the anti-IgG step?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall any specific discussion over what others thought might -- would be appropriate controls.
BY MR. KELLER:
Q. Do you recall ever meeting with the FDA and asking them what appropriate controls would be for plaque reduction neutralization assay?
A. I recall meeting with the FDA talking about what controls we had in the plaque reduction neutralization assay. They did not have any other recommendations that I can recall.
MR. KELLER: Let me mark this next exhibit as Exhibit 28.
- - -
(Exhibit Krah-28, 2/24/99 E-mail with attachments, 95046 - 95053, was marked for identification.)
- - -
MR. KELLER: For the record,

Exhibit 28 is a document that bears Bates stamp number 95046 through 53. The first page is an e-mail from Dr. Chirgwin, dated February 24, 1999, subject: MMR II; Summary of FDA conversation (February 19, 1999).

BY MR. KELLER:

Q. Sir, you are one of the recipients of this document. Want to take a minute and take a look at the document and the attachments.

I want to just start with the first document. We can --

MR. SANGIAMO: He's not done.

MR. KELLER: He can read the other ones when we get to it.

MR. SANGIAMO: No, no, no. No. It's an exhibit, he's reading the exhibit.

MR. KELLER: Sure.

BY MR. KELLER:

Q. Let me know when you're done.

A. Okay.

Q. Do you recall receiving this e-mail and the attachments?



A. Parts of it look familiar to me.

Q. Which parts look familiar?

A. The description or summary of the CBER method. I don't recall -- that's the main part. I don't recall specifics of the -- the important questions or the -- I remember discussion of the challenge virus of how many plaques they were using -- platform units they were using. But I don't recall the specific numbers they have listed here.

Q. If you look on the second page of the e-mail it says, "Attached is a memo summarizing a teleconference with the FDA last Friday during which the methods for the mumps neutralizing antibody assay were discussed.

"Also attached is a fax provided by CBER which briefly outlines their assay methods.

"Under PDUFA Roman numeral II, the FDA is charged with producing meeting minutes."

Do you see that?

A. Yes.

Q. "Attached below is a fax of the meeting minutes provided by CBER."



Do you see that?

A. Yes.

Q. Are you familiar with formal FDA minutes and non-formal FDA minutes?

A. No.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Did you have an understanding that -- did you have an understanding of this rule that required the FDA to generate meeting -- formal meetings?

MR. SANGIAMO: Object to the form.

MR. KELLER: Strike that.

BY MR. KELLER:

Q. Did you have an understanding of the rules that the FDA had to follow for producing formal minutes of meetings?

A. No.

Q. Let me turn your attention to the actual meeting minutes of the FDA of February 19th. It's on 59 -- 95048. It identifies you, sir, as being one of the participants. You recall participating in



this meeting. Correct?

A. I recall a discussion. I don't -- the CBER method description looks familiar to me. So I assume I was there, but I can't say that I remember with 100 percent certainty that I was there.

Q. Do you have any reason to believe that you weren't there since the FDA identified you there at this meeting?

A. No.

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. If you look at the first sentence it says, "Merck wanted to discuss their plaque reduction neutralization assay." And in the second bullet point it says, They want to compare their assay procedure with CBER's assay.

Do you see that?

A. Yes.

Q. Do you recall comparing your assay with CBER's plaque reduction neutralization assay?

A. I recall discussion of the

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procedural differences between our assays. I don't recall at that time physically comparing the two assays.
Q. Under the "CBER method" it says in the second bullet, "Uses no complement or immunoglobin."
Do you see that?
A. Yes.
Q. And immunoglobin would include the anti-IgG step. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: Anti-IgG would be an immunoglobulin.
BY MR. KELLER:
Q. Do you recall discussing the use of the anti-IgG step at this particular meeting?
A. That, I don't recall.
Q. Do you recall CBER saying that they didn't think that maneuver was necessary?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not recall them saying that it was not necessary.

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The assay that they were running did not use it. But they did not say it wasn't necessary for our application.
BY MR. KELLER:
Q. You don't recall them saying that it should not be necessary for running the assay that you guys were going to run for Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall that they said that.
BY MR. KELLER:
Q. Okay. Let's go on. It goes on -- there are two important questions, do you see that, in CBER's meeting minutes?
A. Okay. Yes.
Q. And the first one is, "What is the wild type strain of virus used?"
Do you see that?
A. Yes.
Q. In this case it is the Tennessee strain. Do you see that?
A. Yes.
Q. We've shown you -- I showed you

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the protocol discussion that was used at the investigator's meeting where they talked about using the Tennessee virus. Do you recall whether or not Merck first contemplated using the Tennessee strain?
MR. SANGIAMO: You didn't show that in protocol. You showed him a slide that mentioned the Tennessee virus.
BY MR. KELLER:
Q. Go ahead.
MR. SANGIAMO: So what was your question?
BY MR. KELLER:
Q. You can answer.
MR. SANGIAMO: The question is do you recall whether or not Merck first contemplated using the Tennessee strain. So I object -- if that's the question, I object to the form.
MR. KELLER: Fine.
BY MR. KELLER:
Q. You can answer.
A. I don't recall.
Q. The second question says, "What

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is the appropriate control?"
Do you see that?
A. Yes.
Q. Do you recall what was discussed about what appropriate control would be used for a plaque reduction neutralization assay?
MR. SANGIAMO: At this meeting?
MR. KELLER: At this meeting.
THE WITNESS: At this meeting I recall there -- well, that they have written here the immunoglobulin number 176 as a positive control. I don't see a comment here about media -- response to the media or negative human serum. In our studies we use a media control. I don't recall that CBER suggested an alternative of an additional negative control.
BY MR. KELLER:
Q. So you don't know this reference here, where it says media or negative serum, human serum? Do you see that?
A. I see that, yes.
Q. You don't recall what was discussed about that?

A. No.
Q. And you never attempted to use a negative human serum control. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: We did not have access to a negative serum control, as best I understand.
BY MR. KELLER:
Q. When you say that a positive serum control, what is that?
A. That means a serum that is positive for which a titer could be measured so that one can monitor titer across assays.
Q. Did you use that as a control?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. As part of the AIGENT?
A. We did not use immunoglobulin number 176 in the AIGENT assay but we had additional positive controls that CBER agreed to.
Q. CBER required?
MR. SANGIAMO: Object to the



form.
THE WITNESS: They were part of the assay and CBER required limits on those. As far as I understand, they were part of the assay. CBER required limits on them.
BY MR. KELLER:
Q. Do you understand what is meant by appropriate control?
MR. SANGIAMO: Objection. Calls for speculation.
THE WITNESS: It's a -- it would be a fit-for-purpose application, meaning that controls would be -- what controls apply would be dependent on the assay and a precedent.
BY MR. KELLER:
Q. In this fit-for-purpose application, did anybody evaluate the AIGENT for its fit for purpose in the controls used?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Or was that just you?
A. The procedure that we were



using, proposed using, including the controls, was provided to Merck and CBER for review. I'm not aware that there was any -- so it was provided to others for review and comment, and I don't recall any additional controls that they requested.
Q. Did anybody other than yourself determine what controls would be proposed to CBER?
A. I'm not aware of others. I recall proposing the controls that we planned for the assay. I can't exclude that someone else might have proposed another that was not included.
Q. I see. Fit for purpose, do you know where that comes from? Is that an industry standard?
MR. SANGIAMO: Objection. You can answer.
THE WITNESS: So I can't say at the time whether it was a phrase that was used often, but in the current group that I'm in, when an assay is being developed, a characteristic -- or an objective to the assay is fit for



purpose meaning that the assay meets the expectations as far as reproducibility or other validity criteria that are needed for the application.
BY MR. KELLER:
Q. And so -- but you didn't know what the objective of Protocol 007 was, you only knew one component of that objective which you say was a comparison of the vary -- the three different doses. Correct?
A. Yes.
Q. So the other purposes you didn't know. Correct? The other objectives you didn't know?
A. Yes, that's correct.
Q. So this surrogate of efficacy, that objective, you weren't aware of that. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: At least I don't recall that being or wasn't -- don't recall being aware of that objective.
BY MR. KELLER:

Q. So if you weren't aware of it, you cannot make a determination of the controls were fit for purpose of your AIGENT you developed if you didn't know all the objectives, could you?

A. I wouldn't have all the information, but the information was provided to others who would have that information, and they did not make a contrary recommendation.

Q. Who was it provided that would make those -- that determination?

A. CBER amongst the group.

Q. What about internally at Merck?

A. Internally at Merck, I don't know who the -- there was a clinical assay sub-team I recall that was a group to which the assay development was -- updates were provided to them on the assay development.

Q. Is that a management team that reviews assays for fit for purposes?

A. It's a group that develops, the best of my recollection, clinical assays. I don't -- I can't speak to what their overall responsibilities are, but at that group, clinical assays in development would be



discussed and discussions would be held, include discussions over whether the assay was meeting the requirements.

Q. Were you a member of that group?

A. I remember attending the meetings. Whether I was actually a member of it, I can't say.

MR. SANGIAMO: Jeff, I know it's unintentional, but I think you're starting in with some of your questions before letting Dr. Krah finish his answer. And you commented at the beginning about sometimes there would be a pause before somebody completes. I just ask that you work harder in trying to respect potential -- Dr. Krah's need to finish his answer.

MR. KELLER: Sure.

BY MR. KELLER:

Q. Who do you recall was a member of the clinical assay sub-teams during the time frame of the development of Protocol 007 and the AIGENT?

A. I can't say with certainty. I don't recall.



Q. Do you recall anybody?

A. I couldn't pull a name out of the air.

Q. Let me turn your attention to the memo dated February 22, 1999, that was attached to Dr. Chirgwin's e-mail to you, Dr. Krah. Do you recall receiving this memo from Dr. Chirgwin to Dr. Ukwu summarizing the meeting with the FDA?

A. There are lines in it where the topic looks familiar, but I can't say the document overall is familiar to me.

Q. Was it Merck's practice to create internal memos of meetings with CBER?

MR. SANGIAMO: Answer if you know obviously.

THE WITNESS: I don't --

BY MR. KELLER:

Q. Have you -- sorry, I didn't mean to interrupt you.

A. There are meetings where there are -- there have been, not necessarily mumps specific, but there have been internal minutes, but I don't know what the Merck practice was.



Q. Well, did you review minutes as part of your job duties of meetings that you had with CBER?

A. I can't say with certainty that I did.

Q. So you don't recall whether or not you ever saw those meeting minutes. Is that a fair statement?

A. I may have seen them, but I don't recall. They're not looking familiar to me right now.

Q. This executive summary that was prepared by Dr. Chirgwin and circulated to Dr. Ukwu and circulated again by Dr. Chirgwin to this laundry list of individuals at Merck, it says under the "Executive Summary," number 4 "CBER does not use either complement or IgG to enhance sensitivity and feels that these maneuvers should not be necessary."

Do you see that?

A. Yes.

Q. You don't recall that being discussed at that meeting with CBER, or do you?

A. I recall the anti-IgG and

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complementing discussed with CBER. Whether it was at this meeting or not, I can't say.
Q. Was it something that you proposed to CBER to use in this AIGENT?
MR. SANGIAMO: Object to the form.
THE WITNESS: As best I can recall, the complement, again, whether it's in the context of this meeting or not, but I -- as best I recall, we had evaluated complement and then provided those data. Or we evaluated complement and saw that it was not usable, meaning that neutralized virus on its own in the absence of serum.
BY MR. KELLER:
Q. Just so I'm clear --
MR. SANGIAMO: Were you done, Dr. Krah, with your answer?
THE WITNESS: The other half to it would be anti-IgG, I remember it being discussed at a meeting with CBER. Whether we proposed it or CBER proposed it, I don't know.
BY MR. KELLER:

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Q. Fair enough.
MR. SANGIAMO: We're an hour and nine minutes out.
MR. KELLER: Take a break.
VIDEOGRAPHER: The time is now 3:17. This concludes disc four.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is 3:36. This begins disc five.
- - -
(Exhibit Krah-29, Series of e-mails, 51640 - 51642, was marked for identification.)
- - -
MR. KELLER: For the record, I'd like to mark as Exhibit 29 a document bearing Bates stamp numbers 51640 to 642, which is a series of e-mails.
BY MR. KELLER:
Q. And, sir, I'd like to direct your attention to the January 17, 2003, e-mail to Leonard Rubinstein on the first page regarding -- do you need any help?

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A. Okay.
Q. Could you read what you wrote to Mr. Rubinstein, please?
A. I'm sorry, for the Friday, January 17th?
Q. Friday, January 17th at 3:25 p.m.
A. It says, "Len, Yes - The MMR II Protocol 006 study used a straightforward, non-enhanced neutralization, using several different indicator viruses. The MMR II study...," which it doesn't say here but implies 007, "...used an anti-IgG enhanced neutralization and the low-passage Jeryl Lynn indicator virus. We would have used the same assay used in 006 and 007...," meaning Protocol 006 and Protocol 007, "...except that we could not achieve the 90 percent seroconversion sensitivity with any of the wild-type mumps strains without enhancing the assay sensitivity. We could measure greater than 90 percent seroconversion using the vaccine strain as the indicator, but CBER required us to use a 'wild-type' indicator virus for 007."
Q. Do you recall writing that

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e-mail?
A. I can't say I recall. It's my writing. I can't say it's my writing, but it sounds like my wording and it's from me so I assume that it -- I don't recall writing it. It's from me in language that I would use.
Q. Do you recall that was the reason why Protocol 006, protocol used for Protocol 006 was not used in Protocol 007 because you could not achieve the 90 percent seroconversion sensitivity?
MR. SANGIAMO: Object to the form. Also, Dr. Krah, if you'd like to review the document in its entirety, please read this.
BY MR. KELLER:
Q. I'm only asking about this statement.
MR. SANGIAMO: Well, it's in context.
THE WITNESS: My recollection that the reason for not using one of the viruses, one of the wild type viruses in the Protocol 006 -- the format for Protocol 006 was that we

could not achieve -- and, again, 90 percent here seroconversion with that assay format in any of those indicator viruses.

BY MR. KELLER:

Q. That's why you used Protocol 007 in order to reach the targeted greater than 95 percent?

MR. SANGIAMO: Object to the form.

THE WITNESS: So the AIGENT assay was developed as part of Protocol 007 as an assay that was capable of measuring a 95 percent seroconversion.

BY MR. KELLER:

Q. You couldn't do that with Protocol 006 with a standard PRN assay. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: Independent of this paragraph, I don't recall what the seroconversion rates were with the different indicator viruses. The way this is worded suggests that the



indicator viruses in the Protocol 006, the format of the neutralization assay used for Protocol 006 was not achieving that 90 percent seroconversion rate.

BY MR. KELLER:

Q. So a decision was made to change that assay with what ultimately became Protocol 007 and the AIGENT. Correct?

A. So I would describe it as the AIGENT assay. I wouldn't necessarily link them and say it's Protocol 007 and the AIGENT assay. But it's the AIGENT assay.

MR. KELLER: Let me mark this next exhibit as Exhibit 30.

- - -

(Exhibit Krah-30, 3/30/00 E-mail, 336323 - 336325, was marked for identification.)

- - -

BY MR. KELLER:

Q. For the record, Exhibit 30 is a document bear Bates stamp number 336323 through 325, and it's an e-mail from you, Dr. Krah, dated March 30, 2000, to Emilio Emini, Alan Shaw, Mary Yagodich, update on



mumps Nt studies. Do you recall drafting this e-mail?

A. Again, it's -- I don't recall the specific e-mail, but it's from me in language that I -- looks familiar to me.

Q. So is the purpose of this e-mail to update Emini and Shaw and Ms. Yagodich about your developmental activities with regard to the Protocol 007, praecipe that was going to be used for Protocol 007?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can't tell at least automatically from this that it was specifically for the purpose of Protocol 007.

BY MR. KELLER:

Q. Do you see on the last -- on page 2 of your e-mail --

A. Yes.

Q. -- it says, We also plan to readdress the use of anti-human IgG to enhance Nt, as a back-up if we fall short of our 90 plus percent target.

Do you see that?



A. Yes.

Q. Does that lead you to believe that this was, in fact, related to Protocol 007?

MR. SANGIAMO: Dr. Krah, make sure you've aptly read the e-mail before you respond to questions.

BY MR. KELLER:

Q. Do you see it specifically calls out the 007 study?

A. Some of the variables that we were looking at are ones that are familiar to me from discussions with CBER as part of the discussions about Protocol 007. But I don't see here that it specifically identifies it as part of the Protocol 007 assay development.

Q. The part you're referring to is the use of immunostaining?

A. I think the -- well, immunostaining was part of it. The Spearman-Karber method. The part that I was regarding as the Barnes strain on page 2, the reference to the Barnes strain from Dr. Forghani. As best I recall, that was included as part of some of the discussion with CBER, suggestion to consider

that strain.
Q. For Protocol 007. Correct?
A. Yes.
Q. And the low passage Jeryl Lynn, JL135, that was what was used in Protocol 007, wasn't it?
A. Yes.
Q. So the antihuman IgG was also used in Protocol 007. Correct?
A. Yes.
Q. So I'm confused by your answer why you don't think this was a discussion about updating about your efforts to develop an assay for Protocol 007. Many of the things discussed were discussed about updating Emini and Shaw and Yagodich about your efforts to come up with a methodology to find an answer that would get you to 95 percent seroconversion. Correct?
A. Yes.
MR. SANGIAMO: Object to the form. Misstates his testimony.
BY MR. KELLER:
Q. Here when you say we also plan to readdress the use antihuman IgG to enhance



Nt. Nt, that's neutralizing. Right?
A. Neutralization, yes.
Q. Neutralization. As a backup plan if we fall short of the 90 percent plus target.
Why was it a backup plan?
A. I can't say with certainty, but my best recollection is that we were -- from -- that we would see if we could achieve a 90 percent seroconversion without adding the IgG and then if it wasn't achievable, evaluate addition of that as a CBER suggestion to increase the neutralization sensitivity.
Q. And so -- I'm confused. I apologize if I'm confused. But let me ask you to rectify my confusion. Strike that.
Why was using anti-IgG something that was a backup plan and not used up front?
MR. SANGIAMO: Object to the form.
THE WITNESS: My best recollection is that we were trying to -- our minimizing steps in the assay, minimizing reagents that are needed more for assay simplicity and also are



being more consistent with what CBER had experienced within their testing.
BY MR. KELLER:
Q. And so you saw a memo from CBER saying that they didn't think that step was necessary. So was that one of the reasons why you considered it as only a backup plan if you couldn't get any other methods to get you to reach the 95 percent seroconversion target?
A. I can't say with certainty what the thought process was at the time, but looking back on it, if they thought it wasn't necessary, I would -- if I were doing this today, would try it without and then if it wasn't successful, then go with the anti-IgG.
Q. Do you recall any discussions at Merck about concerns with the use of this IgG maneuver?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not that I recall.
BY MR. KELLER:
Q. Nobody voiced any criticism about using the IgG maneuver --
MR. SANGIAMO: Object to the



form.
BY MR. KELLER:
Q. -- in this assay in Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: No. And, in fact, the assay was based on a publication that CBER had published.
BY MR. KELLER:
Q. Back in 19 -- early 1970s. Correct?
A. Yes.
Q. That was before even ELISA assays had become standard practice in the industry. Correct?
A. That, I can't --
Q. You don't know?
A. I don't know.
Q. Are you aware of any other -- have you ever used the rabbit anti-IgG step after Protocol 007?
A. Me personally?
Q. Yes.
A. There are some discussions I've

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had with others -- I don't recall using it personally, but discussions with other colleagues that I've had of potentially using it.

