23-2553

IN THE

United States Court of Appeals

FOR THE THIRD CIRCUIT

UNITED STATES OF AMERICA EX REL.,
STEPHEN A. KRAHLING; JOAN A. WLOCHOWSKI,

against

MERCK & CO, INC.,

STEPHEN A. KRAHLING; JOAN A. WLOCHOWSKI,

Appellants.

On Appeal from the United States District Court
for the Eastern of District of Pennsylvania
The Honorable Chad F. Kenney, Case No. 2:10-04374-CFK

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were instances where the counts were changed because of them consulting you in that fashion?
A. I don't recall cases of that.
Q. So that didn't happen?
A. I can't say that it didn't happen. I don't recall any cases where it did happen.
Q. So after the counts were marked on the plate, then that number was transcribed into what you called a notebook page or spreadsheet. Is that correct?
A. I described it as a notebook page because I'm thinking -- in the spreadsheet in my mind, I'm thinking of the Excel spreadsheet for that. This is -- the notebook page is basically a page with a list of plate -- a plate code, a space for numbers of plaques, three separate cells or spots to put the plaque counts. So it's basically like a page with blank spaces in which the plaque counts could then be transcribed.
Q. So that was the first place of recording plaque counts after it was recorded on the cell plate?

A. Yes.
Q. You called that a notebook page?
A. I called it a notebook page. I don't know if that's the official description. But that's -- it's a page that was included in the full assay documentation, but I did refer to it as a notebook page.
Q. Was it also referred to as a counting sheet?
A. I believe, yeah, there were -- yes.
Q. And then the next -- after it was entered into the notebook page or the counting sheet, which you're saying is the same, it was then entered into an Excel spreadsheet?
A. Yes.
Q. This is for the interim analysis. Correct?
A. This is for any assay, any of the AIGENT assays.
Q. And then the Excel spreadsheet performed calculations in terms of percent mock and whether it was a positive or negative neutralization?

A. It calculated or had a column that indicated a percent of mock. It was a manual interpretation, meaning an operator would go through and look at the results to decide whether it was positive or negative neutralization.
Q. And you were the operator that you're referring to?
MR. SANGIAMO: Object to the form.
THE WITNESS: Multiple people in the lab did that interpretation.
BY MR. SCHNELL:
Q. Was it the counters that did it?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not in every case.
BY MR. SCHNELL:
Q. So some cases the counters would calculate whether or not their counts led to a positive or a negative neutralization and in other instances it was individuals other than the counters?
A. There are cases where -- so the assays would be counted depending on

availability of the people, what else they were doing, that person may then enter the information in the spreadsheet or they may give that counting sheet to another person to enter into a spreadsheet. The interpretation results could then be the person who entered the spreadsheet or it could be another person. It wasn't -- all the steps weren't done by the same people for a given assay.
Q. Sometimes it involved the counters, sometimes it involved you and sometimes it involved someone else. Correct?
A. As far as entering into the spreadsheet and interpreting the results to determine neutralization titers, yes.
Q. Why was that part of the counting process?
A. Sorry, what part?
Q. Why was the analysis of the data to determine positive and negative neutralization part of the counting process?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't know if I -- I wouldn't characterize it as part

of the counting process, but it's part of the process from having the counts to the final results.

BY MR. SCHNELL:

Q. The final results being?

A. The titers for the samples.

Q. And that was the responsibility of your lab?

A. The responsibility of our lab was to run the assay and report the serum titers.

Q. Okay. And so after the calculations were made on the spreadsheet, then titers were assigned?

A. By interpreting the results in this spreadsheet, we would identify the highest solution that was given, 50 percent or higher neutralization, and then identify the serum dilution that corresponded to, which would, in turn, identify the titer.

Q. That would be entered into the same Excel spreadsheet. Correct?

A. That was written -- it was written on the spreadsheet. I don't recall that it was entered into the spreadsheet, the

electronic spreadsheet, but in some cases I recall it being written in the margins of the spreadsheet.

Q. In terms of what you testified to earlier with regard to you and Dr. Emini reviewing the data for accuracy, was it the counting sheets that you looked at or was it the spreadsheet that you looked at? Was it both or was it neither?

A. I recall when taking the full notebooks, they included all of those, the counting sheet and the spreadsheet. The data that I recall reviewing with them, as best I can recall, were the -- was the spreadsheet. It does not exclude that at some point we looked at the raw data and the counting sheets, but the data that I recall him reviewing with me were the Excel spreadsheets.

Q. And then if it was determined by either you or Dr. Emini that something raised a question, and I'm referring to the four criteria you identified previously, then am I correct that the process would be that you would go back to the counter, tell the counter which sample raised a question, sometimes tell

them what that question was and then direct them to do a recount?

MR. SANGIAMO: Object to the form.

THE WITNESS: I can't say in every case I went back to the original counter. For example, if the original counter was busy, I might have checked the count but the -- for those where I did go back to the original counter, as best I can recall, I would say that there's a question about the counts for this plate or these particular wells, can you please check them, see if you agree that there is a change or not. If you agree that your original counts are accurate, leave them as they are. If there is a correction, to put in the correction.

BY MR. SCHNELL:

Q. And sometimes you would tell them you missed some counts, look at this again. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't -- I recall at least in one case saying I looked at the plate, I see some plaques that it looks like you missed. I didn't say how many. Whether I, in all cases, told the counter if I see something that doesn't look like a plaque or it looks like you missed plaques, I don't recall.

BY MR. SCHNELL:

Q. And then if they did the recount and found that there was a change that -- to be made, they would go back to the notebook page or counting sheet, as we're calling it, and they would cross out the original count and they would write in the new count and then they'd sign it and date it?

A. Typically at a minimum initial and date it. I don't know if it was full signature, but initial and date it typically.

Q. And then they would go back to the Excel spreadsheet and overwrite what was in the spreadsheet?

A. Yes.

Q. So the spreadsheet wouldn't

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reflect the changes, only the counting sheets would. Correct?
A. That's correct.
Q. And the counting sheets never had changes on them that weren't indicated. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: The counting sheets reflected accurately the first whatever the count was that was -- the count from the plates.
BY MR. SCHNELL:
Q. And you're 100 percent certain that every counting sheet had the original counts done on the assay on plate the very first time. Correct?
A. I don't have any -- yes. I don't have any evidence to the contrary or understanding to the contrary. I didn't look at every person running every assay, but I have no expectation of it.
Q. Because that's what you directed your staff to do?
A. To count the plaques and -- what

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I directed the staff was to count the plaques, transcribe the results from the plate onto the counting sheet.
Q. And then what happened to the cell plate after this process was complete?
A. My understanding, we had a quality assurance group that would review the data, review the entire assay packet which included the cover page, notebook page that describes the assay or a brief narrative of the assay purpose, and then there are multiple attachments including a serum code for what sera were part of the assay. I don't recall all the attachments that are part of it, but they would include the counting sheet, the Excel spreadsheet. As best I can recall, a -- for the first time I'm not recalling with clarity whether we included a -- the data were eventually put into a database. I don't recall if that information from the database printout was included as part of the assay packet. At any rate, the assay packet was reviewed by quality assurance. Once that review was completed, my understanding was that those plates were no longer needed. The

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plaque counts on the counting sheet served as a primary data source, and in some cases assays were then discarded after the QA audit was completed.
Q. So the quality assurance group, did they actually go back to the assay plates and double check the counts?
A. Not to my knowledge.
Q. So they only checked to make sure that the transcription that occurred at plaque counts was free of error. Correct?
A. There were multiple things that are part of the review. I don't know all the parts of the review, but as far as I know, they did not go back, to my understanding, to the original plates.
Q. So the quality assurance group played no role in ensuring the quality of the original counts. Correct?
A. To the best of my understanding, they did not serve a role in verifying the transcription of the plaque counts from the plate onto the counting sheet.
Q. Once the quality assurance group was complete or was finished with their task,

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then you said that the assay plates were discarded?
A. My -- not all of them were, but some were.
Q. And who decided which were to be thrown out and which were to be maintained?
A. As best I can recall, when the quality group indicated they were done, they said we are done with the review of these assays, Leah Gottlieb, who is our local quality person, indicated that the plates could be discarded. That doesn't mean that that day I went and discarded those plates. We would -- could get or discard them one at a time or like we have a large number of assays that are completed, we need to free up room in our incubators, we would have potentially discarded blocks of assays at one time.
Q. And who within your lab was responsible for discarding the assay plates?
A. I would say my -- I was responsible for identifying which assays for which the review was completed. As far as who was responsible for the physical discarding, I don't recall, but I would identify which ones

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were not needed further and could be discarded.
Q. Did you discard yourself any of the assay plates?
A. I recall at least in some cases discarding, yes, assay plates.
Q. How did you go about doing it?
A. The plates, once verification matching up that the plates that we were planning to discard were ones that the QA audit was completed for, would place the plate in an autoclave bag, which is part of our normal laboratory disposal process.
Q. Is that a type of incinerator?
A. No.
Q. What's an autoclave?
A. It's a steam sterilizer.
Q. So what happens when you put the plates in a bag in the autoclave?
A. It basically sterilizes them.
Q. So it eliminates any ability to count how many plaques were on that assay?
A. No.
Q. You can go back and count them?
A. One could. The heat distorts the plates a little bit so there's some

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potential warping of the plates. But that heat treatment by itself I would not expect to destroy the plaques.
Q. So if you wanted today to go back and double check all of the plaque counts that were made, you have those plates?
MR. SANGIAMO: Object to the form.
THE WITNESS: We have -- there's -- there are plates that we still have from that testing. It's not all of the assays.
BY MR. SCHNELL:
Q. Where are the rest?
A. Some were discarded for which -- when the QA audit was completed.
Q. But you just said discarded doesn't mean you can't read them.
MR. SANGIAMO: Objection.
BY MR. SCHNELL:
Q. I'm not sure what you mean by "discarded." When you say "discarded," do you mean destroyed?
A. Discarded is a process that ultimately leads to destruction. The first

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step is the autoclaving. Then that material, those are then placed, removed from the lab and then eventually they become -- they're discarded. I don't know Merck's process for discarding.
Q. So anything that entered the autoclave was ultimately discarded?
A. It was on the path of discarding and then eventually it was discarded.
Q. So with the interim analysis, were all the assay plates that were part of that analysis since discarded?
A. I don't recall. We made an inventory of plates that we had or have, but I don't recall whether the interim analysis was among those.
Q. Well, the process, if I understand it correctly, was that once quality assurance completed their audit, then those plates would be discarded. Right?
MR. SANGIAMO: Object to the form.
THE WITNESS: They're eligible for discarding. It doesn't mean that day or that week we discarded them. We

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may, since we're doing other work, we may -- we're not in a -- I'm trying to discard the plates as soon as the audit is done, but we may wait until we have a large stack of the plates and then say that we're going to discard a block of them at a time.
BY MR. SCHNELL:
Q. So did I miss anything -- this is now about the interim analysis. Did I miss anything in terms of the original plate counting all the way through the entering on the various documents or spreadsheets, to quality assurance, to ultimate discard of the assay, is there anything along that path that we haven't discussed?
MR. SANGIAMO: Object to the form.
THE WITNESS: The best of my knowledge, I tried to highlight the key steps, or I can't say that every detail of all the steps that was included.
BY MR. SCHNELL:
Q. Now, was this plaque counting process something that you derived?

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A. Me personally?
Q. Yes.
A. No.
Q. Who derived it?
MR. SANGIAMO: Object to the form.
THE WITNESS: It's a -- I'm sorry. Clarify the plaque counting process meaning the checks or the counting itself?
BY MR. SCHNELL:
Q. The steps, the flow that we just went through. Do you want me to go through it again so it's clear?
MR. SANGIAMO: Same objection.
THE WITNESS: So it's a flow or the assay itself was developed largely by myself and Mary Yagodich. The flow of the assay was -- for example, the flow of the plaque counting and entering --
MR. SANGIAMO: You can continue with your answer.
THE WITNESS: -- entering into the spreadsheet was used in Protocol

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006. So the QA audit part came in with input from QA as to what that flow involved. So the flow of running the assays, entering the counts, entering the data into the spreadsheet, is something we used for many other projects. Whether I was the originator of that, I can't say, but it's something that we had used for multiple applications.
BY MR. SCHNELL:
Q. What other applications did you use it for?
A. Routine plaque assays. For example, for measles, mumps, rubella, varicella, rotavirus.
Q. Was it written down?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall if those specific steps were detailed in the SOP or not. They may have been, I just don't recall.
BY MR. SCHNELL:
Q. Was it GMP compliant?

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MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding -- well, I can't say with certainty. I don't have -- there was a later assessment of the laboratory as far as being GMP compliant, but whether the steps we were doing at the time were GMP compliant, I can't say with certainty with one caveat, that from a later FDA inspection, the cross outs, without a documented reason for the cross outs and plaque changes, were viewed as not compliant with GMP.
BY MR. SCHNELL:
Q. Was it viewed as not compliant with GCP also?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't know.
BY MR. SCHNELL:
Q. You know what I mean by GMP and GCP?
A. I'm familiar with CGMP. GCP I'm not familiar with.

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Q. What about the discarding of plates, was that GMP compliant?
A. From my understanding, yes.
Q. What's that understanding based on?
A. Consulting with other groups at Merck including the manufacturing division where they run potency assays and plaque plates are discarded.
Q. So before you discarded any plates, you checked and got confirmation from that group that it was okay to throw out the plates?
MR. SANGIAMO: Object to the form.
THE WITNESS: It was not checked beforehand. It was verified in follow-up discussions with them.
BY MR. SCHNELL:
Q. With whom was it -- did you confirm it?
A. I don't recall the specifics.
Q. Which group were they in?
A. The varicella group was one of them.

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Q. Was it a man or a woman?
A. That, I don't recall.
Q. This was an oral conversation or in writing?
A. As best I can recall, it was an oral conversation.
Q. By phone or in person?
A. As best I recall by phone.
Q. So let's move now to beyond the interim analysis. Did you have a name for the second two-thirds of the AIGENT testing?
A. We didn't have an official name. I guess I can refer to it as the balance of the testing. I don't know if there was an official name for it.
Q. The interim analysis involved roughly a third of the test subjects. Is that correct?
A. As best I recall, it was approximately a third of the total number of patients enrolled with equal distribution of the three vaccine groups in that third.
Q. And you were done with the interim testing by the first quarter of 2001. Correct?

A. As best I can recall, that was approximately the time frame when we were done that interim -- our part of the interim testing.
Q. And then when did -- did you commence the balance of the testing after you had completed the interim testing?
A. Yes.
Q. And did you commence the balance of the testing after you had done your analysis of the interim testing results?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall the dates when the interim analysis result was finalized and when we began complete testing for the balance of the set.
BY MR. SCHNELL:
Q. Is it fair to say that the bulk of the balance of the testing, if not all of the testing, was done after the interim testing results had been analyzed?
MR. SANGIAMO: Object to the form.

THE WITNESS: I can't say with certainty. Expectation that would be the case, but I don't have a recollection of the dates.
BY MR. SCHNELL:
Q. So the testing of the balance of the samples commenced sometime after the first quarter of 2001. Correct?
A. That's -- yeah, the best of my recollection, it was after the first quarter.
Q. And when was it completed?
A. As best I can recall, sometime in 2002.
Q. Do you know when in 2002?
A. No, I don't remember.
Q. So now I want to go through the same flow of the counting process that we just did for the interim analysis but for the balance of the testing. So tell me if it differed in any way.
A. So the counting did not differ, the counting of the plates. Then transcribing onto the counting sheet did not differ. Transcription of the plaque counts from the counting sheet into the workbook, the

transcription did not differ but it was a different workbook, meaning that in the first third we had an Excel spreadsheet which was, for want of a better description, a generic Excel spreadsheet. For the balance of the testing, another group provided a workbook that had -- was set up as a template with prepopulated cells, including serum dilution, a plate code or plate number. And then would automatically calculate average number of plaques, a percent of mock and then having -- I'll say by flags, I don't recall if flags was just a color flag or an actual set of words, samples or dilutions that triggered certain criteria; for example, extra variability for the three replicate wells in a dilution; an invalid dilution. There were some other descriptions there. Those are two at least that come to mind.
The data from the workbook, as best I can -- from the workbook from the -- the balance of the testing, as best I can recall, I can't recall with certainty, but as best I can recall, I believe it had a column that included the titer, meaning that for the

first third we mainly looked through the data and assigned a titer manually going through and saying what's the highest solution test that provides 50 percent or more neutralization. The workbook for the balance of the testing, as best I can recall, actually calculated or identified a titer.

Q. So to understand the process for the balance, the same as the interim analysis with regard to the counter looking at the plate and then marking on the plate with a magic marker the plaques that they counted. Correct?

A. Yes.

Q. And then like the interim analysis and the balance of the testing, they would then write the count on a counting sheet. Correct?

A. Yes.

Q. And then instead of those numbers then being transcribed onto an Excel spreadsheet where manual calculations were made, they were entered into a workbook where the same calculations were automatically tabulated. Is that correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: As best -- it was a different -- it was -- for the balance of the testing it was a different -- it was a spreadsheet with prepopulated calculations. And as best I can recall, it would do some -- it would do some number of calculations, for example, average number of replicate plates, percent of mock, and best I recall the titer for the serum.

BY MR. SCHNELL:

Q. It would also calculate positive or negative neutralizations. Correct?

A. I don't -- that, I don't recall.

Q. And what you're describing, that's the workbook that you're using, the term. Right?

A. That's the -- what I was referring to in that latter description is the workbook that, as best I recall, the biometrics group prepared for us.

Q. Now, were you still -- like you were with the interim analysis, were you still

looking at the counting sheets as they were being prepared?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't -- in the first third in the balance of the testing what was being looked at were the spread -- the work -- Excel spreadsheet or the workbook. I don't -- I would not say that the counting sheets themselves were being looked at.

BY MR. SCHNELL:

Q. Are you talking about the balance?

A. The review of the data to identify, for example, the single positive dilution was on the Excel spreadsheet, not the counting -- done with the Excel spreadsheet, not the counting sheet.

Q. So in the balance of the testing, were you still looking at the results as they came out in the workbook?

A. In the workbook, yes.

Q. And was Dr. Emini also looking

at the workbook as the results came out?

A. I don't recall for the balance of the testing Emilio looking at the results.

Q. So you don't recall one way or the other, is that what you're saying?

A. I don't have a recollection of him looking at them.

Q. And when you looked at these results, did you undertake the same process that you did for the interim analysis which is where you saw some -- which was if you saw something that made you question the accuracy of the count, you would then go back to the counter and tell them to recount?

A. The first part to that, the workbook had flags that would identify some of the conditions that we identified in the validation plan and from our earlier testing, for example, single positive dilution or extra variability. So just to point out that the workbook would highlight samples that looked unexpected or unusual. In other words, in the first third we were doing that manually. So it was more automated for the validated -- I'm sorry, the balance of the testing.

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Q. And how did the counter come to learn that their counts were being identified in the workbook as questionable?
A. As best I can recall, for ones the original counter was checking, I would say there's a question about this particular plate or these dilutions, could they verify the plaque counts.
Q. So it was still largely you going back to the counter and identifying the question with regard to their counts?
A. In some cases I was -- eventually, as best I can recall, I was the one relaying that information to the counters. Another person in our quality group, Leah Gottlieb, was going through the workbooks and helping to identify samples for the balance of the testing that had these flags for extra variability or single positive dilution, then relay that to me. I would then relay that to the lab members. So it -- ultimately it was me who would typically relay that information to the lab staff.
Q. In terms of the flags that you described on this workbook, were they flagging

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the same criteria that you identified as raising questions with you on the interim analysis, that being positive neutralization at a single dilution, erratic neutralization, plaques in unaffected cell control and pre-positives, post-negatives?
A. I don't recall the specific -- I recall examples of flags that the workbook was capturing. I don't recall with certainty whether all of those flags matched up with observations we were having from the first third of the testing.
Q. Which do you recall?
A. The ones for -- not remembering was one of the -- the one I was thinking of was the single positive dilution. But I don't recall that that was -- if that was a flag, if the workbook was flagging that. I can't say with certainty which ones, which of the flags, which flags matched observations or rationales for checks for the first third.
Q. You can't remember any?
A. I don't recall specifically what is -- what was flagged or what the flags were.

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Q. And then in terms of what happened after the workbook entries, did it then go to quality assurance if there were any recounts -- okay. I'm sorry, take that back.
So if you directed one of your staff to recount, and they did and had a change, would those changes be recorded in the same manner on the counting sheets as they were for the interim analysis?
A. Yes. The result would be counted, there were -- I know or I'm aware of at least two exceptions to what I'm about to say. The majority of the cases, the person would cross out the original result, write in the corrected result, initial, and date it, then put that number into the -- that revised number into the spreadsheet. The two exceptions I'm thinking of, there was one case where in two assays that I recall, there was a large number of samples that were given erratic neutralization. In rechecking the plaque counts, it was noted that the plaque counts were quite consistently -- or consistently not accurate. So in those cases, what was done originally was to -- I recounted

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the entire assay and used those data in place of the original data. What we wound up doing was go back eventually to the original entries and use those and ignore the recounting. I give that as an example where at least -- where two assays were identified as having consistent and extreme plaque count differences from what looked like they were accurate. And instead of correcting individual counts, the entire assay was recounted.
Q. Who came up with the idea of replacing the Excel spreadsheet that was used on the interim analysis with the workbook that was used at the balance of the testing?
A. I don't know who the original -- I can't say who the original idea came from. I can't say that -- I think Joe Antonello in our statistics group was someone who I had -- had discussed with me that that was available for us to use.
Q. But you didn't come up with the idea of switching from an Excel spreadsheet to a workbook, did you?
A. Not that I recall.

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Q. You don't know who did?
A. I don't know who originated it. I can say who provided it to us, but who proposed that, I don't know.
Q. Well, was it someone within your lab?
A. Not that I'm aware of.
Q. Weren't you the one running the test?
MR. SANGIAMO: Objection. The question is, were you the one running the test?
THE WITNESS: Yes, I was the one running the test.
BY MR. SCHNELL:
Q. But this significant -- was this a significant change in the process?
A. To me, it was a way of facilitating the -- obtaining the titer since I did calculations for it. So to me it didn't change -- there were some other criteria that were included as part of the workbook that we were not applying, or one criteria that we were not applying in the first sort of extra variability criteria. To me it was not a

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significant -- at least I personally was not viewing it as a significant change in the process but was just a workbook that allowed cutouts of steps that we had to do manually. So it allowed for more facilitated compilation of the data.
Q. Do you know why the workbook was instituted, implemented into this flow?
A. All I can say, I don't know the ultimate reason. All I can say is that Joe Antonello proposed using it and we adopted using it.
Q. So it was Dr. Antonello who proposed --
A. As best I recall, he was the one who I recall having discussions about the availability of this workbook and using it.
Q. Was he involved in the interim testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: He's in the biometrics group. I don't recall -- he was involved in supporting the statistical analysis of validation

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study that we did, validation protocol that we did. I don't recall whether he had any involvement in the interim analysis.
BY MR. SCHNELL:
Q. But as far as your recollection is, just so that the record is clear, it is Dr. Antonello who came up with the idea of replacing the Excel spreadsheet used in the interim analysis with the workbook that you've been describing for the balance of the testing?
MR. SANGIAMO: Objection. Misstates the testimony.
THE WITNESS: My understanding is that he talked to me and said here's a workbook that's available that you could use. I wouldn't say that he -- I wouldn't characterize as him saying this is one that you should use or must use, but this is available if you choose to use it.
BY MR. SCHNELL:
Q. So you have no idea who came up with the idea then. Am I right?

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A. I don't. As best I recall, he said I have this available. If you want to use it, use it.
Q. But you don't know why he came to you with that suggestion?
A. I recall some aspects of the workbook that he specifically mentioned would include some of the information learned from the validation. For example, the extra variability criteria. So it included some additional analysis of trying to identify samples that were behaving unusually.
Q. Was this workbook GMP compliant?
A. I do not know that it -- it was not validated. I don't know if it was GMP compliant.
Q. It was not validated, is that what you just said?
A. At the time we were using it, my understanding is that it was not validated.
Q. You have no idea whether it was GMP compliant?
A. I don't know what the requirements are for that.
Q. Do you know if it was GCP

compliant?
A. I don't know.
Q. So after quality assurance did its task, and I'm assuming it's the same task that they did for the balance of the testing that they did for the interim testing. Correct?
A. As best I can recall, it's the same general set of steps, like reviewing whatever the experiment documentation was. And then the part I'm not very clear on, the documents that -- I'm trying to think of the words, that support the information that was submitted into the clinical database.
Q. But like with the interim analysis, they did not confirm that the original counts were accurate by going back to the plates and confirming the plate counts. Correct? The plaque counts.
A. That's correct, to the best of my knowledge, yes.
Q. All they did was check for transcription errors?
A. Amongst other parts of the review. But as far as the data, going from

the original -- the plaque count, counting sheet, the best of my understanding, looked at the plaque count counting sheet and looked at transcription into the workbook.
Q. Was the process under which quality assurance acted for either the interim analysis or the balance of the testing GMP compliant?
A. I can't answer. I don't know.
Q. Was it GCP compliant?
A. I don't know.
Q. Was there any aspect of the testing that you led with regard to the AIGENT assay GMP compliant?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not know whether it was or wasn't.
BY MR. SCHNELL:
Q. Was there any aspect of the AIGENT testing that was GCP compliant?
MR. SANGIAMO: Same objection.
THE WITNESS: I don't know.
BY MR. SCHNELL:
Q. Did there come a time in the

August 2001 time period where the members or representatives from the CBER unit of the FDA came to your lab and conducted an inspection of the AIGENT testing?
A. I do recall representatives from CBER, two representatives came to -- were allowed to conduct an inspection. As best I can recall, it was early August. I don't remember the specific date.
Q. Do you know what prompted the inspection?
A. No, I don't.
Q. No idea?
A. No, I don't.
Q. Were there any members of your lab who had complained to you about any of the operations you were conducting relating to the AIGENT testing?
A. The only comment I received from lab -- one member of the lab staff was a comment that we knew which was -- which samples were pre-vaccination and which were post-vaccination.
Q. That was the only comment?
MR. SANGIAMO: Object to the

form.
THE WITNESS: To the best of my recollection, yes.
BY MR. SCHNELL:
Q. And that was a comment by Steve Krahling?
A. Yes.
Q. So no one other than Steve Krahling ever complained about what was going on in your lab during the AIGENT testing period?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not regarding -- or not that I'm aware of.
BY MR. SCHNELL:
Q. So when the FDA came in August 2001, what was your involvement, if any, in the inspection these representatives conducted?
A. My involvement was primarily with Cathy Carbone; Deborah Bennett, I believe, was the other FDA representative there. But my involvement was primarily with Cathy Carbone. That included over the course

of five to six hours giving a tour of the laboratory, giving her an opportunity to talk to some members of the lab to ask questions about the assay. And I say labs, since we had two labs, two lab spaces at the time. And then for the majority of the day to bring over lab notebook documentation and sit next to her reviewing the data side by side with her. And reviewing the data meaning reading through the procedures, the documentation, looking at the plaque counts and then she did independent calculations on the -- our calculations including review of plates that had corrections.