Q. What colleagues did you discuss it with?

A. I recall some colleagues in MMD who were trying to identify means, as best I can recall, means to increase the neutralization capacity of a serum in a tissue -- I think what was called a tissue culture safety test. And one option that I proposed was adding anti-IgG.

Q. Was that a -- was that test at all linked to protection?

A. No.

Q. Do you recall ever -- at any of these CAS meetings you had, nobody voiced any concern about nonspecific neutralization as a result of using rabbit anti-IgG step?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall any objections.

BY MR. KELLER:

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Q. Did Dr. Sadoff ever object?

A. I don't recall.

Q. Do you ever recall discussing the use of the anti-IgG maneuver with Dr. Sadoff?

MR. SANGIAMO: Object to the form.

THE WITNESS: That, I don't recall.

BY MR. KELLER:

Q. What about Dr. Musey?

A. I recall discussing the assay with him, but as far as discussing anti-IgG, I don't recall.

Q. Do you recall discussing the step with Dr. Thaler?

A. That, I don't recall.

MR. KELLER: Mark this next exhibit as Exhibit 31.

- - -

(Exhibit Krah-31, Subcommittee meeting agenda, 2142149, was marked for identification.)

- - -

BY MR. KELLER:

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Q. Do you recall presenting the use of the anti-IgG at a CAS subcommittee meeting or a Clinical Assay Subcommittee Meeting?

A. I recall presenting the data. I don't recall the specific meeting.

MR. KELLER: For the record, Exhibit 31 is an agenda, looks like there's a typo on the title of this, it says, "CRITICAL ASSAY SUBCOMMITTEE MEETING."

BY MR. KELLER:

Q. You understand it to be clinical, correct, October 24, 2000?

MR. SANGIAMO: Objection.

THE WITNESS: I can't -- I don't know.

BY MR. KELLER:

Q. Under "TEAM PRESENTATION," it says -- identifies you, Dr. Krah to present on the enhanced mumps neutralization assay. Do you see that?

A. Yes.

Q. That's the AIGENT. Correct?

A. That's my enhanced mumps -- mumps neutralization assay is what I refer to

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as the AIGENT assay, and I would expect that that's what they're referring to here.

Q. Here it says, "Update on performance of the assay."

Do you see that?

A. Yes.

Q. Do you recall updating the CAS on the performance of the AIGENT?

A. I remember presentations on the assay. I don't remember this particular meeting what was covered.

Q. It says at the invitees, Dr. Thaler was there. Do you see that?

A. Yes.

Q. Mary Yagodich?

A. Yes.

Q. Dr. Chirgwin?

A. Yes.

Q. What was William Long's role in Protocol 007? He was invited as well. Correct?

A. Yes. His name is on here. He wasn't in the same department as I was, and I don't recall what his specific -- what his role was.

Q. Did he also run clinical study -- strike that.

Did he also run any experiments with the PRN assay --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- in developing Protocol 007, do you know?

MR. SANGIAMO: Object to the form.

THE WITNESS: I am aware of, as best I can recall, a CPE-based assay that he was working on, not a plaque reduction, to my knowledge.

- - -

(Exhibit Krah-32, Anti-IgG Enhanced Mumps Neutralizing Assay-Update: October 24, 2000, 26912 - 26918, was marked for identification.)

- - -

MR. KELLER: For the record, Exhibit 32 is a document that bears Bates stamp numbers 26912 through 918, entitled: Anti-IgG Enhanced Mumps



Neutralizing Assay-Update: October 24.

BY MR. KELLER:

Q. Do you see that?

A. I'm sorry, repeat the last part of that?

Q. I'm just reading the title. Do you see the title?

A. Anti-IgG enhanced, okay, yes.

Q. So is this the presentation that you gave to the CAS subcommittee on October 24?

A. It's the same date, but I don't have an immediate recollection of the presentation, but that's the date, the same date as the clinical assay sub-committee meeting.

Q. Do you have any reason to believe that you didn't present it on that date?

A. No. If it's dated, I would expect -- my expectation would be if it's dated that date, that that's the date it was provided.

Q. Did you draft this document, Exhibit 32?

A. The wording looks like my



wording. I can't exclude that someone didn't contribute to it, but at least the majority of the wording looks like it's my wording.

Q. In the experiments that supported this particular document -- did you provide this copy to the CAS subcommittee or was it just a presentation -- strike that.

Did you provide a copy of Exhibit 32 to the CAS subcommittee?

A. I don't recall.

Q. And the individuals on Exhibit 31, D. Arena, Dr. Chirgwin, William Long, S. Olsen, N. Morsy, J. Staub, Dr. Thaler and Ms. Yagodich, were those members of the CAS?

A. I can't say for certain.

Q. And if you look on the first page of 269123 of Exhibit 32, can you read the objective that you wrote?

MR. SANGIAMO: Object to the form.

THE WITNESS: The objective, as listed, is "Identify a mumps neutralization assay format using a 'wild-type' mumps strain that permits



measurement of a 95 percent seroconversion rate in MMR II vaccinees."

BY MR. KELLER:

Q. Is that the objective you used to develop the AIGENT?

MR. SANGIAMO: Object to the form.

THE WITNESS: The AIGENT assay -- development of the AIGENT assay was to determine if we could develop an assay that was capable of measuring 95 percent seroconversion. So it's consistent with that.

BY MR. KELLER:

Q. In fact, you did develop the AIGENT that resulted in -- strike that.

Did the -- strike that.

If you look on the next page, 29 -- I'm sorry, 26913, it says, "Data presented at the August 18, 2000 CAS meeting."

Do you see that?

A. Yes.

Q. Do you recall presenting this data to the Clinical Assay Subcommittee?

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A. I do not.
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Any reason you didn't if that's what it says?
MR. SANGIAMO: Object to the form.
THE WITNESS: If that's what it says, I have no contrary evidence that I didn't.
BY MR. KELLER:
Q. Just so I understand, it says, Evaluation of seroconversion rates achievable in the Anti-IgG Enhanced Nt - results from subset of Protocol 006 and another set of 60 paired PRN assay.
Do you see that?
A. Yes.
Q. So did you use the samples from Protocol 006 to develop Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: The wording of this suggests that those were a subset

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of sera for Protocol 006 and additional sera were included in the evaluation that's listed here.
BY MR. KELLER:
Q. So explain to me serum set number one. It says, "Subset of sera from Protocol 006 (includes set of 12 sera biased toward non-responders to Jeryl Lynn by 'standard' Nt)."
Do you see that?
A. Yes.
Q. Standard Nt, is that the PRN assay that was run in Protocol 006? Were you following that protocol?
A. That --
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say with certainty. My expectation is that they would have had to have been tested at some point. And Protocol 006 wouldn't have been the opportunity. I can't say with certainty that that's where they were tested.
BY MR. KELLER:

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Q. So you took -- you have conversion rates for this set. So you're retesting the same kids in three different experiments to see how those kids respond. Correct? Is that fair to say?
A. No. I'm sorry, you're referring to the seroconversion rate?
Q. You got three -- under "Seroconversion rates for this set," it says Jeryl Lynn "standard" Nt: 31 out of 39, 79.5 percent. JL135 at 1 to 4 anti-IgG 33 out of 36 equals 91.7 percent. Jeryl at 1 to 8 anti-IgG neutralizing 32 to 34, 94 percent.
Do you see that?
A. Yes.
Q. Were they -- these the same kids or different kids?
A. I'm sorry, different kids from what?
Q. I'm asking you, are these retesting the same kids or are you just --
A. I'm sorry. Okay. My best recollection is that they're the same kids tested in three different -- let's start -- I can't say with certainty from this. I have an

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expectation for it, but I can't say the way this is worded, I can't say with 100 percent certainty that they're the same kids tested under three different conditions.
Q. But that's what it looks like from the face of it. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's -- my expectation looking back at it would be that they're the same sera tests at three different formats, but I can't say with 100 percent certainty today.
BY MR. KELLER:
Q. And so if -- okay. Fair enough.
Let me direct your attention to the next page, 26915. It says, conclusion from previous testing of 1 to 4 anti-IgG -- I'm sorry, two pages over. 26915. I apologize. Here you write, Measurement of greater than 95 percent seroconversion in vaccinees is achievable.
Do you see that?
A. Yes.
Q. That's what your experiments

showed, correct, with the use of anti-IgG maneuver?
MR. SANGIAMO: Object to the form.
THE WITNESS: For serum set one, no. Serum set two on the page just before has a 96 percent seroconversion rate including anti-IgG. So there was a condition for one of the two -- one of the serum panels that one is achieving a 95 percent seroconversion.
BY MR. KELLER:
Q. So the standard panel only got you 79.5 percent. But with using different dilutions of anti-IgG, you can get that up to 96 percent. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: At least in serum set one we had approximately an 80 percent seroconversion rate without the anti-IgG. What I can't tell from the wording here is if that is -- refers to JL135 for the anti-IgG part. So what I'm not able to say with



certainty is the contribution of the wild -- of the low passage Jeryl Lynn and the anti-IgG. By using the combination of low passage Jeryl Lynn and anti-IgG, we were able to get 96 percent seroconversion.
BY MR. KELLER:
Q. Did you ever do any experiments running the standard PRN assay with Jeryl Lynn 135 without the anti-IgG maneuver?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall with certainty. I have an expectation of it, but I don't recall with certainty.
BY MR. KELLER:
Q. 26915, second bullet point you say, "Pre-positive rate is higher than desirable." What did you mean by that when you wrote that?
A. My best recollection based on the description for serum set two was that the value was 22 percent, and that that was higher than what was deemed desirable. How that



desirable number was set, I don't recall.
Q. I see. The third bullet point you say, Continue evaluation of results using optimized anti-IgG (target less than equal 10 percent pre-positive rate and greater than/ equal to 95 percent seroconversion).
Do you see that?
A. Yes.
Q. Where did you come up with that 10 percent pre-positive rate?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall where that came from.
BY MR. KELLER:
Q. So at this point you were still developing the assay to try to reach that target. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: My recollection is that we were still developing the assay to see if we could achieve 95 percent seroconversion.
BY MR. KELLER:



Q. Was one of the collateral problems of using the anti-IgG step is a higher pre-positive rate than you would expect in the real world?
A. What we did observe is an increase -- page 26916 is an example of that, using different levels of anti-IgG can give varying levels of pre-positivity rate. As far as what the pre-positivity rate in the real world is, I can't speak to what that is.
Q. I showed you the protocol from February of 1999 that expected -- said it expected a 5 percent pre-positive rate. Do you recall any discussion about the difference between the original 5 percent expectation and your 10 percent expectation?
MR. SANGIAMO: Object to the preamble. You can answer the question.
THE WITNESS: Not that I recall.
BY MR. KELLER:
Q. Did that higher than desirable pre-positive rate continue through when you ran the serums in Protocol 007?
MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall what the pre-positive rate was for the Protocol 007 set.
BY MR. KELLER:
Q. Were you focused on pre-positives when you were running the serums for Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: We were not focused on the pre-positive.
BY MR. KELLER:
Q. You didn't care whether or not it was pre-positive or not, is that your testimony?
MR. SANGIAMO: Object to the form.
THE WITNESS: My testimony is that we -- if we did have a pre-positive, that we were interested to make sure that it was an accurate representation of a plaque number.
BY MR. KELLER:
Q. How did you do that?
A. One way in which it was checked



would be to look at the plaque counts that were recorded for, in some cases, pre-positives but in other cases, specific situations, for example, single pre- -- not pre-positive, but single positive dilution and a number of other I'll say unexpected neutralization results and have either the original counter or other counter look at the plaques and see if plaques were being miscounted.
Q. Did you do that for the post-vaccination positives?
A. Yes.
Q. For both?
A. For the single positive dilution, yes.
Q. So you didn't see from your development of Protocol 007 that if you retested -- I'm sorry.
Did you ever retest pre-positives out of a single dilution?
MR. SANGIAMO: Object to the form.
THE WITNESS: As best I can recall, if a pre-positive -- positive single dilution was confirmed to be



positive, it would be -- the post -- it depends on the post-vaccination serum result, meaning that if a pre-vaccination serum was positive single dilution, and then post-vaccination serum had an invalid result, that pre-vaccination serum will be tested not because it's a pre-vaccination positive.
BY MR. KELLER:
Q. So you didn't retest valid assays in Protocol 007 that had a valid -- that had a pre-positive at one dilution to see whether or not you could -- it would switch to a pre-negative?
MR. SANGIAMO: Object to the form.
THE WITNESS: There were cases I recall where we did have some samples that included examples such as a positive single -- pre-vaccination serum that was positive single dilution that were retested with the intent of trying to verify whether the result was confirmed.



BY MR. KELLER:
Q. So when you were running the protocol samples, you could tell what is a pre-vaccination sample and a post-vaccination sample. Right?
A. Yes.
Q. Let me move on to the document 26917. Here it says, "Proposal for Testing a Subset of Samples from the End-Expiry Study."
Do you see that?
A. Yes.
Q. At a certain point there was a decision made that a subset analysis would be run. Correct?
A. Using the AIGENT assay, yes.
Q. Do you recall what precipitated that decision?
A. I do not require -- I do not recall the specific event that triggered it.
Q. Do you recall general discussion with Emilio Emini where they discussed an emergency that was going on?
A. Yes.
Q. What was that emergency?
A. I don't recall him telling me.

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Q. He didn't tell you that there was a 483 that was issued out of MMD based on an FDA inspection with stability problems in the MMR product?
A. I recall that a warning letter was issued. What that contained or involved, I don't have a recollection.
Q. Do you recall a 483 that came before the warning letter?
A. I do not.
Q. Back to 26917, the second bullet point says, "Validation runs concurrent with clinical serum testing."
Do you see that?
A. Yes.
Q. Henrietta Ukwu had sent an e-mail earlier saying that do not run -- do not run the validation concurrent with testing the serum but finish the validation and then test the serum. Do you recall that e-mail?
MR. SANGIAMO: Object to the characterization of the e-mail.
THE WITNESS: I recall the e-mail that you showed me previously suggesting that the validation be done

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before the clinical testing starts.
BY MR. KELLER:
Q. Here it says validation runs concurrent with clinical serum testing. You understand that what they're saying is validate the AIGENT assay at the same time that you're running the clinical samples?
A. Yes. And that was done in collaboration with CBER. They were informed that that was being done and approved that approach.
Q. When did they approve that approach? Were you at a meeting when that was approved?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall if I was at a -- with certainty that I was at that meeting.
BY MR. KELLER:
Q. Were you at that meeting or not?
A. I don't recall.
Q. So you remember, you recall who told you -- who do you recall telling you that CBER approved running the validation

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experiments for the AIGENT SOP at the same time or concurrently with running the clinical serum in the assay for Protocol 007?
A. I don't recall who --
Q. How do you know that?
MR. SANGIAMO: Whoa, whoa. Jeff, you have to let him finish his answer.
MR. KELLER: Sure.
MR. SANGIAMO: By the way, I object because it's asked and answered.
THE WITNESS: My recollection of how I know that is that the -- someone in authority at Merck indicated that we would do the validation study in parallel -- not necessarily in parallel, but before the clinical testing -- sorry. We would start Protocol 007 testing for the interim, the subset analysis before completing the validation studies.
BY MR. KELLER:
Q. Did they tell you why?
A. I don't recall them telling me why.

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Q. That's what you did, isn't it, you ran the clinical samples while you were validating the SOP? Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: We did, but I recall from the CBER discussion when we indicated we would be running the subset analysis, or the validation and parallel to subset analysis, that the assay would not change. So the validation would be characterizing the assay and the results of the validation study would be applied before the results of the subset analysis were reported.
BY MR. KELLER:
Q. What communication -- when was this? Was this before you started running the assays or after?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say I recall with certainty when that was communicated.

BY MR. KELLER:
Q. Is that -- was that a meeting that you were at that CBER approved of you running the clinical samples for Protocol 007 before you validated the assay?
A. I can't say with certainty that I was at the meeting, but my recollection is that there was an agreement that we were not changing the assay so running the -- doing the validation concurrently with testing of Protocol 007 was acceptable to them.
Q. But you weren't at that meeting, that's just somebody at Merck told you that?
A. I may have been at the meeting. I don't recall with certainty if I was or wasn't.
Q. Was that written down anywhere?
MR. SANGIAMO: Objection. Calls for speculation.
THE WITNESS: I don't recall if it was or wasn't.
BY MR. KELLER:
Q. I see. Have you ever run a clinical study before Protocol 007?
MR. SANGIAMO: Object to the



form.
THE WITNESS: I have -- I and my group have run assays in support of clinical -- at least one other clinical study.
BY MR. KELLER:
Q. That clinical study, is that Protocol 006?
A. Yes.
Q. Did you validate that assay before you ran the serum in Protocol 006?
A. There were some validation experiments, as best I can recall, that were done before starting that testing. I don't recall if the validation was completed for all the viruses before the Protocol 006 testing started.
Q. If you could go back to your journal for 2000. If I could direct your attention to October 27, at 490473 or 393 of your journal.
A. 490473.
Q. There's a reference here to a meeting with Joe Antonello at 9:00 a.m. to review validation protocol for mumps AIGENT.



Do you see that?
A. Yes.
Q. Does that refresh your memory that you were working with Joe Antonello from biologics research?
A. Biometrics.
Q. Biometrics research?
A. I recall he was one of the people from that group who we were talking to in developing the validation plan or protocol.
Q. So did you -- you drafted the validation protocol. Correct?
MR. SANGIAMO: Objection. Asked and answered. Misstates testimony.
BY MR. KELLER:
Q. You don't recall?
A. I don't -- I don't recall who drafted it.
Q. And here, if you look at this discussion, do you recall discussing -- you can feel free to read the reference on October 27 to your communications with Joe Antonello. Do you recall discussing the parameters of what that protocol would look like?



A. So at least the points I have listed here I wouldn't say it's all inclusive of all the points that were discussed, but these are some examples of aspects of the validation that he was suggesting.
Q. If you look at one, two, three, four down, it talks about specificity. Do you see that?
A. Yes.
Q. Can you read that line from your journal?
A. Yeah. Specificity can be addressed from pre/post boost and absorption experiment.
Q. So did you understand that what that pre/post boost was, do you recall any discussion about what that experiment would be?
MR. SANGIAMO: Object to the form. You're asking if he recalls any discussion of it?
MR. KELLER: Yes.
THE WITNESS: I don't.
MR. SANGIAMO: That's different from the first question you asked.

That's why I asked for clarification.
THE WITNESS: I don't recall there being discussion over what he meant by that.
BY MR. KELLER:
Q. So you don't know what a pre/post boost experiment would be for specificity?
A. I am familiar not from mumps or -- from other literature that I'm familiar with, of studies in which that has been looked at, but it requires -- at least ones I'm familiar with requires a monovalent vaccination. Meaning mumps, mumps alone not in the context of MMR.
Q. Did you ever consider running that experiment as part of your validation of the AIGENT?
A. As best I understand or can recall, we didn't include that. I can't say that we -- I don't recall if we considered it or not.
MR. KELLER: Let me mark -- let me mark this next exhibit as Exhibit 33.
- - -



(Exhibit Krah-33, Series of e-mails with attachment, 759836 - 759847, was marked for identification.)
- - -
MR. KELLER: For the record, Exhibit 33 is a document that bears Bates stamp numbers 79 -- 759836 through 847. It's a series of e-mails and an attachment of a validation protocol.
BY MR. KELLER:
Q. Can you tell me -- can you take a minute to look at this document and see if you recall receiving these e-mails and writing these e-mails that are identified in Exhibit 33. Let me know when you're done.
A. Okay.
Q. Let me direct your attention to 79 -- sorry, 759837, which is your e-mail of October 10, 2000, to Dr. Schofield, amongst another -- Joe Antonello, William Long, Michael Washabaugh. Do you see that?
A. I'm sorry?
Q. The bottom.
A. Oh, okay. Okay. Yes.



Q. Sorry. The earlier e-mails start in --
A. Yeah. Yes. Okay.
Q. Here the subject was, Validation protocol for anti-IgG enhanced mumps neut assay. Do you see that?
A. Yes.
Q. That's Protocol 007. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's the neutralization assay that was used in Protocol 007.
BY MR. KELLER:
Q. That's the AIGENT. Correct?
A. The AIGENT assay, yes.
Q. Here you say, The following are some thoughts on the validation protocol for the mumps neut assay to be transferred to Dick Ward's lab -- Dick Ward's group. Do you see that?
A. Yes.
Q. It says, "I am providing these to get the ball rolling on developing the validation protocol."



Do you see that?
A. Yes.
Q. So you were involved in developing the validation protocol. Correct?
A. I was involved in it. What my specific role was, I can't say for sure.
Q. Was the purpose -- was the idea as -- back in October 10th, that the validation would be -- the validation analysis and experiments would happen at Dick Ward's lab?
MR. SANGIAMO: Object to the form.
THE WITNESS: That, I don't recall.
BY MR. KELLER:
Q. That appears to be what you said in this e-mail, though. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: It comments on validation protocols for the assay to be transferred to Dick Ward's group. I don't read it to mean whose -- whether validation would be done at Dick Ward's

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lab or at Merck. Validation protocol would be prior to the potential transfer to Dick Ward's lab.
BY MR. KELLER:
Q. So as of October 30, the decision was made to run that 600 subset out of your lab. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: The date?
BY MR. KELLER:
Q. As of October 30, after the October meeting with the CAS, do you recall having discussion with Emilio Emini where you were informed that you would run the subset out of your lab?
A. I recall being informed by Emilio that our lab will be running the subset. I don't recall the date, the specific date.
Q. Fair enough. Here on October 30, on the first page of Exhibit 33, there's an e-mail from Joe Antonello to you, Dr. Krah. Do you see that?
A. Yes.

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Q. Again, it's, Validation of protocol for the anti-IgG enhanced mumps neut assay.
Do you see that?
A. Yes.
Q. It says, "Dave, To help in preparing a Mumps PRN Validation Protocol, two recently completed validation protocols are attached."
Do you see that?
A. Yes.
Q. So does that lead you to believe that you were, again, helping prepare that validation protocol or refresh your memory to that effect?
A. To my understanding, reinforces that I was involved in trying to identify conditions for the validation protocol. It doesn't clarify to me who the author would be.
Q. Fair enough. So in the second, third paragraph under "Sero-Status Cutoff (information on Pre- and Post-Vaccination Rates)," Joseph Antonello writes, Test around 100 pediatric pre- and post-vaccination samples (since approximately half of these

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samples have already been tested, the remaining samples can be divided among six runs used to assess precision).
Do you see that?
A. Yes.
Q. Then it says, "The test sample data will be used to establish a 'sero-positivity' cutoff and provide estimates of pre- and post-vaccination sero-positive rates."
Do you see that?
A. Yes.
Q. This 100 pediatric sample, that was the proposal by Joseph Antonello. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. For the validation protocol? Is that a fair statement?
MR. SANGIAMO: Object to the form.
THE WITNESS: That -- according to the way this is written, that's his recommendation for the serostatus cutoff part of the validation protocol.

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BY MR. KELLER:
Q. That's part of the mock control limits as well. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Is that how you calculate the mock control units?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't believe so. The mock -- my understanding of the mock control, it's a no serum control. So it's virus, control medium, anti-IgG that has limits that are set that are, my understanding, not related to the serostatus cutoff.
BY MR. KELLER:
Q. So seropositivity, that's -- how would these 100 pediatric pre- and post-vaccine samples be used to set the seropositivity cutoff?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall how

it would be applied. I can say that he's suggesting that that number of samples would be recommended to allow him to do that part of his analysis. But beyond that, I don't have any information.

BY MR. KELLER:

Q. You're not -- you don't know how the sero classification cutoffs are generated, that's for the statisticians?

A. The statisticians -- my understanding of the process is that the statisticians confirm what serostatus cutoff is appropriate. So we'll have data, meaning percent of mock and a titer, the statistician then would be able to, through the validation protocol, evaluate what's a statistically supported cutoff.

Q. So this mock control, you testified that it's control medium, IgG, and virus. Correct?

A. Yes.

Q. What was the purpose of having the control medium?

A. The -- my -- it doesn't just



apply to this assay but other assays. My objective for the control, the mock control is to have it be everything that's in the assay but the serum. So control for everything but the one variable. So it then serves as the plaque number to use to compare to the serum-containing samples.

Q. So would the -- if you removed the IgG, would that have an effect on the mock control?

A. We did do studies where we evaluated the impact of anti-IgG on virus infectivity and did not see that effect in the absence of serum as well as the similar observation from the publication from the FDA on their anti-IgG assay development. So in a practical way, I would not expect an effect of not having the anti-IgG present but for the sake of better control or minimizing variables in the assay, meaning having the only variable be serum dilution, the mock contained everything but the serum.

Q. There could have been -- what was done in the original studies in 1972, those are very limited studies. Correct?



MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. A handful of kids, like four kids in there?

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. Do you recall?

A. I don't recall the number of kids, but the mock serum control is not -- are not related to the performance of the -- the question about whether anti-IgG is neutralizing on its own or not is not relevant to that assay.

Q. Did you see any effect of -- you said you ran these assays to say that there was no effect with or without the anti-IgG?

A. In the absence of serum.

Q. But in the absence of serum there's a huge effect. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: It depends on the serum. It depends on the serum.



BY MR. KELLER:

Q. So because the IgG would interact with not only mumps antibodies but measles antibodies, rubella antibodies, and antibodies for influenza, RSV, whatever antibodies are in that kid's serum, the rabbit antibodies -- the rabbit anti-IgG is going to interact with that and bind it. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: It has the potential, the anti-IgG has the potential to bind to any IgG that's in the sera.

BY MR. KELLER:

Q. So when you did these experiments with or without the IgG and the mock, what indicator virus did you use?

A. I don't recall with certainty.

Q. Was it Jeryl Lynn 135?

A. I have an expectation that that was it, but I don't have a recollection that that was the indicator virus.

Q. Do you know whether or not you actually ran 100 pediatric samples for the

validation of the AIGENT?
A. I don't recall.
Q. Do you recall that those 50 samples identified by Antonello, those were samples that were run as part of your developing the assay. Correct?
MR. SANGIAMO: Object to the form. Calls for speculation.
THE WITNESS: I can't say with certainty that that was once -- I'm sorry, they were once part of the assay development. One arm of the assay development would have included whatever anti-IgG, whatever the conditions were that we wound up using in the assays. The development included different concentrations of anti-IgG, for example, one concentration was chosen for the final assay application. So a subset of the sera would be eligible if the indicator -- if all the other assay conditions and the indicator virus and anti-IgG concentration were the same as what was being used in the eventual assay.



Whether those particular samples were included as part of that 50, I can't say for sure.
BY MR. KELLER:
Q. Except you may have had a different control because the controls were not set until after October of 2000, correct, by CBER?
A. I'm sorry, what controls are you referring to.
Q. Positive controls?
MR. SANGIAMO: Object to the form.
THE WITNESS: The -- my best recollection is that the controls were run in -- so in those development studies, I can't verify, I don't recall if the controls were included in those. The limits to the control sera were set, as best I understand, from the results of the validation study. CBER asked for limits to be set but the date or the limits were set to -- the best that I can recall, was a value that came out of the validation study.



BY MR. KELLER:
Q. Was it your testimony that these 50 samples -- that these 100 samples that are identified here had controls that were used in the actual running of Protocol 007, the same positive controls?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't have -- I don't have a recollection of whether they were or weren't.
BY MR. KELLER:
Q. And if they weren't running the validation samples, would that be a concern for you, if they had controls that were not the same as the controls that were run in the actual SOP, running kids serum in Protocol 007?
A. I need to defer to Joe Antonello whether those data would be usable for that -- appropriate to include in that.
Q. Do you recall -- sorry. Go ahead and finish.
A. Whether they would be appropriate to include that combination of



data.
Q. Do you recall ever hearing that the data that was generated as part of the validation was insufficient to generate reliable data to validate Protocol 007 AIGENT?
A. Not that I recall.
Q. Would that surprise you to learn that?
MR. SANGIAMO: Objection. Form.
THE WITNESS: I don't recall hearing that.
BY MR. KELLER:
Q. Let me direct your attention back to Exhibit 33. On the second page at 759837 Dr. Schofield, on October 12, responded to your October 10 e-mail in the middle of the second page. He says, "Some comments highlighted below." If you look on your e-mail at the bottom of 759838, there's a statement that says should the validation also include a requirement for up-front testing to evaluate pre- and post-rates?
A. Where are you?
Q. Sorry. Right there.
A. Okay.

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Q. So you wrote, Should the validation also include a requirement for up-front testing to evaluate pre-positive rates (around 10 percent target?) and..., typo, ...seroconversion rates (greater or equal to 95 percent) for a panel of 50 to 60...pediatric sera.

Do you see that?

MR. SANGIAMO: You left out paired.

BY MR. KELLER:

Q. Pediatric sera.

MR. SANGIAMO: You left out paired.

BY MR. KELLER:

Q. I'm sorry, paired pediatric sera. Thank you.

Do you recall writing that?

A. It's in an e-mail from me, but I don't have an independent recollection.

Q. Below that --

MR. SANGIAMO: Jeff, you did it again. You got to let him finish.

THE WITNESS: In the -- I don't have an independent recollection of

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writing -- the wording is -- looks and says -- it was wording I would use, but I don't have an independent recollection of writing that.

BY MR. KELLER:

Q. Below that it says, "This would be the 'clinical validation' that I mentioned before. Yes, I think it's useful to reliably establish these characteristics, since these were the metrics that drove your development."

Do you see that?

A. Yes.

Q. So here do you believe that to be Dr. Schofield's comment to your statement about the target of less than 10 percent pre-positives and greater than or equal to 95 percent seroconversion?

A. It's looks like a different font, see comments highlighted below. So I can't say with 100 percent certainty that that's his comment, but it looks like the comment that was added by someone.

Q. So that target, is that consistent with your understanding, your belief that that target drove your development

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of the AIGENT?

MR. SANGIAMO: Object to the form.

THE WITNESS: A goal in the development of the AIGENT was to have an assay that was capable of measuring 95 percent seroconversion and had a minimum -- in my mind a minimize or minimal pre-positivity rate, whatever that wound up being.

BY MR. KELLER:

Q. And the goal was 10 percent -- around 10 percent pre-positive rate. Correct?

A. That was at least the target that was in some of the documents.

Q. So that's what you -- that's what drove your developing the assay to get to that target. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: The goal was to find an assay that was capable of meeting those two targets.

BY MR. KELLER:

Q. Fair enough. Have you ever

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developed an assay where you developed the assay to get a certain result --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- a predetermined result --

MR. SANGIAMO: Object to the form.

BY MR. KELLER:

Q. -- before Protocol 007?

MR. SANGIAMO: Object to the form.

THE WITNESS: I would not characterize it as getting a predetermined result. I would characterize it as developing an assay to achieve sensitivity that was meeting the requirements for the assay.

BY MR. KELLER:

Q. Have you done that at Merck in the past where you set a target result for an assay and developed an assay to reach that target?

MR. SANGIAMO: Object to the form.

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THE WITNESS: Not that I recall, but I remind you that the target that was set here was a CBER-imposed target.
MR. KELLER: Let me mark this next exhibit as Exhibit 34, which is a document that bears Bates stamp number 1218 through 1221, which is a memo from Manal Morsy to a series of individuals, including you, Dr. Krah, regarding a teleconference with CBER on November 29.
- - -
(Exhibit Krah-34, 11/29/00 Memo, 1218 - 1221, was marked for identification.)
- - -
BY MR. KELLER:
Q. Do you see that?
A. Yes.
Q. Do you recall -- why don't you take a minute to review this memo and let me know when you're done.
MR. KELLER: Off the record so I can use the restroom real quick.
MR. SANGIAMO: We're going to take a break, take a break. That's

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fine.
VIDEOGRAPHER: The time is now 4:41. This concludes disc five.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is now 4:57. This begins disc six. You may proceed.
MR. KELLER: I'd like to mark for the record Exhibit 35.
- - -
(Exhibit Krah-35, Plaque Reduction Neutralization Assay for Mumps Analytical Validation Protocol (v.01), 780112 - 780116, was marked for identification.)
- - -
MR. KELLER: For the record, Exhibit 35 is a document bearing Bates stamp number 780112 through 116, entitled: "Plaque Reduction Neutralization Assay for Mumps Analytical Validation Protocol (v.01)."
BY MR. KELLER:

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Q. Do you see that?
A. Yes.
Q. Was that your handwriting on page 2 at 780114?
A. It doesn't look like my handwriting.
Q. Do you recall on 78 -- back up. Do you recall ever seeing this document before, Exhibit 35?
A. I recall there are parts of the protocol that look familiar to me. Whether I saw it in its entirety I can't say. In fact, looking on page 3, looks like it's a draft version since it has underlining. So I don't know, depending on who made the edits, if I would have seen those parts.
Q. So this is a -- this Exhibit 35 is a draft. Correct?
A. I can't say with certainty other than page 3 and -- on page 3 at least there are edits made, which would imply a draft.
Q. And so this reference on page 780114 where there's a circle around the 100 pre- and post-vaccination paired pediatric samples, it says 100 or fewer due to

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contamination. Do you believe that half of the samples that were being proposed to be tested as part of the pediatric samples were not usable because of contamination in your lab?
A. I don't recall.
Q. Let me direct your attention --
A. If I may add to that, at the end you put in in my lab. The source of the -- if there was contamination, I do recall some sera we tested at some point, where there was contamination was the sera, not something introduced in the lab.
Q. So it's your testimony that you recall there being contaminated serum but that was contaminated from someplace else but not in your lab. Correct?
A. Yes. I don't recall if it was this particular set, but I do recall a period where a panel showed, that we were evaluating, had a contamination problem.
Q. Let me direct you to the 2001 journals. Can you pull those in front of you?
A. Okay.
Q. If you could direct your

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attention to January 21, 2001, at 490623.
A. I'm sorry?
Q. 490623. January 21, 2001. Do you see that reference to the last entry? Can you read the last entry for me?
A. Sorry, on Sunday 21st was that?
Q. Yes. Sorry.
A. Review Manal's info for CBER. Revise validation protocol to be approximately 50 pediatric sera instead of 100.
Q. Does that refresh your recollection that you, in fact, were at least editing the validation protocol at this point?
A. That indicates that the validation protocol was edited, revised, if you will, on the 21st of January, 2001.
Q. And this revision of the protocol from around 50 pediatric sera instead of 100, do you recall that was due to contamination of the sera that you received?
A. I don't --
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall the rationale for that change.