Q. Before I forget, going back to the plaque counting process that occurred with the balance of the testing, after quality assurance did their task, did you then discard the assay plates like with the interim analysis?

MR. SANGIAMO: Object to the form.

THE WITNESS: We made a list of plates that were -- that are available and were available at the time. I know

that some plates were discarded. Not all of them were discarded.

BY MR. SCHNELL:

Q. And was there -- is there anything in the flow of the plaque counting process for the balance of the testing that you haven't identified?

MR. SANGIAMO: Object to the form.

THE WITNESS: In what way? As any part of the process?

BY MR. SCHNELL:

Q. Did we cover the highlights like we did for the interim testing? For the balance of the testing, did we cover the highlights of the plaque counting flow?

MR. SANGIAMO: Object to the form.

THE WITNESS: I guess -- well, the one -- I guess one aspect to the flow that, as best I can recall, is in the review of the -- I don't recall being -- systematic part of the process for the first third was that for the balance of the testing, Leah Gottlieb,

who was in our quality assurance group, served a role of reviewing the spreadsheets to flag the samples, or dilutions and/or samples that were providing flags in the workbook or providing single positive dilutions. In the first third, either I or other members of the lab did some of that review. In the balance of the testing, Leah Gottlieb was doing the majority of that to help facilitate the flow of identifying samples to recheck.

BY MR. SCHNELL:

Q. By the time the FDA came for this inspection in August 2001, how much of the balance of the testing had been completed?

A. I don't recall specifically, but my -- I have a general sense that we were nearly complete. I don't know if that's -- I wouldn't say that that's accurate, but my general recollection was that we were winding down the testing. I can't say that with certainty.

Q. Why is that your general recollection?

A. Just because I recall at the time thinking about other projects that we'd be doing after this work was done.

Q. You said that you introduced Carbone and Bennett to members of your staff to be interviewed. Is that correct?

A. I don't remember Deborah Bennett coming through the lab. Cathy Carbone and Deborah Bennett were in a meeting room with myself and other Merck representatives. Cathy Carbone came through the lab. I don't recall introducing her, but she just walked through the lab and would ask questions of people I'd say at random, but I don't recall specifically introducing her to anyone.

Q. Do you recall, other than speaking with you and Dr. Shaw, either Carbone or Bennett speaking with any members of your lab?

MR. SANGIAMO: Objection.

THE WITNESS: I'm sorry, repeat that.

\- - -

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

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- - -

THE WITNESS: I recall Cathy Carbone talking to -- when she was going through the lab, asking questions of people in the lab.

BY MR. SCHNELL:

Q. Who did she speak to?

A. I don't recall specifically.

Q. And then you reviewed data side by side with Carbone?

A. Yes.

Q. Not with Bennett, just Carbone?

A. As best I recall, Cathy Carbone was sitting immediately to my left and Deborah Bennett was at the other end of the table.

Q. You were in a conference room?

A. Yes.

Q. Were you looking at -- well, what were you looking at with them?

A. They were experiments from the AIGENT testing. I don't recall if -- how the -- how many assays were from the interim analysis set and how many were from the balance of the testing.

Q. How many assays did you -- how

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many assay samples did you look at?

A. I don't recall. I remember it being several -- we brought over several binders, each of which would have multiple experiments in it. But I don't recall -- I can say it took -- we did it for several hours. We did the review for several hours. I don't recall how many assays were --

Q. And it was the counting sheets that you were looking at?

A. The whole assay set.

Q. So it would be the counting sheets, it would be the Excel spreadsheet or the workbook, depending on which part of the testing it was?

A. Yes, and the titer assignments.

Q. What did they, if anything, did they ask of you with regard to this review?

A. I don't recall specifically what they asked. All I can say is that I answered every question they asked truthfully and completely.

Q. And that process lasted several hours. Yes?

A. Yes, they came, I think, as best

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I recall, sometime in the morning and then left like 5:00 or later. So it was the majority of the day. So several hours.

MR. SCHNELL: I'm about to turn to a document if you want to take a break.

VIDEOGRAPHER: The time is now 11:36. This ends disc two.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is now 11:55. This begins disc three. You may proceed.

MR. SCHNELL: I want to mark as Krah Exhibit 40 an e-mail dated August 7, 2001, from Karen McKenney, M-C-K-E-N-N-E-Y, Bates-numbered 52249 through 53.

Before we circulate that with our group, Dino, I want to point out it's marked highly confidential. I don't think it is. I'll honor if you want to keep it. But if you just want to take a gander, I don't -- I mean,

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we'll excuse Mr. Krahling and Ms. --

MR. SANGIAMO: I prefer if we just honor --

MR. SCHNELL: If you guys step out for maybe a couple minutes.

- - -

(Exhibit Krah-40, 8/7/01 E-mail with attachment, 52249 - 52253, was marked for identification.)

- - -

BY MR. SCHNELL:

Q. Mr. Krah, you are marked as a recipient of this document. Do you see that? Third line next to Dr. Emini.

A. Yes.

Q. You have no reason to believe that you didn't get a copy of this. Right?

A. I don't have a reason to suspect that I didn't.

Q. The first -- on the second page -- first of all, who is Karen McKenney?

A. I don't know, the bottom of the page lists a GMP Compliance person that I don't -- the name is not familiar to me.

Q. The second page of the document

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is the 483 report that CBER issued in connection with the inspection in August 2001 that we've been discussing. Is that correct?

MR. SANGIAMO: Obviously take your time to look at it.

THE WITNESS: Yes, it looks like that's dated August 6, 2001.

BY MR. SCHNELL:

Q. Yeah. You've seen this before. Right?

A. Yes.

Q. This is the write-up of the four areas that CBER had issues with in connection with the inspection. Correct?

A. There are four areas that they deemed appropriate to issue the 483 report.

Q. What is a 483 report?

A. I'm sorry, I'm not familiar with -- I recall seeing it. I don't know all aspects to it.

Q. Is that the only 483 report that involved work you did at Merck during your time your time at Merck?

A. I'm not aware of any other work during my time at Merck that anything that I

was doing received a 483.

Q. I'm going to go through this. If you need time after I ask a question to look at it, feel free. This is a summary purportedly prepared by Ms. McKenney and a few others, that summarizes the inspection we've been referring to, and I just want to follow up on some of the observations that are in this report?

MR. SANGIAMO: How about if you just give him a minute or two to look it over, and then if you go through line by line and he feels a need to look further, he can do it then.

MR. SCHNELL: If you want to take a like bit, like a minute or so, but I'm not really going to go line by line. I have a couple questions. Maybe some of it is line by line.

BY MR. SCHNELL:

Q. Have you seen this document before?

MR. SANGIAMO: Hold on, I think he's still looking.

THE WITNESS: Yes, I have seen

it before.

BY MR. SCHNELL:

Q. When have you seen it?

MR. SANGIAMO: You should exclude any review with attorneys.

THE WITNESS: My best recollection is that I saw it at some point after the inspection. But I don't recall specifically when. I don't -- I can't tell -- it has "To Distribution." I don't recall if I was part of that distribution.

BY MR. SCHNELL:

Q. Other than Dr. Shaw and yourself, are you aware of any other Merck employees who met with either Carbone or Bennett at the inspection?

A. There were other Merck employees present.

Q. Who?

A. It was a room full of people. I'd estimate a table similar to this size with Merck people there and even perhaps some sitting separate from the table, but I don't recall --

Q. When you were going --

MR. SANGIAMO: You don't recall?

THE WITNESS: I don't recall specific names of people who were there other than Alan and myself.

BY MR. SCHNELL:

Q. When you were going through the data, was Dr. Shaw with you?

A. When we were going through the data, my -- Cathy Carbone was sitting to my left. My focus was on answering her questions. I don't recall if Alan was -- it was in the conference room. Other people were in the room. I don't recall if Alan was there or not. I wasn't really paying attention to who else was there.

Q. So do you recall if anyone else from Merck was there?

A. The room was full of Merck -- other people. So there were other people from Merck there.

Q. Now, if you look at the line right above "DAILY ACTIVITIES," it says, "While not an observation, Ms. Bennett voiced her expectation that data generated from human

subjects be controlled under the requirements of CGMP."
Do you see that?
A. Yes.
Q. You were not aware of that expectation. Correct?
A. That's correct.
Q. That was the first you heard of it?
A. That was the first I heard of it personally.
Q. And then in the next paragraph, towards the bottom, the last sentence actually, it says, "Also discussed during the tour were laboratory practices for evaluating variability in the plaque neutralization assay to determine the need for plate recount."
Do you see that?
A. Yes.
Q. Do you recall what you discussed with either Carbone or Bennett with regards to that subject?
A. I don't recall specifically to it, but I do see in the copies provided there's, in addition to the SOP, for example,

memo to file, all "'Responses to Flags for Questionable Values in the Data Spreadsheet,'" the seventh bullet point down.
Q. That's the one dated June 21, 2001?
A. Yes. Yes. I don't recall the Memo D. Krah to FILE, Review of MUMPS AIGENT Neutralization Data, August 1, 2001. I don't recall that one.
I recall there was a document provided that gave a summary of criteria for the recount. I don't recall with certainty that that's the one, but amongst these, my understanding was that that information was provided to her at the -- as part of this meeting.
Q. So that was the August 1st document you're talking about?
A. I believe that's what I'm talking about. I'm not completely certain that that's the one, but amongst the documents provided or the -- sorry, the copies provided list here, one of them is that, as best I can recall, description of the recount process.
Q. And did the discussion you had

with Dr. Carbone or -- and/or Bennett about the variability process follow a similar line of questions that we were -- a similar line of discussion that we were having earlier in the day about the plaque counting process you employed?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall specifically. I would say that whatever questions primarily Cathy Carbone and Ms. Bennett, I don't recall her asking personal questions or -- whatever questions Cathy Carbone asked, I answered as best I could and truthfully and completely. And whatever -- she seemed satisfied with the completeness. So whether I included all the details with the same flow description I provided earlier, I can't say with certainty. But I did answer all the questions.
BY MR. SCHNELL:
Q. The next paragraph says, "During the tour, Dr. Carbone was interested in

procedures for handling pre- and post-vaccination sera steps taken to minimize the effect of inter-assay variability."
Do you see that?
A. Yes.
Q. What did you tell her in regard to that subject?
MR. SANGIAMO: So if you feel you need to read the rest of the paragraph, do so. That seemed to address that.
THE WITNESS: I don't see the description of that in this paragraph. I don't recall my specific answer to that question. What I would say today would be my answer. I don't recall what I provided to her as an answer at that time.
MR. SCHNELL: I'm sorry, can you read the answer back?
\- - -
(The court reporter read the pertinent part of the record.)
\- - -
BY MR. SCHNELL:

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Q. So you don't recall a single thing you told her with regard to this inquiry?
MR. SANGIAMO: Object to the form.
THE WITNESS: I recall answering every question that she asked to her satisfaction. I just don't recall my response to this -- I have an answer that I would give today if she asked the question, but I don't recall at the time what I said.
BY MR. SCHNELL:
Q. Even one thing?
A. I don't recall my specific answer to -- about this. Today, I would say what I would answer today. I can't say with certainty that that's what I said during the inspection. It's what I expect I would have said during the inspection, but I don't recall specifically what I said at the inspection.
Q. If you turn over to the next page, the first paragraph -- I'm sorry, the second paragraph, it says, "Dr. Carbone was interested in the trigger that would result in

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re-evaluation of assay raw data."
Do you recall anything that you spoke to with Dr. Carbone to respond to that interest?
A. Comments on -- I don't have a direct recollection, I'm just reading what it says here. I explained, for example, the extra variability criteria which was a criteria that was in the workbook that was part of the -- I'm sorry, the balance of the testing is sometimes referred to, the balance of the testing, as the second third and third third. So I was preventing myself from rephrasing, re-describing that. That was, I believe, an example of her concern that for the first third we did not have that workbook. So, therefore, the extra variability criteria was not applied. For the balance of the testing in 2001, the workbook was available, didn't have an extra variability flag. So that meant that those -- the data from those sera were being flagged differently than the first third.
Q. Did you tell her that for the first third you actually did apply that extra

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variability criteria but you did it manually?
A. We did not -- from my understanding, we did not apply the extra variability criteria. The extra variability criteria to me means the variability between triplicate wells or duplicate wells. We were looking at things, for example, like single positive dilution, erratic neutralization. That is separate from extra variability. I don't recall that we were -- I don't recall that we were manually assessing extra variability for the first third.
Q. Did you disclose to either Dr. Bennett or Carbone that you were -- the criteria we discussed earlier which you looked for in terms of directing the plaque counters to do recounts?
A. As best I --
MR. SANGIAMO: Object to the form.
THE WITNESS: As best I can recall, I described to her what I described to you of, if a plaque count, a sample in question was identified, that the preference would be to go to

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the original counter, have them recheck the count. If there was a correction, make it. If there was no correction, to leave it as it was.
BY MR. SCHNELL:
Q. Did you tell Dr. Carbone or Bennett that on some occasions you would tell the counter why they needed to recount?
A. I don't recall. I answered all the questions she posed. I don't recall that -- I don't recall if I indicated that.
Q. In the fourth paragraph it says that Bennett ".. requested SOPs for handling laboratory worksheets and raw data, notebook documentation, spreadsheet validation, calibration of pipettes, and QA audit procedures for a research lab performing clinical testing."
MR. SANGIAMO: This paragraph here.
THE WITNESS: Oh, okay. Sorry. Okay.
BY MR. SCHNELL:
Q. Do you see what I just read?
A. Yes. Yes.

Q. Do you recall discussions of that?
MR. SANGIAMO: Make sure you read it.
THE WITNESS: So I recall whatever she requested and she needed from me or our group we provided. So what I can't tell from this is if all of that was provided at the inspection or whether there was any follow-up provision or documents provided.
BY MR. SCHNELL:
Q. Did you have an SOP for handling laboratory worksheets and raw data?
MR. SANGIAMO: Object to the form.
THE WITNESS: We had the MRL policy 23 which, the best I recall, was available for the data documentation and raw data, as it indicates raw data handling. I don't recall that we had an SOP specifically for the worksheet.
BY MR. SCHNELL:
Q. Did you have an SOP for the notebook documentation?

A. Not to the best of my knowledge to have an SOP, but we did have MRL policy 23.
Q. So MRL policy 23 was what you responded with when Bennett asked for SOPs for all of the items I previously identified in this paragraph?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall specifically what was provided to her. And I read this to be that she requested certain items and then it identifies what was provided to her. Beyond that, I can't say what else was provided to her.
BY MR. SCHNELL:
Q. With respect to the handling laboratory worksheets and raw data, notebook documentation, spreadsheet validation, calibration of pipettes, and QA audit procedures for the AIGENT testing, was any of it GMP compliant?
A. That, I don't know.
Q. Was any of it GCP compliant?
A. I don't know.

Q. Now, in the two paragraphs up, the last sentence, so we're in the second paragraph on this page, the last sentence, Dr. Carbone stated that if changes in the data were made after results were calculated and selective wells reviewed, then the practices were not consistent with GLP. This topic was further discussed later in the day.
Do you see that?
A. Yes.
Q. Do you recall discussing that topic with Dr. Carbone?
MR. SANGIAMO: Object to the form. Just so the record is clear, Gordon, I think you might have said wells reviewed and the documents says wells re-reviewed.
MR. SCHNELL: Thank you.
THE WITNESS: I remember -- I recall discussions with her -- or Dr. Carbone about the re-review of the data and corrections or changes. I don't recall -- and I recall discussions with Deborah Bennett about the GMP aspects. I don't recall the

discussion with Cathy Carbone about the GLP topic.
BY MR. SCHNELL:
Q. Now, it's true, isn't it, that in the AIGENT testing that you ran, changes in the data were made after results were calculated and selective wells were re-reviewed. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: Changes were made to the data, meaning the data being coded serum samples were -- we don't know which study group the samples are in. And to the extent of having a sero -- either a positive or a negative -- I'm sorry, a seropositive or seronegative status at end of titer. So the data were calculated -- the data were calculated to the point of having those -- a serum titer and serostatus when corrections were made.
BY MR. SCHNELL:
Q. I'll ask the question again. Listen to the question.

Isn't it true that in the AIGENT testing you ran, changes in the data were made after results were calculated and selective wells were then re-reviewed?

MR. SANGIAMO: Objection. Asked and answered. He just answered that question very directly, Gordon.

MR. SCHNELL: Object to the form is all you need to say, Dino.

MR. SANGIAMO: I can say whatever is appropriate to say.

THE WITNESS: There were -- the calculations were completed for the calculated percent of mock end titers, for example, and re-review of the data was made so samples were blinded as to which treatment group they received. And the -- it is correct that they were re -- sorry. They were selective wells, wells identified by some of the criteria that we identified earlier as flags for like, for example, single positive dilution.

BY MR. SCHNELL:

Q. So your answer is yes?

MR. SANGIAMO: Object to the form. He gave his answer. Results is a vague term. You know that. He answered your question.

I'm sorry, so what's your question, Gordon.

There's no question pending, don't say anything.

MR. SCHNELL: Do you need to hear the question again?

MR. SANGIAMO: What's the question? I need to hear the question again. What's the question?

MR. SCHNELL: No, you don't. You're not answering my questions. Your witness is. You need to be quiet. I'm not going to take this, Dino.

MR. SANGIAMO: I'm here to represent Merck and I'm entitled --

MR. SCHNELL: Will you repeat the question, please?

MR. SANGIAMO: I'm entitled to find out what the question is. I don't think there is a question, but if there is one, I'd like to hear it.

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

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MR. SANGIAMO: Objection. Asked and answered.

THE WITNESS: So, yes, with the results meaning the titers and serostatus of individual coded serum samples.

BY MR. SCHNELL:

Q. If you look at the bottom of this document, this is the second to the last paragraph, the last sentence, "After this review a tally was made of the direction (plaque count going up or down) of the corrections."

Do you see that?

A. Yes.

Q. Was that a tally that you conducted?

A. No. That's one that Dr. Carbone conducted.

Q. Was that written down?

A. She was writing it down.

Q. Did you get a copy of that?

A. I did not personally receive a copy. I don't know if she provided Merck a copy.

Q. Dr. Carbone remarked that the frequency was low. What frequency was low?

A. My understanding of that was that the frequency of the corrections was low.

Q. Is that true?

A. From my view, looking at the data, the frequency to me seemed like a subjective term but seemed low to me, and all of the changes were ones that were supported by an attempt to try to make the data more accurate.

Q. That's what you shared with Dr. Carbone?

MR. SANGIAMO: Object to the form.

THE WITNESS: As best I can recall, in the discussions with her about the reasons for the recheck and the results of the recheck were that we identified, for example, single positive dilution or erratic

neutralization. And by rechecking our -- the intention was to try to increase the accuracy of the data.

BY MR. SCHNELL:

Q. You think you succeeded?

A. Succeeded in?

Q. Increasing the accuracy of the data.

A. To me, on a case-by-case basis, serum-by-serum, I believe yes.

Q. Did you disclose to either Dr. Carbone or Dr. Bennett or anyone at the FDA that you and your staff collectively make thousands of changes to the data?

MR. SANGIAMO: Object to the form.

THE WITNESS: What we did at a follow up -- at this meeting, all I can say is that Cathy Carbone looked through a number of assays, I don't recall the specific number, made an assessment of the changes. In a subsequent follow up that Merck made, we listed all of the changes made in every assay for whatever reason the

change was made, included a justification where the reason was known and then provided that to the FDA.

BY MR. SCHNELL:

Q. Did you disclose that the total collective number of changes was in the thousands?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall the number.

BY MR. SCHNELL:

Q. Do you recall what percentage of the assays involved changes?

A. I don't recall.

Q. Did you ever disclose to the anyone at the FDA that the percentage of assays that had changes was close to 90 percent?

MR. SANGIAMO: Object to the form.

THE WITNESS: I did not provide that. I'm not aware of that.

BY MR. SCHNELL:

Q. And you did not disclose that to the FDA?

MR. SANGIAMO: Object to the form.

THE WITNESS: I'm not aware of it.

BY MR. SCHNELL:

Q. Did you disclose to anyone at the FDA that in your recounts you were targeting pre-positives?

MR. SANGIAMO: Object to the form.

THE WITNESS: We were not targeting pre-positives. We disclosed to them that we were targeting single -- looking at single positive dilutions amongst other recheck criteria.

BY MR. SCHNELL:

Q. So you did not disclose to the FDA that you were targeting pre-positives in your recount?

MR. SANGIAMO: Object to the form.

THE WITNESS: We did not

disclose that because that's not what we were doing.

BY MR. SCHNELL:

Q. Did you disclose to the FDA that -- anyone at the FDA that positive neutralizations that you were targeting at a single dilution were predominantly in the pre-vaccination samples?

MR. SANGIAMO: Object to the form.

THE WITNESS: I do not know that that is a correct statement, that they were predominantly in the pre-vaccination sera. I do not recall providing to the FDA or anyone at CBER at least personally relative amount of pre-vaccination, of single -- of pre-vaccination positives versus post-vaccination single positives. Single positive dilution.

MR. SCHNELL: Can you read back the question and his answer, please?

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

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BY MR. SCHNELL:

Q. I'm going to ask the question again.

I'm not asking you whether or not this is true. I'm asking whether or not you disclosed to the FDA that the vast majority of positive neutralizations at a single dilution occurred at the pre-vaccination sample?

MR. SANGIAMO: Object to the form. Asked and answered. He answered this.

THE WITNESS: I don't believe that it's an accurate statement, and I personally did not -- don't recall providing CBER a proportion of sera that were single dilution positive pre-vaccination versus post-vaccination.

BY MR. SCHNELL:

Q. Did you disclose to the FDA, anyone at the FDA, that you were directing your staff members to increase their plaque counts on the pre-vaccination samples to eliminate pre-positives?

MR. SANGIAMO: Object to the form.

THE WITNESS: That was not an accurate -- that's not an accurate statement and we did not disclose that. We didn't make that statement to the FDA.

BY MR. SCHNELL:

Q. Did you disclose to the FDA that you were directing your staff to make inaccurate plaque counts?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's not an accurate statement and we did not disclose that. We did not say that to the FDA.

BY MR. SCHNELL:

Q. Did you disclose to anyone at the FDA that you were directing your staff to selectively review pre-vaccination samples versus post-vaccination samples?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's not an accurate capturing of the practice, and we did not communicate that to the FDA.

BY MR. SCHNELL:

Q. Did you disclose to anyone at the FDA that the vast majority of changes that were made to the plaque counts were in the pre-vaccination samples?

MR. SANGIAMO: Object to the form.

THE WITNESS: Again, I don't know that that is an accurate statement, and to the best of my knowledge, that was not communicated to the FDA.

BY MR. SCHNELL:

Q. Did you disclose to the FDA that a large number of the plaque count changes that you or your staff committed changed pre-positive samples to pre-negative samples?

MR. SANGIAMO: Object to the form.

THE WITNESS: Again, I do not know that that's an accurate representation of the data and the effect of the plaque count corrections.

The -- I don't recall making a statement to CBER that the majority of the samples were in effect, that were pre-positives.

BY MR. SCHNELL:

Q. Did you disclose to the FDA that there were instances where you or your staff retested a sample that was pre-positive in a subsequent assay? Let me restate that. Did you disclose to anyone at the FDA that you or your staff engaged in retesting when you found a pre-positive in the sample?

MR. SANGIAMO: Object to the form.

THE WITNESS: Well, the retesting of a pre-positive sample depends on the results of the post-vaccination serum. I don't know that whether we disclosed to the FDA a retesting of a paired set where pre-vaccination serum was positive and post-vaccination serum, for example, was invalid. As I mentioned previously, we tested the samples in the same assay, the pre-vaccination and

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post-vaccination samples in the same assay. For example, if in a pre-vaccination result, whether it's positive or negative and the post-vaccination is invalid, that pair would be retested because one of the components of the pair was invalid. So that's the case where a retest would be done where the pre-vaccination serum could be positive but the post-vaccination serum was not valid.

BY MR. SCHNELL:

Q. Did you disclose to anyone at the FDA that you retested samples specifically because you found a pre-positive in the original assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: As best I recall, in the interim analysis set there was one experiment where we were -- was on line or intended to be further understanding the assay performance that there was an example in there of a pre-positive sample that was retested

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to confirm the results of trying to verify the result. For the clinical database, only the original result was reported. But those -- to the best of my understanding, that experiment was included in the data that was subsequently provided to the FDA.

BY MR. SCHNELL:

Q. Other than that, did you disclose to the FDA that there were other instances where you retested an assay because it registered a pre-positive in the original assay?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall or don't believe that it's accurate that they would have been retested if there was a valid post-vaccination serum result. So I do not recall disclosing the indications of retesting a sample just because it was pre-positive.

BY MR. SCHNELL:

Q. Do you recall telling the FDA that you recounted plaque counts in the

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controls that originally showed invalid assays?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall -- I do recall at least one assay where a plaque count in the -- did you say unaffected control or what was the -- I'm sorry.

BY MR. SCHNELL:

Q. That you recounted when you found -- instances when you found that there were plaque counts in the controls that made the assay invalid?

MR. SANGIAMO: Object to the form.

THE WITNESS: There were examples or are examples of cases where a plaque count in a control was rechecked to verify accuracy. I don't recall that that was provided to the FDA.

BY MR. SCHNELL:

Q. Did you disclose to anyone at the FDA that you destroyed the assay plates

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after quality assurance did whatever they did?

MR. SANGIAMO: Object to the form.

THE WITNESS: Yes, I did. Yes.

BY MR. SCHNELL:

Q. Who did you disclose that to?

A. Cathy Carbone and Deborah Bennett.

Q. You disclosed that during the inspection?

A. Yes.

Q. How many plates did you tell them you destroyed?

A. I don't recall what we did -- actually, I just indicated it was at the inspection, there was a follow-up meeting, but I don't recall it was at the inspection or one of the follow-up meetings when Deborah Bennett came back, we made a list of all the assays and the plates that we had available. I don't recall numbers of how many assays there were and how many plates were still available. But we provided to them a list of each -- a list by assay and then which plates were available.

Q. What did you tell them was the

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reason for your destruction of the assay plates?
A. As best I recall, my understanding of this was that retention of the plates was not a requirement. That the plaque counting sheet was the primary source of the data and the assay plates were not -- wasn't required to retain them as the primary data source.
Q. Did you give them a reason for destroying the assay plates?
MR. SANGIAMO: Objection.
THE WITNESS: The explanation I gave them was that in previous assays that we had run another -- at the time, my best recollection, I indicated other assays that we had run, once the QA audit was done, we did not feel the assay plates were required to be kept and we were then able to discard them.
BY MR. SCHNELL:
Q. What other assays did you run where you discarded assay plates?
A. As best I recall, Protocol 006 and all of our other lab experiments.