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BY MR. KELLER:
Q. Let me direct your attention back to your journal from 2000. If you can go to 490489, which is dated November 14, and ask you questions on the end of that journal entry on 489, which is pages 408 and 409 of your journal, if that helps.
A. Yes, okay.
Q. So on 409, which is 490489 in the Bates numbers, it says, Assign MMRV-715-00 to the receipt of serum set number 24 from Serologic group (from October 31, Kelly Buckley: 60 paired sera...).
Do you see that?
A. Yes.
Q. Did you get the sera for the validation samples from Kelly Buckley?
A. I don't recall who we received them from.
Q. If you look on 490500, which is page 420 of your -- which is November 25, 2000, there's a reference to Saturday. Can you read your Saturday entry?
A. Okay. It says, Leave message with Kelly Buckley re most of the sera from

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set number 24 are contaminated - any ideas of the source?
Q. So does that lead you to believe that the sera that you had anticipated testing for the validation protocol that we had seen documents earlier where Antonello was recommending running 100 paired samples, and here on January 21st, you reference needed to revise it from 50 -- down from 100 to 50, and in conjunction with the draft protocol in Exhibit 35 where there's a reference to contamination, that, in fact, those 50 samples of sera that you had anticipated to be run for the validation pediatric sera was contaminated and, therefore, you didn't have it and you need to revise the validation protocol for that purpose?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't tell from the wording here. But I can't confirm that that sera set number 24 was intended for the validation study or not.
BY MR. KELLER:

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Q. But it's fair to say that on January 21st, you have a reference in your journal to revise the protocol to be around 50 ped sera instead of 100. Correct?
A. I'm sorry, what's the date again for that one?
Q. Right here.
A. January 21, 2001?
Q. Yes.
A. Yes.
Q. And when you say ped, you mean pediatric?
A. Pediatric, yes.
Q. So did you revise the validation protocol from 100 to 50?
A. I don't recall.
Q. Do you recall any discussion with any e-mails from Dr. Schofield stating that if you reduced the number of pediatric serum that were tested in the validation protocol, that the results would be of limited data and unusable?
MR. SANGIAMO: Objection. Form.
THE WITNESS: I don't recall a discussion on those lines.

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MR. KELLER: Let me mark this next exhibit as Exhibit 36.

- - -

(Exhibit Krah-36, Series of e-mails, 52848 & 5284, was marked for identification.)

- - -

BY MR. KELLER:

Q. Let me back up for a second.

You made a point of saying that there was no contamination of sera in your lab. During the time that you were running Protocol 007, you had a very serious problem of mold problems in your incubators, didn't you? Do you remember that?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't -- I remember we had mold occasionally in the incubator, but I don't recall it being at that particular time.

BY MR. KELLER:

Q. Do you recall having problems in -- at the end of 2000?

MR. SANGIAMO: Object to the

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form.

THE WITNESS: I don't recall.

BY MR. KELLER:

Q. Do you recall having problems in -- during the time that you were running the preliminary subset, having mold problems in your incubators that those samples were run on?

A. Not that I recall.

Q. But you recall a mold problem in the incubators, just not during that time frame?

A. I recall occasional mold in some incubators. Whether they were incubators associated with this testing, I don't recall. And if it was at that time, I don't recall.

MR. KELLER: Fair enough.

Let me mark this next exhibit.

MS. SCANLAN: Marked it already.

BY MR. KELLER:

Q. Let me mark -- show you Exhibit 36, which is a series of e-mails bearing Bates stamp number 52848 through 52849, and feel free to read these e-mails. Let me know when you're done.

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A. Okay.

Q. On the second page of this e-mail there's an e-mail from you, Dr. Krah, dated January 21, 2001, to Emini, Shaw, Washabaugh, Schofield, Heyse, Antonello and Yagodich, Karen Hencken and Jerry Sadoff. Do you see that?

A. Yes.

Q. And the subject was the "Anti-IgG Enhanced mumps neutralization assay validation protocol draft."

Do you see that?

A. Yes.

Q. Who was Karen Hencken?

A. I don't recall. I know of Karen. She's had different positions over the time I knew her. I don't recall her position at the time of this e-mail.

Q. Was she involved in -- do you know if she's involved in GMP compliance?

MR. SANGIAMO: Object to the form.

MR. KELLER: Strike that.

BY MR. KELLER:

Q. Do you recall if she is involved

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in any kind of quality control, quality assurance functions?

MR. SANGIAMO: Object to the form.

THE WITNESS: At some point of -- the time that I knew her, she wasn't involved in a quality control function. I don't recall at this specific time what her role was.

BY MR. KELLER:

Q. And here in this e-mail on January 24th you write, "Attached is a draft of the validation protocol, prepared in collaboration with Joe Antonello, for the anti-IgG enhanced mumps plaque-reduction neutralization assay."

Do you see that?

A. Yes.

Q. It says, "This is a slight revision to the one circulated by Manal last week. Please review and return to me with your comments and/or signatures."

Do you see that?

A. Yes.

Q. This one has version .01. And

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what I showed you in Exhibit 35 is also version 1. Do you see that?
MR. SANGIAMO: Object to the form.
THE WITNESS: Yes.
BY MR. KELLER:
Q. And so do you recall circulating versions of the draft validation protocol?
A. I don't recall.
Q. On February 12, about, what is that, three weeks later, you followed up with an e-mail to the same folks, same topic saying, "Please review the attached draft that was sent out in late January and either provide comments or the signed cover (signature) page." It says, I only received 1 signature back (and 1 comment from the same person) so far.
Do you see that?
A. Yes.
Q. So on February 15th, based on your prompting, Timothy Schofield responded. Do you see that?
MR. SANGIAMO: Object to the form.

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THE WITNESS: I see a reply from him, yes. And he says --
MR. SANGIAMO: Wait, hold on a second. Did you finish your answer, Doctor?
THE WITNESS: I see a reply following as listed on the February 15th.
BY MR. KELLER:
Q. And here it says, Schofield states, "David, I reviewed the protocol, and have one comment, and a couple of typos.
Comment: On page 3 (and in the last section) you mention using the data that you collect on the controls to establish control limit. This will be far too little data to set reliable units. You must add that "The control criteria will be updated after a sufficient number of runs have been performed, to obtain reliable estimates of assay performance (total N equals 20 runs)."
Do you see that?
A. You used the word must, you must add. I'm sorry.
Q. You might have.

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A. Might have.
MR. SANGIAMO: Did you get that, Linda? The document says you might have, not must have.
MR. KELLER: I'll reread it. Strike the prior question.
BY MR. KELLER:
Q. Comment: On page 3 (and in the last section) you mention using the data that you collect on the controls to establish controls limit. This will be far too little data to set reliable limits. You might add that "The control criteria will be updated after a sufficient number of runs have been performed, to obtain reliable estimates of assay performance (total N equal 20 runs)."
Do you see that?
A. Yes.
Q. Did you address that language to the draft protocol?
A. I don't recall.
Q. And so if you go back to Exhibit 35, can you tell what he's talking about? Page 3, in the last section. Is he talking about the seroclassification cutoff?

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A. My understanding and recollection of what he was referring to there are the control limits, second paragraph, Each validation run will also include testing on the mock control, and in parentheses, and on low and high positive control samples (adult sera)..., as I recall discussion with Joe Antonello when the validation report was being assembled that -- my understanding, my recollection of the procedure that he would follow would be a tentative control limit would be set based on the available data that number or value, or values, if there are multiple controls, would be updated as more data became available.
Q. And the data, as more data became available, is that running sera from Protocol 007 or running sera from sera outside of Protocol 007?
A. My understanding of that comment and best recollection is that that refers to the adult -- the positive control sera which are adult lab volunteer sera. So sera outside of Protocol 007.
Q. So your testimony is that these

20 runs were supposed to be sera outside of Protocol 007 sera. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't believe you're capturing the assay format accurately. In a given assay, sera from a given study can be tested and there are control sera tested. So these are not 20 assays of only control sera but 20 assays, as best I understand this, 20 assays in which control sera were included.
BY MR. KELLER:
Q. That control sera, you said that would include the mock?
A. Sorry, that -- in the paragraph it's listed as one of the controls, but the control sera that, my understanding, Tim Schofield is referring to are the positive control sera.
Q. The adult sera?
A. The adult sera, the lab volunteers.
Q. You don't think he was talking



about the reduction from 100 pediatric sera down to 50?
A. My reading of this and my recollection of this was that he was referring to the number of runs that we had with the control sera. So it was not related to the dropping from 100 to 50 but was referring to how many assays in which the adult lab volunteer control sera were run.
MR. KELLER: Let me mark the next exhibit as Exhibit 37.
- - -
(Exhibit Krah-37, Plaque Reduction Neutralization Assay for Mumps Analytical Validation Protocol (v.02), 337307 - 337318, was marked for identification.)
- - -
MR. KELLER: For the record, Exhibit 37 is a document that bears Bates stamp number 337307 through 318.
BY MR. KELLER:
Q. Can you tell me if you recognize this document as the -- as a version of the plaque reduction neutralization assay for



mumps for the AIGENT?
MR. SANGIAMO: Object to the form.
THE WITNESS: It's version .02 of at least -- from the title version .02 of the "Plaque Reduction Neutralization Assay for Mumps Analytical Validation Protocol."
BY MR. KELLER:
Q. Is this the final?
A. It's marked -- sorry. The signatures are initial review. I cannot tell from the document whether it's final or not.
Q. If you look on the first page, that's your signature. Correct?
A. Yes.
Q. That's February 12, 2001, when you signed this?
A. 21st of -- February 21, 2001.
Q. And what was the date of the last signature? Is that March 6, 2001?
A. Looks like -- March 6th looks like the last signature.
Q. In the first paragraph of the signature part of this validation protocol, do



you recall whether or not there was a final validation protocol different from this exhibit?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall.
BY MR. KELLER:
Q. Here it says, quote, the final review is not circled, only the initial review. Do you see that on the first page?
A. Yes.
Q. You don't recall ever seeing a final review that was circled. Correct?
A. I don't recall.
Q. Here it says in the first paragraph, Your signature below indicates your acceptance of a validated protocol -- of the attached validation protocol, given that no comments are provided by any of the reviewers. If comments are received, the protocol will be revised and recirculated, with the comments appropriately incorporated or addressed. Do you see that?
A. Yes.
Q. Can you turn your attention to

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page 337314, Karen Hencken.
A. Okay.
Q. So she is identified as a "World Wide Quality Assurance." Do you see that?
A. Yes.
Q. She checked off "Comments." Do you see that?
A. There is a check mark next to comments.
Q. Here under your instructions for signing this document it states that if comments are received, the protocol will be revised and recirculated, with the comments appropriately incorporated or addressed. Do you see that on the first page, on every signature page?
A. Yes.
Q. Would you be -- would you expect that since Karen Hencken had checked the box as having comments, that there would have been another version of this based on the instructions of this signature page?
A. I would not say -- given the wording that is here, I would not say with certainty that a new version would be issued,

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but indicates that the protocol would be if comments are received, the protocol will be revised and circulated, with comments appropriately incorporated or addressed. If they're addressed in a way that doesn't require incorporation, it may not require a new version. In this case, I can't speak to what the comments were or whether a new version was issued.
Q. You don't know -- you don't recall what her comments were?
MR. SANGIAMO: Object to the form.
THE WITNESS: At least from this document, I don't see, or nothing looks -- I don't have any indication what the comments were.
BY MR. KELLER:
Q. If you go on in the signature instructions, in the first -- in front of every signature page it says, It is understood that these experiments will be produced in a GLP compliant laboratory to ensure the validity of the data. Do you see that?
A. Yes.

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MR. SANGIAMO: Objection to the form. You said produced.
MR. KELLER: Sorry. I'll start over. Getting tired here. Strike my last question.
BY MR. KELLER:
Q. "It is understood that these experiments will be performed in a GLP compliant laboratory to ensure the validity of the data."
Do you see that?
A. Yes.
Q. Do you know whether or not these submissions were ever given to CBER?
A. I don't -- that, I don't know.
Q. Who -- do you know, was that something that you put into the signature page, this is only done pursuant to a GLP compliant laboratory and not a GMP or G -- Good Clinical Practices laboratory?
MR. SANGIAMO: Object to the form.
MR. KELLER: Strike that.
BY MR. KELLER:
Q. This reference to GLP, do you

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recall who put that in the signature line?
A. I don't --
MR. SANGIAMO: Object to the form.
THE WITNESS: -- recall with certainty. I don't recall that I put that in there.
BY MR. KELLER:
Q. And that really is -- that's a true statement, that your lab was only compliant to GLP. Correct? Strike that.
Was your lab compliant with the GLP requirements --
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- as of the date of this document?
A. At this moment I'd say -- my understanding of GLP is not extensive, so I can't comment on whether we were or weren't compliant with GLP.
Q. Let me direct your attention to the body of the protocol. Have you -- when was the last time you reviewed this protocol?

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A. I don't recall.
Q. I assume you read it before you signed it. Correct?
A. Yes.
Q. If you want to take a minute to review this protocol, why don't you do that. Let me know when you're done.
A. Okay.
Q. Let me direct your attention to page 2 where it says, "Assay Validation Experiments."
Do you see that?
A. Yes.
Q. Here it says, The plaque reduction neutralization assay will be performed according to the Department of Virus Biologic Research Procedure Number 474.3489, rev. 00 ("Anti-IgG Enhanced Mumps Plaque-Reduction Neutralization Assay").
Do you see that?
A. I do. It's 874.3679. You said 4.
Q. Sorry. I apologize. 874- -- .3489. Correct? That's the SOP for the AIGENT. Correct?

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MR. SANGIAMO: You also misidentified the department. You said virus and biologic research. It's virus and cell biologic research.
MR. KELLER: Strike that whole thing.
BY MR. KELLER:
Q. Dr. Krah, under "Assay Validation Experiments," the second sentence it says, "The validation experiment will include sera from 4 adults and approximately 50 pre- and post-vaccination paired pediatric samples."
Do you see that?
A. Yes.
Q. And in the prior draft of this protocol on Exhibit 35, on page 870114, it said, "...100 pre- and post-vaccination paired pediatric samples," and circled is a reference to "or fewer due to contamination."
Do you see that?
A. Yes. In the document 780114.
Q. Do you recall that the number of pediatric sera that was proposed went from 100 down to 50 because of a problem with the sera

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that was going to be used to run those experiments?
A. I can't -- I don't recall with certainty.
Q. Would you -- would it be fair to say that the protocol reduced by half the number of pediatric sera to be tested as part of the validation experiments from what was proposed by Joe Antonello in October of 2000 to what ended up in the final or in this draft of the validation protocol?
A. I would say numerically I can't see if there are other pediatric sera included in this, but it looks, at least from my reading of it, approximately half the number of pre- and post-vaccination paired pediatric samples were included, but I would point out that amongst the evaluation or the validation evaluations, the -- I'm sorry, the validation evaluations, it looks like the pediatric samples will be divided among multiple assay runs that is not a number reduced from the original proposal.
Q. So is it your testimony, sir, that there was 100 paired samples tested of

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pediatric serum as part of this validation protocol?
MR. SANGIAMO: Objection. Misstates testimony.
THE WITNESS: No, that's not what I was saying.
BY MR. KELLER:
Q. So these runs that you're saying, the 50 runs that you're talking about, are you testifying that those 50 runs represent 100 pairs of pediatric samples?
MR. SANGIAMO: Objection. Misstates the testimony.
THE WITNESS: What I'm representing is that there are -- this is written that there are approximately, in addition to the four adults here, there's approximately 50 pre- and post-vaccination paired sera. Pediatric samples will be divided among the next -- sorry, the first paragraph on page 337317, "The pediatrics samples will be divided among multiple (7) assay runs with pre- and post-vaccination sample pairs being

tested together in the same assay run."
That the number of replicate runs is not reduced from the original proposal.
BY MR. KELLER:
Q. So it's your understanding that there would be additional samples run as part of this validation protocol in order to -- is it -- strike that.
Is it your belief that because it says, "The pediatric samples will be divided among multiple (7) assay runs...," that that was going to happen in the future?
A. My understanding and my interpretation of that is that those -- the 50 pre- and post-vaccination serum pairs would be split up among seven different assays.
Q. Did you believe as of the date of this --
MR. SANGIAMO: I'm sorry, Jeff.
BY MR. KELLER:
Q. I didn't mean to cut you off.
A. As part of this -- as part of the validation.
Q. I see. Did you understand that those runs were already -- those assay runs



were already completed by the time you drafted this protocol? Correct? Strike that.
Those experiments, those 50 paired serum through seven assay runs were already completed when this protocol, validation protocol was signed. Correct?
A. I can't say that with certainty.
Q. Well, Joe Antonello on October 30th said we've already run half of them. Right? So half of the 50 -- half of the 100 is 50. Correct?
A. I can't say with certainty that the 50 that he's referring to is the 50 that we wound up using.
Q. I see. And so he goes on in the next paragraph to state that, Each validation run will include testing on the mock control, and on the positive control sample (adult sera). Note that some of the pediatric serum assays and specificity assays include a single control serum. All assays of clinical sera will include two control sera (low and high titer). The data arising from the validation experiment will be used to establish assay validity criteria in the form of tentative



specification limits for the mock and positive control samples.
Do you see that?
A. Yes.
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Did you understand that the mock control samples that they're talking about there, that they were all run in pediatric samples, in those 50 paired samples run over seven assay runs?
A. I'm sorry, the mock is an inherent part of each assay, so it would be run in every assay regardless of what sera are tested.
Q. I see. So the control criteria will be updated after a sufficient number of runs have been performed to obtain reliable estimates of assay performance (N equals 20 runs).
Do you see that?
A. Yes.
Q. That's what Schofield had recommended that you put into the protocol.



Correct?
A. That looks like -- appears to be the wording that he recommended, at least N equals 20 runs, and updating it -- updated after a sufficient number of runs had been performed.
Q. You don't know whether or not those runs were from runs using Protocol 007 sera or runs using sera from -- that Merck had acquired through other sources?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall which sera were --
BY MR. KELLER:
Q. Can you -- as you sit --
MR. SANGIAMO: Jeff.
BY MR. KELLER:
Q. I'm sorry. Go ahead.
A. I don't recall which sera were -- where the source -- I can't tell from this document what the source of the pediatric sera was.
Q. As you sit here today, do you see any problems with Merck using the sera

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from Protocol 007 to run those 20 runs?
MR. SANGIAMO: Object to the form.
THE WITNESS: I have a general understanding of the -- sorry, I'm not familiar with the specific requirements for a validation study. I have a general perception, this is personal perception, that the sera from a pediatric sera -- the pediatric sera from a clinical study would not be used as part of a validation study. That would not apply, in my view, to adult lab volunteer sera.
BY MR. KELLER:
Q. Correct. Because those adult sera are not run in the Protocol 007 sera. Those are Protocol 007 sera from the kids that were gathered as part of the protocol in the study. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. Strike that. That was a terrible question. I'll leave it at that.

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Let me have you turn -- did you ever discuss with Joe Antonello those -- I showed you a document earlier where you state you started running samples in Protocol 007 on December 6, 2000. Do you recall that?
A. I don't recall the specific date.
Q. Do you recall that you were already running clinical samples from Protocol 007 during the time that you were validating the protocol?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not able to confirm dates.
MR. KELLER: Let me mark the next exhibit, Exhibit 38, which bears Bates stamp number 52242.
- - -
(Exhibit Krah-38, 12/10/99 E-mails, 52242, was marked for identification.)
- - -
BY MR. KELLER:
Q. It's a single-page e-mail from

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you, Dr. Krah, dated December 10, 2001. Actually two of your e-mails. I'll draw your attention to the first e-mail on December 10th at 12:22 p.m.
A. I'm sorry, what was that?
Q. The third paragraph down.
A. Bottom e-mail, okay.
MR. SANGIAMO: Read the e-mail.
BY MR. KELLER:
Q. You write, "The testing of the..." --
MR. SANGIAMO: Hold on, he hasn't read it.
MR. KELLER: I'll read it.
MR. SANGIAMO: He hasn't read the e-mail.
MR. KELLER: He can read it.
MR. SANGIAMO: He's going to read a particular paragraph and when he's done reading the e-mail, then you ask the question.
BY MR. KELLER:
Q. I'm just going to ask you questions about this one sentence. It says, quote, The testing of the interim analysis set

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started on December 6, 2000, and ended January 26, 2001.
My question is, is that a true and correct statement as to when the sera from Protocol 007 preliminary subset was run? That's all I want to ask about this document.
MR. SANGIAMO: Read the e-mail and then answer the question.
MR. KELLER: He doesn't need to read the entire e-mail to do that, but go ahead.
THE WITNESS: I can't verify this independently, but I interpret that next to -- the next to the last paragraph to mean that no testing of protocol sera was started prior to the start date listed as 06, December 2000.
BY MR. KELLER:
Q. That's not my question. My question is -- okay. That's fine.
MR. SANGIAMO: That is your question.
MR. KELLER: That is my question. You're right. Got you.
BY MR. KELLER:

Q. So is it -- other than this e-mail, you don't recall starting -- running samples from Protocol 007 before you had validated the SOP. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall the dates. This has listed dates for the validation. There are assays to evaluate variability inter and intraassay for the adult lab sera panel that are after that start date.

BY MR. KELLER:

Q. And so going back to Exhibit 38, the assays that are identified here, it says -- you write to Alan Shaw, "The following summarizes the timing of the experiments done to support validation studies of the mumps AIGENT assay."

Do you see that?

A. Yes.

Q. Those are the validation studies that are -- that were to be run -- described in the validation protocol?

MR. SANGIAMO: Object to the



form.

THE WITNESS: I can say that -- would say that those are experiments that are -- experiments done in support of the validation studies that would be part of the validation protocol. Whether this is all inclusive, I can't say.

BY MR. KELLER:

Q. Do you have any reason to believe that this is not the list of experiments that were used to validate Protocol 007's AIGENT?

MR. SANGIAMO: Object to the form.

THE WITNESS: All I can tell you, this lists assays that are indicated in support of validation studies. I don't have any information to the contrary that they were not part of what was used in the validation protocol.

BY MR. KELLER:

Q. Let me bring you back to your journal of February 15, 2001, after you signed



the validation protocol. February 15, 2001, was before the final signature on the validation protocol of March 6, 2001. Correct?

A. I believe the --

Q. This is before you even signed the validation protocol. Correct?

A. Let's see. I signed it February 21st of 2001.

Q. Can I direct your attention to February 15th in your journal which is at 490641 -- 640. Let me know when you're there.

A. 641?

Q. Right. 640, Tuesday, February 15th, do you see that? Or Thursday, February --

A. Thursday.

Q. I mean Thursday, February 15, 2001. The second page of that, there is a reference to you having a meeting with Dr. Emini at 1:30 p.m. to update the MPS Nt data. Do you see that?

A. Yes.

Q. Do you recall -- you testified earlier that you recall having a meeting with



Dr. Emini regarding him describing a warning letter. Can you read, for the record, what you wrote in your journal?

MR. SANGIAMO: Object to the preamble. If you want him to read what's written in the journal, that's fine.

BY MR. KELLER:

Q. Out loud, please.

A. What it says, it's a meeting with Emilio 1:30 p.m. to update the mumps neut data. Merck has been issued a "warning letter" from the FDA regarding mumps titers data - The data that we have generated will be needed to include in the response (due within 14 days from receipt) to provide a "comfort factor" with the vaccine dose. The full data set from Protocol 007 would be needed to change the label/license.

Q. Do you recall that conversation with Mr. -- with Dr. Emini?

A. I have a recollection of a meeting where Emilio mentioned the warning letter. I don't recall all the other aspects that are in this journal entry.

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Q. So your reference to comfort factor in quotes, you don't recall what he said about that?
A. No, I don't.
Q. Do you recall -- but you understood that the results of the preliminary subset would be used to respond to a warning letter from the FDA. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: My interpretation is that, as it says, the data that we have will be needed. I don't know what needed means. Needed to include.
BY MR. KELLER:
Q. Do you recall whether or not the results of the preliminary subset that was run by your lab was submitted to the FDA in response to the warning letter?
A. I recall that the data, or at least my -- I recall that the data from that subset analysis were provided. Whether it was in response to the warning letter, I can't say with certainty.
Q. In the reference here to the

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full data set from Protocol 007 being needed to change the label/license. Do you understand what you meant when you wrote that?
A. No.
Q. Do you recall what Protocol 007, the purpose of Protocol 007 was to change the end expiry specifications for the mumps component of the MMR II product?
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding of the purpose of the study was to compare the immunogenicity of three different doses of mumps. As far as what it's -- the data would be used for, I don't have a recollection.
BY MR. KELLER:
Q. Let me direct your attention to February -- your February 21, 2001, journal entry on Wednesday, which is 490648.
A. Okay.
Q. If you direct your attention to page 490650, there's a reference to Robin. "Robin indicates that she expects to have a draft validation report Thursday/Friday."

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Do you see that?
A. "...draft validation report Thursday/Friday."
Q. So Robin -- that's Robin Wolchko. Correct?
A. The sentence -- there are a couple of sentences before it, it says, "Note: all data sent to Robin Wolchko...." I don't know any other Robin.
Q. And Robin -- sorry, I didn't mean to cut you off.
A. That is the Robin.
Q. Robin worked -- she worked with Joe Antonello working on the validation report. Correct?
A. As best I can recall, she was on the validation report, one of the authors of the validation report along with Joe Antonello.
Q. Here, can you read what you wrote under that statement about her having a draft validation report Thursday/Friday? Strike that.
Does this indicate that you had a conversation with Robin Wolchko --

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MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. -- on February 21, 2001? Is that a fair statement, to say that you spoke to Robin on that date regarding the draft validation report?
A. All I can say is that she indicated she expects to have a draft validation report Thursday or Friday which would indicate some communication. Whether it was a conversation or e-mail, I don't know.
Q. Can you read what you wrote under that?
A. It says, "I commented on my observations from the Protocol 007 serum set assays-mock value 8.67 was not...," there's a typo of some kind Y-E-D. I don't know what that -- might be -- I don't know what that is. Comma, ...and all other runs were approximately 10.25 to 30.5 pfu for mock; control sera were with a range of fourfold across all assays.
Q. Is it fair to say that at this point on February 21st, you were updating

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Robin about your observations from running the serum from Protocol 007?
MR. SANGIAMO: Object to the form.
THE WITNESS: I take the comment to mean that I was providing feedback to her on how the mock value was performing in the assays. Not the assays overall, but just what the mock pfu value was.
BY MR. KELLER:
Q. And the assays you're referring to are the serum that was run as part of Protocol 007. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: No. They're in assays where serum was tested. The mock results are in the absence of serum.
BY MR. KELLER:
Q. But those are in the Protocol 007 experiments, correct, the kids serum in Protocol 007?
MR. SANGIAMO: Object to the

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form.
THE WITNESS: They're data from experiments in which Protocol 007 were tested but not directly involving -- they're not data from the clinical sera.
BY MR. KELLER:
Q. I see. But you were updating Robin about your experience from running the Protocol 007 assay using the SOP and the AIGENT. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: Yes, but only in the context of what the mock value was --
BY MR. KELLER:
Q. And in the content of that -- I see what you're saying. Then it goes on to --
MR. SANGIAMO: Did you finish your answer?
THE WITNESS: I was going to say the mock values in those assays.
BY MR. KELLER:
Q. I see. And the next you have a

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"Note: signatures were...," can you read the next reference?
A. Yes. Note: Signatures were received from first round of reviews of validation protocol from everyone except Jerry Sadoff.
Q. In the validation version .02 that we have as Exhibit 37, he didn't sign the protocol, the validation protocol, did he?
A. I see next to his name an NA.
Q. And is that your handwriting, the NA?
A. That looks like, yeah, that's my handwriting.
Q. And did you talk to Dr. Sadoff as to why he didn't sign the validation protocol?
A. I cannot say with certainty, but I can say I would not have put NA next to his name without some feedback on whether that was appropriate.
Q. Did Dr. Sadoff voice any reservations about signing the protocol?
A. Not that I recall.
Q. Did you get his approval to

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write NA next to that -- his name on the protocol?
A. I don't recall.
Q. Let me direct your attention to the next day, which is February 22nd, there's a reference in the middle of 490650 to a Meeting at 1:00 for our lab and Emilio... do you see that? "...(in his office)."
A. Yes.
Q. Do you recall that meeting happening?
A. I recall meetings with Emilio. I don't recall what that particular meeting was about.
Q. Do you recall a meeting with Emilio where there was discussions of bonuses if the Protocol 007 assay was completed successfully?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not recall that discussion.
BY MR. KELLER:
Q. Let me direct your attention to the next page at 490651 which is the day after

you spoke to Robin. There's a reference in the middle at top of the page, it says, "Reply to Joe Antonello's phone call..."

Do you see that?

A. I'm sorry, 1651?

Q. Right here. Do you see that?

A. Okay.

Q. So under that -- can you read what you wrote under that?

A. Yes. It says, "Extravariability evaluation - he can add this to our spreadsheets? I proposed - not for current set - no time to reevaluate and reaudit."

Q. So this was for the preliminary subset, you were not going to use whatever extravariability flags that were set up on a preliminary subset. Were those run? Is that true?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can't tell with certainty what set that applies to.

BY MR. KELLER:

Q. And under that you say, "For the plaque count limit proposed by CBER." Can you



read that?

A. Yes. It says, "use 10 as lower limit. For upper limit, he proposes using whatever is the upper counting range (50-60?). 50 seems okay to me (although a range of 10 to 40 seems best to me, as an average of 20 plus or minus twofold range)."

Q. So you're -- can you tell me what you're doing here when you're -- this is your -- this is a conversation you're having with Joe Antonello. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: There is a proposal that -- and I don't recall the specific CBER proposal of a limit that suggests for the plaque count limit based on the validation study that Joe analyzed he is proposing. A limit, and I don't -- I can't tell from this what -- how that -- actually how that compares to CBER's description. But as I'm reading this, the wording is such for the plaque count limit proposed by CBER. I don't recall that CBER



actually proposed the limit or said we would like a limit. So as I -- my first thought was that there may have been a limit that CBER suggested, but in reading this, I'm -- my understanding is that he's suggesting ten is a lower limit, and the upper limit there's some exchange of what we mutually agree would be a suitable upper limit.

BY MR. KELLER:

Q. Is he proposing ten or are you proposing ten?

A. He is proposing ten.

Q. How do you get that? Is that something you recall or just how you read this?

A. I don't -- it would not be a limit that I would have a basis on providing or generating. I recall subsequent discussions with him to understand his rationale for ten is a lower limit.

Q. So you weren't proposing using ten?

A. To the best of my recollection, Joe was the one, Joe Antonello was the one



proposing ten as the lower limit.

Q. You discussed with him the upper limit. He talked about 50 to 60 and you said 10 to 40 seems best to you. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's what it says there.

BY MR. KELLER:

Q. Is there any clinical significance to the mock control range?

MR. SANGIAMO: Object to the form.

THE WITNESS: Not that I'm aware of.

BY MR. KELLER:

Q. Is that used to set the serostatus cutoff?

A. No.

Q. What is the mock range set for -- what is it used for in an assay?

A. It is used to calculate the percent value -- percent plaque numbers for test sample relative to a -- to the mocks and then determine whether a sample is

neutralizing or not.
Q. So whether or not it's a -- the sample is a seroconverter or non-seroconverter. Correct?
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. It's used in that calculation. Correct?
A. Not directly. It's used on an individual sera basis to calculate the number of plaques as a percent of the mock value. So it identifies whether a given serum, it identifies the titer for a given serum. The seroconversion is a second calculation.
Q. And does the 10-40 play into that calculation at all?
MR. SANGIAMO: Object to the form.
THE WITNESS: The range is only used, from my understanding, to calculate the plaque count toward test sample relative to the mock for a given serum sample.
BY MR. KELLER:



Q. So later on you write, "Fax summary of results from Protocol 007 testing to Joe Antonello...mock pfu, MKY titer, CM titer, by assay."
Do you see that?
A. Yes.
Q. Why did you submit that data to Joe Antonello?
A. I can't say with certainty. I have an expectation of that, but I don't -- I can't say with certainty.
Q. What's your understanding, your best understanding?
A. My understanding is that Joe, since he -- in the validation report it indicated to have tentative specification limits for the control sera, that I would provide additional control serum results periodically to increase that number and allow him to reassess the -- whether the control limits were appropriate.
MR. KELLER: Let me mark two exhibits.
- - -
(Exhibit Krah-39, 2/22/01 Fax,



780093 & 780094, was marked for identification.)
- - -
BY MR. KELLER:
Q. Let me mark as Exhibit 39 a document that bears Bates stamp numbers 780093 through 94. It's a fax from you, Dr. Krah, to Joe Antonello, dated February 22, 2001. And is that your handwriting on the second page?
A. Yes, it looks like my handwriting.
Q. Is this what you faxed to Joe Antonello that's referenced in your journal on February 22, 2001?
A. I don't have an independent recollection of it. It indicates I'm sending a summary of the mock serum pfu and titers for MKY and CM serum, which is included in the data on the back of page 2 of that. So I can't independently confirm it, but it looks consistent with what was on the -- is on the back pages, captures the same classification or categories of data.
Q. So looking at -- this is your handwriting, though. Correct?
A. Yes.



Q. And here there's a listing of 44 assays. Do you see that? There's a reference to -- the bottom right-hand corner says, "To transfer 44 assays..."?
A. Yes.
MR. SANGIAMO: Object to the form.
BY MR. KELLER:
Q. That's your handwriting. Correct?
A. Yes, it is.
Q. And here you're capturing for 44 assays that were run as part of Protocol 007 the mock averages for those 44 assays. Is that a fair statement?
A. The mock value for those 44 assays.
Q. And it also references the low and high controls for those assays as well?
MR. SANGIAMO: Object to the form.
THE WITNESS: The two controls, I don't recall that they were referred to as high and low, but they are the two controls that were run in the --
BY MR. KELLER:

Q. You also --
MR. SANGIAMO: Jeff, I shouldn't have to enforce Dr. Krah's right to finish his answers.
BY MR. KELLER:
Q. Are you done?
A. The control sera that were used in each of the assays, adult lab volunteer control sera.
Q. There is a chart that you provided. Can you -- it says number -- I can't quite read your handwriting.
A. Number of assays at titer.
Q. What are you trying to convey in this reference here?
A. My -- or I can't say with certainty at the time what I was conveying, but I can say what I have there, which is a distribution of how many assays. For example, the MKY serum was providing a titer of 1,024 versus 2,048, down to 512 at the far right-hand column. And then for the CM serum, the titers in -- how many times a serum had a given titer in an assay.
Q. Is it fair to say that Joe



Antonello was using the data generated during the Protocol 007 clinical runs to establish control runs?
MR. SANGIAMO: Object to the form.
THE WITNESS: Control -- my understanding is that the control, tentative control runs were set based on the validation protocol. Validation protocol indicated that additional assays would be run to gather additional data to verify or further support the control limit titers. These results are adult lab volunteer sera and the mocks that are involving -- they're from assays that involve Protocol 007 sera but these are not results related to Protocol 007 samples.
BY MR. KELLER:
Q. But they're run, each one of these assays runs a paired sera from kids in Protocol 007. Correct?
A. Each assay does, the data that were provided do not include those results.



Q. And each assay that's run has a mock control limit, an N2 positive control limit that are run in that assay. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: Each assay has a mock N2 positive control samples that are run. Each of which has limits for a valid assay.
BY MR. KELLER:
Q. So based on your review of the 44 assays that you captured the MKY controls, was the MKY control performing consistently throughout these 44 assays, based on your opinion?
A. Not being a statistician, I can't comment with statistical certainty, but I'd say 39 of the assays that had one titer of 1,024, six times it was within a twofold range of that. And in one case it was five -- sorry, two cases it was 512, which is twofold lower than 1,024.
Q. Do you recall ever providing Joe Antonello before you finalized his validation report all the data from Protocol 007



including the serum runs?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall which, if any of the Protocol 007, the mocks N2 and adult lab volunteer control sera from -- that were included in Protocol 007 were provided to Joe.
BY MR. KELLER:
Q. Let me direct your attention to 490656 which is on February 26, 2001. Let me know when you're there. If you look in the middle of the page under "Transferred," can you read what you wrote in your journal?
A. It says, "Transferred Excel files to Joe Antonello and Robin from Protocol 007 data summaries and the raw data files (44 files each.)"
Q. And those 44 files, are those the same 44 assays that you faxed to him, list the controls -- the control data?
A. It's the same number of samples. I can't say with certainty that it's the same sample. It's the same number of assays.
Q. Why did you provide Joe

Antonello the raw data from Protocol 006 before -- at this time frame? Why did you do that?

MR. SANGIAMO: Object to the form. Are you going to let him read the rest of it?

BY MR. KELLER:

Q. Strike that.

Dr. Krah, why did you provide Joe Antonello on February 26th all the raw data from Protocol 007?

MR. SANGIAMO: Feel free to read the rest of the entry, Dr. Krah.

THE WITNESS: I can't recall. Certainly I can read what it says, that they would -- this was that "They will apply the extravariability criteria test" to the data.

BY MR. KELLER:

Q. Do you know whether or not Joe Antonello used any of the data you used to validate Protocol 007 to add information to those 20 runs --

MR. SANGIAMO: Object to the form.



BY MR. KELLER:

Q. -- that were requested as part of the protocol that were tentative?

MR. SANGIAMO: Object to the form.

MR. KELLER: Let me strike that.

BY MR. KELLER:

Q. Could one of the reasons that you provided the raw data to Joe Antonello to help him update those tentative results with more information to finalize the validation report?