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Q. None of those were clinical studies, though, other than Protocol 006. Correct?
A. That's correct. But I didn't know that there was a different -- I wasn't aware that there was a different requirement.
Q. Did you disclose to anyone at the FDA that quality assurance did not review the original plaque counts?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall. I don't recall the question being asked. I don't recall whether that information was relayed or not.
BY MR. SCHNELL:
Q. Did you disclose to anyone at the FDA that you had a concern that there were too many pre-positives in the AIGENT testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not recall CBER questioned the characterization of being too many pre-positives. I don't know that that's an accurate statement.

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BY MR. SCHNELL:
Q. I'm just asking, did you disclose to anyone at the FDA that you had a concern that there were too many pre-positives in the AIGENT testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not aware of a communication on that line.
BY MR. SCHNELL:
Q. Did you disclose to anyone at the FDA that quality assurance did not review the assay plates before they were destroyed?
A. As best I can recall, during the discussion of the assay plate and the flow of the -- the flow of the assays and disposal of some of the assay plates, that by indication, as best I recall, was that the QA, once the audit was completed, that the assay plates were then able to be discarded. So I would say with the meeting with Deborah Bennett and Cathy Carbone, at a minimum with Deborah Bennett, that the flow of the QA audit and then disposal was discussed.
Q. So is your testimony that you

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did disclose to the FDA that quality assurance did not review the plates before they were destroyed?
A. Yes. Or they did not review the plates. They completed their review -- their audit of the documents and review, but they did not review -- they did not review the plates. Again, I will say I do not know that that was disclosed and I don't know that the -- I don't recall the question being posed during either of the inspections.
MR. SCHNELL: You can bring back Steve and Joan.
BY MR. SCHNELL:
Q. One of your earlier answers you referenced blinding. What type of blinding, if any, was employed in the AIGENT testing?
A. In the AIGENT testing, we did know which was a pre-vaccination, which was a post-vaccination sera that was required to run the same sera in the same assay. The blinding that was involved was that there were three vaccine dose groups in the study. All the analysts for the AIGENT testing were blinded as to which serum -- sera went with which

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vaccine dose.
Q. What's the purpose of blinding?
A. The blinding, as best I understand, is to prevent a knowledge of which treatment groups are involved so that there isn't -- minimizes the chance of a biased standard result, one group versus another.
Q. In what way could have the AIGENT testing been biased if there had been no blinding with respect to the three treatment groups?
A. In that case, the best of my understanding, we would know which individuals received which vaccine, and there could be a biased towards a response in one dose versus another.
Q. How could there have been a bias if that knowledge was there?
A. Well, it would require that someone was selectively identifying serum samples that corresponded to a given treatment group and treated those differently than the other groups.
Q. Now, would that same type of bias have existed with the counters of the

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plaques knowing which were pre-samples and which were post-samples?
MR. SANGIAMO: Object to the form.
THE WITNESS: Counting the plates, I'm not aware that plaques were necessarily counted sequentially, meaning those plaques -- plates are counted, it's not obvious which is the pre-vaccination, which is the post-vaccination serum.
BY MR. SCHNELL:
Q. When you went back -- well, when you were doing the analysis, you knew. Right?
A. Yes.
Q. And Dr. Emini knew. Right?
A. Yes.
Q. And when you went back to the counters for recounts for a variety of reasons, at that point they knew. Right?
A. Yes.
Q. And you don't think that introduced any bias into the AIGENT testing?
MR. SANGIAMO: Object to the form.

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THE WITNESS: No, because whatever -- if a check was made, if the counter confirmed that there were corrections that were made, in other cases confirms there were no corrections to be made, the results were left as is.
BY MR. SCHNELL:
Q. But then why do you ever need blinding in testing if you're relying on the integrity of the tester?
A. I think in this case the blinding in my view, not being a clinician or not having experience in designing the clinical assays, would be more -- I would offer would be more relevant to the interpretation of the data comparing the three different treatment groups.
Q. Wasn't the objective for each of the three treatment groups to have a lower confidence interval of 90 percent or higher for seroconversion?
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding

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of the study from an assay perspective was to compare the immunogenicity of three different treatment groups.
BY MR. SCHNELL:
Q. Wasn't it the goal for each of those treatment groups to have the same seroconversion rate?
A. That, I don't know.
Q. You ran this test.
A. I ran the test. I did not design the clinical study or develop the protocol for the clinical study.
Q. Who did?
A. I don't know. Someone other than me.
Q. You don't know?
A. I don't recall offhand who that was.
Q. You ran the test, but you don't know who designed the test?
MR. SANGIAMO: Objection. Asked and answered.
THE WITNESS: I know who designed the assay.
BY MR. SCHNELL:

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Q. You designed the assay?
A. I designed the assay. Who designed the clinical trial, I don't know, and I would say is not relevant to me running the assay.
Q. Who came up with the blinding protocol?
A. That, I don't know.
Q. Was there a blinding protocol?
A. I know the three treatment groups were blinded. I don't know what that involves as far as a protocol of something, I'm not familiar with.
Q. Was the blinding protocol you used in running the AIGENT test GMP compliant?
A. That, I don't know.
Q. Was it GCP compliant?
A. I don't know.
Q. Did you have any input into the blinding protocol?
A. Not that I'm aware of. Not that I recall.
Q. In running the testing, did you see any evidence of bias?
MR. SANGIAMO: Object to the

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form.
THE WITNESS: I did not see any evidence of bias in terms of favoring of pre- versus post-vaccination serum. I can't comment on the blinding of the study group because I was blinded to the study group.
BY MR. SCHNELL:
Q. Do you think the potential for bias would have been less in the AIGENT testing if the plaque counters were blinded to which was a pre- and which was a post-vaccination sample?
A. Without being a statistician and having experience in that area, I don't know what the expectation would be that that blinding would have made a difference in what impacted a bias, a potential bias.
Q. Do you believe that the potential for bias in the AIGENT testing would have been less if you did not perform an analysis of the neutralization results while the testing was going on?
MR. SANGIAMO: Object to the form.

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THE WITNESS: No, I don't believe that would have been -- I don't believe that would have introduced more -- less bias by not doing that analysis while the study was going on.
BY MR. SCHNELL:
Q. Do you believe that the potential for bias would have been less if Dr. Emini did not analyze the neutralization results while the testing was going on?
A. I do not believe that his results, his review affected the bias, but the attempt was to try to increase accuracy of the results. The statistical -- not being a statistician, I can't speak to the chances of all these options providing increased biased or not, but I do not believe in my personal opinion that his review increased the risk of bias.
Q. Do you believe the potential for bias would have been reduced if you had different counters performing the recounts?
MR. SANGIAMO: Object to the form.
BY MR. SCHNELL:

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Q. Let me make that clear. Do you believe the potential for bias would have been reduced if you did not have the original counter perform his or her own recount?
A. No. In fact, I believe it would -- my personal opinion is it would be the opposite, meaning that if you have another person doing the count on selective wells only, there could be increased risk of variability even though the counters are qualified, there could be an increased risk of variability between the original counter and the recounter that would introduce a bias in the counts.
Q. What does that say about the variability of the plaque counting process altogether?
MR. SANGIAMO: Object to the form.
THE WITNESS: My understanding and personal opinion is that I try to do -- is have an assay, having a counter count an assay, controls it for that counter. If you had -- there is what we established or proposed as an

acceptable range of variability between counters which, the best I recall, was 10 percent. It doesn't mean that if one person was counting, they were maybe at like 9 percent difference, but if you're looking at the absolute numbers, that second person, the absolute numbers would change but the trends within the assay would not change.

BY MR. SCHNELL:

Q. Did the validation protocol take this into account?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall -- I recall the aspects of the validation on different operators on different days. I don't recall how the validation report addressed the different counters, plaque counters.

BY MR. SCHNELL:

Q. Validation didn't address plaque counting at all, did it?

A. I don't recall.

Q. Would the potential for bias have been reduced if all of the plaque counts were reviewed for error?

A. Not being a statistician, I can't speak to how likely that would be to reduce bias or error. The question -- I can't answer the question directly. What if you did a full recount, would it be more appropriate to average the results, and I don't have experience in this area. Full recounts are verified counts or numbers are different, average them or what would the next step be.

Q. Would the potential for bias have been reduced if the individuals recounting the plaques that you -- the samples that you identified for them had not known the reason for your asking them to do a recount?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall in all cases that I identified the reason for the recount. I don't recall how many times I just said there is a question about this plaque count, could you please check it versus this is a

single positive dilution. But my expectation would be that the plaque check would be to try to give the most accurate count and there would not be a biased towards that the accuracy if the person didn't know what the reason for the recheck was.

BY MR. SCHNELL:

Q. So is it your testimony that on those occasions that you previously testified to when you went up to an individual in your lab who had done a plaque count, you said, hey, you missed some, recount it, you don't think that introduced bias into the recount?

MR. SANGIAMO: Object to the form. Misstates testimony.

THE WITNESS: No, I believe there is a -- looks like there's -- plaques were missed, can you please verify whether you would agree that plaques were missed or not.

BY MR. SCHNELL:

Q. You admit you did that. Right?

MR. SANGIAMO: Object to the form.

THE WITNESS: I did go to an individual and say here is a well or a plate that was identified with some flags or single positive dilutions or flags from the workbook. Plaques looks like they're being miscounted, can you please verify whether you agree that they're miscounted or not.

BY MR. SCHNELL:

Q. And on those occasions you don't believe that you're disclosing the reason for your asking them to recount the plaques introduced potential bias into their recount?

A. My understanding is that that was trying to get the most accurate plaque count, that the person would make the best effort to get the best, accurate plaque count, not necessarily a bias.

Q. Did you disclose to anyone at the FDA that you went to individuals in your lab and asked them to recount plaques that you found had been missing plaques?

MR. SANGIAMO: Object to the form.

THE WITNESS: The best I recall,

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when I was talking to Deborah Bennett about -- not Deborah Bennett, to Cathy Carbone about the plaque count corrections, that was an example I gave to her.

BY MR. SCHNELL:

Q. So you told Cathy Carbone during the inspection that I would go to individuals in my staff and I would tell them recount this because you missed some?

MR. SANGIAMO: Object to the form.

THE WITNESS: I recall going to her and saying some of the checks involved cases where I -- in checking the plates, I noticed plaques that were being counted or overcounted, I would go to the individual and ask them to verify the plaque count that had been entered.

BY MR. SCHNELL:

Q. Did you tell Dr. Carbone in this instance that you told the plaque counter that they missed counts?

MR. SANGIAMO: Object to the

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form.

THE WITNESS: As best I recall, I told them that the count, I looked at the plate and I see a different count than what they had.

BY MR. SCHNELL:

Q. But I'm asking about with your conversation with Dr. Carbone, did you disclose to her that you at times went to individuals in your staff and told them I want you to recount this because I see you missed some plaques?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall, I recall telling her that if I looked -- saw plaques were being missed or overcounted, I would let the person know or ask them to verify the counts. Whether I told her specifically cases, there were cases where I told them they were undercounted, I don't recall.

BY MR. SCHNELL:

Q. Did you disclose to anyone with the FDA the blinding protocol employed in

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AIGENT testing?

A. That's not an area I'm responsible for. I don't recall disclosing that to them.

Q. Who is responsible for that area?

A. I don't know.

Q. You ran the AIGENT testing. Right?

A. The assay.

Q. If you had a question about the blinding -- who told you about the blinding procedure?

A. All I recall is that we were given samples identified by -- I forget all the identification of information, but that they would be blinded between -- all the three treatment groups would be -- are not visible to us. We wouldn't be able to disclose which of the three treatment groups.

Q. Who gave you that --

MR. SANGIAMO: Hold on, Gordon. I don't think he had finished.

THE WITNESS: We weren't be able to tell which sera belonged to each of

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the three treatment groups.

BY MR. SCHNELL:

Q. Who provided you with that blinding information?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall who told us that the samples were blinded. We never received the blinding code. I don't recall who told us that they were blinded or if it was a given that the samples in the study would be received blinded to the treatment group.

BY MR. SCHNELL:

Q. Where did you learn that you were supposed to be blinded with respect to the treatment groups?

A. I don't recall a specific document where I indicated that.

Q. Sitting here today, can you think of how you learned about what you were supposed to do in terms of blinding?

A. No. From my perspective, my responsibility was running the assay. I received samples and ran them. The blinding

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was something not part of our lab activities. That we received samples, the blinding was not -- from my view, not relevant to our testing of it not being unblinded.

Q. Did you consider blinding an important part of clinical studies?

A. I'm not a clinical person so I can't speak to the -- in which cases blinding is critical and when it's not.

Q. Was blinding critical, in your opinion, with the AIGENT testing?

A. All I can say is the samples were blinded. Whether that's critical to the study, I can't say.

Q. You have no opinion?

A. No.

Q. Other than the blinding of the treatment groups, you had no other restrictions in terms of blinding. Correct?

A. What do you mean by "restrictions"?

Q. Other than the blinding restrictions in terms of the individuals running the test, knowing which of the treatment groups were being tested, you had no other restrictions in terms of what

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information the individuals in your staff running the lab had?

MR. SANGIAMO: Object to the form.

THE WITNESS: They would have information from the identifier on the vial and then whether it was a pre- or post-vaccination serum. I don't know what -- that's the information that was available to us. I don't know what other information --

BY MR. SCHNELL:

Q. Who designed that aspect --

MR. SANGIAMO: Hold on.

MR. SCHNELL: I'm sorry.

THE WITNESS: I don't know what other information would be considered.

BY MR. SCHNELL:

Q. Who designed that aspect of the AIGENT testing?

A. I'm sorry, what aspect?

Q. What was blinded and what was not?

MR. SANGIAMO: Objection. Asked and answered.

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THE WITNESS: In the neutralization assay format, we as part of validation determined to run the pre- and post-vaccination serum in the same assay. So we needed to know which samples were pre-vaccination, which was the corresponding post-vaccination serum. From my perspective, that's all I needed to know to run the assay. As far as other blinding for the study groups, that's not related, from my perspective, to the assay or to us running the samples.

BY MR. SCHNELL:

Q. So is it your testimony that it would have been impossible to blind for pre- and post-vaccination samples?

A. I would say it's not impossible. But someone -- someone -- I don't know someone would have been -- would have to come up with some other way of coding the samples and then providing us with a decode to allow us to identify pre- and post-vaccination samples that can be put in the same assay.

Q. Wouldn't that have been easy if

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you separated the group who counted the plaques from the group that analyzed the results?

MR. SANGIAMO: Object to the form.

THE WITNESS: Not necessarily.

BY MR. SCHNELL:

Q. Why would it have been difficult for the plaque counters to not know whether they were counting a pre- or a post-sample?

A. One aspect to the testing was that if we ran a pre- and post-sample together -- pre- and post-vaccination serum together, each serum required, as best I can recall, two plates, each plaque of four plates was a pre- and post-vaccination -- a pre- and post-pair. So basically every four plates became a new set of pre- and post samples. The way the plates were -- the samples were inoculated onto the plates, they were sequential pre/post-pairs one after the other. So the counter could in theory know every multiple of four becomes another pre-vaccination serum.

MR. SANGIAMO: We've been going over an hour, getting close to 1:00.

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So if you can wrap up soon.
BY MR. SCHNELL:
Q. So my question is, wouldn't that have been an easy fix if you were concerned about potential bias from not being blinded to whether samples were pre or post for counting purpose, wouldn't it have been an easy fix to make it random or engage in some other process that would have blinded the plaque counters from what they were counting?
MR. SANGIAMO: Object to the form.
THE WITNESS: It could have been a solution, but it wasn't one, from my perspective, that I deemed necessary at the time. The way we were running the assay was the way it had been run during the development studies and through the interim analysis; and would have, from my perspective, have been more complicated to juggle the serum distribution throughout the assay with a concern that we might mispair sera with each other.
BY MR. SCHNELL:

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Q. Does Merck have any in-house blinding procedures that are generally applied to the clinical testing?
A. I don't know.
Q. You've never seen any?
A. Not that I recall.
Q. With respect to the --
MR. SCHNELL: We can stop now.
VIDEOGRAPHER: The time is now 12:59. This concludes disc three.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is now 2:06. This begins disc four. You may proceed.
- - -
(Exhibit Krah-41, Summary of findings, 2021754 - 2021761, was marked for identification.)
- - -
BY MR. SCHNELL:
Q. Dr. Krah, I've marked as Exhibit -- Krah Exhibit 41 a document with the Bates range 2021754 through 761. It purports

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to be a summary of findings prepared by Drs. Bennett and Carbone of the FDA relating to the August 6, 2001, inspection we've been -- that we were discussing before lunch. I just want to ask you about a couple of things in this.
My first question is, have you ever seen this document before?
A. It doesn't look familiar to me, but I can't exclude that I saw it at some point, but I don't recall seeing it.
Q. I could turn your attention, again, if you have any -- in response to one of my questions you need to review any part of the document, obviously please feel free. On page 2 where it has --
MR. SANGIAMO: Hang on a second. I think you should at least give him a chance to look over the document.
MR. SCHNELL: I don't think he needs to because --
MR. SANGIAMO: Well, are you going to be asking him did you ever tell the FDA this, did you ever tell the FDA this? He needs to see the

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document if something --
MR. SCHNELL: Well, why don't we -- let me ask the question and then if he needs to --
MR. SANGIAMO: At a minimum, just look it over, Dr. Krah, so you're at least familiar with it in general.
BY MR. SCHNELL:
Q. Dr. Krah, on the second page of the document --
MR. SANGIAMO: Have you completed your review?
THE WITNESS: I got to the third page of it.
BY MR. SCHNELL:
Q. I only have a question right now on the second page. So let me ask you that.
MR. SANGIAMO: Well --
MR. SCHNELL: Dino, you're just wasting time.
MR. SANGIAMO: I'm not wasting time. You hand him a document, he's got to look at the document.
MR. SCHNELL: If he needs to review it -- you don't know what my

questions are. Hear my question and then you can tell me if he needs to review the document.

MR. SANGIAMO: Or I can -- let's hear your first question.

BY MR. SCHNELL:

Q. So if you look to the second page, the bottom paragraph which begins, "According to Dr. Shaw...," do you see that?

A. Yes.

Q. "According to Dr. Shaw, this is a novel assay developed uniquely for this study...."

Do you see that?

A. Yes.

Q. Is that a true statement with regard to the AIGENT?

A. I would say parts of the assay were previously published, the combination of virus strain and the assay conditions I don't believe have been provided by anyone else. So I would say that parts of the assay are not unique but the overall combination of the assay including the different -- the virus strain and the immunostaining method were a

unique combination.

Q. So what parts of the assay, of the AIGENT assay were not unique?

MR. SANGIAMO: Object to the form.

THE WITNESS: What I recall at least, as background for the AIGENT assay, is the publication from Sato, I believe et al. in 1978, I believe, where he -- the authors described an anti-IgG enhanced mumps neutralization assay. I don't recall details of the plaque visualization that were included as part of that. But the concept of using anti-IgG to enhance neutralization was included as well as other additions such as complement in that publication.

The use of JL135 -- JL135 I don't recall, there were some -- sorry. I don't recall if earlier studies that Dr. Hilleman did included that strain of virus. If I'm trying to tease out perhaps steps of the virus that's used, ever been used in a previous study, I

don't recall if JL135 was used in a previous study or not.

The immunostaining by itself is done in a unique procedure, but my interpretation of the comment would be a novel assay, says a combination of the anti-IgG, the JL135 virus, and the immunostaining as a unique combination.

BY MR. SCHNELL:

Q. Are you aware of any other clinical trials that involved that combination?

A. By Merck or anyone?

Q. Anyone.

A. Yes.

Q. Who?

A. GlaxoSmithKline. I'm sorry, not with the virus strains. Sorry. Similar assay, but not with the same virus strain.

Q. And what clinical trial are you referring to?

A. I don't know what -- I don't know the specific trials, but I've seen publications from GlaxoSmithKline where they included anti-IgG in the neutralization assay.

Q. But not with the JL135 strain?

A. I don't recall what strain. I don't recall it being JL135, but I don't recall what strain it was.

Q. Any other clinical trials in which that combination was used?

A. Not that I'm aware of.

Q. Are you aware of any other neutralization test that Merck has ever conducted using anti-IgG?

A. Clinical trial or in any study?

Q. First let's start with clinical trial.

A. I am not aware or do not recall any other clinical trial in which it was used for -- at least in my experience. I can't speak for all of Merck, but in assays I was involved with, I'm not aware of others.

Q. And then what about any trial?

A. There was a study --

MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: There was a series of experiments that I was involved with in the mid-1990s that involved clinical sera for varicella where we developed

an anti-IgG, an assay that used anti-IgG in the neutralization assay. I don't recall that that was part of a clinical trial evaluation but was -- from my recollection was a comparison between different assays of varicella antibodies.

BY MR. SCHNELL:

Q. Did you run that testing?

A. Yes. I ran the mumps -- I'm sorry, mumps. The varicella neutralization testing.

Q. How many subjects were in that study?

A. I don't recall an exact number. My best recollection is something on the order of 75 or so.

Q. What was the purpose of the study?

A. The purpose of the study, as best I can recall, the purpose of the experiments that we were doing -- I was doing was part of a group in our department to compare antibody titers measured by different antibodies -- different -- sorry, different

assays.

Q. What were the different assays involved in the study?

A. The assays, they included some version of an ELISA, something called a FAMA assay, F-A-M-A. So fluorescent-antibody-to-membrane antigen assay. And then the neutralization assay.

Q. And the 75 subjects were tested in each of the three assays?

A. Actually, I believe, as I'm recalling this, I believe there were four assays. I don't recall if the fourth assay was another version of the ELISA or not. But as best I can recall, the intention was to test each of the sera in each of those assays. Whether that was completed for every individual sera, I can't say with certainty.

Q. The goal was to compare the sera conversion results using the different assays?

A. I don't -- I'm sorry. I don't recall if it was a -- the two measurements that we would have made would have been seroconversion and then geometric mean titer. I don't recall if the comparison was both or

only seroconversion.

Q. What were the controls used for those three assays?

A. I can't speak to the ELISA controls or the FAMA, the FAMA assay control. In the neutralization assay, you would have had a no serum control. I don't recall -- I don't recall if the assay included positive controls or not.

Q. What was the no serum control?

A. That all of the reagents except sera, meaning virus, anti-IgG. In this assay we used complement in addition to the anti-IgG.

Q. Why?

A. In developing the assay we identified that anti-IgG enhanced neutralization, complement enhanced neutralization, when we used the two together, we got enhancement that was beyond either of them alone. Our goal was to increase the sensitivity of the assay to more accurately detect antibodies to varicella.

Q. You thought by adding complement to the control, that would help you get there?

A. Not to the control, but to every sample.

Q. You did it differently for the AIGENT testing. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: We did not use complement in the AIGENT testing but we did use the anti-IgG added to each sample.

BY MR. SCHNELL:

Q. What were the difference between the two tests that caused you to use complement in the varicella testing but not in the AIGENT testing?

A. I wouldn't characterize them as differences, but I can say we did evaluate complement. Complement has been used by others for multiple viruses to enhance neutralization. We did evaluate that for mumps. In discussions with CBER, they had asked if we considered complement as a supplement. As best I can recall, the complement -- in these development studies that we did, complement alone, in the absence

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of serum, neutralized mumps significantly. So we did not proceed with including it in the assay. In the case of varicella, complement alone at the concentration we were using did not neutralize virus on its own in the absence of sera.

Q. You thought the test would be more accurate, the varicella test would be more accurate using both complement and anti-IgG?

A. My belief at the time and still now is that that assay provided a more sensitive measure of varicella antibodies. So it would be a more accurate indicator of whether varicella antibodies were present or not.

Q. Do you equate sensitivity with accuracy?

A. I'm not a statistician. I understand that there is a formal definition to accuracy. So I would, on a statistical description, would not equate them.

Q. In your experience, is an assay that's more sensitive more accurate?

MR. SANGIAMO: Object to the

form. Asked and answered.

THE WITNESS: My experience is limited to the assays that I have developed or read about. I would say that the more sensitive assays are a more accurate measure of antibodies, whether that qualifies as from a statistical definition of what constitutes an accurate assay, I can't say.

BY MR. SCHNELL:

Q. But in your experience, a more sensitive assay is a more accurate assay in terms of measuring antibodies?

MR. SANGIAMO: Object to the form. Asked and answered.

THE WITNESS: It's a more accurate means to or provides -- a more sensitive assay provides a more accurate way of measuring antibodies, meaning that if antibodies are present, you have a greater chance of detecting them.

BY MR. SCHNELL:

Q. So the control used in the

varicella neutralization testing had complement, anti-IgG, the virus and some form of diluent?

A. Yes. Yes.

Q. And the control used in the AIGENT testing didn't have complement but did have anti-IgG virus and some form of diluent?

A. Yes.

Q. Was the diluent used in each of these respective controls the same?

A. I don't recall what the diluent was in the varicella studies, so I can't say.

Q. But the diluent used in either study wouldn't have had antibodies in them. Correct?

A. That's -- well, in the case of mumps, it has bovine serum, so it has serum which could have antibodies, but no human antibodies.

Q. Other than bovine antibodies, could it have other antibodies?

A. There were none added to the reaction, so no.

Q. Does the existence of bovine antibodies in the control used for the AIGENT

testing pose any risk of combining with the anti-IgG to provide an artificial picture of what's actually going on in the control?

MR. SANGIAMO: Object to the form.

THE WITNESS: My understanding is that the anti-IgG is antihuman IgG and specific for human IgG, and there's no expectation of a reaction with bovine antibodies.

BY MR. SCHNELL:

Q. Going back to this document, which was Krah-41, if you turn to the next page, this is page 3, under 1 where it says, "Raw data is being changed with no justification...," do you see that?

A. Yes.

Q. It says, "As the immunological correlate for efficacy of mumps vaccination, Merck has developed an assay to measure anti-mumps antibodies in the serum of vaccinated subjects."

Do you see that?

A. Yes.

Q. Now, that is an incorrect

statement of what the AIGENT assay was developed for. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: That's beyond my expertise. As far as the application, my job was responsibility was to develop an assay to measure mumps antibodies. The clinical application or connection is something I'm not responsible for or trained in.

BY MR. SCHNELL:

Q. Dr. Krah, you developed the AIGENT test. Correct?

A. Yes, along with other members of the lab.

Q. You and Mary Yagodich developed the AIGENT assay. Correct?

A. Yes.

Q. Other than you two, you can't identify anyone else involved in that development. Correct?

MR. SANGIAMO: Object to the form. Misstates prior testimony.

THE WITNESS: There are others

in the lab who contributed to experiments that were part of the development. Mary and I were the leads in designing the experiments for the development.

BY MR. SCHNELL:

Q. And here the FDA wrote that Merck has developed an assay as an immunological correlate for the efficacy of mumps vaccination.