A. I don't recall that it was related to the validation report.

Q. Do you know when the validation report was finalized?

A. I don't recall.

Q. You don't recall. Did you ever disclose to CBER that you provided Joe Antonello data from the Protocol 007 runs to help validate the AIGENT SOP?

MR. SANGIAMO: Object to the form.

THE WITNESS: The control -- providing to Joe the mock and control



serum, the MKY and CM control limit titers, from my interpretation, was the only way to generate additional -- or any way to generate additional data would be using data from the actual Protocol 007 testing. So my expectation was when there was a request to have data from additional assays, the Protocol 007 assays would be the source of those control limits to include.

BY MR. KELLER:

Q. You testified earlier that you didn't expect that those tentative runs would be run with sera from Protocol 007 or run through -- the assays run through Protocol 007 but would be run separately through different assays?

MR. SANGIAMO: Objection. Mischaracterizes testimony.

BY MR. KELLER:

Q. You didn't testify to that?

A. Not -- that's not what I believe I testified to.

Q. Let me have you go back to



Exhibit 38, which is your e-mail dated December 10, 2001. Exhibit 38. You've read this e-mail already. Correct?

A. Yes.

Q. In the second paragraph you write, "The pediatric serum sample panels (sets 8 and 5 from Bev Rich's group) were used to evaluate seroconversion rates, pre-positivity and the assay cutoff (titer of 32 assigned negative)."

Do you see that?

A. Yes.

Q. And those pediatric serum panels, those are the ones that where Antonello proposed running 100 paired sample and you ultimately only had 50 paired sample. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can't -- from this, reading this, I can't tell how many samples were in those sets.

BY MR. KELLER:

Q. I see. You go on to write, "As recommended by Biometrics Research, the limits

were re-evaluated after interim analysis set was run to use a larger data set to establish the limits (I believe they recommended re-evaluating after 20 runs, since the number of runs in the validation studies were too low to provide an evaluation of the limits to be set for these)."

Do you see that?

A. Yes.

Q. And so -- and that is -- is that your understanding why you provided Joe Antonello the results of running the controls in Protocol 007 assays to help provide sufficient data to set reliable controls?

MR. SANGIAMO: Object to the form. Dr. Krah, you should feel free to read the parts of the paragraph that Mr. Keller elected to skip.

THE WITNESS: I believe, as instructed, that the 20 runs that we had, it indicates that the number of runs in the validation study was too low to provide an evaluation of the limits for those.

BY MR. KELLER:



Q. It's your testimony that those 20 runs were run in the assays that were used in Protocol 007. Correct?

A. The 20, I'm sorry.

Q. The 20 runs to validate the control limits were run through running the assays in Protocol 007?

A. My understanding and recollection is that those 20 runs are assay runs as part of the validation and not from Protocol 007.

Q. So is it your testimony that when -- in the validation protocol you stated that these results were tentative and that 20 more runs needed to be run, that those in order to validate the protocol with sufficient enough reliable data, that you had to look to the running of the Protocol 007 data to get sufficient data to have reliable data for the controls?

MR. SANGIAMO: Object to the form.

THE WITNESS: In order to -- my understanding is in order to get the data from a large enough or



sufficiently large number of runs, control serum values from assays that were run as part of Protocol 007 were included in that analysis.

MR. SANGIAMO: I got a feeling we're pretty much right at seven hours. I think we got five minutes.

VIDEOGRAPHER: Yeah. About two minutes.

MR. KELLER: We're at our seven-hour limit, Dr. Krah. Thank you for your time.

VIDEOGRAPHER: The time is now 6:14. This concludes the video deposition.

- - -

(Witness excused.)

- - -

(Deposition concluded at 6:14 p.m.)



CERTIFICATE

I do hereby certify that I am a Notary Public in good standing, that the aforesaid testimony was taken before me, pursuant to notice, at the time and place indicated; that said deponent was by me duly sworn to tell the truth, the whole truth, and nothing but the truth; that the testimony of said deponent was correctly recorded in machine shorthand by me and thereafter transcribed under my supervision with computer-aided transcription; that the deposition is a true and correct record of the testimony given by the witness; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WITNESS my hand and official seal this 20th day of July, 2017.

Linda Russi-Rios, RPR, CSR
Notary Public

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.



ACKNOWLEDGMENT OF DEPONENT

I have read the foregoing transcript of my deposition and except for any corrections or changes noted on the errata sheet, I hereby subscribe to the transcript as an accurate record of the statements made by me.

_____
DAVID KRAH

SUBSCRIBED AND SWORN before and to me this ____ day of _____, 20___.

_____
NOTARY PUBLIC

My Commission expires:



ERRATA SHEET

IN RE: USA ex rel. vs. MERCK

DATE: 7/11/2017

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(DATE) DAVID KRAH

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

| | | |
|---|---|---|
| UNITED STATES OF AMERICA ex rel., STEPHEN A. KRAHLING and JOAN A. WLOCHOWSKI, Plaintiffs, | : | CIVIL ACTION NO. 2:10-04374(CDJ) |
| vs. | : | |
| MERCK & CO., INC., Defendant. | : | |
| IN RE: MERCK MUMPS VACCINE ANTITRUST LITIGATION | : | Master File No. 2:12-cv-03555(CDJ) |
| THIS DOCUMENT RELATES TO: ALL ACTIONS | : | |

** HIGHLY CONFIDENTIAL - ATTORNEYS' EYES ONLY **

July 12, 2017

Continued videotaped deposition of DAVID KRAH, taken at the offices of Spector Roseman & Kodroff, 1818 Market Street, Suite 2500, Philadelphia, Pennsylvania 19103, beginning at 9:05 a.m., before LINDA ROSSI-RIOS, a Federally Approved RPR, CCR and Notary Public.

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- - -



I N D E X



E X H I B I T S





E X H I B I T S (cont'd.)

- - -

VIDEOGRAPHER: The date today is July 12, 2017. The time is approximately 9:05. This begins disc one of the continuation deposition of David Krah. You may proceed.

- - -

DAVID KRAH, after having been previously duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

BY MR. SCHNELL:

Q. Good morning, Dr. Krah.

A. Good morning.

Q. As I introduced myself, I'm Gordon Schnell and I'm going to be asking you questions today.

A. Okay.

Q. In your opinion -- well, let me -- let's get the record straight because I want to make sure we understand what the AIGENT test is. We got it yesterday. It's spelled A-I-G-E-N-T. Correct, Dr. Krah?



A. That's the acronym that we use for it, yes.

Q. And that stands for anti-IgG enhanced neutralization test. Right?

A. Yes.

Q. In your opinion, was the AIGENT test a reliable test?

A. In my opinion it met the appropriate criteria that were set in the validation plan, and as such, would be a reliable assay.

Q. And it was a reliable assay, in your opinion, for what purpose?

A. It was a reliable assay for the purpose of testing human sera for mumps neutralizing activity.

Q. Was it a reliable test for measuring the immunogenicity of the mumps component of MMR II?

A. I would say it was a reliable test to measure antibody to mumps. As such, the measurement of -- our intention was to use the antibody measurement as a means to assess the immunogenicity of the mumps component of MMR.



Q. That wasn't my question.

MR. SCHNELL: Can you repeat my question, please?

- - -

(The court reporter read the pertinent part of the record.)

- - -

MR. SANGIAMO: Object to the statement. Object to the implication that he hasn't answered the question, but you're asking that question again?

MR. SCHNELL: Could you just object to form and leave the coaching out, please.

MR. SANGIAMO: I'm not coaching. I will make the objections that are appropriate.

MR. SCHNELL: Are you objecting to form?

MR. SANGIAMO: Are you asking that question again?

MR. SCHNELL: I am asking that question again. Please limit the objection --

MR. SANGIAMO: Then I object.



MR. SCHNELL: -- to object to the form.

MR. SANGIAMO: I'll object consistent with the way objections are supposed to be made.

THE WITNESS: I would say it was, in my view, a reliable test to measure antibody. If antibody measurement was -- as antibody with the criteria that antibody measurement in the neutralization assay was an assessment of immunogenicity, I would say it was a reliable measure of immunogenicity.

BY MR. SCHNELL:

Q. And was the antibody assessment an accurate measure of immunogenicity?

MR. SANGIAMO: Object to the form.

THE WITNESS: I would say the -- all I can say is that the assay in my view was a reliable assay to measure antibody. If antibody is the criteria measure of immunogenicity, then the assay was reliable and suitable to be

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able to measure the immunogenicity.
BY MR. SCHNELL:
Q. I'm asking, is the antibodies that were measured in your AIGENT test an accurate measure of immunogenicity of the mumps component of MMR II?
MR. SANGIAMO: Object to the form. Asked and answered.
THE WITNESS: It was an assay format that was agreed to in discussion with CBER as a means to measure antibody responses to measles -- to measles, I'm sorry. To mumps.
MR. SCHNELL: Can you, please, repeat my question?
- - -
(The court reporter read the pertinent part of the record.)
- - -
THE WITNESS: I would say the assay, in my view, was a reliable assay. The measurement endpoint of measuring antibodies with the AIGENT assay was discussed and agreed to in collaboration with CBER. So given

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those statements, the expectation would be that it was a reliable measure of immunogenicity to mumps.
BY MR. SCHNELL:
Q. Do you believe it was an accurate measure of immunogenicity?
A. That's beyond my scope of responsibility and training. I can speak to the assay performance itself, not to the clinical implications.
Q. That's what I'm asking. In your opinion, did your assay give a reliable measure of the immunogenicity of the mumps component of MMR II?
MR. SANGIAMO: Objection. Asked and answered.
THE WITNESS: That's beyond the scope of my responsibility and training.
BY MR. SCHNELL:
Q. So your testimony is you don't have an opinion one way or another whether the AIGENT assay is an accurate measure of the immunogenicity of the mumps component of MMR II?

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MR. SANGIAMO: Objection. Asked and answered.
THE WITNESS: I have an opinion that the assay was reliable in measuring antibodies to mumps. As far as the impact on -- or the conclusion about whether it was reliable assessment to immunogenicity, I can't say.
BY MR. SCHNELL:
Q. Do you have an opinion as to whether or not the AIGENT assay was a reliable measure of how well the mumps component of MMR II protects vaccine recipients from getting the mumps disease?
A. I don't have any opinion on that.
Q. Do you have an opinion on how well the mumps component of MMR II works today in protecting vaccine recipients from contracting mumps?
A. I don't have an opinion on that.
Q. You have no idea?
MR. SANGIAMO: Object to the form.

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THE WITNESS: I read reports and taken part in meetings discussing protection from mumps, but I have no independent knowledge of -- or no independent opinion other than what I've read or discussed in meetings.
BY MR. SCHNELL:
Q. And all the clinical testing that you did while at Merck on the mumps component of MMR II has given you no indication one way or another as to how well the vaccine works at protecting vaccine recipients from contracting mumps?
MR. SANGIAMO: Objection. Asked and answered.
THE WITNESS: That's correct, none of the work -- the work that I did was involved in the assay development and using the assay, not in connecting those results to project on how well the mumps component works.
BY MR. SCHNELL:
Q. In terms of the data that resulted from the AIGENT test, is it your opinion that the data was reliable?

A. Yes.
Q. And there were two sets of data that came out of the AIGENT testing. There was what Merck has described as, quote/unquote, original data, and what Merck has described as, quote/unquote, corrected data. Is that true?
MR. SANGIAMO: Object to the form.
THE WITNESS: Could you clarify what you mean by came out of Merck? I believe you said data that came out of Merck.
BY MR. SCHNELL:
Q. I don't know if I said that, but have you heard of the term "original data and corrected data" as it relates to AIGENT -- the AIGENT study results?
MR. SANGIAMO: Object to the form.
THE WITNESS: To the data -- I do recall hearing those terms used in connection with the data.
BY MR. SCHNELL:
Q. What's your understanding of



what, quote/unquote, original data means in that context?
A. My understanding of that term is that those are the plaque counts as recorded -- as the primary data recorded in counting the plaques.
Q. What do you mean "primary data"?
A. The first -- the data that the person counting the assay recorded first.
Q. And then what's your understanding of what, quote/unquote, corrected data means as it relates to the AIGENT study results?
A. My understanding of the corrected data, those are values that had been changed from whatever the original entry was.
Q. And if an original data point was changed to become a corrected data point, and then it was changed again, would you consider that still corrected?
A. I would consider anything beyond the original entry as a corrected value.
Q. And if an original data point was changed so it became corrected but then it was changed again back to the original data



point, would you consider that original or corrected data?
A. My view of the original data was whatever the first number that was written down was for the plaque count. So if -- I would still consider that -- it's a number that's -- gets into semantic argument. The number would be a -- I would say it's a corrected number, but it's the same as the original -- in that description, as I understood it, it's the same as the original number.
Q. In your earlier answer when you testified that in your opinion the AIGENT data was reliable, were you referring to both the original data and the corrected data?
A. Yes.
Q. Do you have an opinion one way or another as to which, if either, of the sets of data was more reliable than the other?
A. I have an opinion based on analysis that our -- I don't recall if it was the biometrics group or another group did at Merck comparing corrected data with the original data.



Q. And what's your opinion based on that?
A. That the -- both results are comparable.
Q. In terms of what?
A. Seroconversion rate, as best I recall.
Q. What about in terms of pre-positive rates?
A. That, I don't recall what difference there was between the groups.
Q. What about in terms of invalid assays?
A. That, I don't recall.
Q. So, again, is your opinion that both sets of data are equally reliable?
A. Yes.
Q. So you don't believe the corrected data is more reliable than the original data for the purposes of the AIGENT test?
A. In looking at the global compiled data, I feel that they're both -- they both gave comparable seroconversion rates. Both are comparable estimates of

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providing data that are equally usable.
Q. Equally usable for what?
A. For assessing seroconversion rate.
Q. What about for assessing the reliability of the AIGENT test, do you have an opinion one way or another as to which was the better set of data if one was indeed better than the other in your view?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't have an opinion on that.
BY MR. SCHNELL:
Q. I want you to take me through the process in your lab that occurred with the AIGENT testing as it related to the counting of plaques. So could you kind of give me the narrative of call it a flow as to what your lab staff and you did in trying to calculate plaque counts from the various assays that were being tested in the AIGENT?
A. As best I can recall, the -- start from the point where the plates are stained and the plaques are visible, a counter

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would look at the plate typically with a light box to give some better visualization of the plaques, mark plaques with a Sharpie pen or an ink -- a laboratory ink pen, and then write the plaque count typically on the, could be the plate bottom or the plate lid. Different people had different preferences as to where to record the number. Those -- after an assay was counted, then those plaque counts would be transcribed into a notebook page which listed the plate number and then for each sample there are four -- sorry, three replicate wells, so it would be a spreadsheet capturing the plaque counts by plate and by replicate column row. Those plaque counts then would be transcribed into an Excel spreadsheet where a calculation would be done of the average number of plaques for the replicates and then a calculation of the plaque count as a percent of the mock value. And then an analyst would look at the data and assign a titer to the sample based on the highest serum dilution providing 50 percent or more neutralization.
Q. Is that the total path of the counting process?

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A. They're all the steps that come to mind right now that capture the general flow, the flow.
Q. Now, there was a correction log at some point that was instituted into this flow as well. Right?
A. There were plaque count checks that were driven by observations from the workbook, meaning flags that -- it's different for the first third of the data versus the second third and the third third of the data; meaning that in the second third and the third third a workbook was available that was implemented or included flags for various criteria that were identified as -- some of them I recall being part of the validation plan. They would identify samples that were deemed or warranting a check to verify that the plaque counts were accurate.
Q. That was only for the first third?
A. I'm sorry. That was for the second third and the third third. For the first third we did not have that, a workbook that displayed flags identifying samples

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warranting every check to verify accuracy.
Q. How did you check accuracy for the first third?
A. As best I recall, some examples were looking for or screening -- looking through the data. Sample sera are tested at multiple dilutions. We identify sera that were positive at a single dilution. Another example would be if we had samples where the -- there was -- I'm trying to think of the term, inconsistent neutralization or erratic neutralization, meaning that it was jumping back and forth in multiple dilutions between positive and negative. And at least in one other example, if we saw -- or one of the validity criteria for the test was to have no plaques in the unaffected cell control. So if we had an assay where there were plaques in the unaffected cell control, we would verify that they were indeed plaques. I can't say that that's all of the criteria that we used at first, but at least those are the ones that come to mind.
Q. So I want to make sure I understand this. So with the first third of

the data, and was that also referred to as the preliminary subset analysis?
A. I recall it as an interim analysis, but it may have had different descriptions.
Q. You recall a term "interim analysis," is that what you said?
A. That's the term that I'm recalling. I don't know what the official, if there was an official description of that first third.
Q. Did I say it right, interim analysis or was it interim subset analysis?
A. I can't recall with certainty, but the phrase that's coming to mind is interim analysis. But I can't say that's the -- that is necessarily an official description.
Q. What period of time did the counting of plaques for the interim analysis take place?
A. I don't recall specific dates, but it would have been in the time frame of when we were running assays for that first third. As best I recall, it was towards the



end of 2000. I don't recall -- and into the early part, meaning, as best I can recall, the first quarter of 2001.
Q. So does November 2000 to February of 2001 sound about right?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall. I only recall it was late 2000 into the first quarter of 2001.
BY MR. SCHNELL:
Q. So let's talk about that period of time and the counting that was done for the interim analysis. By the way, why was there an interim analysis done?
A. I don't have a full understanding of the reason for it. I have a general understanding. I don't know if that's the official reason. My general understanding is that it was to provide an analysis of an earlier read on the results of the immunogenicity testing for Protocol 007 before waiting till we had the full testing for the full set done.
Q. And what's your understanding as



to why you wanted an early read on the data?
A. I don't have a general -- I don't have a recollection of the reason. The only recollection I have was a discussion we're getting -- having -- rather than waiting till the full study is done, have a read into the results from a subset of the data. I don't recall the official reason for that.
Q. In the clinical trial work that you've done at Merck over the last, it's been about 30 years. Right?
A. I've been at Merck about 30 years.
Q. Yeah. In the clinical trial work that you've done there, is it typical to have an interim analysis done on the data that you're testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say that it's typical. In other studies that I've been involved in, it's one other study, I don't recall there being an interim analysis.
BY MR. SCHNELL:



Q. You've only been involved in one other study at your time at Merck?
A. One other clinical study that I can recall.
Q. Is that Protocol 006?
A. Yes.
Q. Those are the only two clinical studies that you've been involved in at your 30 years at Merck?
A. As best I can recall, yes, as far as running antibody assays, or any assays.
Q. What was -- was there anything special about Protocol 006 and Protocol 007 that led to you being tasked with running those assays?
MR. SANGIAMO: Objection. Answer if you know.
THE WITNESS: I'm not aware of anything special about the studies. I would offer that at least my manager Alan Shaw approached our group to develop the assays given our virology expertise.
BY MR. SCHNELL:
Q. So going back to the interim

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analysis which occurred, as you say, in late 2000, towards the first quarter of 2001, who were, during that period, the staff members in your lab who were involved in counting?
A. I can't say certainly who all of them were. We had -- there were some personnel changes during that time, so I would not be able to recite all of the people who might have been involved in the counting.
Q. Can you tell me who you do recall?
A. At least some of the assays would have included myself, Mary Yagodich, Colleen Barr. I believe some with Elizabeth Thoryk. I expect there are two other people, Stephen Krahling and Joan Wlochowski were in the lab in the first quarter. I don't recall -- I expect that there would be assays that they counted. I don't recall that with certainty.
Q. You didn't mention Jennifer Kriss, was she one of the ones also?
A. Jennifer Kriss was in the lab. I expect that she would have been one of the counters. I expect that she would be. I

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can't say with certainty that she was one, but I expect that she would have been one.
Q. Any others you can recall?
A. None that come to mind.
Q. In your opinion, were there any individuals within that group, including you, who were better at counting than others?
A. To my understanding, the best of my recollection, each of the counters was compared to a -- their counting accuracy was compared against a reference counter. So there was a reference counter, but in the -- as part of the training, the plaque counting -- as best I can recall, the plaque counting verification was done with a subset of plates from, I'll say, an assay. It may not be any particular study but just a set of plates that had plaques on them and to -- and verify that the new counters were counting within a targeted range of the reference counters.
Q. And that was something that was done before the actual counting of plaques and the AIGENT study commenced?
A. As best as I recall, that plaque

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counting training was done before any -- before those individuals counted plaques independently.
Q. So you wouldn't allow someone to count plaques unless they pass that preliminary test of counting ability. Is that correct?
A. That's the best of my recollection, yes.
Q. In the course of the counting, and now I'm extending it not only to the interim analysis but the full range of counting, were there any counters that you found particularly good or particularly bad?
A. I did -- later in the year I did a review or a verification of plaque counts against all the counters in the lab. As best I recall, there was one counter who had some assays that were given beyond the 10 percent counting consistency target.
Q. Just one?
A. As best I recall it was just one.
Q. Was that Mr. Krahling?
A. Yes.