Is that what you developed the AIGENT assay for?

MR. SANGIAMO: Object to the form.

THE WITNESS: My objective and our lab's objective was to develop an assay that would be capable of measuring 95 percent seroconversion. The clinical application is something that's beyond my responsibility of assigning.

BY MR. SCHNELL:

Q. So is your question -- is your answer, then, that you did not develop the AIGENT assay as an immunological correlate --

MR. SANGIAMO: Objection.

BY MR. SCHNELL:

Q. -- for the efficacy of mumps vaccination?

MR. SANGIAMO: Objection. Asked and answered. We've gone over this, Gordon.

THE WITNESS: The AIGENT assay was developed to provide a measure of mumps antibody and seroconversion that was consistent with CBER's requirement. Its application or interpretation of what the data would be applied to is beyond my responsibility and understanding.

BY MR. SCHNELL:

Q. So did the FDA get it wrong here?

MR. SANGIAMO: Gordon, come on. Let's go one more round. You can give your answer again, Dr. Krah, and hopefully we're done.

THE WITNESS: I defer to the FDA and their interpretation. That's beyond my responsibility.

BY MR. SCHNELL:

Q. During the inspection, did you discuss with anyone at the FDA what you developed the AIGENT assay for?

MR. SANGIAMO: Dr. Krah, if you want to read the rest of the document given that it may document those discussions, feel free to do so.

THE WITNESS: I would say I personally did not -- I don't recall indicating to the FDA the purpose for the assay development other than it was a mumps neutralization assay to support Protocol 007.

BY MR. SCHNELL:

Q. Now, further on this page, the last paragraph it's the second sentence beginning with the word "Thus...."

Do you see that?

A. I'm sorry?

Q. On page 3, last paragraph, second sentence beginning with the word "Thus..."

A. "Thus, there is no...."

Q. "Thus, there is no guarantee

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that the numbers on the worksheet were the original data, even at time of transfer of count from plate to worksheet."

Do you see that?

A. Yes.

Q. Do you recall having that discussion or a discussion on that topic with Drs. Bennett and/or Carbone?

A. I recall having that discussion with Dr. Carbone, yes.

Q. And you told her that the numbers on the worksheet were the original data. Correct?

A. The original entry on the -- I told her that the numbers recorded on the counting sheet were the original counts from the plates.

Q. Here the FDA is saying there's no guarantee that that's the case. So I'm wondering in your discussion with Dr. Carbone or Bennett, or both on this topic, did they believe, as you recall, that there was no guarantee that the numbers on the worksheet were the original data?

MR. SANGIAMO: Objection. Calls

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for speculation. I also just want to make an objection for the record that chunks of this paragraph discussing this particular issue are redacted. But if you're able to answer Mr. Schnell's question, Dr. Krah, you can.

MR. SCHNELL: The redactions are how Merck produced this document to us.

MR. SANGIAMO: The redactions were put on there by the FDA.

MR. SCHNELL: I don't know where they came from.

MR. SANGIAMO: I'm telling you where they came from. They were put on there by the FDA.

MR. SCHNELL: Can you repeat the question?

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

- - -

THE WITNESS: Those are the words -- as best I recall, those are the words she has listed here. In

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subsequent discussion with her, we explained the flow of accounting, the reasons for the checks. My understanding was that she -- that that -- still say there was no guarantee but she was not having a reservation. I wouldn't say as best I recall that was like an absolute guarantee that they were the original counts, but she, from my understanding, did not question that they represented the original counts.

BY MR. SCHNELL:

Q. So is your testimony that, as you understand it, you convinced Dr. Carbone that the numbers on the worksheet were the original data in every case?

MR. SANGIAMO: Object to the form.

THE WITNESS: I recall indicating that to her. And I don't recall her making a contrary -- a comment against it, that reply.

BY MR. SCHNELL:

Q. Are you aware of any instances

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where a counting sheet was discarded?

A. No.

Q. Are you aware of any instances where a counting sheet was overwritten?

MR. SANGIAMO: Object to the form.

THE WITNESS: Can you explain what you mean by "overwritten"?

BY MR. SCHNELL:

Q. Well, maybe there were a lot of changes so a new counting sheet was created?

A. I don't recall cases for that.

Q. Now, if counting sheets had been thrown out and new ones created, you would be aware of that. Right?

MR. SANGIAMO: Objection. Calls for speculation.

THE WITNESS: I wasn't looking at every lab member every day for every assay. So I can't be sure that if that did happen, I would have necessarily seen it.

BY MR. SCHNELL:

Q. How can you be sure that there weren't instances where recounts were made but

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not recorded on the counting sheets?
A. To the best of my understanding, original counts --
MR. SANGIAMO: Object to the form. I'm sorry. Go ahead.
THE WITNESS: -- were -- the instructions to the lab staff recorded the original counts on the counting sheet.
BY MR. SCHNELL:
Q. Do you know if those were carried out?
A. To the best of my understanding, yes.
Q. Were there instances where someone wasn't sure about a particular count and they consulted with you or another member of the lab before they recorded that count on the counting sheet?
A. I recall cases where an individual counting a plate, if they were having difficulty counting, for example, faint plaques, they would ask if -- someone to look at the plate and see if they were counting accurately.

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Q. So in those instances, would they have written on the counting sheet their original count and then if someone disagreed with them and convinced them that their original count was wrong, they'd cross that out and write a new count?
MR. SANGIAMO: Object to the form.
THE WITNESS: That would be my expectation.
BY MR. SCHNELL:
Q. Do you know if that was carried out?
A. I don't have any evidence to the contrary. I'd say -- from my expectation, I would say that it was carried out.
Q. Did that actually happen on occasions where someone wrote down a count and then came to you and said I'm not sure if I got this right, will you recount this for me. And you did, and then you got a different count and they crossed out the one they had just written down and then five minutes later put a new count in that you calculated?
A. I don't recall an example such

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as what you just described. I do recall a case where somebody was counting or had counted and said I had trouble counting this assay, I'm not sure if I'm counting accurately, could you, please, check. Check doesn't necessarily say recount, but just look at the plate and see if I agree, for example, the plaques are difficult to count.
Q. So in those instances did they tell you what their count was?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall.
BY MR. SCHNELL:
Q. So you don't recall in those instances if they told you what their count was, you came up with a different count and then they recorded as the original count what your count was?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall that situation.
BY MR. SCHNELL:
Q. You don't know one way or the

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other?
A. No.
Q. The last question I have on this document is on page 4.
Again, this -- I'm going to point you to language, similar, not identical to language we saw on the earlier document. It's in the first paragraph, the second to the last sentence beginning with the word, "Moreover...."
A. Okay.
Q. It says, Moreover a selective review of specific assays or wells was undertaken after data analysis of pre- and post-neutralizing antibody titers (e.g., with specific knowledge of matched samples and of pre- or post-vaccination status of samples), providing clear opportunity for selective bias to change.
My question to you is, is that a true narrative of the recounting procedure that you oversaw in the AIGENT testing?
MR. SANGIAMO: Object to the form. Also I think you said review where you should have said re-review.

THE WITNESS: So the comment about review of specific assays or wells was undertaken after data analysis. I would say that is or were cases where that happened but following the rules that we tried to capture in the defining recheck criteria. They were selective but the selectivity was based on a result for a sample regardless of whether it was pre- or post-vaccination.

BY MR. SCHNELL:

Q. Which rules are you talking about?

A. What I was referring to was rules that I -- as far as like a single dilution positive sample, extra variability criteria, invalid dilutions that would affect -- assigning a titer to a sample.

Q. The criteria we discussed before lunch?

A. Yes. Yes.

Q. So is there anything about that statement that's inaccurate as it relates to how the AIGENT testing process was conducted

in your lab?

MR. SCHNELL: Object to the form.

THE WITNESS: So the first half of the sentence, there were selective re-reviews of specific assays or wells, they provided these flags or check flags was undertaken after data analysis, meaning with data analysis, meaning percent of mock values and titers for samples. So the data meaning the results of the neutralization assay. So I would say that that re-review of assays after the percent of mock failures or some indication of whether it's seropositive or seronegative and a titer was done. Given the way the plates are laid out in the assay, we would then know which matched serum sets went together between the post-vaccination pairs.

BY MR. SCHNELL:

Q. Do you agree with the part of the statement where it says, "...providing clear opportunity for selective bias to the

change"?

A. That's whoever wrote this document's opinion. I don't agree that it's necessarily a clear opportunity for bias.

Q. Did you discuss the potential for bias with the FDA during the inspection?

A. As best I can recall, the discussions with the FDA, mostly Cathy Carbone during the inspection, were -- I don't recall her using the word bias, but looking at the data, the changes or corrections that had been made and evaluating the impact on the results. So from that point there was a discussion over the impact of the changes.

Q. And your position during your discussions with Carbone and Bennett was that the recounting process that you employed did not result in any bias?

MR. SANGIAMO: Object to the form.

BY MR. SCHNELL:

Q. Is that correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: My best

understanding is that the recheck that Cathy Carbone did in her narrative summary, the document we looked at earlier today was that the changes were both up and down, it wasn't a systematic change and there weren't many of them.

BY MR. SCHNELL:

Q. Is that true?

A. That's my understanding, yes.

Q. So if we were going to analyze all the changes that were made in the AIGENT testing, you would expect to see an equal distribution of changes made to the pre-vaccination samples as to the post-vaccination samples?

A. I don't know that I would say equal, but in some statistical evaluation of that. So what constitutes equal, I can't say. I'm not familiar with what would qualify as equal.

Q. Well, would you expect there to be more changes on the pre-vaccination side than on the post-vaccination side?

A. Not being a statistician, I

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can't give a statistical, accurate number, but it could be a numerically larger number but maybe not -- perhaps not statistically, significantly different from the post.

Q. Well, would you expect there to be more changes on the pre-vaccination than the post-vaccination?

A. Not -- I would say not from -- not as best I can -- I wouldn't expect that to be the case.

Q. Would you expect there to be more changes that increased plaque counts than decreased plaque counts?

MR. SANGIAMO: Object to the form.

THE WITNESS: I recall seeing both. My best recollection is that the majority of the changes were more plaque counts. There were cases where plaques were being overcounted and then the correction led to a lower plaque count. But whether -- how much -- how many samples fell into a higher plaque count versus a lower plaque count, I can't say with certainty.

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BY MR. SCHNELL:

Q. Do you have any understanding as to why changes would be in one direction versus the other?

MR. SANGIAMO: Object to the form.

THE WITNESS: My understanding is that the -- a lower -- an increase in plaque counts would indicate that plaques were being missed through some aspect of the staining and that the higher plaque counts being recounted as lower would mean that there was some other precipitator debris in the assay that was being confused as a plaque.

BY MR. SCHNELL:

Q. Would you expect -- with your experience in this kind of assay, would you expect there to be more of one kind of change versus the other?

MR. SANGIAMO: Object to the form.

THE WITNESS: I'd have to say I don't have a clear expectation because the changes varied. It was a different

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aspect of different assays. So I don't have a memory or recollection of what the consensus, like what's more likely, is it more likely to be a higher count or a lower count.

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(Exhibit Krah-42, 2/20/01 Memo, 26443 & 26444, was marked for identification.)

\- - -

BY MR. SCHNELL:

Q. I'd like to mark as Krah Exhibit 42 a memo dated February 20, 2001, from Dr. Krah to lab staff, Bates number 26443 and 4. Do you recognize this document, Dr. Krah?

A. Yes.

Q. And this was a memo you prepared during the AIGENT testing for your lab staff. Correct?

A. It was prepared at the time we were doing AIGENT testing for distribution to the lab staff.

Q. What was the purpose of your preparing this memo?

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A. As best I can recall, reading the description of this indicates that there were audits done of mumps neutralization assays with the assays being assays from the AIGENT testing, and there were some observations that the auditors identified. What I -- my goal here was to try to capture the comments and then communicate that to the lab staff to correct those deficiencies and increase the likelihood that we wouldn't have similar observations in subsequent assays.

Q. So this is based on feedback you received from quality assurance?

A. As best I can recall, this is a summary based on comments made during review by the quality assurance group of the assays.

Q. Would that explain why among the potential errors not listed here are plaque counting errors?

A. I would say I don't recall during the audit of the data that the quality assurance group had questioned the cross outs and changes.

Q. Well, they would have no basis to make any evaluation of whether or not the

plaque counts were correct. Right?
A. They would have no basis for the plaque count changes, but what they could have done is made a comment that there were corrections made and not with -- an explanation not given in the experiment.
Q. But they didn't. Right?
A. Not -- at least I don't have it captured here.
Q. And explanations weren't given when cross outs were made. Correct?
A. For at least as best I can recall, for the majority of the samples, there was -- an explanation was not provided next to the cross out or change.
Q. Did you direct your staff to justify the changes that they made to the plaque counts?
MR. SANGIAMO: Object to the form.
THE WITNESS: Could I ask for clarification of what point as counting or in a review of the data or what -- can you further explain what you mean by asking the lab staff to justify the

changes.
BY MR. SCHNELL:
Q. All the changes that the lab staff were making to the plaque counts following up on the criteria for determining accurate plaque counts, did you direct the staff to explain anywhere why they were making these changes?
MR. SANGIAMO: Object to the form.
THE WITNESS: For the interim analysis I don't recall. I don't recall instructing the staff to indicate the reasons for those changes.
BY MR. SCHNELL:
Q. Did you not want them to?
A. No, it was an oversight on my part of not asking for the explanation of the changes or even for changes that I made to put an explanation next to them.
Q. When did you correct that oversight?
A. As best I can recall, that oversight was corrected in response to the FDA and then resumption of the Protocol 007 AIGENT

testing in 2002.
Q. So for all of the testing that was done from late 2000 through August of 2001, so we're talking about at least nine months of testing, the changes to the plaque counts that were made were never justified or documented?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say that no cases had a justification or explanation, but as best I can recall, the majority of the changes, again, as best I can recall, did not have a justification written in the plaque counting sheet.
BY MR. SCHNELL:
Q. Other than it being an oversight, was there any other reason why that was not done?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not -- no.
BY MR. SCHNELL:
Q. Are making changes to plaque

counts without justification compliant with CGMP?
A. I'm not familiar with CGMP. Sorry. CGMP is what I said. It's -- I'm not fully fluent in CGMP. My understanding is that that would not be compliant with -- there's a caveat to this that, as I understand it, it's a limited understanding of the CGMP, is that changes are -- the explanation of the changes are to be documented unless the change is obvious, the reason for the change is obvious.
MR. SANGIAMO: Could you show an objection to the form to the last question, please.
BY MR. SCHNELL:
Q. Are making changes without justification -- without documenting the reason compliant with GCP?
MR. SANGIAMO: Object to the form.
THE WITNESS: Not something I'm familiar with.
BY MR. SCHNELL:
Q. What would be an obvious reason

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for changing a plaque count that would not, in your opinion, need to be justified?

A. Some examples that I can think of would be someone intended to write a number, for example, eight, and really wrote six and realized, oh, I put the wrong number down, so they would cross out the correction to whatever the intended count was. Or if these plaque count values were entered into the wrong cell of the spreadsheet or the counting sheet and then they realized that the values were put in the wrong cell for that assay.

Q. If I'm a plaque counter and I wrote a six but I meant to write an eight and I go back and change it, how would that be obvious to anyone but me?

A. It wouldn't be. And there's --

Q. So that's not an example of an obvious change?

MR. SANGIAMO: He's in the middle of an answer.

BY MR. SCHNELL:

Q. So that's not an obvious --

MR. SANGIAMO: You have to let

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him finish his answer.

BY MR. SCHNELL:

Q. Do you want to finish your answer?

A. I was going to say the transcription error part -- I'm sorry, transcription error. The entering the data into the wrong cell of the counting sheet where all the values, for example, they get moved down four spaces. In looking at the assay, one could say this looks like all four values got moved down. So it looks like they were entered in the wrong cell. I've seen cases where it's viewed as an obvious correction that they were mis-entered into the right space in the spreadsheet. The entering, the -- a number, you realize you just wrote the wrong number down. Technically, I guess, would -- someone looking at it would not know automatically whether that was a correction or the original counter entered it and changed it.

Q. So other than the first example which was, I forget how you described it, but recording the number in the wrong part of the

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spreadsheet or moving it up?

A. Yes.

Q. Other than that example, are there any other examples of plaque count changes that would have been so obvious that they wouldn't need to be justified?

A. None are coming to mind, but I can't exclude that there were other situations where that would apply.

Q. So looking back at Krah Exhibit 42, the first error identified as transcription error, it says, it's a difference between data in the handwritten file and the Excel file. So is that when the counting sheet number did not match the Excel final number?

A. That's my recollection of what that indicates, yes.

Q. So in those instances, which was the number that was picked as the original count?

A. As best I can recall, it would be the handwritten value.

Q. Why?

A. Because that was -- the plaque

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count on the counting sheet was the primary data that was then transcribed into the workbook. So that original count was the number to be used in the workbook.

Q. So in that instance, if there was a five on the counting sheet and a ten in the Excel file, what would happen in terms of reconciling the two to make the information correct in your view?

A. My understanding of that, my best recollection is that the value in the Excel file would be changed to match whatever was in the hand count and recorded file.

Q. Was there any indication in the Excel file that the Excel file had been changed?

A. Not that I'm aware of.

Q. And, in fact, if there was originally a five in the counting sheet and a five was entered into the Excel file, and then you directed that counter to go back and recount and they came up with a ten, they would then go back to the Excel file, delete the five and put in the ten. Correct?

MR. SANGIAMO: Object to the

form.
THE WITNESS: The original entries in the -- the entries that were made into the spreadsheet were -- did include corrected count. So in the original data summary before we went back and used the original plaque count entries in the Excel file. So there was a period where the corrected counts were being used for the calculations in which case that, for example, if a five was corrected to a ten, that ten would be put into the spreadsheet.
BY MR. SCHNELL:
Q. Calculation errors, self-explanatory as to what it was. My question is, were you finding that there was a relatively high number of calculation errors?
A. I don't recall. I recall it being observation during the audit. I don't recall that it was a high percentage or a low percentage.
Q. All the calculations were performed by you. Correct?
MR. SANGIAMO: Object to the

form.
THE WITNESS: Not by me. The calculations were done by, as best I can recall, in Excel for the -- some cases the mock value, I believe, was done manually with a calculator. But the percent of mock value would have been calculated by the -- as best I can recall, with Excel. Assignment of a titer would have been done manually, not -- it could be by me or by others in the lab.
BY MR. SCHNELL:
Q. So it was most likely -- or strike that.
Was it the individual who was inputting the data into the Excel spreadsheet also the one who made the calculations of percent mock value and average plaque number for mock sample and other calculations?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't say with certainty that that's the case. That would be the typical flow, but I can't

say that that always was the case.
BY MR. SCHNELL:
Q. When you were getting the counting sheets from your lab staff as they were preparing them, were you going through them and making calculations?
A. Once the plaque count sheets were available, calculations were done to determine seroconversion rates and also, at least in the first third of the testing by assay, evaluating the number of pre-positives. So there were some summaries of the data that were being done by me but the calculations would have been part of the Excel spreadsheet and subsequent determination of titer.
Q. And what specific calculations were you performing as it related to pre-positives?
A. As best I can recall, I remember -- recall cases whereby assay would have listed percent pre-positives in that assay.
Q. And why were you performing those calculations?
A. As best I can recall, that was

something Emilio Emini had asked for to help understand the assay performance.
Q. Why would that help him understand the assay performance?
MR. SANGIAMO: Objection. Calls for speculation.
THE WITNESS: I don't have -- I didn't ask him directly why he was asking for it. So I don't have an explanation for his ultimate goal in asking for it.
BY MR. SCHNELL:
Q. He never told you why?
A. Not that I recall.
Q. And you have no idea. Is that right?
A. I have an idea, but it would be speculation.
Q. So what's your idea?
MR. SANGIAMO: Objection. Calls for speculation as he just said.
THE WITNESS: My speculation is that in development of the assay we had a seroconversion -- I'm sorry, a pre-positivity rate that we observed.

And this would be a way to see if the pre-positivity rate that we're seeing in testing of Protocol 007 was consistent with the result we were getting in the development studies. But that's just my guess at what he's was looking for.

BY MR. SCHNELL:

Q. As the person who was running and leading the study, you didn't care one way or the other why he wanted this pre-positive information?

MR. SANGIAMO: Object to the form. Object to the characterization of Dr. Krah's role.

THE WITNESS: Emilio asked whatever -- typically if he asked for a summary or data, I provided it and didn't typically ask about the explanation for the reason behind it.

BY MR. SCHNELL:

Q. You reported to Dr. Shaw at the time. Right?

A. Yes.

Q. Was Dr. Shaw also asking for

this information?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't recall. I recall Emilio Emini asking for it. I don't recall if Alan Shaw was as well.

BY MR. SCHNELL:

Q. Were you involved in any other clinical studies at Merck where you were working as closely with Dr. Emini as you were with the AIGENT testing?

A. No.

Q. If you look at number 9, it says, "Over-writing data." What's that?

A. It means -- I'm trying to recall the examples of this or definition. The data would be, for example, if you wrote a sentence on a page and -- I'm trying to think, not recalling specific examples of this. Something had been written on a page by pen and then something else had been written over top of it to the point where it might be potentially difficult to see the underlying number.

Q. Are we talking about the

counting sheets here?

A. That, I don't know. I recall examples. For example, if we were putting a lot number of the reagent, someone put the wrong lot number and they had like put in a number, for example, six, they meant -- they realized that it's an eight so they make the six an eight. That would count as an overwrite, because there was a six entered originally and then modified.

Q. But you don't know if they're referring to counting sheets here?

A. The way it's worded -- I don't recall specifically what they were referring to. And the way it's written, I can't tell what that refers to.

Q. That's all I have on this one.

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(Exhibit Krah-43, 6/21/01 Memo, 63805, was marked for identification.)

\- - -

BY MR. SCHNELL:

Q. I'd like to mark as Krah Exhibit 43 a memo from Dr. Krah to files, dated June 21, 2001, Bates number 63805.

Do you recognize this document?

A. Yes, I do.

Q. What is this document?

A. This is a memo that was intended to capture impact of extra variable plaque counts that were flagged in the workbook and categorize them by the codes listed on the far right-hand column where that code would then be put into the workbook to explain the impact or describe the impact of that extra variability result on the data, on the overall data for that serum sample.

Q. Is there a flag here that relates to positive neutralization of a single dilution?

A. The ones I see are extra variable plaque counts. They're plaque counts for given dilution and then they consist of pattern of neutralization. So I do not see one for every single positive dilution.

Q. But there was one flag for that in the AIGENT workbook. Right?

A. I don't recall -- single positive dilutions were part of the -- I'm sorry, I don't recall with certainty. I have

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an expectation that that was a plaque in the workbook, but I don't recall with certainty that that was the case. These are -- there's -- explain the impact of these flags versus something like a single positive dilution. The impact of these flags is that you could have an extra variable. Each serum has eight dilutions that are tested. There could be an extra variable plaque count or no plaque count or inconsistent pattern of neutralization at some dilutions of the serum that don't impact the titer assignment. For example, if you have extra variable plaque counts at the first three dilutions but your fourth and fifth dilutions are positive, one could still assign a titer that the higher dilution to the serum sample. So the results that are not -- are extra variable become unusable or meaningless as far as determining whether the serum is neutralizing or not. If the serum is neutralizing at a higher dilution, that result at the lower dilution becomes irrelevant. So you can still assign a titer.

If the extra variable plaque

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count is -- another example is all the values are giving less than 50 percent neutralization, they're extra variable but they're all less than 50 percent, that means even though they're extra variable, none of them are neutralizing. So that would have no impact on the difference between a positive and a negative serum. If an extra variable plaque count was in, for example, one row, and all other rows were negative, you couldn't tell if that extra variable count would have been positive or negative so you wouldn't be able to assign a titer to the sample.

So the objective from this is to take cases where the impact of that extra variable plaque count or no plaque count depended on where it fell in the dilution scheme; or depended on where that dilution fell -- where the extra variable flag or another flag fell in the dilution series. So that you wouldn't always say, oh, there's an extra variable plaque count for this row, therefore, that sample is an invalid sample. It would depend on where that result fell.

Q. So this doesn't purport to

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represent all of the flags marked questionable in the workbook. Correct?

A. I don't recall with certainty what all the flags were in the workbook. This represents at least some of the flags. Again, whether it's all of them, I can't say with certainty.

Q. I believe, you can tell me if I'm wrong, but I believe this morning you testified that there was a flag for positive neutralization at a single dilution. Is that not your testimony?

MR. SANGIAMO: Objection. Misstates the testimony as I recall.

THE WITNESS: As best I recall, I indicated that I thought that there was a flag for that, but I wasn't certain.

BY MR. SCHNELL:

Q. Are there other flags that were in the AIGENT workbook that are not identified here that you're aware of?

A. I don't -- these are ones that I can say with certainty were part of the workbook. Whether there were others that are

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part of it, I don't recall.

Q. Now, if you look at the fifth one down, the second sentence says, "Data from this set are not reported in this assay."

Do you see that?

MR. SANGIAMO: Sixth one down, Gordon?

THE WITNESS: The fourth one down?

BY MR. SCHNELL:

Q. Fourth one down.

A. This is, "Extra variability prevents reliable measurement of neutralization --

MR. SANGIAMO: Slow down.

THE WITNESS: Sorry. "Extra variability prevents reliable measurement of neutralization, serum is being retested. Data from this set are not reported in this assay. Data will be presented in the retest assay spreadsheet."

So to me my recollection of --

MR. SANGIAMO: Dr. Krah, he hasn't asked you a question.

THE WITNESS: I'm sorry.
BY MR. SCHNELL:
Q. So what did you mean by "Data from this set are not reported in this assay"?
A. What I -- my best recollection of what I meant from that is that that meant that basically is an invalid sample, that it doesn't have an assignable titer. And since it's not assignable, it's not being reported in that assay.
Q. Then in the sentence that preceded that sentence, "Extra variability prevents reliable measures of neutralization, serum is being retested," what did you mean there?
A. That means that if -- in the series of eight dilutions of serum that are tested, depending on -- the extra variability means that there is more variability than expected between the replicates at that dilution. If that number exceeds the expected variability, the extra variability flags indicates that those are not reliable values. Depending on where that -- so that then becomes a value for which you cannot calculate

a reliable percent mock and then in turn cannot determine whether it's neutralizing or not. If -- it depends on where that dilution falls and what the results of the other seven dilutions are as to whether that falls into this code number 4 or one of the other codes.
Q. So if you don't count a count in some way for extra variability, is it impossible to have a reliable measure of neutralization? Is that what you're saying here?
A. My understanding is that if the count is extra variable, it's not a valid count which means that there's no count, no valid count for that dilution of a particular serum, which means you cannot assess neutralization for that dilution.
Q. Did you account -- did you take any measures to address extra variability in the interim analysis?
A. The interim analysis, I did not. I don't know if someone else did, but I did not.
Q. Well, who else would have other than you that you wouldn't have been aware of?