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Q. So what action, if any, did you take in response to that?
A. I recall talking to Mr. Krahling about the plaque counts were identified as being extra variable, and asked him to be extra careful in counting plaques in subsequent assays.
Q. So you didn't stop him from counting plaques?
A. I don't recall that I stopped him, but I don't recall that he had any -- that any other assays were counted by him after we had identified the plaque count accuracy question.
Q. Who was the reference counter that you earlier testified about?
MR. SANGIAMO: Object to the form.
THE WITNESS: The reference counter that originally was established was Mary Yagodich.
BY MR. SCHNELL:
Q. Was that because you thought she was a highly qualify counter?
A. That's because she was the

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person in my view, who developed the assay and was the most experienced person in running the assay.

Q. Mary developed -- Mary Yagodich developed the assay?

A. In collaboration with me and others in the lab.

Q. Who else was involved in the development of the assay?

A. I was -- there were others -- there were other people in the lab who may have contributed experiments. I don't recall who -- I don't know who first was involved in running any of the development experiments.

Q. But in terms of who came up with the assay, that was you and Mary?

A. The assay was developed in discussion with CBER as far as the assay design and specifics including the virus strain, use of anti-IgG, the endpoint, the staining method. We had -- Mary and I and others in the lab had done experiments to evaluate effects of variables in the assay and then relay that information to CBER to get a consensus on the format for the assay.

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Q. But in terms of who at Merck led the design and development of the AIGENT test, that was you and Mary. Correct?

A. To the best of my recollection, yes.

Q. In terms of who led the testing, the AIGENT testing, that was you. Correct?

A. I was in charge of the lab that was running the AIGENT testing, the mumps AIGENT testing.

Q. Was Mary Yagodich the only reference counter in the AIGENT testing?

A. I was -- I considered myself a reference counter as well.

Q. Anyone else?

A. I don't recall. I don't recall.

Q. So getting back to the flow of the counting process, we'll start with the interim analysis because you said it was different for the first third of the AIGENT test than it was for the second two-thirds. Correct?

A. The analysis, the calculation of percent of mock was no different. What was different was the second third and the third

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third, and the assignment of a titer was no different between the first third and the second third and third third. The difference was that in the second third and third third there was a workbook that indicated flags for various results being extra variability, invalid dilution as examples.

Q. Let's look at that because you also mentioned for the first third there wasn't a flag system set up, but there was, I think you described it as the counters looking for certain things. Were the things -- you gave a couple of examples. Before we go through those examples, I want us -- were the things that counters were looking for in the first third of the AIGENT testing for accuracy purposes ultimately incorporated into the flagging system or was there a difference in terms of measuring the accuracy between the two portions of the AIGENT testing?

MR. SANGIAMO: Object to the form.

BY MR. SCHNELL:

Q. Let me make this easier. So for the first third when you I asked earlier about

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how you confirmed the accuracy of the counting, you identified the counters would look for data at a positive neutralization at a single dilution? Correct?

A. Yes.

Q. And you also mentioned they would look for erratic neutralizations. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: That was an example of a case where plates were checked for accuracy.

BY MR. SCHNELL:

Q. But that was something that you directed the counters to be looking for when they were doing these counting for the first third of the test?

A. I don't recall -- in some cases -- so I don't recall necessarily directing the counters to look for that in each assay, but in some cases, I would review the data and notice these conditions and then relay that information to the counter.

Q. And is that the same for the

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positive neutralizations at a single dilution?
A. There are cases for the single positive dilution where I relayed that information to the original counter.
Q. Is that the same for the plaques in the unaffected cell control plate?
A. Yes.
Q. Were there -- other than those three items, and, again, that's positive neutralization a single dilution, erratic neutralization or plaques in unaffected cell control plate, were there any other criteria that you were looking for in these -- in the interim analysis to ensure the accuracy of the counts?
A. I do recall some other conditions. I can't say that I recall each one of them. One example is a sample that would have an unexpected result, meaning, for example, pre-positive but post-negative. Pre-vaccination positive and post-vaccination negative.
Q. That would be an example of -- would that be an example of an unexpected result?

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A. It would be an example of an unexpected result with -- at least from my best recollection a question of whether there's a chance that the sera were reversed in the assay inadvertently.
Q. Any other criteria you were looking for to ensure accuracy with respect to the interim analysis?
A. I believe there were others, but I can't -- I don't recall others off the top of my head.
Q. Now, for the first -- for the interim analysis were you the only one who was looking through the data for these types of criteria to ensure accuracy?
A. No.
Q. Who else was looking through the data?
A. Emilio Emini.
Q. Anyone else?
A. I don't recall. I can't exclude anyone else, but I don't recall anyone else.
Q. And the process under which you and Dr. Emini went through, was it a formal process where you looked -- you or he or both

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looked at every single counting sheet for these criteria to ensure accuracy of the data?
MR. SANGIAMO: Object to the form.
THE WITNESS: As best I recall, the reviews that were done with Emilio Emini were going through, as best I recall, each counting sheet.
BY MR. SCHNELL:
Q. So your testimony is Dr. Emini reviewed every counting sheet in the interim analysis?
A. I can't say for the full interim analysis, but at least some number of assays from the interim analysis.
Q. Was there any rhyme or reason as to which assays he reviewed?
A. No. As best I can recall, they were whatever assays were available at the time.
Q. When he would review them, would he come to the lab or you would bring them to him?
A. I would bring them to him.
Q. He directed you to do that?

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A. Yes.
Q. What about what you did during the interim analysis, did you review every counting sheet for these criteria to ensure accuracy?
A. I recall at least looking through each counting sheet for the single positive dilution criteria. My best recollection is that I applied the rules uniformly across all the assays. So I would say that each -- I did review each assay, each counting sheet for those criteria.
Q. So in the instances where Dr. Emini reviewed the -- are we calling them counting sheets, is that the right term?
A. What actually is reviewed is not the counting sheet but the Excel spreadsheet where the counts are transcribed into.
Q. And that Excel spreadsheet would contain what information?
A. That would contain a plate code, the serum dilution, the plaque counts and average number of counts and percent -- average number of plaques and then a percent of mock that correlates with that number of

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plaques.
Q. So it would have all the information you would need to calculate whether something was a pre- or post-positive or a pre- or post-negative. Correct?
A. The counting sheet -- I'm sorry, not the counting sheet. The spreadsheet would not necessarily include the identification of which was a pre-vaccination or post-vaccination serum.
Q. Isn't that -- the spreadsheet does not contain that information?
A. At least the spreadsheet that we used for the first, as best I recall, we -- as best I recall, we wrote the -- I don't recall that the spreadsheet had -- as best I can recall, the spreadsheet had the plate code and the plaque counts and then we wrote, as best as I can recall, the serum identification in the right-hand column. So when the data was being reviewed with Emilio, I don't -- or -- with Emilio, I don't recall whether that information was on the spreadsheet or not.
Q. But didn't you say earlier that one of the criteria you looked for was whether

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there was a pre-positive and a post-negative?
A. Yes.
Q. So how would you be able to determine that if you didn't know which were the pres and which were the posts?
A. Eventually we would assign a titer to those samples and compile the results. At that point we'd know which -- what titer was corresponding to what pre- -- the post-vaccination serum.
Q. So for this review of accuracy you ultimately had all the information you needed to determine which was a pre- or post-positive or a pre- or post-negative. Correct?
A. Ultimately that information was available. It doesn't necessarily follow that the review always included that final compilation that included those details.
Q. Your review of the data did. Correct?
A. Some of it did, not all of it.
Q. So how did you determine whether you were going to do a complete review or a review that didn't have all the information

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you needed to identify the criteria you identified before for accuracy purposes?
A. I'm sorry, you referenced a full review?
Q. Well, a review that would enable you to look for positive neutralizations at a single dilution, erratic neutralizations, plaques in the unaffected cell control plate and whether a pre-positive went to a post-negative or other what you might describe as unexpected behavior?
A. Often the first two of those, the single positive dilution or erratic neutralization could be viewed without knowing whether it's a pre-vaccination or post-vaccination serum just looking at the data in column form where you have dilutions of the sera and looking at the percentage of the neutralization across the dilutions of the sera. To do the assessment of, for example, pre-positive or post-negative or verify whether there were plaques in the unaffected cell control, at that point we would -- I would need the code to know what data cells corresponded with what plate code.

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Q. Sometimes you had information and sometimes you didn't?
A. The data would be eventually available. I can't exclude that I didn't do review of the -- the single positive dilution or erratic neutralization before all that data was compiled.
Q. Is it you don't recall? Is it -- I didn't understand your answer. You said you can't exclude --
A. I can't exclude that there weren't cases that the data were -- the review of the single positive dilution and extra variability was assessed before doing the compilation of sera codes to go along with the samples.
Q. So were there instances when after you delivered to Dr. Emini the spreadsheet pages that had the information you discussed on it, that he came back to you and said this looks questionable to me, have the counter go back and take a second look?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do recall cases

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reviewing the data with Emilio that he did -- I would have particular dilutions of samples where he had said this looks like, for example, single positive dilution, this looks unusual, please have -- or have the counter verify the count for accuracy.

BY MR. SCHNELL:

Q. And were there other criteria that you recall him pointing out to you which led him to direct you to have the counter do a recheck?

A. I don't recall. The one I recall is a single positive dilution. I don't recall others.

Q. And when you say a single -- a neutralization at a single positive dilution, what does that mean?

A. It means that there are eight dilutions of -- or actually rephrase it. Neutralization at a single dilution. It means that there are eight dilutions of a serum tested. In the anti-IgG assay there is something called a prozone effect, meaning that the neutralization -- as the serum

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dilutes out, there may not be neutralization at the early dilutions, but then the prozone means that there's a region of antibody concentration where the anti-IgG is not effective in enhancing neutralization. So instead of having a neutralization curve where you'd have neutralization that's diluting out, you can have a sample where there's no neutralization and at one or several dilutions neutralization is detected. What single dilution neutralization means that only one of the eight dilutions is showing neutralization.

Q. And why would that be a result that would lead you to believe that there was a potential issue with accuracy?

A. At least one of the thoughts for that was that the -- there may be something about the staining or plaque visibility in those wells that allowed for an inaccurate count that then led to a reduced number of plaques being counted.

Q. Didn't you testify that it had to do with the anti-IgG?

A. The anti-IgG has an effect on the prozone. The plaque count itself is not

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directly -- the plaque visibility or clarity is not directly related to the anti-IgG.

Q. And when you found a positive neutralization of the single dilution, was it always the case that it was an unreliable result?

A. No.

Q. So sometimes they're reliable and sometimes not?

A. Yes.

Q. Would you always retest those?

A. No.

Q. You would recount those?

A. We would check the plaques to verify accuracy if there was a correction, if the count was not accurate, in recounting it, it turned out to not be neutralizing, that result would be reported.

Q. Would you do a third time to make sure that the second one was the accurate one and not the first one?

A. I'm sorry, for the counting or testing?

Q. For the counting.

A. Not that I recall.

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Q. Well, then, how could you be sure that the second one was more accurate than the first one?

A. In the recheck, the counts were only -- changes to the counts were only made if there was confidence that the plaques were miscounted in the first time.

Q. Why would there be more confidence that the second count was more accurate than the first count?

A. The confidence was that one was looking more -- it's my interpretation that someone was looking more carefully at the well to make sure that something wasn't being missed or miscounted.

Q. So it's your opinion that your staff, when they did a recount, did it more accurately the second time than the first time?

A. Not -- I wouldn't say that as a global statement, meaning that, for example, in some rechecks the plaque counts there were inaccuracies noted in some wells but not globally across the assay. So if someone counted the second time, it did not mean that

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they saw differences but they were specific dilutions of samples that were more typically showing inaccurate counts.

Q. You didn't institute any kind of two out of three rule with recounts?

A. Not that I recall, no.

Q. Wouldn't that have been more accurate than just recounting a second -- recounting once and picking automatically the second count?

A. I don't have a view on that.

Q. You don't have a view that if you had a first count that you had a question about and you did a second count, that relying on the second count is more accurate, would be just as reliable as doing a third count and taking whichever was two out of three?

MR. SANGIAMO: Object to the form. Asked and answered.

THE WITNESS: Not necessarily. In fact, part of the recheck, recount -- I can't say with certainty that it was applied in every assay but the intention was to have the original counter recheck the counts and verify

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whether they agreed that there were miscounts or miscounted counts.

BY MR. SCHNELL:

Q. So when you had a question about the accuracy of a count, you would go back to the same counter?

A. I can't say that that happened in -- well, I can't say it didn't happen in all cases, but that was in some of the assays my intention.

Q. And it was your intention that having the same counter recount the original count would be more accurate than having a different counter come in?

A. That in -- my interpretation at the time was that rather than add on the additional potential variability between counters, even though we had qualified all the counters, that it would be more reliable to have the original counter count. But in subsequent assays that wasn't always practical, meaning that those people might not be available to recheck plaque counts.

Q. When you went back to the original counter and told them to recount, you

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would tell them to recount the entire assay?

A. As best I can recall, I would identify that there was a question, identified for particular sample or plate and could they recheck that plate. I don't recall necessarily saying -- I don't recall saying to recheck the full assay.

Q. So you would tell them to recheck the individual plate with which you had a question. Correct?

A. I asked them to recheck the individual plate. I don't recall if I asked them to look at additional plates, but I don't recall them -- asking them to recall the full one -- to recheck the full assay.

Q. When you asked them to recheck the plates because of a concern you had on accuracy, did you tell them what your concern was?

A. As best I can recall, at least one example said there's a question about this. Well, in looking at it, at least one example, I said I see plaques that are missed, can you please verify whether or not you did it -- when you check it, that you get -- you

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see something. I don't think -- didn't give them a number to say, but just said I see a difference in counts than what you recorded, can you please recheck.

Q. So you would actually do the recount first and then you would send it back to the counter for them to do the recount?

MR. SANGIAMO: Object to the form.

THE WITNESS: As best I can recall, the example I'm thinking of, I would look at -- the most straightforward one to me is looking at a plate, spots were put on the plate to identify where a plaque was counted. I would look at the plate and say I see spots that aren't marked by a Sharpie. So those look like plaques that were missed. Or I see spots next to something that doesn't look like a plaque. That would tell me that it looks like they're -- they counted something that wasn't a plaque.

BY MR. SCHNELL:

Q. So you wouldn't go back to the

counter and say, hey, we have a question about this one, recount it, you would say, hey, we have a question about this one because of X, Y and Z, recount it to make sure you're accurate?

MR. SANGIAMO: Object to the form.

THE WITNESS: As best I can recall, I would say that I -- can you verify the counts for this. In some cases saying I looked at the plate, I see a different plaque, I see more plaques or less plaques than what you have got, can you please recheck. It doesn't mean that I counted the plate but I -- just looking at the plate, I can see that something was either not being counted or counted as a plaque that didn't look like a plaque.

BY MR. SCHNELL:

Q. Now, this positive neutralization of a single dilution occurs predominantly in pre-vaccination samples because of the prozone effect. Correct?

A. I don't know that that's



correct. I agree with the prozone effect but I don't recall that it's specific or happens more frequently in the pre-vaccination sera.

Q. In your experience with this assay, that wasn't the case. In virtually every instance when there was a positive neutralization at a single dilution, it was a pre-positive and not a post-positive?

MR. SANGIAMO: Object to the form. Asked and answered.

THE WITNESS: As best I can recall, there were -- I don't recall the actual numbers but there were single positive dilution samples in post-vaccination sera as well as pre-vaccination sera.

BY MR. SCHNELL:

Q. But I'm saying in terms of the vast majority where this occurred, it occurred on the pre-vaccination side. Isn't that correct?

A. I do not know that that's correct.

Q. Well, in terms of how the prozone effect works, wouldn't it make more



sense that it happened on the pre-vaccination side?