A. Joe Antonello in the biometrics group was the one who proposed the idea of extra variability. I can say that in our compilation of the data and calculation of titers we did not implement extra variability -- extra variable -- extra variability assessments. What I cannot exclude is that he didn't retrospectively apply an evaluation of the extra variability to the data and look at the impact of it on the result -- on the assay results.
Q. Now, if you had done that, and there were changes that followed, those would have been recorded on the counting sheets. Correct?
A. Whatever changes would have been made, regardless of the reason, would have been recorded on the counting sheet.
Q. Are you saying it's possible that Joe Antonello implemented changes on the counting sheets that you were not aware of?
A. No, not for the first third.
Q. The second two-thirds?
A. The second two-thirds he provided the worksheet.

Q. Are you saying he also could have implemented changes to the counting sheets that you would not have been aware of?
A. No, I'm not saying that. What I was attempting to say, that he may have, and I'm not aware that he did, looked at the data from the interim analysis, the experiments from the interim analysis, look at whether the extra -- what the results would be if he put in an extra variability flag. There would not -- those would not have been the data that were reported to CBER. But I can't exclude that he might have done some sort of -- included those in his review of frequency of extra variability.
Q. But the interim results that were reported to CBER did not control for extra variability. Is that correct?
A. The interim results that were provided to CBER did not have a flag for extra variability, yes.
Q. Well, there were no flags at all for the interim results. Correct?
A. There were no flags, yes.
Q. So my question is, you did

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control for, or tried to control for other potential errors that were made in the plaque counts on the interim analysis. Correct?

A. There were changes in the data that were intended to try to make the data more accurate for the interim analysis.

Q. But none of those involved extra variability. Is that correct?

A. Correct. As best as I understand it, there was no -- I wasn't aware of that as a potential -- potential criteria for check so I did not implement knowingly an extra variability evaluation.

Q. So it was only after the interim analysis was completed when you implemented an extra variability check on the data to control for that potential error. Is that correct?

A. It's correct that the first, the workbook that we -- the Excel spreadsheet that we used for the first third did not have an extra variability criteria. The second third -- the balance of the testing in the second third and the third third did have a different workbook that didn't include an assessment of extra variability.

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Q. So if extra variability wasn't accounted for in the preliminary analysis, did that prevent a reliable measure of the neutralization for that part of the AIGENT testing?

A. I can't comment on the reliability, the impact -- the statistical impact on the reliability. Joe Antonello suggested this as a means to monitor the assay. Whether that led to an actual affect on the reliability, I don't know.

Q. But it might have?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't have -- or I guess it could have, but it could equally have well not have. I don't have a view one way or the other.

MR. SANGIAMO: Gordon, we're about an hour and nine minutes out. Take a break.

VIDEOGRAPHER: The time is now 3:15. This concludes disc four.

- - -

(A recess was taken.)

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- - -

VIDEOGRAPHER: The time is now 3:33. This begins disc five. You may proceed.

- - -

(Exhibit Krah-44, 7/30/01 Memo, 00002211 - 00002230, was marked for identification.)

- - -

BY MR. SCHNELL:

Q. Dr. Krah, I've handed you what we've marked as Krah Exhibit 44. It's a memo dated July 30, 2001, from Dr. Krah to files. It attaches a series of counting sheets. Bates range is 2211 through 2230.

Dr. Krah, do you recognize this memo and the attached counting sheets?

A. I recognize the memo. The counting sheets in general I recognize. I can't say the actual specific content is familiar.

MR. SANGIAMO: Can I ask, did you intend to include 2227 through 223 --

MR. SCHNELL: I don't have questions about it, but I think that's

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the way it was produced to us.

MR. SANGIAMO: Okay.

BY MR. SCHNELL:

Q. So, Dr. Krah, what were the circumstances surrounding your drafting this memo?

A. As best I can recall, as I mentioned earlier, Leah Gottlieb had -- was -- sorry, let me take a step back.

Once the plaque counts were entered from the counting sheet into the workbook, Leah Gottlieb would review the workbook to identify samples that had flags and then summarize those and meet with me on a periodic basis and identify with a goal -- at least from my perspective, identify sera that were ones that were flagged for rechecks or for the like -- and then an assessment, for example, the extra variable plaque counts and the implications of that on being able to assign a titer to the sera -- I'm sorry, being able to assess a -- assign a titer to the samples. As best I can recall, Leah identified two assays that were counted by Steve Krahling where they had, as best I can

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recall, a large number of flags. I don't recall what large number of flags meant. So she suggested checking the assays to see if there were errors in the plaque counting. So what I did as part of that follow up with Leah was do 100 percent recheck of -- recount of the plaques for, as this indicates -- as best I can recall, there were two assays that -- I think what's listed here as MMRV-170-01 and MMRV-179-01, it had large recounts. Let me refresh my memory if these -- which assays these are.

Q. Just to help you along, these are assays 210, 214 and 245 that you indicated that you recounted 100 percent.

A. So my best recollection is that Leah identified the two assays, MMRV-170-01 and MMRV-179-01, that had a number of counting errors. My recollection of this document was that as follow up to those counting errors, I monitored three assays that, double checking that these are all --

MR. SANGIAMO: Take your time to look through.

THE WITNESS: Three assays that

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appear to be ones that Steve had counted subsequent to that -- subsequent to those two assays to verify whether the plaque counts in these three assays were within the targeted plus or minus 10 percent count difference between me as the reference counter and Steve. And if not, to continue rechecking until the counts fall within that -- sorry, not keep rechecking the same data, but recheck subsequent assays to -- until we can verify that the plaque counts were falling within that 10 percent range.

BY MR. SCHNELL:

Q. So Leah Gottlieb was in quality assurance. Right?

A. She served a -- I don't recall what group she was in, what her official group name was. She served a quality assurance function to our department at the time of the protocol virus and cell biology. I don't recall what department she was in in serving that function.

Q. This references counting errors,

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not extra variability flags, so are you talking about the same thing here?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't -- to me -- I can't say with certainty based on the word "count" -- the words "counting errors," but my best recollection is that there were a lot -- a large number of flags of one kind or another in those two assays of MMRV-170-01 and MMRV-179-01.

BY MR. SCHNELL:

Q. But there was no flag for counting errors, was there?

A. There's no flag for counting errors, but I can't exclude that I genericized that as counting errors, meaning flags from the workbook.

Q. So if we looked at -- so that was with respect to 170 and 179 which is what prompted your re-review of the three assays attached here. Correct?

A. That's my understanding of what prompted the review -- re-review of the three

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assays attached here.

Q. So what you did was you went back to the assay plates and then you did all the recounts yourself?

A. Yes.

Q. And you recorded them on these counting sheets. Is that correct?

A. Yes. As the numbers to the right of -- as best I recall, the numbers to the right of what Steve had entered in here originally.

Q. And the first recount -- this is assay 210, you conducted on July 1st as indicated by your signature and date. Correct?

A. Yes.

Q. And then the second assay which is number 214 and begins on --

A. I'm sorry, may I correct that? It looks like the plaque counts were checked by D. Krah, 30th of June 2001, and then results were entered into a new spreadsheet 01, July of 2001.

Q. So June 30th is when you made these changes. Right?

A. That's what this indicates. At least for that experiment, 210-01.
Q. And then for assay 214 which begins on the page ending in 217, the Bates number ending 217, lower right corner, not the EDPA one, but the MRK-KRA. Do you see it?
A. I'm sorry, 2217 is the last --
Q. Yeah.
A. Yes.
Q. So that indicates that you did these changes on July 17th. Am I correct?
A. That's -- yes.
Q. And then for assay 245 it looks like Merck produced an incomplete assay here, but it looks like on the pages they did provide -- actually, I can't tell. Can you tell when you did that one?
MR. SANGIAMO: Let me just say that this is a document that you're producing here at this deposition. If you're suggesting that we did not produce a complete set of this assay, I certainly don't accept that proposition. This may not -- you may not have included all the

appropriate things here.
MR. SCHNELL: You can look at the Bates number and tell for yourself. But in any event --
MR. SANGIAMO: Well, no, this is the Bates number for this particular document. I just want to avoid any suggestion that our production in general did not include complete documentation for this assay.
MR. SCHNELL: Are you finished?
MR. SANGIAMO: Yeah, I'm done talking. Isn't that evident?
BY MR. SCHNELL:
Q. So this last assay 245, when did you make the changes?
A. The pages that I see here indicate that the 17th of July 2001.
Q. Okay. So all of these were made on or after the end of June, correct, in 2001, all of these changes you made?
A. The end of June, 30th of June through the 17th of July.
Q. And these changes were made by you, isn't it true, after a time that

Mr. Krahling had raised serious concerns he felt with how you were conducting the AIGENT testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: The only concerns that I recall hearing from Mr. Krahling were that we knew the pre- and post-vaccination sera.
BY MR. SCHNELL:
Q. And you had heard those concerns prior to the time you did these changes. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall the date at which those questions were posed.
BY MR. SCHNELL:
Q. So I have a few questions about some of your changes. If you could turn to the second page of this packet with the Bates number ending 212, if you look at sample 122, do you see the changes you made there?
A. Yes.

Q. You went from eight -- so Mr. Krahling recorded eight, you recounted by checking the assay plate. Right?
A. Yes.
Q. And you recorded nine. But then you crossed that out and you wrote ten. Why was that? Did you check it twice?
MR. SANGIAMO: Objection.
THE WITNESS: I can't recall with certainty looking at this. I don't expect that -- I don't -- I would not expect that I would have rechecked it twice.
BY MR. SCHNELL:
Q. So how could you explain, then, that you have two corrections there?
A. I do recall, I can't say it's this particular assay, but assays where I count the number of plaques, record the number on the plate, and then when I -- as I'm recording the number, looking at the plate, I see a plaque that I missed. So I can't exclude the possibility that this is something where I counted nine as I'm looking at the plate and then I write nine down and looking

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at the plate one last time and see a plaque that I missed so I changed it to a ten to reflect what the -- the fact that I missed a plaque.

Q. So what about plate number 130, Mr. Krahling recorded nine, you didn't like that so you crossed it out and then you wrote your own nine?

MR. SANGIAMO: Object to the form.

BY MR. SCHNELL:

Q. So how do you explain that?

A. I don't -- that I can't explain. I expect that would be I crossed it out and realized that it was not justified being crossed out, then wrote a nine in next to it.

Q. Why would you cross it out before reaching a conclusion as to what the numbers should be?

A. In filling out the -- I can't say with certainty, but in filling out the form, the large number of wells, I can't verify that I wouldn't have crossed out, for example, a wrong row or crossed out and realized that wasn't one to be crossed out.

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Q. Okay. If you could flip a few pages down, the Bates number ending 215, you look at plate 166 and 167, there for 166 Mr. Krahling wrote -- recorded 21 plaques. You crossed it out and wrote 14. And then you crossed that out and wrote 21 again which is what Mr. Krahling originally counted. You did the same thing with plate 167, Mr. Krahling wrote 11 plaques, you crossed it out and wrote eight. Then you crossed that out and wrote 11 again. How do you explain that?

A. I'm sorry, what was the second one -- what was the second example that you gave?

Q. They're right next to each other, 166 and 167.

A. I don't recall.

Q. If you keep flipping through, there's others examples if you go through it, but I'd like to turn your attention to assay number 214.

A. I was going to say the -- in doing the plaque count comparison, I rechecked well by well. My objective was to count -- to make sure I'm counting the right well that

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Mr. Krahling recorded. There's the plate -- there's three replicate wells and one can count the plate upside down or right side up. The middle well will always be the middle well regardless. I can't exclude the possibility that in some cases I counted a top well when really it matched up the number that Steve had for the bottom well and then the reverse would apply. But the evaluation that I do as far as -- at least from my recollection, is that the evaluation, whether someone is counting plus or minus 10 percent of the reference counter is not well by well but taking the average of the three replicates. So then it wouldn't matter -- it's the three values that matter. It wouldn't matter if I got things mixed up in recording.

Q. Turning to assay 214, which begins on Bates number page ending 217, I just want you to flip through that assay and then the pages that are in this packet from assay 245 which follow. You crossed out virtually every single number that Mr. Krahling, not every one, but I'd say 75, 80 percent or in some cases looks like close to 100 percent of

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the counts that he wrote. Do you see that?

MR. SANGIAMO: Object to the form.

THE WITNESS: I agree that there's a large percent -- large number of the samples that were crossed out with corrections.

BY MR. SCHNELL:

Q. Did that give you concern that Mr. Krahling was just not a capable plaque counter?

A. It gave me a concern that he had become not -- at least based on the results of this, not a reliable plaque counter. In the original training for the assay, training was done to show ability to count plaques accurately. And my objective, as best I recall from this, was to look at assays around this time to see what other assays were also showing counts that were -- had excess variability from a reference counter.

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(Exhibits Krah-45, Counting sheets, 00683926 - 00683930 and Krah-46, Counting sheets, 00683514 - 00683518,

were marked for identification.)
\- - -
BY MR. SCHNELL:
Q. I'm going to hand you two more counting sheets. This is what we're going to mark as Krah Exhibit 45 and 46. Krah-45 is a counting sheet for assay 762 recorded by Mr. Krahling on January 3, 2001. And Krah-46 is a counting sheet for assay 754 recorded by Mr. Krahling on December 27, 2000. Do you see these?
A. Yes, I do.
Q. If you look at these, look at Krah-45, of all of these counts, I see one correction on the third page. On sample 1285. I don't see any other corrections. Do you?
A. No.
Q. And the correction that was -- the one correction that was done was Mary Yagodich made that. Right?
A. There's a note there, "plaques missed - MKY...," which is Mary Yagodich checked. '01 -- I'm sorry, January 8, 2001.
Q. So obviously his counting sheet was reviewed. Correct?

MR. SANGIAMO: Object to the form.
THE WITNESS: I cannot say that the full counting sheet was reviewed. All I can say is where there is a -- there's no indication that the full counting sheet was reviewed. There's only the note next to the third line, second line and third line for sample 1285 that shows cross-out correction.
BY MR. SCHNELL:
Q. Then if you look at Krah-46, nothing on the first page, nothing on the second page, two changes on the third, and two samples that had changes on the third page. One change on the next page. No changes on the next page. Is that correct?
A. That looks correct to me, yes.
Q. So how do you reconcile the assays that Mr. Krahling performed that you reviewed where you found literally hundreds of errors with the counting sheets that I just showed you where there was just a few?
MR. SANGIAMO: Object to the form.

THE WITNESS: All I can say is that the plaque counts, there was -- Steve was trained initially, passed the training qualification, which led to him being able to count plaques initially. What happened between then and the assays, were a large number of miscounts were noted, I can't speak to. What I would offer, which was, as I recall, an unusual event more typically I think, as I mentioned earlier, the tendency is to miss plaques either through faint plaques or just plaques that were missed. Some of these assays that I recall reviewing with Steve were ones where the plaque counts were higher. So Steve was counting plaques that weren't plaques. I can't explain what happened between these earlier assays where the counts looked like they were -- the counts were accurate and then what happened at this later time when they became -- had a large proportion of inaccurate numbers.
BY MR. SCHNELL:

Q. So when you did these checks on 210, 214 and 245 and identified what you saw as such a large number of incorrect counts, did you go back to all the other assays that Mr. Krahling counted to make sure that there weren't a large number of incorrect counts?
A. I don't recall -- other than the ones I listed here, I don't recall other assays that were checked.
Q. Weren't you concerned that if he made what you saw as such a large number of incorrect counts on these assays, that he had made an equally large number of incorrect counts on the other assays?
A. As best I can recall, the assays that are listed here as experiment 170-01 and 179-01 were the first ones that had, as I phrased here, a large number of counting errors which, to the best of my recollection, meant flags from the workbook. I don't recall assays before that having similar large proportions of flags.
Q. Most of the changes that you make here are one, two, maybe three. So it doesn't suggest extra variability issues, does

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it?
MR. SANGIAMO: Object to form.
THE WITNESS: That extra variability is not -- the criteria that's evaluated in the rechecks is percent values -- I wouldn't say that I -- of these changes, I don't know how many of them fall outside of the 10 percent counting range, but the objective is to have the reference counter and the counter be within 10 percent plus or minus of the reference counter. So it's not extra variability that's assessed but the average number of plaques for the replicate wells.
BY MR. SCHNELL:
Q. Has the individual responsible for conducting the AIGENT testing, did you feel an obligation to ensure that the data that you and your staff were finding in the AIGENT testing was accurate and reliable?
A. My objective was to have the data be as accurate a representation of the actual numbers of plaque counts as possible.
Q. Yet despite finding what you saw

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as so many errors in these three assays by Mr. Krahling, you didn't think it would be a good idea to go back and check his other assays?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall, again, if -- the trigger for me was experiment 170-01 and 179-01, if they had a large number of flags from the counting sheets. Assays before that did not have that. That would not have been an immediate indicator that the other assays were being counted inaccurately.
BY MR. SCHNELL:
Q. So you had no concern that Mr. Krahling had inaccurately counted on his other assays?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't recall looking -- I don't recall what other assays I might have looked at as part of an evaluation of when the counting

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accuracy might have dropped off.
BY MR. SCHNELL:
Q. Now, the FDA inspection occurred a week after you wrote this memo. Right?
A. I believe it's the first week of August, so approximately a week.
Q. Are there any other memos in your files where you call out a particular member of your lab for engaging in what you characterize as inaccurate plaque counting?
MR. SANGIAMO: Objection.
THE WITNESS: As best I can recall, in response to the observation of potential miscounting by Steve, I went to every one of -- assays that every one of our lab counted and did 100 percent recheck of those to assess whether other people were having a similar tendency of miscounting.
BY MR. SCHNELL:
Q. But you just said you didn't go back and check his other assays, so what assays are you talking about?
MR. SANGIAMO: Object to the form.

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THE WITNESS: I don't recall the specific assays I looked at, but there were assays that were available at the time where people had counted -- I say counted and then I did 100 percent verification of the plaque counts that they had made.
BY MR. SCHNELL:
Q. So you selectively chose certain assays from the lab staff and you checked them?
A. I wouldn't say selectively. I picked, as best I can recall, two assays, as best I recall, from every individual in the lab. They're not completely at random, just two that were available at the time. So not completely -- not selectively, but not completely randomly selected.
Q. And you went through every count that they had made for that particular assay?
A. As best I can recall, I did 100 percent check of counts for everyone in the lab.
Q. And you went back to the assay plates and you -- that's how you checked it?

A. Yes.
Q. Do you have a record of that counting?
A. Yes.
Q. What's the record?
A. I don't know if it's a memo to files. I recall documenting the specific way in which I did it, whether it was a member of the files or some other form. I don't recall, documenting who was checked and what dates and what the results showed.
Q. And the counting sheets would be attached?
A. I can't assure that the counting sheets are attached. It may just -- I may just reference the experiment numbers.
Q. Who at the time would have been the lab counters or the staff in your lab who did the counts that you checked?
A. Well, Steve, Joan Wlochowski, Colleen Barr. We had two summer interns, Jon Gombola and Suzanne Maahs, I believe. I forget. There was Frank Kennedy who was in our lab, I don't recall when he joined the lab. So as best I can recall, it was everyone

who was in the lab and counting at the time.
Q. And how did Leah Gottlieb communicate to you the issue with assays 170 and 179 that are referenced in your July 30th memo?
A. As best as I recall, when I met with her to go over her review of the assay results, meaning the -- review meaning the flagging or identifying sera for which there is a flag in the workbook that would trigger verification of the plaque counts, that she presented these two assays and said these look like they have a large number of flags, something doesn't look right.
Q. Did she call you or did she write you?
A. This is in person. I met with her in person.
Q. There's nothing in writing about this?
A. The initial communication to me was verbal. I don't recall that she documented it in any other way.
Q. Before lunch we talked about the discarding of assay plates from AIGENT

testing. You said that Merck still has in its possession some of the assay plates that were used in AIGENT testing but not all of them. Correct?
A. Yes.
Q. And you don't know how many. Correct?
A. At the time of the -- at the time or shortly after the FDA inspection, I contributed to developing a list of the assay plates that we -- the assays that we ran and the assay plates that we had. I don't recall the numbers of plates that are -- assay plates that are still available.

- - -

(Exhibits Krah-47, Series of e-mails, 00026555 - 00026559 and Krah-48, Spreadsheet, 00050333 - 00050342, were marked for identification.)

- - -

BY MR. SCHNELL:
Q. Hold off on the first one. Let's talk about this one first. I'm sorry.
So I'd like to mark as -- we're going to skip and go to Krah-48, because I

already marked 47. We'll come back to 47.
This is a spreadsheet. Is the this the spreadsheet that you were just referring to?
A. No.
Q. So there's another spreadsheet that you prepared that identifies what plates were -- from the AIGENT testing were thrown out and what had been maintained. Correct?
A. As best I can recall, there was another spreadsheet that had a list of experiment numbers and then which assays for which plates were still available.
Q. So this is, for the record, a document with Bates range 50333 through 342 This is your handwriting. Right, Dr. Krah?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm sorry, on?
BY MR. SCHNELL:
Q. On Krah-48.
A. That's not -- some of it, the discarded entries look like my handwriting. The other entries do not look like my handwriting.

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Q. So I'm interested in the discarded handwriting, which you confirm is your handwriting.
A. Sorry, looking at the other pages, the first two, three, four, five, six, seven, the entries on the first page look like my writing of discarded. On the second page, experiment 163-01 does not look like my writing. Discarded on the subsequent page is not my writing. So the entries on the first page look like -- the discarded entries on the first page look like my writing. But none of the other entries look like my writing.
Q. Do you recognize this spreadsheet?
A. I don't have a -- it lists experiments that are familiar and the information that's familiar, but I don't recall this specific format, seeing this specific format. I don't recall this specific format.
Q. What was the format of the other spreadsheet you referenced where you identified the assay plates from the AIGENT testing that had been discarded?

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A. I don't recall with certainty.
Q. Do you have any reason to believe that the -- on the first page the assay numbers meant -- on the spreadsheet have the word you wrote "discarded" on them does not indicate that those assay plates were discarded?
A. I don't have a -- all I can say is that it says they're discarded. I don't have an independent recollection of whether they were or weren't.
Q. Can you think of any other reason why you would have written discarded there?
A. No.
Q. Now, if you look at what we've marked as Krah-48.
MR. SANGIAMO: You mean 48? You said 48.
BY MR. SCHNELL:
Q. I'm sorry, 47. This is a series of e-mails, the top one being from Dr. Krah to Gary Swantner, S-W-A-N-T-N-E-R, dated February 7, 2011, Bates range 2655 [sic] through 60. And I want to direct your

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attention to the page with the -- second to the last page, Bates number ending 559. There you wrote on January 20, 2011, to Luwy Musey and Deitra Areha that We have been retaining the mumps neutralization assay plaque -- assay plates from MMR Protocol 007 as the primary data for this assay. This was part of a commitment to CBER to retain the primary data (the assay plates).
Do you see that?
A. Yes.
Q. There's nothing incorrect about what you wrote there. Right?
A. There's nothing incorrect my understanding after the FDA inspection that the assay plates were the primary assay data. It's not correct before the inspection I understood that.
Q. Your belief was that counting sheets were the primary assay data. Right?
A. Yes.
Q. The FDA's view was that it was the assay plates. Correct?
A. I can't say that with certainty or commitment to CBER was -- after the

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inspection was to retain the plates. I don't recall hearing a conclusion from them of what -- whether the counting sheet would be acceptable as the primary data or the plates would be needed. I don't recall getting an answer to that question.
Q. Answer or not, at the time you wrote this memo, it was your understanding that the assay plates were the primary data for the AIGENT assay. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: The first sentence I have written that as a primary data for this assay. My understanding was that -- at least I don't recall a response from CBER to confirm that. Those are words I used here, but I can't say that that's accurate.
BY MR. SCHNELL:
Q. You can't say that your words here are accurate?
A. I can say my words are accurate. I can't say that my conclusion -- well, I can say that my words are -- that are written

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there are my understanding at the time, but I did not -- when I wrote this, I did not have confirmation from CBER whether the asset plates would indeed be needed as the primary data.

Q. If you look to the very first page -- and this was all about trying to understand, was it not, whether you were permitted to destroy the remaining assay plates. Right?

MR. SANGIAMO: Dr. Krah, why don't you read the e-mail exchange here to answer what this all about.

THE WITNESS: As best I recall the fundamental question was -- that I was asking was, we still have the assay plates, does CBER require us to keep storing them or do they consider the primary data to be the counting sheet.

BY MR. SCHNELL:

Q. And you wrote according to your records, ...there are 36 boxes and each box should contain at least 1 assay (which typically is 45 plates) so there would be approximately 1600 plates, that's 36 times 45.

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Do you see that?

A. I'm sorry, what page?

Q. On the first page, your e-mail at the bottom of the page. Do you see where you wrote, "According to my records...."

A. Yes.

Q. What records?

A. I can't tell from this what I was referring to.

Q. And you don't independently recall records regarding the assay plates that have not been discarded that you would have had as of February 2011?

A. That, I don't recall.

Q. You estimated that you had 36 plates from 36 assays. Is that correct?

MR. SANGIAMO: Objection.

THE WITNESS: That's not an accurate description here. I think that there are 36 boxes and each box should contain at least one assay. Some boxes may contain more than one assay.

BY MR. SCHNELL:

Q. Your ultimate estimate was

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around 1,600 plates. Right?

A. That was my estimate that was provided in this e-mail.

Q. That was based on your review of your records. Right?

A. No. Another -- I can't say with certainty. Another option could have been I went to where the boxes were kept and counted them, and I don't recall that I did that, but it could be -- I don't recall specific -- I do have written here that according to my records, but I don't recall what that specifically refers to. Another option may be that I may have counted the number of boxes and assumed each box contains at least one assay and physically counted how many boxes were present.

Q. And you wouldn't consider that part of your records?

A. At the time I can't say for sure right today. If I counted something and that was the number I counted, I would say that that's what I counted and I would consider that part of my records.

Q. So the 1,600 plates at 45 plates

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per assay comes to about 36 assays. You're saying you're not sure if it's 36 assays. Do you have a rough sense of how many assays you still have?

A. If this indicated there are --

MR. SANGIAMO: Object to the form. You can answer.

THE WITNESS: The only -- all I can say is if this says there are 36 boxes, I'm assuming that there are 36 boxes. I can't say with certainty that I didn't intend approximately 36 boxes or this is exactly 36 boxes, and each box contains at least one assay.

BY MR. SCHNELL:

Q. Could a box contain two assays?

A. It depends on the size of the box. Potentially, yes.

Q. What's the most assays the box could contain?

A. That, I don't know.

Q. Do you have a sense of approximately how many assays were discarded from the AIGENT testing?

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A. No, I don't.
Q. Would you be surprised if it was more than 100?
A. I don't have any sense of what that number was.
Q. So that wouldn't surprise you or not surprise you, you just don't have a sense one way or the other?
A. I don't have a sense. The guidance that we were following at the time was that after the QA audit was done, those plates were -- we could discard them. I don't recall how many assays we run -- we ran so I really don't have a sense of how many assays were discarded.
Q. If I told you you ran 172 assays, would that change your answer to my question as to whether you'd be surprised if over 100 assays had been destroyed?
MR. SANGIAMO: Object to the form.
THE WITNESS: I would say no because the guidance that we were following at the time was once the QA audit was done, that we were able to

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discard the plates.
BY MR. SCHNELL:
Q. Would it surprise you if more than 120 assays had been destroyed?
A. No.
- - -
(Exhibit Krah-49, 8/1/01 Memo, 00026864, was marked for identification.)
- - -
BY MR. SCHNELL:
Q. I'd like to mark as Krah-49 another memo to files from Dr. Krah, dated August 1, 2001, Bates number 26864.
Do you recognize this, Dr. Krah?
A. The general document I recognize. I recall preparing a document of this sort.
Q. Have you seen this document recently?
MR. SANGIAMO: Don't answer with respect to any documents you reviewed with counsel. So excluding anything you might have reviewed with counsel, have you seen this document recently?
THE WITNESS: No.

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BY MR. SCHNELL:
Q. Why did you write this document?
A. I can't say with certainty what the reason for preparing this was.
Q. Did anyone ask you to prepare it?
A. I don't recall.
Q. Now, at this point the FDA inspection was five days after. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: As best I recall, the inspection was early August, which would have been after the 1st of August.
BY MR. SCHNELL:
Q. August 6th. Right?
A. I don't recall the date.
Q. Were you concerned that the FDA was about to come visit?
A. No.
Q. You had no idea they were about to come visit?
A. That's correct.
Q. You had no idea that any members

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of your lab had complained and threatened to go to the FDA?
A. That's correct.
Q. So it was just pure coincidence that you happened to write this memo five days before the FDA inspected?
A. Yes.
Q. At this point in time, the AIGENT testing had been going on for more than nine months, hadn't it?
A. It had started towards the end of 2000, wasn't running consecutively, but there was a span from late 2000 to this date, August 1st, during which the AIGENT assay was being run at some point.
Q. And so for nine months this testing had gone on and it was only at this point in time, five days before the FDA inspected on the AIGENT testing, that you decided to put this memo -- or put this stuff in writing. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: I would not characterize it that this was a date

where I decided to put this in memo form. I cannot exclude that I was planning to put this together. This is when I did it.

BY MR. SCHNELL:

Q. Can you think of any reason why it took you nine months to put this in writing?

MR. SANGIAMO: Object to the form.

THE WITNESS: Other than we're busy running the assay, and there was a practice that we were following and the data review, the assay running in data review with Leah Gottlieb, I did not understand the need to have that documented as we were doing it. So this is a process that we were following that I hadn't acknowledged needed to be put in some documented form. So the shortcoming is postponing or delaying not having time available to put this -- not setting time aside to prepare this in a more timely way.

BY MR. SCHNELL:

Q. Now, why didn't you just amend the standard operating procedure rather than write a separate memo?

MR. SANGIAMO: Object to the form.

THE WITNESS: I'm sorry, did you say why didn't I write a new or amend the SOP rather than write the memo?

BY MR. SCHNELL:

Q. None of this was in the standard operating procedure. Right?

MR. SANGIAMO: Object to the form.

THE WITNESS: We did not have -- although the first point would have been in the original SOP. That's a given for running the assay. I don't recall that we had a comment in the original SOP about if questions arise during the original counting. We did not have the mumps AIGENT workbook. We didn't have an indication that plaque counts were entered into a spreadsheet. All the flag comments were points for review with 3 on 5, or any recheck 6,

corrections are -- in 7 and 8 as best I can recall not part of the original SOP.

BY MR. SCHNELL:

Q. Now, this wasn't even circulated to lab staff, right, just the files?

MR. SANGIAMO: Object to the form.

THE WITNESS: As this is worded, it's sent to files.

BY MR. SCHNELL:

Q. Don't you think it would be a good idea for the lab staff to see this memo?

A. I don't recall with certainty that it was not reviewed with lab staff. As a memo, the policy does not exclude that I would have reviewed it with lab staff.

Q. It doesn't indicate that it was either?

A. No.

Q. This was at a time when virtually all the AIGENT testing was complete. Correct?

A. As best I can recall, approaching August, again, my best recollection is that we

were beginning to complete the planned testing for the AIGENT assay.

Q. Other than being busy, can you think of any other reason why you waited nine months to write this, all these, this clarification of data collection on the AIGENT testing when the AIGENT testing was almost complete, and not send it to lab staff?

MR. SANGIAMO: Object to the form.

THE WITNESS: I would say in a practical sense, if we're almost done the testing, and this is the package we were following, it would be less critical -- or less important to present it to the lab staff because we had already -- we're wrapping up the testing. It's not that all the lab staff would still be continuing with additional testing.

BY MR. SCHNELL:

Q. So why is there a need to document it at all?

A. As best I can recall, this is an effort to document the steps and whether it's

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just that I -- I don't recall whether -- I don't recall the actual -- I don't recall the reason for writing it other than having it or the -- what initiated the writing of it, but the intent was to capture the steps in the workbook and flags and rechecks and corrections and comment on things like invalid dilutions.

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(Exhibit Krah-50, 007 Summary, 00054460, was marked for identification.)

- - -

BY MR. SCHNELL:

Q. I'd like to mark as Krah Exhibit 50 a document with Bates number 54460. Dr. Krah, is this your handwriting?

A. Yes, it is.

Q. What is this?

A. This, as the title indicates, is an 007 summary, which, as best I can recall, is an attempt to tally the frequency of different categories of results from the -- I'm not sure what the assay span, which range of assays this includes other than it was written, initialed and dated by me on

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February 15th of 2001; including pre-negative, post-negative, the three different columns, pre-negative, post-positive and then pre-positive. And then some comments about experiment 743 and experiment 101. Then a summary of it looks like, as best I can see, taking those, the numbers for the different categories and compiling a percent value.

Q. Given a date of February 15, 2001, and the number of subjects which looks to be in the low to mid-500s, do you believe that this was an analysis of the interim AIGENT testing?

A. Given the date and, best of my recollection, it included sera from the interim analysis still blinded as to which study group the patients belonged to. It indicates 007 as the study. So my -- best of my recollection, this is -- these are data from the interim analysis.

Q. Do you know why you compiled this data?

A. I don't recall with certainty.

Q. Can you think of any reason why you compiled this data?

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MR. SANGIAMO: Objection. Calls for --

THE WITNESS: It would be speculation.

BY MR. SCHNELL:

Q. Do you have any educated speculation as to why?

A. I -- I don't know.

MR. SANGIAMO: Dr. Krah, don't speculate.

THE WITNESS: Yeah. I don't know.

BY MR. SCHNELL:

Q. You have no idea?

A. No.

- - -

(Exhibit Krah-51, 9/21/00 Memo, 00014572 - 00014575, was marked for identification.)

- - -

BY MR. SCHNELL:

Q. I'd like to mark as Krah Exhibit 51, a memo dated September 21, 2000, from Dr. Krah to Alan Shaw, subject "Monthly report for September, 2000."

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Were you in the practice of preparing monthly reports for Dr. Shaw?

A. Yes. Or whoever was my manager at the time.

Q. Did you have a manager that -- other than Dr. Shaw during the AIGENT testing?

A. No.

Q. If you could turn to the third page of the document. And if I -- I want to point you to the first paragraph.

MR. SANGIAMO: Dr. Krah, it's not that long a document, why don't you read the whole thing.

THE WITNESS: Okay.

BY MR. SCHNELL:

Q. You wrote this in September 2000 -- September 21, 2000. Right?

A. Yes.

Q. This is at a time before the AIGENT testing began. Right?

A. Yeah, as best I recall, the AIGENT testing was later in 2000.

Q. So this was at a time when you were still developing the assay. Correct?

A. That's my --

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MR. SANGIAMO: Object to the form.
THE WITNESS: Given the date and the description here, I would say that this is during a time when we were in development, a time when development of the assay was still in progress.
BY MR. SCHNELL:
Q. Part of that development was determining the proper dilution of anti-IgG to be used in the assay. Correct?
A. That's at least one of the variables that was part of this study.
Q. In the first paragraph in the middle you referred to "The majority of the pre-positive sera were positive at a single dilution."
Do you see that?
A. Yes.
Q. So that's what you found when you were doing the pilot studies that led up to the AIGENT testing. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: This says that of

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the sera that were pre-positive were positive of a single dilution.
BY MR. SCHNELL:
Q. That's an observation that you found in the experimenting you did prior to commencing the AIGENT testing. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: Noting of the sera that were pre-positive, they were positive single dilution was -- looks like -- this indicates that it was an observation at the time during development of the assay.
BY MR. SCHNELL:
Q. Then in the next paragraph you wrote, "An option under consideration is to classify sera (pre and post-vaccination) that are positive at a single dilution as 'equivocal', and perform a retest to confirm the serostatus."
Do you see that?
A. I'm sorry, what -- I've lost where you are.
Q. Second paragraph starting with

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the second sentence. "An option under consideration is to classify sera (pre and post-vaccination) that are positive at a single dilution as 'equivocal,' and perform a retest to confirm the serostatus."
A. Yes. Yes.
Q. You ultimately adopted that not as a measure for retesting but as a criteria for recounting. Correct?
A. The single positive -- the single positive neutralization was adopted regardless whether it was -- it's correct that it was adopted, but independent whether it's a pre-vaccination or a post-vaccination serum.
Q. But the purpose you adopted that was to address the pre-positive problem that you were facing with the AIGENT testing. Right?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not agree with that conclusion.
BY MR. SCHNELL:
Q. Well, the very next sentence you wrote, "This could reduce the pre-positive

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rate (and allow for analysis of more serum pairs), while maintaining assay sensitivity."
So isn't it true that you knew that the instances of positive neutralization at a single dilution were occurring more often on the pre-vaccination side than the post-vaccination side?
A. I don't interpret that in the data --
MR. SANGIAMO: Object to the form.
THE WITNESS: -- the comments on the pre-vaccination. So it doesn't -- I don't see any comment on post-vaccination sera.
BY MR. SCHNELL:
Q. I'm not necessarily limiting you to this memo. I'm asking you in terms of you as a scientist and the experiments you did here, it was not your experience that the majority of instances where positive neutralization occurred at a single dilution were in pre-vaccination samples?
A. I do not, I don't have a recollection one way or the other what the

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frequent was.
Q. It's your testimony also that you did not implement this criteria for rechecking as an effort to eliminate pre-positives in the AIGENT testing?
A. That's correct. It was an effort to obtain the most accurate data in the case of a single positive dilution, whether it was in a pre- or post-vaccination serum.
Q. And that's your testimony still even though with the very next sentence you wrote implementing "This could reduce the pre-positive rate"?
A. That's -- that was my thought at the time. It doesn't say that it would or wouldn't have independent confirmation if that was the case.
\- - -
(Exhibit Krah-52, 8/15/00 E-mail, 00068546, was marked for identification.)
\- - -
BY MR. SCHNELL:
Q. I'd like to mark as Krah-52 an e-mail from Dr. Krah to Dr. Shaw, dated

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August 15, 2000, Bates number 68546.
A. Okay.
Q. I point you to third paragraph where you wrote, "Retesting of the pre-positive sera from other serum sets have shown that the pre-positives often do not repeat (although post-positives do repeat). Although it would likely drive the testing lab mad, a retest policy on all sera might reduce the pre-positive rate...."
Do you see that?
A. Yes.
Q. Is it still your testimony that the majority of instances where positive neutralization occurs at a single dilution doesn't occur on the pre side versus the post side?
MR. SANGIAMO: Objection. Misstates his testimony.
THE WITNESS: I don't have a recollection of the frequency of post-vaccination versus pre-vaccination single positive dilutions.
BY MR. SCHNELL:
Q. Does this refresh your

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recollection that in the experimenting you did leading up to the AIGENT testing, that you found that the positive neutralizations that occurred at a single dilution were more often on the pre side than the post side?
A. That was -- that's in the development of the assay. That's an observation from that. Whether that would continue to be the case in larger scale testing, I can't say.
Q. So you do agree, though, that that was the experience you observed in the testing leading up to the commencement of the AIGENT testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: I wouldn't say that that's a description of the results for that one sera set. Whether that's a description of the overall results, I don't -- I can't say.
BY MR. SCHNELL:
Q. And does this also refresh your recollection that it was because of this occurring more on the pre-vaccination side

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than the post-vaccination side, that implementing a recheck or a retest policy for these instances of positive neutralizations at a single dilution might reduce the pre-positive rate?
MR. SANGIAMO: Object to the form.
THE WITNESS: Does that characterize the reason for implementing the recheck of the single positive dilutions.
BY MR. SCHNELL:
Q. If we did a statistical analysis of the AIGENT testing results, would you be surprised if more than 75 percent of the positive neutralizations that occurred at a single dilution occurred on the pre-vaccination side?
A. I don't really have a feeling one way or the other. And I don't recall what that percentage is.
Q. And you didn't gain any experience on that when you were doing all this analysis of the AIGENT testing?
MR. SANGIAMO: Object to the

form.
THE WITNESS: Not that I'll recall.
BY MR. SCHNELL:
Q. Do you recall any instances where plaque counts were rechecked when there was a positive neutralization on the pre-vaccination sample?
A. Do I recall any cases where there was a plaque check on a sample that was a pre-vaccination positive sample? I recall plaque checks that were made on single positive dilutions, some of which I would expect would be pre-vaccination sera.
Q. I'm asking if you recall any?
A. I don't recall a specific case, but my expectation would be that there would be some since some of the -- since we were checking all single dilution positive samples, some of which would be pre and some of which would be post, some subset of those would be pre-vaccination samples.
Q. But your experience with the AIGENT testing doesn't give you any sense of whether or not there was an equal distribution

of the positive neutralizations on the pre- and post-vaccination samples. Right?
A. Not that I recall.
MR. SANGIAMO: Going about an hour ten minutes here, Gordon.
MR. SCHNELL: Take a break.
VIDEOGRAPHER: The time is now 4:41. This concludes disc five.
- - -
(A recess was taken.)
- - -
VIDEOGRAPHER: The time is 5:03. This begins disc six.
BY MR. SCHNELL:
Q. Dr. Krah, I want to refer you back to what we marked Krah-49, is the memo to files that you wrote -- Krah-49 is the memo you wrote to files dated August 1, 2001. I had asked you if you had any idea as to why you wrote the memo that day.
A. Yes.
Q. And I believe you said you don't recall why you wrote it that day?
A. Yes.
Q. Did you meet with your lawyers

that day from Merck?
MR. SANGIAMO: Object to form of that question. Dr. Krah had a privileged meeting that day with Merck with --
MR. SCHNELL: Can I hear that --
MR. SANGIAMO: -- including Merck counsel.
MR. SCHNELL: Can I hear that testimony?
BY MR. SCHNELL:
Q. You had a meeting with, a privileged meeting that day with lawyers. Is that correct?
A. I had a meeting that day that included --
MR. SANGIAMO: Just yes or no.
THE WITNESS: Yes.
BY MR. SCHNELL:
Q. I don't want to get into the substance of your meeting.
A. Yes.
Q. You had a meeting that day. Was it before you wrote the memo?
A. I don't recall.

Q. Who was at the meeting?
A. As best I can recall, John Shiver, Kathrin Jansen and Alexis Pinto.
Q. And which of those three were lawyers?
A. Alexis Pinto, I believe, was a lawyer.
Q. Who were the other two?
A. They were members of our department of virus and cell biology.
Q. Was that the first time -- strike that.
Did you meet with any lawyers in any of the intervening days between August 1st and August 6th?
A. Not that I recall.
Q. Did you meet with any lawyers after the FDA inspection?
A. Not that I recall.
MR. SANGIAMO: Is there an end date on that question?
MR. SCHNELL: That's fine.
BY MR. SCHNELL:
Q. Do you recall if you destroyed any assay plates on that day?

A. I don't recall.
Q. Did there come a time in the course of the AIGENT testing when you were directed by Dr. Emini to do a separate test of a certain selection of the Protocol 007 samples but with different parameters in terms of the dilution of the anti-IgG and in terms of the indicator strain?
A. I recall some experiments that Emilio suggested. I don't recall that they met the -- what you just described.
Q. What do you recall of what Dr. Emini asked you to do in that regard?
A. I don't recall any details other than -- I don't recall any specific details of it.
- - -
(Exhibit Krah-54, Collection of papers, 00064825 - 00064831, was marked for identification.)
- - -
BY MR. SCHNELL:
Q. I'd like to mark as Krah Exhibit 54 a document with the Bates number 64825 through 831. Do you recognize what this

collection of papers is?
A. I can't say I recall this specific experiment, but I would say that the collection includes the notebook page, assay information sheet, plate code and immunostaining of plaque assay page, so pages that would be used in neutralization testing.
Q. And this is all your handwriting. Right?
A. It looks like -- yeah, all the pages look like they're my handwriting.
Q. At the very top you wrote, "data being generated for information only - not part of formal testing for Protocol 007."
Do you see that?
A. Yes.
Q. Does this refresh your recollection at all as to what was going on here?
MR. SANGIAMO: Object to the form.
THE WITNESS: That description does not refresh my recollection.
BY MR. SCHNELL:
Q. So the date of this is March 6,

2001. Correct?
A. Yes.
Q. Now, were there instances that you recall where you were doing testing for information only during the course of the regular AIGENT testing?
A. There is an assay that I recall that was after, as best I recall, after -- shortly after we did the interim -- the testing for the interim analysis set that had included -- that included sera that had some of the neutralization patterns that we discussed previously, meaning pre-vaccination positive, post-vaccination negative. I forget all the -- what all the detailed descriptions of the sera that were included there that were, as best I recall, performed or tested to confirm the results with the intention of using it as scientific confirmation but using the original data from the original valid assay as the date it was reported to the database.
Q. Here you wrote the Neutralization is being tested without an anti-IgG enhancement, and using Jeryl Lynn

vaccine virus and JL135 as indicator viruses.
Do you see that?
A. Yes.
Q. Does that give you further recollection as to what you were testing here?
A. No. The next sentence gives more detail about the format of the assay, but that additional description doesn't refresh my memory any further.
Q. Above the passage I just read speaks about selecting samples from Protocol 007 that were low or nonresponders. Do you see that?
A. It says, ...(low/nonresponders from previous testing in the anti-IgG enhanced mumps neutralization assay).
Q. So am I correct that you took a sample of what looks to be two, four, six, eight, ten low/nonresponder samples from the AIGENT testing and retested them with a neutralization test, one of which -- both of which -- or two neutralization tests, both of which -- neither of which had anti-IgG, and one of which used the vaccine strain of the mumps virus as the indicator virus and the

other one using JL135 as an indicator virus. Is that true?

MR. SANGIAMO: Object to the form.

THE WITNESS: It says, Neutralization is being tested here without anti-IgG enhancement, and using Jeryl Lynn vaccine virus and JL135 as indicator virus.

Just looking at the info, at PRN assay info sheet. Mumps house standard listed in the middle of the page which is the vaccine passage. JL135 is the low passage, I do not see anti-IgG listed here. So that it was tested without anti-IgG using two different, vaccine strain and low passage. JL135 is the indicator virus. And also pointing out being tested at higher serum dilutions than were used in the AIGENT assay. I mean, higher concentration, sorry, in the AIGENT assay.

BY MR. SCHNELL:

Q. What was the higher concentration?

A. The serum concentrations.

Q. So does that make it easier or harder to neutralize?

MR. SANGIAMO: Object to the form.

THE WITNESS: It does not impact -- it doesn't impact directly whether it's easier or harder to neutralize when it -- testing more concentrated serum allows one to detect lower levels of antibody.

BY MR. SCHNELL:

Q. And the cutoff for neutralization is lower, too. Correct?

A. For this particular assay we started testing at a 1 to 4 initial dilution. So there would be a -- I can't speak to what the cutoff is. There was a cutoff used for Jeryl Lynn vaccine virus in Protocol 006 testing, and I don't recall what that cutoff was. I don't know if that same cutoff was applied in this assay.

- - -

(Exhibit Krah-55, Test result, 00069449, was marked for identification.)

- - -

BY MR. SCHNELL:

Q. I want to hand you what we marked as Krah-55. Are these the results of that test -- of those tests?

For the record, it's a single page with a Bates number 68448, and that's your handwriting, right, Doctor?

A. Yes, that is my handwriting. So the very top of the page, X46-01, which to me indicates that it's that -- the same experiment MMRV-46-01. The sera listed, serum 231, 133, 166, 174, 223, 678, 1124, 1715 and 1716. And then two lab volunteer sera, one of which is not the volunteer or control serum used in the AIGENT assay, the DK serum. Pre- and post rows with titers then for Jeryl Lynn vaccine JL135. Without seeing the results or a counting sheet from that assay, I can't verify that those results match up. But the serum numbers match. It indicates that there was vaccine tested in JL135. The anti-IgG plus JL135, my expectation would be that that's the historical value, but I can't say with certainty where that number came from.

Q. Can you think of -- do you have any reason to believe that those aren't the historical values from the AIGENT testing? I'm talking about the right-hand column under anti-IgG plus JL35?

A. As far as I know, this was not audited so there was not an independent Verification that these were the titers. But it was my best -- as I best can recall, my best representation was I understood at the time of the titers.

Q. And would you say the same with respect to the other two columns, the first column being that under JL vaccine and the second being that under JL135?

A. My expectation would be whatever titer I have listed here is my understanding of what number titer that was obtained against the two different indicated indicator viruses.

Q. And just so we go through this quickly, but for the first column it lists under -- does that say sera or serum?

A. That's sera. It might be serum or sera. I'm not sure.

Q. So that would be -- for number

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2, that showed a negative neutralization or a nonresponder for all three of the tests that are identified here. Is that correct?

A. I wouldn't characterize them as nonresponders. It's the -- we did not establish a cutoff for sera positivity. But this -- my interpretation of this it means, for example, sera that had a titer of less than eight meant that it did not have a detectable titer at the highest serum concentration tested which was the 1 to 8 dilution. It does not indicate that they were negative or failed to seroconvert.

Q. And then for the -- for test 31 under the AIGENT test, does that show a low/responder?

A. I don't have -- in my -- the front page to the experiment I don't have -- I don't see indicated what constitutes, which -- like what a serum titer of 256 can constitute a low/responder. I can't say with certainty that that is of a responder. The description of the sample in the assays indicate low/nonresponders. So my expectation is that that would represent a low/responder, but I

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don't have independently indicated on the documents that -- what constitutes a low/responder.

Q. Based on your workbook notes that say you were testing low or nonresponders, do you have any reason to believe that this wasn't a low/responder?

A. I can't say with certainty what I -- at the time, but looking back at the data I could say that that would be my expectation, since there are negatives or values less than 32 and then samples were titers, that if the indication was that they were going to be low and nonresponders, less than 32 would be a nonresponder, so a value other than less than 32 would be a low/responder.

Q. And then the same with sera 174, that was also 256, so that would also be a low/responder. Correct?

A. Yes.

Q. All of the other sera that were tested, are all of the other samples taken from the AIGENT testing that was used in this assay were nonresponders -- in the AIGENT testing. Correct?

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A. When you say that I've seen them, the others would -- I've seen serum 31, and 174 are the only ones where I see a titer other than less than 32 for the AIGENT assay.

Q. And then with respect to the results you wrote here for the JL135 without anti-IgG on those same samples, looking at the numbers and other than the eight that is listed for sera 678, all the others are listed as less than eight. Correct?

A. Is that the JL135?

Q. Yeah.

A. The only one I see with an eight is 678.

Q. What you previously said is less than eight means that there was no detectable level of antibodies that was detected in the testing of these samples in the JL135?

A. No, what it indicates is at the -- at a 1 to 8 dilution, there's not sufficient antibody to be detected. It does not mean the serum is -- that there's no detectible antibody in that serum, but at that concentration no detectable activity was measured.

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Q. Then you also wrote the results here for the testing that was done on these samples with just the Jeryl Lynn vaccine which would be the vaccine strain of the Jeryl Lynn virus. Correct?

A. Yes.

Q. What do you recall was your take away, if any, from this testing that you did?

A. I don't have a recollection at the time I was running this of what the takeaway was.

Q. To whom, if anyone, did you deliver your results?

A. I don't recall.

Q. So you don't recall who asked you to do this testing. Correct?

A. I don't recall who asked for it.

Q. And you don't recall why you did the testing. Correct?

A. That's correct.

Q. You don't recall who, if anyone, you reported the results of your testing to. Is that correct?

A. That's correct. I would just point out its 16 years ago, it's like -- I'm

not sure that I would have complete memory of every activity that was done at the time.

Q. Do you recall disclosing this testing to anyone at the FDA?

MR. SANGIAMO: Object to the form.

THE WITNESS: I do not recall discussing or disclosing these data with the FDA.

BY MR. SCHNELL:

Q. Are you familiar with Dick Ward?

A. I know him. I met him.

Q. During the time of the AIGENT testing, the plan originally had been that his lab at the Children's Hospital in Cincinnati was going to conduct the AIGENT testing. Correct?

A. The best of my -- best recollection of the plan was for our lab to develop the assay and have it be transferred to another lab. I don't recall with certainty that Dick Ward's lab was the one that the plan was to transfer it to.

Q. Who decided that it was originally going to be Dick Ward's lab that

was going to conduct the testing?

MR. SANGIAMO: Object to the form.

THE WITNESS: I don't -- it wasn't me. I don't know who made that decision.

BY MR. SCHNELL:

Q. Were you involved in any training of any staff in Dick Ward's lab to conduct the AIGENT testing?

A. I was involved in providing documents to help his lab get set up. I don't know if that qualifies as training, but I did provide documents to him and responded to e-mails with questions as they were preparing to run additional experiments with the assay.

Q. So then you do have a recollection that originally Dick Ward was going to do the AIGENT testing. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: My experience with Dick -- sorry. To clarify, my experience with the training or providing documents to Dick Ward's lab

was that we did the -- our lab did the interim analysis, and that the plan then was Dick Ward's lab, have the assay transferred to Dick Ward's lab and have his lab do the second third and the third third, the balance of the testing. So that training was -- or documentation was provided in support of the transfer after we were done with the interim analysis. Before we started testing, I -- my assumption, my understanding was that some of the lab would be running the assay, but I don't recall specifically it was Dick Ward's lab or someone else.

BY MR. SCHNELL:

Q. Did members of his lab come to your lab and get trained by Mary Yagodich?

A. I do recall at least one -- there was two people from his lab who I knew. I recall at least one of the people coming to the lab. Whether they were trained by Mary Yagodich, I don't recall. But I do recall at least one of the members coming to our lab.

Q. How long were they there?

A. My best recollection is one or two weeks. I can't say with certainty, though.

Q. Do you recall a decision was reached to keep AIGENT testing in-house and cancel the plans to send it to Dick Ward's lab?