A. No.

Q. Doesn't the prozone effect mask neutralization?

A. No.

Q. It doesn't?

A. It doesn't mask neutralization that was going to happen in the absence of anti-IgG.

Q. Is there a difference in terms of neutralization depending on whether anti-IgG is part of the solution?

A. There's -- if one titrates serum, I don't believe there's a difference in quality of the antibody that's being detected. If you had -- part of the -- this is largely not based strictly on Protocol 007 experience but other neutralization experiments, for example, Protocol 006 where we tested at higher serum concentrations. For example, we could have a serum that neutralizes at 1 to 2 or 1 to 4 -- I don't recall 1 to 2 is the first exposure. For example, 1 to 4 dilution or 1 to 8 dilution, that would neutralize



whether you had anti-IgG or not at that dilution. It's much more likely at a higher dilution. In the anti-IgG assay, knowing that there's a prozone effect and to conserve sera volumes, we started a 1 to 32 dilution. So we did not have the capability of seeing whether or not serum would have been positive at 1 to 4, 1 to 8 or 1 to 16 dilution. So my expectation is that the anti-IgG would not mask neutralization if it was going to happen at a higher serum concentration. But we did not test those higher serum concentrations.

Q. The neutralization that you're talking about when it comes to anti-IgG, are you talking about just mumps neutralization?

MR. SANGIAMO: Object to the form.

THE WITNESS: I'm talking about mumps plaque reduction.

BY MR. SCHNELL:

Q. Anti-IgG also leads to neutralization of non-mumps antibodies. Correct?

MR. SANGIAMO: Object to the form. And asked and answered actually.

THE WITNESS: The anti-IgG is not specific for mumps antibodies so it's capable of binding to other antibodies. Whether or not it neutralizes or not, I don't -- I can't say.

BY MR. SCHNELL:

Q. So how do you know, then, if you're using anti-IgG, whether the neutralization that occurs is mumps neutralizing or non-mumps neutralizing?

A. That was addressed in the -- the specificity was an aspect that was addressed as part of the validation plan to demonstrate mumps specificity.

MR. SCHNELL: Can you, please, repeat the question?

- - -

(The court reporter read the pertinent part of the record.)

- - -

THE WITNESS: So anti-IgG on its own does not neutralize mumps. We showed in a paper by Sato from the FDA for a similar effect. In our studies



we did -- did studies absorbing sera with measles, mumps, rubella antigens to demonstrate mumps specificity of the neutralization.

BY MR. SCHNELL:

Q. So if you mixed anti-IgG with human serum, it's going to neutralize -- it's going to show neutralization of mumps neutralizing antibodies and it's also going to show a neutralization of non-mumps antibodies. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: It could -- in this assay we have -- there's -- the indicator virus is mumps in the assay. So we're detecting mumps specific neutralization.

BY MR. SCHNELL:

Q. But how? If there is anti-IgG in there, how do you know if it's the antibodies that are mumps neutralizing or the other types of antibodies that the anti-IgG combined with?

A. In an example I gave, the



specificity studies that were part of the validation, we took sera, absorbed it with measles, mumps, rubella antigen, given these were MMR recipients and we're comparing pre- and post-vaccination sera. The boost in titer would indicate -- between pre- and post-vaccination sera would indicate that within that time frame between the two bleeds there was a boost in the antibody. And then with the absorption of measles, mumps, rubella antigen demonstrated mumps, that absorbed with mumps antigen reduced the neutralization capacity of the serum more than the other antigens, suggesting that the antibodies were being attacked that were mumps specific.

Q. I think it was 50 percent specificity. Correct?

A. That's not my interpretation of the results.

Q. What was your interpretation?

A. My interpretation of the results was that the antibody titers were reduced more significantly by mumps than any of the other -- than measles or rubella. And some of the sera, some of the sera were, from my view,



not a valuable, meaning they were negative for all the absorbing antigens.

For the pediatric sera, as best I recall, two -- I don't know pediatric or adult sera, two of the four showed less or some effect of rubella absorption on titers, but I would argue that those, the lack of absorbing -- more efficiently absorbing out mumps antibodies for those who are -- absorbing out the antibodies for mumps from those sera may be a reflection of the titer of those sera rather than the specificity itself, meaning that we're adding a fixed amount of antigen to absorb the antibodies. We don't have a guarantee that we're adding enough antigen to absorb out all of the antibodies.

Q. So the test that you say you conducted, measles, mumps, and rubella, didn't show that 100 percent of the neutralizing antibodies were mumps neutralizing. Right?

MR. SANGIAMO: Object to the form.

THE WITNESS: No, in fact, there are published absorption experiments. I've never seen one that showed 100

percent reduction of antibody specificity with the absorption.
BY MR. SCHNELL:
Q. So some of the neutralization that occurs when you're using anti-IgG in the mumps testing that you did would have resulted from non-mumps neutralizing antibodies. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: From my interpretation, that's not a conclusion that I would make from that -- from the specificity data.
BY MR. SCHNELL:
Q. So is your testimony that 100 percent of the neutralization that occurred in the AIGENT testing was mumps neutralizing antibodies?
A. My testimony is that the specificity study demonstrated that the assay was showing specificity for mumps. I can't speak to whether it's 100 percent. I don't have familiarity or insight into the application to say whether one can say it's



100 percent. All I can say is that the assay from my view demonstrated specificity -- absorption experiments demonstrated specificity. Whether one can assign 100 percent, that's -- it's not a term that I'm familiar with or have any familiarity with to say whether the 100 percent value applies.
Q. So you just don't recall one way or the other?
MR. SANGIAMO: Object to the form.
THE WITNESS: I would say my recollection is that the absorption experiment showed mumps specificity. How one then assigns what -- not saying it's specific or nonspecific, I'm not familiar with how one assigns a percent value.
BY MR. SCHNELL:
Q. You can see that anti-IgG binds with any kind of antibody in the blood. Right?
A. No.
Q. So it binds with mumps antibodies, right, mumps neutralizing



antibodies?
A. Only IgG antibodies.
Q. Okay. So is mumps the only one?
A. There are other potential IgG antibodies.
Q. Flu? Could it bind with flu antibodies?
A. I can't exclude it. I don't know what sera -- what the recipients of the vaccine, what antibodies they would likely have. But I would agree in theory, if it's an appropriate IgG antibody, it could bind to the anti-IgG.
Q. So what are some other IgG antibodies that it could potentially bind to?
A. Any -- whatever IgGs are in serum.
Q. What are those?
A. In an infant I don't know what --
Q. Do you know any?
A. I don't -- I just would be pulling virus names out of the air.
Q. It could be measles. Right?
A. Yes.
Q. It could be rubella?



A. Yes.
Q. It could be flu?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't know. The measles, mumps, rubella I agree to because they're given more vaccine. As far as flu, I don't know. Again, I would agree in theory a flu antibody could bind. Whether or not the infants would have flu anti-IgG, I don't know.
BY MR. SCHNELL:
Q. So what steps, if any, did you take to control for the possibility that the anti-IgG was showing a false neutralization because it was detecting or it was allowing you to detect in the AIGENT testing non-mumps neutralizing antibodies?
MR. SANGIAMO: Objection. Asked and answered.
THE WITNESS: The absorption experiments from my view demonstrated the mumps specificity. Another aspect which is my -- I've seen it in other publications, I don't -- I can't recall

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with certainty if this was included in the discussion of the current assay, is that we have a pre-vaccination serum and then a post-vaccination serum. If they're given MMR, you only -- the expectation would be that the infants are only going to make antibodies to those three viruses in that time period. So if one had a question about flu antibodies or other antibodies, it would be unlikely that those -- comparing the pre- and post-vaccination titers, that they would change concomitant with the MMR vaccination or integral between bleeds with the MMR vaccination.

BY MR. SCHNELL:

Q. Were the subjects in the AIGENT testing screened beforehand to make sure that they didn't -- their blood didn't contain any other IgG?

A. I'm not aware of any screening.

MR. SANGIAMO: Gordon, we've been going about an hour and five minutes. If you get to a good stopping

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point.

MR. SCHNELL: A few minutes.

BY MR. SCHNELL:

Q. So the AIGENT testing had controls. Right?

A. The AIGENT assay had a control of those serum, meaning virus anti-IgG in the absence of serum. It had a, call it a control, but a mock sample which is the control -- sorry, that's not right. The control which is the virus anti-IgG and no serum. Virus anti-IgG and no serum. And then there were adult -- two control sera in each assay. And then uninoculated controls.

Q. For the negative control you used the mock control I believe you said?

A. That's not a negative -- I guess one could call it a negative control. I don't view it as a negative control. I view that as the baseline.

Q. So how did that control, if at all, control for the possibility that anti-IgG was going to lead to false neutralization?

A. That sample included anti-IgG in the absence of serum. So it would -- that was

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a control to verify that the anti-IgG was not -- would account for -- would verify the anti-IgG was not neutralizing mumps.

Q. How could it do that if the control didn't have serum?

A. That's the -- the intent of that control was to demonstrate -- or in previous experiments we looked at adding anti-IgG or not to virus, and there was no impact and confirming the results of the Sato paper. So it's a control not for serum but for the anti-IgG. We did not have a control for -- for example, we did not have a negative serum control.

Q. Did the Sato paper talk about controlling for anti-IgG?

A. I'm sorry, in what way?

Q. In any way.

A. I recall that they -- the publication described dilutions of anti-IgG. As best I can recall, they had a -- no serum control. I don't recall if they had other -- what other controls, if any, were described.

Q. Again, if there's a risk that using anti-IgG will bind with non-mumps

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neutralizing antibodies, how can you control for that possibility if you don't use serum in the control?

A. As we state here, in the case of a paired sera, the pre-vaccination serum is not intended as a control but it serves as a -- in effect a control, meaning that if pre-vaccination serum are predominantly negative, post-vaccination serum are seroconverting, that that pre-vaccination serum indicates that -- negative pre-vaccination serum result indicates that there's no detectable mumps antibody or other -- it is my interpretation no mumps antibody from your description would -- if there's any potential -- would address the absence of mumps specific antibody in those sera. Whether or not other antibodies that were in there could or would or could neutralized mumps, we don't have other viruses in there to see what other viruses might be present and neutralized.

Q. So how could you be sure, maybe this wasn't important to your experiment, but I would assume it would be, how could you be

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sure that the neutralization results you were getting in the AIGENT testing was specific, 100 percent specific to not -- to mumps neutralizing antibodies?

MR. SANGIAMO: Object to the form.

THE WITNESS: Again, going back to the validation study, as best I recall, those -- the results of the validation study were presented both to Merck and to CBER. They did not raise concerns over that specificity. My conclusion from that was that the assay was specific, demonstrated to be specific for mumps.

BY MR. SCHNELL:

Q. If you had used a non-immune serum, a non-immune control, meaning non-immune serum in the control, and anti-IgG, wouldn't that have told you exactly whether or not there was neutralizing antibodies caused by the anti-IgG that were not mumps neutralizing antibodies?

MR. SANGIAMO: Object to the form.

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THE WITNESS: No. That has one major caveat to my understanding in that negative serum is, from my understanding, not an absolute value, meaning it depends on the assay that's used to show that it's devoid of antibodies to mumps.

BY MR. SCHNELL:

Q. Didn't you use it for the ELISA testing?

MR. SANGIAMO: Object to the form.

BY MR. SCHNELL:

Q. Wasn't that critical to the ELISA testing?

MR. SANGIAMO: Object to the form.

THE WITNESS: I'm not familiar with the ELISA -- it's a different assay, so I don't --

BY MR. SCHNELL:

Q. You don't know what controls, if any, they used?

MR. SANGIAMO: Object to the form.

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THE WITNESS: I'm not -- yeah, I don't know the specific controls that they used.

MR. SCHNELL: Okay. We can take a break.

VIDEOGRAPHER: The time is now 10:16. This ends disc one.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is now 10:33. This begins disc two. You may proceed.

BY MR. SCHNELL:

Q. Dr. Krah, in terms of the interim analysis, taking us back to the flow of the plaque counting process, in terms of the interim analysis, when you were reviewing the spreadsheet which had the data that derived from the plaque counting, and you were looking for criteria to confirm accuracy, was that something that you were directed to do?

A. I would say the single positive dilution aspect, as best I recall, was something in reviewing the data with Emilio

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Emini that he, I wouldn't say directed, but pointed out that those were ones that he thought were worthy of verifying plaque counts. So I wouldn't call it a directive, but in doing that and realizing that some of the counts were not accurate became something that seemed appropriate to continue, from my interpretation to continue doing. So one point it is a directive but something that came out of initial discussions with Emilio.

Q. When you say that in reviewing this and you finding out that the plaque counts weren't accurate in this regard, how did you confirm that they weren't accurate?

A. Well, not -- the original counters were, as I indicated, I can't -- I don't recall in each case the original counter was the one that verified it, but I had confidence that the person doing the recheck was taking an accurate count. I would point out that not all of them -- some were accurate and some weren't. So it wasn't always -- in each case where there was a check, it did not result in a correction.

Q. But you always believed that the

second count was more accurate than the first count. Correct?
A. That's my best recollection, yes.
Q. What's that based on?
A. My confidence -- it's based on my confidence in the first count plaques were miscounted, the person realized that in the recount and then had a -- in some cases, not all the cases resulted in a change, but that their recount verified whether the original result was accurate or the correction was accurate and that recount, the recheck gave me confidence that the person verified the accurate plaque count.
Q. So these were criteria for checking views to determine whether or not there should be recounts. Correct? That's what we've been talking about, this criteria for the interim analysis was the criteria that you were guided by in determining whether or not there should be recounts?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not sure I



understand the question.
BY MR. SCHNELL:
Q. So the four criteria you outlined, positive neutralization single dilution, erratic neutralization, plaques and unaffected cell control and pre-positives to post-negatives, those were criteria that you identified before that you looked at to determine whether or not you were going to direct a recount?
A. Those were conditions in which we looked at the plates and did a recount to verify the accuracy of the counts.
Q. So what about for retesting, was there also a set of criteria that you were governing -- that you were looking towards to determine whether or not a retest was appropriate?
A. There was a criteria for -- there was a criteria for retest that involved an invalid result for -- in the first part I don't recall if this applies. The point I was trying to -- I was thinking I was trying to make is that in one of the -- if there was an aspect to our pre-vaccination serum or a



post-vaccination serum that made that sample result invalid, the pair would be retested. We always tested the sera as a pair in the same assay. Which the point there being that if, for example, one of the serum -- like a pre-vaccination serum result was valid, a post-vaccination serum was not valid, we would retest the pair together. To get a valid result, you needed a valid pre- and post-vaccination serum result.
Q. So what were the circumstances that would lead to a pre- or post-vaccination sample being invalid?
A. In the first third, I don't recall the specific example. The second third and third third, for example, there were, I believe, what was described in the workbook as an invalid dilution, meaning a -- for example, if for a given serum dilution we have triplicate wells, the samples are inoculated in triplicate wells, we need at least two -- values for two of those wells to have a valid result for that well; meaning that if we only had one result out of the three replicates, that would be an invalid dilution. So there



would be no opportunity to determine whether that serum was neutralizing or not.
Q. Any other examples?
A. No. We had cases where, besides the extra -- there was extra -- extra variability criteria was part of that. And in some assays we're having, for want of a better description, tearing of the monolayers, they need some healing of the cells that prevented getting an accurate count for those wells. Those would then result in, from my interpretation, a similar invalid dilution. There may be other cases. Those are two that comes to mind.
Q. So with the extra variability criteria, what would that entail?
A. That -- as best I understand it, it was a value established by our statistician. It's not an area I'm fluent in. My general understanding is that it looked at the variability between the triplicate well values or having duplicate wells would still be valid. So looking at variability between the duplicate and triplicate wells. And then there was a calculation involved to, as best I

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recall, identify a range that is statistically acceptable between, as best I recall, the high and the low value in that range. So my understanding it's basically looking to see if the numbers, if the replicate values are unusually unlike each other.

Q. Was positive neutralization in a single dilution ever used as a criteria for retesting?

A. Positivity of a single dilution was used, not specifically for pre-positive.

Q. So that was also used as a criteria for retesting?

A. As best I can recall, a single positive dilution was flagged for not necessarily -- I'm sorry, not for retesting. For plaque count as a first check, not -- there are some samples that were tested, retested as part of an understanding the assay and monitoring the assay. There were single positive dilutions. But in those cases, the result of the original test was always reported if the original result was valid.

Q. So getting back to the interim analysis, I want to make sure I understand the

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path. So the counter would first look at the plate, count the plaques, and each time they counted the plaque, they would mark somewhere on the plate a dot for each plaque they counted. Correct?

A. That's my understanding and recollection of the -- how they were counted.

Q. Then the plaque count, would they double check that?

A. Not that I'm aware of. From my own personal experience, as part of the counting of the plate, I would mark the spots and then give a second look, not recheck, but look to see that I didn't miss something.

Q. And were there instances where you missed something?

A. I recall cases where the plates -- occasionally the plaques aren't visible. It may be like -- hard to describe, but they could be at the corner of the well so you need to tilt the plate back and forth a bit to make sure that you're seeing all the surface of the wells. But I considered that not a recheck but part of the original counting. Because I hadn't finalized the

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number, the count number for that well yet.

Q. So you recall instances at least where you were counting where you would do a count, and you'd mark it on the plate and then you would check your count and get a different number?

A. It's not a -- I wouldn't characterize it as a check. As part of the routine counting, after I put spots in the plate, I tilt the plate back and forth to make sure that I wasn't missing something. So it's not a recount or a check but a verification that something wasn't being missed.

Q. So you didn't double check your work, you would just count once, give it a little look and that's that. Right?

MR. SANGIAMO: Object to the form. And asked and answered.

THE WITNESS: As best -- as far as -- I don't recall doing -- unless it was part of a recheck of additional assay plates later, I would not recheck or recount that particular plate.

BY MR. SCHNELL:

Q. And you didn't direct your staff

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to either?

A. No.

Q. Would that have made the counting more accurate?

A. From a statistical criteria, I can't say whether it would have. My understanding was that when we're doing the plaque count qualification, it's typically a person counts the plate, set of plates, another person counts the set of plates. We were doing the plaque count comparison with a single round of counting. So whether or not a second round of counting would have had an impact, I don't have a thought.

Q. Do you recall during the counting process that you would on occasion go to some of your counters while they were counting and help them count?

A. I recall some counters when they were counting saying I'm having trouble seeing these plaques, they look kind of faint or they're not readily visible, can you take a look at this and verify that I'm counting accurately.

Q. Do you recall finding that there