A. All I can say is that our lab did the balance of the testing. So the assay -- the completion of the Protocol 007 testing was not done in Dick Ward's lab. The reasons for that I don't -- I'm not aware of.

Q. Have you ever worked with Dick Ward?

A. I know of him. Did I ever work with him directly? Not that I -- other than this trying to or work with him to have the assay methods transferred to his group, I don't recall working with him directly. As best I recall, there was some rotavirus work that he was doing. Our lab was involved in rotavirus work. I don't recall if there was any exchange of discussion between our two groups, but I don't recall directly working with Dick.

Q. Can you think of anything about Dick Ward or his lab that would have made them incapable of conducting the AIGENT testing?

A. No.

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(Exhibit Krah-56, 10/9/00 Memo with attachment, 00065695 - 00065703, was marked for identification.)

- - -

BY MR. SCHNELL:

Q. I'd like to mark as Krah-56 a memo dated October 9, 2000, from Dr. Krah to Emilio Emini, among others, attaching an October 8, 2000, document titled "Anti-IgG Enhanced Mumps Neutralization Assay-Update." Bates range for the entire packet is 65695 through 703. A lot of this is something that -- different document you saw yesterday from an earlier update. So I'm not going to go over the same stuff that was discussed yesterday. I do have a question on the first page on the short e-mail you wrote.

It's the last sentence. You wrote, The following attachments provide an update to the status of optimization of the

anti-IgG dilution, and a 1 to 6 dilution appears to provide an 'ideal' sensitivity.

My question to you is, what did you mean by "'ideal' sensitivity"?

MR. SANGIAMO: As you're doing, Dr. Krah, feel free to look at the document to answer the question.

THE WITNESS: I can't say with certainty at the time what I was thinking, but looking at the results on page ending in 65700, the sixth page, I believe, looking at the result summary where the serum classification is listed using four -- I'm sorry, three different anti-IgG dilutions, 1 to 4, 1 to 6, 1 to 8, look at pre-positive rate seroconversions, the 1 to 4 dilution gives 95 percent seroconversion, 24 percent pre-positive. 1 to 6 dilution of anti-IgG gives 100 percent seroconversion, 11 percent pre-positives. 1 to 8 dilution of anti-IgG gives 96 percent seroconversion and 8 percent pre-positives. To me the 1 to 6 and 1

to 8 pre-positivity rate are, in my view, the same. A higher pre-positivity rate for 1 to 4. So using a 1 to 6 dilution would give us a balance of acceptable seroconversion and a pre-positive rate that was low of additional dilutions. Was low and -- I can't say it's flattening out, but when it's -- the 1 to 6, 1 to 8 are given the same pre-positive rate, no impact at seroconversion. So the ideal then would be a concentration of anti-IgG that gives a balance of seroconversion and low pre-positivity rate. And 1 of 6 dilution would meet that.

BY MR. SCHNELL:

Q. The 24 percent pre-positive rate that you found at the 1 to 4 dilution, that doesn't really mean that 24 percent of the samples were pre-positive, does it?

MR. SANGIAMO: Object to the form.

THE WITNESS: My interpretation means that they are indeed pre-positive.

BY MR. SCHNELL:

Q. Well, then how can the same samples not be pre-positive with a different dilution of anti-IgG?

A. In our studies and studies of Sato and his publication reported the enhancement -- magnitude of the enhancement of neutralization depended on the anti-IgG concentration. So the more anti-IgG is used, the more enhancement neutralization can be achieved.

Q. So the 24 percent isn't showing a false neutralization?

A. We did not do a specificity test of those particular samples, but my interpretation of this is that that is showing or reflecting mumps antibodies present at a low level in those sera.

Q. What does that mean, at a low level?

A. Low level meaning they're detected or requiring in this case a high level anti-IgG to be detected.

Q. But if the mumps antibodies are really there, aren't they going to have a neutralizing effect regardless of whether you

have anti-IgG or not?
A. No.
Q. So when you have a mumps anti-IgG, there's a qualitative difference of how well it neutralizes?
MR. SANGIAMO: Object to the form.
THE WITNESS: A quantitative difference, meaning that the assay -- think of this as a window, that if your assay is capable of measuring neutralization from one dilution and up, and the antibody level is within that range, you'll have a value. If the level is low but below that range that you're testing, it doesn't preclude there being antibody there, it just means that it's at a lower concentration that can be detected with that assay format.
BY MR. SCHNELL:
Q. Isn't the goal of developing these tests to develop a test that has the highest sensitivity?
MR. SANGIAMO: Object to the

form. The goal of the test are -- charged with this test was to develop an assay that was capable of detecting a 95 percent seroconversion. There was a target, as it indicates here, a targeted range of approximately 10 percent for the pre-positive rates. So I cannot exclude that some assays may be developed with the sensitivity as the requirement. This assay was developed with the requirement to meet the seroconversion target and a target of -- as stated here, of pre-positivity rate.
BY MR. SCHNELL:
Q. Your goal in developing the AIGENT assay wasn't to develop the most sensitive test. Correct?
A. My -- one could argue, so my interpretation of the requirement stated by CBER was -- discussion with CBER was to have an assay that was capable of protecting a 95 percent seroconversion rate. My interpretation of that was to identify conditions that would allow us to be able to

measure that seroconversion rate and not try to have it be the most sensitive assay, but allow us to have the capability of measuring 95 percent seroconversion.
Q. But in not trying to develop the most sensitive assay, weren't you sacrificing accuracy?
A. That I can't -- I don't have a sense of how accuracy factors in.
Q. So, again, on the front page when you talked about having -- providing the ideal sensitivity, the goal was not to find the assay with the greatest sensitivity, but it was to find the assay with the sensitivity that would allow you to find results with post-positives greater than or equal to 95 percent and pre-positives below 10 percent. Is that correct?
A. Or approximately -- at least it's indicated here, approximately 10 percent pre-positives.
Q. And even though at a 1 to 4 dilution of an anti-IgG, it detected a lot of neutralization that wasn't detected in the 1 to 6 or 1 to 8 dilution, you weren't

interested in that because that fell outside your parameters. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: That was -- if we wanted to have the same result at 1 to 4, 1 to 6, and 1 to 8, then we would have had to reassess the parameters. In looking at the data, the 1 to 4 -- the use of the 1 to 4 dilution does not offer us any improvement in seroconversion rate versus 1 to 6 or pre-positivity rate.
BY MR. SCHNELL:
Q. Are we talking about improvement in rate or are we talking about finding the most accurate result of what's really going on?
MR. SANGIAMO: Object to the form.
THE WITNESS: The goal is, of this assay was to be able to measure seroconversion in 95 percent of the people with a high pre-positivity rate. If you had an extremely sensitive assay

that detected maternal antibody as an example -- maternal antibody in sera, those -- you could not then assess whether the person seroconverted. So as far as -- again, I can't speak to the accuracy. What would be the most appropriate -- what accuracy is required for this -- for the assay. Our -- my goal and my understanding for developing the assay was to have an assay that would allow us to have the capability of measuring 95 percent seroconversion and have a pre-positivity rate of approximately 10 percent without -- from my personal perspective, without considering the impact on accuracy.

BY MR. SCHNELL:

Q. And did you share this understanding you had as to what was guiding your development of the AIGENT assay with anyone at the FDA?

A. I recall that we disclosed the data that we had for the assay development with the FDA. So, yes, we did -- I don't

recall specifically. I know specifically we communicated to them they indicated the requirement of a 95 percent seroconversion. I don't recall whether the pre-positivity rate was -- target was communicated to them.

Q. I asked if you disclosed to the FDA what it was that was guiding your development of the assay?

A. What I described to the FDA were the plans and progress in developing the assay. Whether that -- I can't say with certainty whether that included -- all I can say -- what I can say is that the plan's progress, the plans and progress of the assay were fully disclosed to the FDA. Whether we actually used a phrasing of or a comment -- I don't recall a discussion on accuracy, so whether we included a description of accuracy in the discussion, I don't recall.

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(Exhibit Krah-57, 3/29/01 Memo, 00015702 & 00015703, was marked for identification.)

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BY MR. SCHNELL:

Q. I'd like to mark as Krah-57 a memo dated March 29, 2001, from Alan -- am I using the wrong one?

MR. SANGIAMO: I don't think so.

BY MR. SCHNELL:

Q. Okay. Same thing, a memo from Alan Shaw to Emilio Emini, dated 29, March 2001, Bates number 15702 and 3. I have one question on this document. Feel free to read it if you want. I'm going to tell you what my question is. It's in this first paragraph where Dr. Shaw says -- where it starts with the word "Second...," it's the second -- it's the third to last sentence, do you see that where it says, "Second..."?

A. Yes.

Q. "...a preliminary run of about one-third of the serum set has revealed an unanticipated tightness of data from the Krah laboratory. We doubt that the contract lab would be able to match this level of precision."

Do you have any idea of what Dr. Shaw was telling Dr. Emini there?

A. I do not.

Q. That's all I have for that document.

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(Exhibit Krah-58, 6/18/01 E-mail, 00048555, was marked for identification.)

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BY MR. SCHNELL:

Q. I'd like to mark as 59 --

MR. SANGIAMO: 58.

BY MR. SCHNELL:

Q. -- Krah-58 an e-mail from Dr. Krah to Dr. Emini, dated June 18, 2001, Bates 48555. I'd like you to read this e-mail, and I have a couple of questions for you.

A. Okay.

Q. Do you recall writing this e-mail?

A. It's from me. I don't have a specific recollection of this.

Q. You reference concerns you sensed from Emilio Emini regarding the conditions of your lab. Do you have any recollection of what you were describing

there?
A. I have a recollection of someone approaching either Alan or Emilio with -- again, I don't recall the specific concern. But, again, I don't recall whether it was Alan or Emilio or both. And that then, as best I recall, Alan communicated that concern or a concern to me.
Q. So you wrote that some of the staff left your group, indicated that they did so because of issues with you or the lab operations. Who are you referring to there?
A. The two people I was thinking of, at least that I recall as being ones who -- I can't say for certainty who I was thinking at the time, but I recall two people, DeeMarie Watson and Krista Getty who left the lab with concerns over in one case, as best I recall, it was dissatisfaction with a performance review. And the other was someone who was interested in more visibility and more opportunity for growth who I worked with to try to identify opportunities to meet that, but before we could implement the plan, she had moved.

Q. Were either of them involved in AIGENT testing?
A. Krista Getty, as best I recall, was out of the lab before that testing. DeeMarie Watson, I don't recall if she was in the lab at any point of the AIGENT testing. I don't recall when -- the date when she left the lab.
Q. What were the concerns of the lab operations that you referenced here?
A. I don't know what specific ones I'm referencing here. I could offer that in the case of DeeMarie Watson, her concern was that she had worked on, as best I recall, mumps neutralization assays that were not part of the clinical study, and that she felt she should have been given more credit for development of the assay, and was claiming that another lab member was given more credit than she had been given.
Q. And then you reference Steve Krahling and Joan Wlochowski and your expectation that they won't remain in your lab much longer. You reference "perceived concerns/issues" they had. What were you

talking about there?
A. Well, I do recall questions that Steve raised. I don't recall if Joan was also raising them about the distribution of work within the laboratory and whether the work was being equitably -- or appropriately distributed.
Q. You don't recall them raising concerns about the -- how the AIGENT testing was being conducted?
A. The only recollection I have was Steve at, I believe, two lab meetings commenting that we know which is a pre-vaccination and which is a post-vaccination serum. That's the extent of the comment that I recall.
Q. You don't recall any complaints about -- from Joan Wlochowski on how the -- how you were running the AIGENT testing?
A. I do not.
Q. You don't recall concerns raised by either of them relating to any fraud in connection with the AIGENT testing?
A. No.
Q. I'd like to mark as Krah-59 an e-mail from Dr. Krah to Mary Yagodich, dated

June 20, 2001. If you take a -- if you don't recognize it, if you take a moment to review it.

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(Exhibit Krah-59, 6/20/01 E-mail, 00048558, was marked for identification.)

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THE WITNESS: Okay.
BY MR. SCHNELL:
Q. And do you recall the circumstances surrounding your sending this to Ms. Yagodich?
A. I don't recall the specific occasion for sending this. Given the wording, my expectation is that Mary was out -- I recall that Mary went out on maternity leave. The way this is worded to me suggests that it's something that was sent while she was out on leave, but I can't confirm that.
Q. Were you concerned that you were going to be removed from the lab, from your responsibilities in the lab that you were running?
A. When Alan approached me about

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the concerns with the laboratory, the options that he provided to me were to try to work through and resolve those concerns or to be removed from the laboratory, move to another location out of sight essentially, and then have someone else come in to take over for my responsibilities. So there was an option presented of me trying to work to resolve the concerns or to have me removed from the lab at least temporarily.

Q. How did you work through those issues?

A. I worked through the issues by meeting with each of the lab staff and discussing their concerns and trying to work towards understanding what those concerns were and address them where possible.

Q. Which of the lab staff did you meet with in this regard?

A. As best that I can recall, was all the lab staff.

MR. SCHNELL: Okay. Let's take a break.

VIDEOGRAPHER: The time is now 5:51. Going off the video record.

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(A recess was taken.)

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VIDEOGRAPHER: The time is 6:04. We're back on the video record.

BY MR. SCHNELL:

Q. Dr. Krah, do you have an understanding as to whether or not CBER ultimately rejected the results of the AIGENT test?

A. I do not recall what CBER's -- I don't recall CBER's -- I don't recall the specific wording of CBER's conclusion. At least for the -- I don't recall their response to the data.

Q. So you don't have an understanding one way or another as to whether or not CBER accepted the results of the Protocol 007 AIGENT test?

MR. SANGIAMO: Object to the form.

THE WITNESS: I recall that there was -- after the inspection and response to the GMP or the audit, there were concerns that CBER had raised. We

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addressed those and resumed testing. As best I can recall, that testing included -- that included use of the original plaque counts were submitted to CBER. I don't recall what the eventual decision was on that -- those data.

BY MR. SCHNELL:

Q. Were the original plaque counts in any way reviewed before sending them to CBER?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: I do not recall what review was done before sending them to CBER. As part of the quality assurance audit, we verified transcription from accounting sheets to the workbook. Beyond that, I don't have any knowledge.

BY MR. SCHNELL:

Q. Is that Verification done after the August 6, 2001, inspection?

A. Verification of the transcription was done routinely as part of

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the assay audit by quality assurance. The audit of using only the original plaque count data would have been -- that requirement was applied after the August inspection, does not mean that there might have been assays for which there are no correction where the same data would be used in the later submission.

MR. SCHNELL: Can you repeat his answer, please?

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

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BY MR. SCHNELL:

Q. I didn't understand that.

A. The point there was that the original data would be used but in some of the testing before the inspection there may have been assays for which there were no corrections. So the same data would be applied.

Q. And you testified previously, didn't you, that the bulk of the AIGENT testing had been completed by the time the FDA inspection occurred in August 2001?

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A. I can't say with certainty, but my best recollection is that we were beginning to wrap up the testing -- the plan testing for the Protocol 007 around that time.

Q. Were you involved in the decision by Merck to submit the original AIGENT testing results to CBER?

MR. SANGIAMO: Object to the form.

THE WITNESS: I was in meetings where the proposal to include the original counts in the submission to CBER was discussed.

BY MR. SCHNELL:

Q. And at any point in those meetings did you object?

A. No.

Q. Did you believe that the original data was accurate and reliable?

A. My understanding of the -- so I don't have a thought -- my expectation -- I'm sorry. My expectation is that the original data were as a composite reliable. CBER in their discussion with Merck about the corrections and the flags, for example, that

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were part of the workbook was that they thought that those checks were actually an improvement to the assay performance but was not documented before we started testing. So their view was that the plaque count checks were an improvement, but that for documentation purposes we would need to use the original data. From my own personal perspective, I don't have a feeling one way or the other whether one set of data is more -- accept them to be equally reliable or equally reliable representations of the data.

Q. So if you could turn back to Krah Exhibit 44, these are the counting sheets of Mr. Krahling where you identified incorrect counts or what you perceived as incorrect counts on the lion's share of the samples for these assays. If I can in particular point you to, let's take assay 214, which begins on page 2217.

A. Okay.

Q. Is it your testimony that what Mr. Krahling originally counted and you crossed out on all of these pages is just as reliable as the numbers you found?

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A. I can't tell from this. In the recheck, one of the criteria or the criteria for the recheck is to see if the plaque counter is within 10 percent of the reference counter. I can't tell from these numbers whether -- even if there's a change or a correction to the count, whether it takes it outside of that range of 10 percent.

Q. So is that your measure of reliability, plus or minus 10 percent?

A. That's my measure or the measure that our lab implemented to compare plaque counting between two different counters.

Q. So sitting here today, you don't have an opinion one way or another as to whether what Mr. Krahling originally counted or what you counted is -- which of those two is the more reliable count?

A. My personal feeling is that the counts that I had were more accurate. Whether his counts for accurate -- less accurate enough to not be reliable, I can't say.

Q. So of all the changes that were made during the course of the AIGENT testing which we've calculated to be in the thousands,

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is it your testimony that those changes were meaningless?

MR. SANGIAMO: Object to the -- you don't have to accept his premise --

BY MR. SCHNELL:

Q. You don't. You don't.

MR. SANGIAMO: -- that it was in the thousands.

BY MR. SCHNELL:

Q. That of all the changes you've made, you and your staff made over the course of the AIGENT testing which you would admit is a lot, is it your testimony that those changes did not make the data more reliable?

MR. SANGIAMO: Object to the form.

THE WITNESS: It would not constitute -- I don't have a number to differentiate a lot from not a lot. So I wouldn't agree to there being a lot. As far as whether those regards -- results are less reliable, I don't have a feeling one way or the other whether they're more or less reliable.

BY MR. SCHNELL:

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Q. Didn't you represent to the FDA that all the changes that were made were for legitimate purposes?
A. Yes.
Q. So then --
A. Sorry.
Q. Sorry.
A. Well, I would agree for legitimate purposes where we had an explanation for that specific reason we documented. There were other cases where we might not have been able to identify the reason for the check.
Q. So despite telling the FDA that all the changes that were made were for legitimate reasons, you can't say one way or another whether those changes made the data more accurate?
A. I don't have the experience to be able to make that comparison.
Q. What kind of experience would you need?
A. I would expect -- what I'm thinking of would be a statistician, for example, to compare results with and without

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the corrected values. And at least in the interim analysis that comparison was done and the results were statistically comparable.
Q. You're talking about seroconversion results. Right?
A. Yes.
Q. You're not talking about pre-positive results, are you?
A. There was a difference using the corrected counts versus the original counts as far as the number of pre-positives.
Q. There was also a difference in terms of number of invalid assays. Correct?
A. There were assays that were invalid. I don't recall how many, but assays that were invalid and on recheck were identified to be not invalid.
Q. And the original data showed a significantly higher number of pre-positive samples than the corrected data. Correct?
MR. SANGIAMO: Object to the form.
THE WITNESS: It showed an increased number of pre-positives. Whether it was a statistically

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significant number, I can't comment on.
BY MR. SCHNELL:
Q. The original data showed a significantly higher number of invalid assays than the corrected data. Yes?
MR. SANGIAMO: Object to the form.
THE WITNESS: I would say that there are some assays that were invalid, when the plaque counts were checked, that the assay was deemed not invalid. So there were some assays that moved from invalid to valid. There is also an opportunity for some assays to become -- perhaps not be -- or be valid initially and on recheck they become invalid. So I can't exclude that there could be a two way -- for some assays, some becoming invalid that were valid, some going the other direction.
BY MR. SCHNELL:
Q. So in assessing the comparative reliability between the original data set and the corrected data set, wouldn't you also want

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to consider -- besides just the comparative seroconversion rates, wouldn't you also want to consider the comparative pre-positive rates and the comparative invalid assay rates?
A. As far as what criteria would be appropriate to evaluate the data in that way, I'm not -- that's something I'm not familiar with.
Q. So just so the record is clear, you didn't have a problem with Merck submitting the original data set from the AIGENT testing to CBER as a reliable and accurate representation of the results of the AIGENT testing. Is that correct?
A. It's correct that the original uncorrected data were provided to CBER to indicate the serostatus and seroconversions from Protocol 007.
Q. My question is, is it your opinion that that represents an accurate and reliable data set from the AIGENT testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: Again, I don't have, again, a statistical training to

be able to make an appropriate conclusion on the reliability and accuracy.

BY MR. SCHNELL:

Q. I'm not sure why you would need a statistical training in that. You ran the test. And all I'm asking is, did you feel comfortable that the original data set was an accurate and reliable representation of the AIGENT testing?

MR. SANGIAMO: Objection to form. And asked and answered.

THE WITNESS: As a personal opinion, I'd say I felt that they were -- it was a -- as a composite an accurate representation of the data.

BY MR. SCHNELL:

Q. What does that mean, "as a composite"?

A. Means that when all the data combined, they're looking at study groups. If there were changes that were effected in individual sera, that those would be averaged out in doing the overall summary for each of the study arms.

Q. And what's that based on?

A. That's a personal opinion.

Q. And what's that opinion based on?

A. It's not based on any scientific training I have. It's just like a personal opinion.

Q. Your opinion is no way swayed by the significant difference in the pre-positive samples between the two sets of data. Correct?

MR. SANGIAMO: Object to the form.

THE WITNESS: The using original data at least, as best I can recall -- the agreement with CBER was to use the original plaque count data and I was comfortable providing that. So the difference in the pre-positivity rate was not something that was a concern.

BY MR. SCHNELL:

Q. Now, the original data set did not control for any errors in plaque counts that may have resulted from extra variability issues. Correct?

A. The original meaning the interim analysis -- I'm sorry, the original plaque counts?

MR. SCHNELL: Could you reread the question, please.

- - -

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

- - -

MR. SANGIAMO: Object to the form.

THE WITNESS: If I can clarify, by original data, you mean the original plaque count that was recorded on the counting sheet?

BY MR. SCHNELL:

Q. Yes.

MR. SANGIAMO: Object to the form.

THE WITNESS: That would be -- yes, those counts would not factor in -- not include an assessment based on extra variability.

BY MR. SCHNELL:

Q. And now if I could return you to

Krah-43.

A. Okay.

Q. The passage we looked at before, the fourth one down, you wrote, "Extra variability prevents reliable measures of neutralization...."

Do you see that?

A. Yes.

Q. So if the original data set did not account for extra variability, doesn't that prevent the original data set from being a reliable measure of neutralization?

MR. SANGIAMO: Object to the form.

THE WITNESS: No. I believe this is not in context. The context of this is that the -- for the assays that the extra variability would impact the measure of neutralization if indeed that extra variability flag was imposed, meaning that if the original plaque counts were applied, even if there was extra variability, one could assign a titer to the sample.

BY MR. SCHNELL:

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Q. You wrote this memo as a response to questions that came about as to the reasons for having extra variability flags. Is that correct?
A. As best I can recall, the reason I wrote this was to clarify different scenarios that would occur depending on where the extra variability flag would occur, where it would occur meaning what dilution it would occur.
Q. So even though you spent nine months on the AIGENT testing and implied a whole series of flags and criteria for ensuring the accuracy of the data and used that to go back and make numerous changes to the data count, even though you did all that, you still believe without all that work, the data as uncorrected was still reliable?
MR. SANGIAMO: Object to the form. And asked and answered.
THE WITNESS: My personal opinion is that it was as composite, meaning averaging all the sera in each study group together was a reliable measure of the immunogenicity of the

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vaccine doses.
BY MR. SCHNELL:
Q. And if there were instances where the original data showed a non-seroconversion as the same sample showed a seroconversion with the corrected data, would that change your opinion as to the comparative reliability of the two sets of data?
MR. SANGIAMO: Object to the form.
THE WITNESS: My expectation is that the changes could -- there's going to be some sera where there's going to be a change in titer and some which there's not, and some where you could have -- what always -- the change would not always be in one direction. So if you look on a sera-by-sera basis, that it would affect, in my personal view, the reliability of the titer for that particular patient. But in the overall data were lumped together, that would -- it would still provide a reliable measure of immunogenicity as measured by antibody responses.

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BY MR. SCHNELL:
Q. If you were asked by CBER, well, which of the two data sets is the one that more accurately represents the results of the AIGENT testing, what would you tell them?
MR. SANGIAMO: Object to the form.
THE WITNESS: That's, as I indicated, a personal opinion, but as far as communicating with CBER, we indicated to them all of the corrections, the reasons for the corrections; that we were going to provide original uncorrected data as part of the analysis package, and as best I understand, they accepted that proposal. So the conclusion of whether -- from CBER's perspective whether it's reliable or not, I can't -- I don't know what their position is.
BY MR. SCHNELL:
Q. Now, when -- the kids who were enrolled in Protocol 007 were throughout the country. Right?

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A. That, I don't know.
Q. Do you know how it was that their blood was drawn?
A. I do not.
Q. Do you know any protocol that was set up in terms of revaccination for kids whose samples were taken and found not to seroconvert?
A. I do not know.
Q. Did you disclose to the clinical investigators the original data set?
MR. SANGIAMO: Object to the form.
THE WITNESS: I do not know. My responsibility was to provide the assay data entered into a clinical database. I don't know -- I'm not familiar with what -- how it was reported beyond that.
BY MR. SCHNELL:
Q. If a parent wanted to know, a parent whose child was enrolled in these studies wanted to know if that child, based on your AIGENT testing, was protected from mumps, which data set would you look to to make that

determination?

A. I do not agree that the data were designed to indicate whether they were protected or not. They're looking at immunogenicity and antibody responses, not -- to the best of my understanding, not correlating it with protection. The second paragraph of your question as far how they would determine or obtain the result for their infant, I don't know how that -- what that process would be.

Q. What about if the parent are interested to know what the most accurate measure of the kid's titers were with the vaccine?

A. I would not characterize the mumps, I would not be able to say that the AIGENT assay is the most accurate measure of mumps antibody. It's an assay that's intended as an imperfect model for looking at immune response in terms of an antibody response to the vaccine. Whether it's accurate or not, that's beyond my expertise.

MR. SCHNELL: I'm going to move on to discussions with the CDC mumps

outbreaks.

MR. SANGIAMO: The 30(b)(6) is what you're saying?

MR. SCHNELL: I mean, for the most part I mean, yeah. I mean, I think there's like ten minutes left so -- but it's -- I think it -- you'll see. So it's going to be confined.

MR. SANGIAMO: I guess the only thing I just need -- we need to know when it is that he's speaking on behalf of Merck and when he isn't.

MR. SCHNELL: Oh, it's -- on the questions I'm asking about any -- I think this covers the topic related to any testing that was done in collaboration with the CDC with regards to outbreaks. Right?

MR. SANGIAMO: Okay.

MS. DYKSTRA: Are you going to be asking that now? So we don't -- just to make sure Dr. Krah understands he's testifying on behalf of Merck or in his own personal knowledge.

MR. SCHNELL: Yes. If it's a

question that maybe it's hard to do a fine line --

MR. SANGIAMO: We'll see how it goes.

MR. SCHNELL: Yes for now.

So this is in response to a 30(b)(6) deposition notice that had many topics, one of which was someone to speak on behalf of Merck with regard to any collaboration Merck did with the CDC and the FDA.

MR. SANGIAMO: I don't think that's actually the way it was defined. I think -- I don't have the notice in front of me. I think it was testing or some research or something like that in connection with mumps outbreaks. I think what we told you was Dr. Krah can -- a component of that is neutralization testing that Dr. Krah's lab did and it was a collaborative aspect of that with the FDA and CDC. So as to that part of what Merck did, he's the guy.

BY MR. SCHNELL:

Q. So in response to the 2006 mumps outbreak, you worked, you personally worked with representatives from the CDC and the FDA in terms of testing?

A. So I worked with them in terms of discussing experiments to conduct and identify which lab would do what aspects of the work. So we didn't physically work together but had activities that were coordinated to try to address questions regarding the outbreak.

Q. And this was the 2006 outbreak?

A. As best I can recall, that was the outbreak. I recall the studies that we were doing in the laboratory in the 2006 time frame. I tend to recall it like the Iowa or, slash, Nebraska outbreak which I, as best I can recall, was the 2006 outbreak.

Q. Were you involved in any other testing in connection with mumps outbreaks other than the 2006?

A. There were some -- I don't recall that we wound up doing neutralization assays, but there were, for example, I forget the individual's name, a person in Israel who

we contacted to try to see if we could obtain any virus that was associated with an outbreak in Israel just to see if we could include in some characterization the breadth of neutralization with sera, with different sera.

Q. When was that?

A. I'm not remembering offhand if that was in the 2006 time frame or perhaps a couple of years afterwards.

Q. So with respect to the testing that was done in 2006, that was plaque reduction neutralization testing?

A. Our lab's contribution was plaque reduction neutralization assay.

Q. Was your -- and that was your lab. Correct?

A. Our lab did it, but CBER and FDA also did plaque reduction neutralization. So we did -- it was my lab. But we weren't the only lab doing the plaque reduction neutralization testing.

Q. Other than your lab and Rubin's lab, was anyone else doing plaque reduction neutralization testing in connection with the 2006 outbreak and your collaboration with the

CDC?

A. I am not aware of another group that was doing plaque reduction neutralization assay as part of this collaboration. There may have been other collaborations that CDC had that I'm not aware of where plaque reduction neutralization was done.

Q. Did the testing that your lab performed have a name or an assay number?

A. The indicator viruses that were included were the Iowa strain and the Pennsylvania strain. So as a description, I offer calling it like the Iowa neutralization testing. There were -- there also was a Jeryl Lynn indicator virus used in that assay so it wasn't exclusively using the Iowa strain, but a proposed shorthand for the testing, just to refer to it, would be calling it the Iowa neutralization testing.

Q. And was another one done with the Arkansas strain?

A. The Pennsylvania strain. In development studies, meaning that when we first became involved in trying to support the neutralization testing of sera, as part of the

outbreak investigation with the CDC and FDA there were two strains of virus, one referred to as Iowa and the other as Pennsylvania. We had -- as best I can recall, we received both of those and did pilot neutralization assays with lab volunteer sera just to get an idea of the neutralization, relative neutralization of those two viruses relative to Jeryl Lynn. In subsequent testing we focused on the Iowa strain, but I don't recall it's because CDC was saying that Iowa was adequate but -- or there was another -- I recall some issues with the plaquing visualization of the Iowa strain -- I'm sorry, the Pennsylvania strain, meaning that some of these isolates don't form nice, clean, distinct plaques and cell cultures so they make it difficult to do a plaque reduction assay because it's hard to visualize the plaques. The bottom line there is that when we focused on the Iowa strain, then, to test two panels of sera against the Iowa strain and Jeryl Lynn to compare neutralization titers.

Q. What was the goal of this testing?

A. The goal, from my understanding --

MR. SANGIAMO: Object to the form. Go ahead.

THE WITNESS: The goal, from my understanding, was to obtain neutralization titers against the vaccine strain of varicella, Jeryl Lynn, and the Iowa strain and determine whether there was -- if there was any difference in the neutralization sensitivity -- sensitivity may not be the -- probably isn't the right word there. Meaning that if you tested a serum against Iowa and Jeryl Lynn, are the titers the same or is the titer higher for one virus versus another virus. So my focus was to -- as best I understand it, Steve Rubin's focus with the FDA was also running the neutralization -- plaque reduction neutralization assay was to determine titers to Iowa and to Jeryl Lynn for two panels of sera as well as -- two panels of sera as well as some reference sera that FDA provided. And

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then compare the titers obtained and compare -- as best I can recall our approach was to do a ratio, for example, the titer to Iowa to Jeryl Lynn or vice versa. So you'd have a titer determined for individual -- for sera against an individual virus and then have a ratio titer so you're solving the relative titer, the difference in titer, if there is one, with two different indicator viruses.
BY MR. SCHNELL:
Q. Who came up with the assay to be used in this testing?
A. The assay, as best I can recall, is the assay that we initiated -- as best as I recall, again, it was the format that we used for the -- there was discussion with the FDA and CDC about what format to use. The format that we moved ahead with is the format that we used with some modification in Protocol 006.
Q. And was that what you recommended?
A. We proposed an option of running that format versus the anti-IgG enhanced assay. The discussion, as best I recall, with

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Steve Rubin at the FDA and Bill Bellini at the CDC was since CBER was running a plaque reduction neutralization without anti-IgG, the preference would be to us -- have it once run another assay without anti-IgG but not follow the exact procedure that his lab was using. So it was a group discussion over the general assay format but a decision to leave it to Merck to decide the details of the plaque reduction neutralization assay, meaning we did not intentionally try to match our -- all details of the assay with the assay as run by Steve Rubin.
Q. How many subjects were in the Merck test?
A. There were two panels of sera. One was a set of sera from Nebraska. My best recollection of that, there was 100 some odd, 108 approximately sera. The Merck -- and then Merck provided a panel of sera, as best I recall, that was collected before and after a second dose of MMR vaccination. That group, as best I recall, was about 50 paired sera. And then additionally there were two reference immunoglobulins that Steve or the FDA

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provided, one referred to as lot 3 and one referred to as lot 176.
Q. What were the results of the test?
A. The overall results of the test, I would offer as results -- as we had results available, we forwarded them to Bill Bellini as the coordinator. So results as we were getting them were forwarded both to Steve Rubin and Bill Bellini; Bill Bellini having the charge to compile them. The overall results were slightly different for Steve Rubin's testing than ours, meaning that in Steve Rubin's hands, if we look at the ratio of titers to Iowa versus Jeryl Lynn, in his hands the majority of the sera were not showing, as best I recall, more than about a twofold difference between titers. In our testing we were seeing a slightly bigger difference, meaning that Iowa was less well neutralized than Jeryl Lynn to a greater difference than what Steve Rubin was seeing. Steve Rubin's conclusion was that the majority of the patients would still likely be -- they still had detectable titers to Iowa as well as

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to Jeryl Lynn and that they likely would still be protected. My personal -- one of the questions I had personally in the study or in the outbreak investigation was, is the virus that was occurring in Nebraska a mutant of mumps that had become something that would not be capable of being neutralized by antibodies to Jeryl Lynn vaccine. The testing that we did and that the FDA did, did not support that that was happening. This virus was not a mutant that was resistant to neutralization with antisera to MMR -- or antisera to mumps generated by MMR.
Q. Did this testing in any way relate to whether vaccine recipients were protected from these various strains of mumps?
MR. SANGIAMO: Object to the form.
THE WITNESS: I recall that Steve Rubin had -- was discussing with it a comment or statement that he thought that since these -- the majority of the patients had detectable antibodies to Iowa, that they would be protected against viral strain. I

don't have a personal preference or any other data to support whether -- what correlates protection. The fundamental aspects of that being that there is no correlative protection from mumps.
BY MR. SCHNELL:
Q. So you didn't get any insights from this testing as to how well the mumps components of MMR II protects vaccine recipients from these various strains of mumps?
A. The conclusion that Steve Rubin made, from my understanding, was that the MMR vaccine would provide adequate protection against the Iowa strain of mumps. Me personally, I didn't -- other than Steve Rubin's comment, I don't have any other insight to be able to comment on the protection.
Q. You don't have your own insights?
A. No. I defer to Steve Rubin on topics of that sort.
Q. Have you met with representatives from the CDC in connection with any outbreaks

other than the 2006 outbreak?
A. I recall some -- at least a meeting that included CDC representatives that was, as best I can recall, in the 2010 time frame, which I attended by telephone, that, as best I can recall, discussed a summary not just from Merck but many people in attendance about thoughts on the outbreaks in general and data from evaluations of serological testing of previous outbreaks.
MR. SANGIAMO: Gordon, just so we're clear, when he's talking about this 2010 meeting, he's not --
MR. SCHNELL: Right. So now I'm going off 30(b)(6). I have ten minutes left and then I'll close out.
BY MR. SCHNELL:
Q. So now you're back to your speaking on behalf of yourself.
So other than the testing we just discussed that was done in 2006 and this 2010 meeting, have you ever met with the CDC in connection with any of the mumps outbreaks?
A. I don't recall any others.
Q. You haven't met with them

recently in regard to outbreaks that have occurred over the last couple of years?
A. I can say with certainty not within the last four years.
Q. And with respect to the times you did meet with the CDC in connection with the mumps outbreaks, did you share with them your experience from the AIGENT testing?
MR. SANGIAMO: Object to the form.
THE WITNESS: I had provided the AIGENT assay as an option to consider. Steve Rubin was at the FDA when the AIGENT test was going on. I do not recall independently summarizing our results of the AIGENT study, nor would I have results of the AIGENT study, the final results to share with the CDC and FDA.
BY MR. SCHNELL:
Q. You didn't share with the CDC, anyone from the CDC, anything relating to the FDA inspection in August of 2001. Correct?
A. I did not.
Q. Do you have any understanding as

to what's causing the recent outbreaks in mumps in the US?
MR. SANGIAMO: Object to the form.
THE WITNESS: I have a general understanding which is only based on reading publications of some circumstances of the outbreaks. As far as what's actually causing it, I don't have an understanding.
BY MR. SCHNELL:
Q. And the work that you did -- or that you've done on mumps testing doesn't give you any idea as to what could be a possible factor contributing to mumps outbreaks?
A. The factor -- I would say no and my -- in starting these studies, my interest was in understanding whether the mumps strain had mutated to the point where it would not be neutralized by antisera generated by MMR. The results of the testing that we did and the FDA did, did not support that there was a significant, at least by FDA, a significant shift in neutralization of the virus. So that then -- the conclusion that I would make from

that is that the reason for the outbreaks, it's not that the virus is drifting away or mutating in a way that's drifting it away from the Jeryl Lynn sequence to the point where the antibodies generated against Jeryl Lynn are no longer able to neutralize the virus.
Q. So that suggests to you what may not be cause of the outbreaks?
A. Yes.
Q. So is there any suggestion you have as what could be a cause of the outbreaks?
A. I would say I -- I'm familiar with some of the circumstances of outbreaks, meaning as best I understand, college age adolescents or young adults in close quarters, that's just an observation. My understanding, the close quarters seems to be the most common theme. The other aspect of this is that the outbreaks, as best I understand, aren't happening in infants or older adults. It's this 18 to college age students category, as best I recall. So -- and I don't have any perspective on why other than people being in close quarters. If you have an infected individual there, the challenge, the virus

challenge may be more efficient, meaning that in a population -- this is speaking not as -- certainly not as an expert in the field, but as a general statement, if you had someone who is infected and then exposed to people infrequently, the likelihood of transmitting infection is low; but if you have a room full of people who may have some level of immunity or even be immune to typical exposure, if there in a close space with someone who -- given a high transmission, that the risk of transmission of the virus to those individuals would be higher. That's just kind of a personal interpretation of the options.
Q. Last question or last subject. Do you recall in the AIGENT testing that one of the test subjects actually developed mumps?
A. I do have -- I don't have a specific recollection of that, but I have a -- I do recall some issue with one patient. I don't recall what that issue was.
Q. And do you recall whether or not that subject seroconverted with regard to his particular test?
A. That, I don't know.

Q. Would it surprise you if he had?
A. If he had? I don't have knowledge of the correlation of the AIGENT assay, seroconversion and protection from disease to see whether that would be unexpected or not.
Q. Does that lead you to conclude one way or the other whether or not the AIGENT -- I'm sorry. Yeah, whether the AIGENT testing had any connection with correlating protection?
MR. SANGIAMO: Object to form.
THE WITNESS: I would say that the AIGENT assay was developed to meet specific -- a specific requirement -- may be able to measure -- have the capability of measuring antibody responses. I'm not -- I don't have an expectation of what the correlation of that assay would be with protection.
BY MR. SCHNELL:
Q. Does the fact that one of the subjects of the test actually caught mumps even though the testing showed that he seroconverted in any way weigh into your sense

of how reliable the testing was in demonstrating protection from the disease?
MR. SANGIAMO: Object to form.
THE WITNESS: I would say no in that -- I'm not a clinician. I would expect a clinician would have more details about the case, the situation of the person's infection or disease and also be able to assess whether having that individual have an exposure to someone who is infected in a way that would challenge the immunity, or is the vaccine expected to be 100 percent protective or is one case of mumps out of a larger number an acceptable number, that's not something I'm familiar with.
MR. SCHNELL: Okay. That's all the questions I have. Thank you.
VIDEOGRAPHER: The time is now 6:52. This concludes the video deposition.
(Witness excused.)
(Deposition concluded at 6:52 p.m.)

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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 26th day of July, 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.

____
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: 7/12/2017

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(DATE) DAVID KRAH

10/25/2019

Declaration of G. Reilly

EXHIBIT 123

Mumps Neutralization Assay Development

Objectives:

- Develop an assay using different wild-type mumps strains to evaluate immune responses to M-M-R®II and Priorix (Protocol 006 Competitive Trial)

Background:

- M-M-R®II contains a mixture of at least 2 virus populations (JL-2 and JL-5)
- Mumps in Priorix is a homogeneous population of JL-5
- More heterogeneous vaccine may give rise to a broader range of neutralizing anti-mumps antibodies

Objectives (continued):

- Develop an assay which permits detection of ≥95% seroconversion rates in M-M-R®II vaccinees (Protocol 007 Expiry Trial)

Background:

- CBER requirement to demonstrate ≥95% seroconversion by a neutralization assay (90% lower limit)

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
- Plate format (12-, 24-, 48-well)
- Enhancements to Nt
  - Complement (≤8-fold enhancement)
  - anti-human IgG (~100-fold enhancement)

DK, 15June 2000

Mumps Neutralization Assay Development: Results of Preliminary Experiments

- Assay format
  - Plaque-reduction neutralization assay
  - Evaluate adult lab volunteer sera against selected mumps strains
  - Neutralization titer = highest tested dilution providing ≥50% neutralization ("mock serum" control)

- Results

Serum	Neutralization titer against indicator mumps strain				
	JL vaccine	JL2	JL5	TN	SA
MKY	16*	<2	8	8	2
	16	<2	16	8	2
	16	<2	16	8	2
AS	32	8	128	128	16
	32	8	64	128	16
	64	8	64	128	16
DW	1024	256	512	16	256
	1024	256	512	16	256
	1024	256	256	16	256

JL vaccine = Jeryl Lynn™ vaccine virus
* Results of replicate assays

Adult Lab Volunteer Serum Panel Used in Mumps Neutralization Assay Development

Initials	Age	Source of Immunity
DK	42	Vaccination-monovalent mumps vaccine
MKY	28	Vaccination-monovalent mumps vaccine
CK	24	Vaccination-measles, mumps, rubella vaccine
PK	52	Natural mumps infection
AS	47	Natural mumps infection
CM	24	Vaccination-measles, mumps, rubella vaccine
JD	24	Vaccination-measles, mumps, rubella vaccine
DW	28	Vaccination-monovalent mumps vaccine; exposure to wild-type case at age 20

Effect of Virus Indicator Strain on Mumps Neutralization Sensitivity

Virus	Expt Number	Neutralization Titer for indicated test serum: AS	PK	DW	DK	CM	CK	KS	Ref IG
Jeryl Lynn™ vaccine	478-99	64	≥256	1024	8	≥128	32	32	512
	480-99	64	≥256	1024	<4	≥128	64	64	256
	481-99	64	≥256	512	4	≥128	32	32	512
	499-99	64	≥256	1024	4	≥128	32	32	≥1024
Lo1	478-99	16	64	512	4	32	32	32	128
	480-99	64	≥256	512	8	64	≥128	64	256
	481-99	32	128	512	8	64	≥128	32	256
	499-99	≥128	128	1024	16	≥128	64	≥128	128
JL2	478-99	<16	<32	256	<4	16	16	<16	128
	480-99	<16	<32	256	<4	16	<16	<16	128
	481-99	<16	<32	256	<4	16	<16	<16	128
NY	478-99	32	<32	512	<4	32	32	16	128
	480-99	32	64	512	16	16	64	64	256
	481-99	16	<32	256	<4	32	16	16	128
	499-99	32	64	256	<4	16	16	32	128
Sw1	478-99	<16	<64	<256	<4	<16	<16	16	<128
	480-99	<16	<32	<256	<4	<16	<16	<16	<128
	481-99	<16	<32	<256	<4	<16	<16	<16	<128
	499-99	<16	<32	<256	<4	<16	<16	<16	<128
TN	478-99	≥128	64	1024	<4	32	16	32	512
	481-99	64	64	512	4	32	16	nt	256
	499-99	64	32	512	8	32	64	16	256

Neutralization titer = highest tested dilution providing ≥50% plaque-reduction against a "mock serum" control
Ref IG = FDA reference immune globulin, lot 176.
All sera were heat-inactivated prior to assay
nt = not tested
Virus stock titers were approximately 10^5 (Jeryl Lynn™, diluted prior to filling; NY), 10^6 (Lo1, JL2, Sw1) and 10^7 (TN) pfu/mL

CONFIDENTIAL

MRK-KRA00336910
MRK-CHA00336910

Initial Evaluation of Seroconversion Rate in Mumps Plaque-Reduction Neutralization Assay

- Test format:
  - Sera = pediatric sera from MMRV studies
  - Paired sera tested (1:2 starting dilution)
  - Seroconversion measured against Jeryl Lynn™, Lo1 and JL2 mumps preparations
  - Seroconversion = 4-fold titer increase from pre-vaccination negative serum
- Results summary:

Mumps indicator Virus	Seroconversion rate (% [number/total])
Jeryl Lynn™	90% (62/69)
Lo1	66% (41/62)
JL2	56% (18/32)

Evaluation of Mumps Neutralization Responses from M-M-R®II Protocol 006

- Study Design and assay:

- Study = Randomized double-blind comparison of M-M-R®II and PRIORIX in infants 12 to 24 months of age

- Infants given 0.5 mL vaccine subcutaneously

- Sera collected pre-vaccination (day 0) and 42 days after vaccination

- 169 vaccinees (85 M-M-R®II and 84 PRIORIX)

- Sera assayed in plaque-reduction neutralization assay against Jeryl Lynn™ vaccine, Lo1 and JL2 mumps preparations
1:2 initial serum dilution

- Neutralization titer = highest tested dilution providing ≥50% plaque-reduction against a "mock serum" control

- Seroconversion = 4-fold titer increase from pre-vaccination negative

Summary of Observed Responses for Mumps Neutralization Antibody Assay for the London 1, JL-2 and Merck Jeryl Lynn™ Mumps Isolates - Per Protocol Analysis

Vaccine Component (Assay)	Parameter	Group A M-M-R®II N=85		Group B PRIORIX N=84		Observed Difference/ Fold Difference (95% CI)[†‡]
		n	Observed Response[†]	n	Observed Response[†]	
London 1	SCR	78	75.6%	73	69.9%	5.8 (-8.5, 20.0)
	GMT	78	9.6	73	8.2	1.2 (0.7, 1.9)
JL-2	SCR	83	53.0%	77	44.2%	8.9 (-6.7, 24.0)
	GMT	83	3.4	77	2.5	1.4 (1.0, 1.9)
Merck Jeryl Lynn™	SCR	80	96.3%	77	90.9%	5.3 (-2.7, 14.4)
	GMT	80	37.7	77	25.3	1.5 (1.0, 2.3)

N=number vaccinated.

n=number of subjects in each treatment group with serology evaluable for the individual component.

[†] Observed responses, observed differences, observed fold differences, and confidence intervals are computed from a statistical analysis model adjusting treatment group.

[‡] Observed difference is the difference in observed seroconversion rates, SCR_A-SCR_B. Observed fold difference is the fold difference in observed geometric mean titers, GMT_A/GMT_B.

CI = Confidence Interval.

Candidate Enhancements to Mumps Neutralization Assay

- Suggestions agreed upon by CBER for evaluation in enhancing the mumps neutralization assay

  - Evaluate alternate "wild-type" mumps strains
    Barnes
    "Low-passage" Jeryl Lynn™ (between passages 7 and 12)

  - Evaluate anti-human IgG to enhance neutralization

Comparison of Mumps Nt Titers for Adult Sera Using different Indicator Viruses

	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

JL-135 = low-passage Jeryl Lynn™, passage 8
JL-vaccine = Jeryl Lynn™ vaccine
ND = not tested

DK 8June 2000

Enhancement of Neutralization with Anti-human IgG

- Incubate 30 minutes with anti-human IgG following virus + serum incubation

- Typically enhances Nt titers ~100-fold
  Previously applied to viruses such as measles, VZV, polio

- Mechanism:
  - Aggregate "sensitized" virus
  - Increase affinity of binding of primary antibody to virus

DK 19June2000

Effect of anti-human IgG on Mumps Neutralization Titers of Adult Sera

Serum	Neutralization titer to Jeryl Lynn™	
	- anti-IgG	+ anti-IgG
MKY	<4	1024
DK	<4	512
DW	512	16384

Enhancement of Mumps Neutralization of Pediatric Sera with Anti-Human IgG

Serum #	Neutralization titer to Pre-serum -anti-IgG	+anti-IgG	Historical	Neutralization titer to Post-serum -anti-IgG	+anti-IgG	Historical
98	<32	<32	<2	<32	≥4096	32
99	<32	<32	<2	<32	2048	8
101	<32	<32	<2	128	2048	128

Mumps indicator virus = low-passage Jeryl Lynn™ (passage 8)
Sera = from protocol 006
Historical titer = using Jeryl Lynn™ vaccine passage without anti-IgG treatment

DK 15 June 2000

10/25/2019
Declaration of G. Reilly
EXHIBIT 124

July 2, 2000 **DRAFT**

TO: CAS

FROM: Vera Byrnes

SUBJECT: Minutes of CAS meeting: June 20, 2000

I. Administrative:
Approval of May minutes: Approved as written.

REDACTED – OMP

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[redacted]

III. Mumps Expiry Trial:
Attachment 2

Status of wild type neutralization assay: A mumps neutralization using a wild type virus strain which results in >95% seroconversions rate is required for the M-M-R®II end-expiry trial. The efforts to enhance the sensitivity of the plaque reduction neutralization (PRN) assay are nearly complete. Discussions with CBER have indicated that low passage JL (between passages 7~~2~~ and 12~~7~~) and the Barnes strain would be acceptable wild type strains. Several assay enhancements, including revised assay

format, inclusion of anti-human IgG, and revised calculation method (Spearman-Karber) to interpolate titers were also evaluated. A series of assays were conducted using adult lab volunteer sera and Barnes, TN, Lo1, JL135p8 and vaccine strain. Neutralization titers of JL135p8 were comparable to those with vaccine strain, and 2-4 fold higher than the other strains. A subset of pediatric sera which historically had high titers against the vaccine strain were tested against both Lo1, JL135p8 and vaccine strain; the low passage JL virus was nearly as sensitive as vaccine passage virus. Based on these data, the JL135p8 was selected as the wild-type strain. While the Spearman-Karber calculation slightly increased the number of seroconversions, the effect was modest and not expected to reach the target ≥95% rate. Further evaluation of this calculation method with enhanced assay conditions will be conducted. The inclusion of human anti-IgG in the assays resulted in significant enhancement of neutralization titers. However, depending on the dilution of antibody, the baseline pre-immunization titers were also increased. Over the next 4-5 weeks the anti-IgG concentrations will be optimized, assay format will be defined and the sera from protocol #006 will be tested to estimate seroconversion rates under optimized assay conditions. The position paper for CBER will be available T- mid August. Timing for transfer of the optimized assay is T- SEPT*?? (Dave Krah/ Mike Washabaugh- correct timing??)-Vera-The transfer should be able to start in September, but it won't be completed-From my view, transfer can begin once we define the assay and establish whether or not we can reach 95% seroconversion-Validation of the assay will be done after this demo, and in parallel witht he transfer..*

Team recommendation on conduct of subset analysis: In response to a CAS assignment, the M-M-R®II team considered evaluating a subset of the end-expiry sera to get an early "disaster check" on the data. The power statements for the study cannot be made, since the final assay characteristics are unknown. Results from a subset analysis could be very misleading due to the inherent variability in estimating proportions. Furthermore, CBER is likely challenge the selection of a subset for analysis because of the potential for introducing bias. The team recommends not conducting a preliminary analysis.

DISCUSSION/ DECISIONS: The recent assay optimizations are very promising for meeting the goals of the assay. There was discussion of how the team intended to bridge the final vaccine formulation (with rHA/ improved stabilizer) with the current product. The M-M-R®II PDT is developing this strategy, and will review the vaccine stabilizers at an upcoming BPC meeting. The CAS recommended using the M-M-R®II control arm from the failed ProQuad study for clinical validation of the enhanced neutralization assay. Once the clinical validation is complete, the team should rapidly assay the samples from the end-expiry study.

The CAS agreed with the team's recommendation to not conduct an interim analysis on a subset from the end-expiry study.

ASSIGNMENTS:

D. Krah: consider evaluating the Lo-1 strain in the optimized assay.

D. Krah, T. Schofield, M. Washabaugh: Develop clinical validation protocol for the enhanced PRN assay. Present results of the clinical validation at the 8/00 CAS meeting. *(TIMING??)*

IV. ProQuad™

Attachment 3

Selection of a mumps antigen for development of a WT ELISA: A panel of 25 per and post vaccination sera were evaluated against several WT mumps strains, including Lo-1, JL135p8, TN, TN#2, Barnes, SBL-1 and vaccine strain. Barnes and JL135p8 were the only strains that showed consitently low pre- vaccination titers, whereas post vaccination titers were fairly comparable for all strains tested. The team concluded that further study should be limited to JL135p8 and Barnes strains. 84 additional sera will be tested to confirm the selection of the WT strain. ELISA assay optimization and validation experiments are pending.

REDACTED – OMP

[redacted]

REDACTED – OMP

[redacted]

10/25/2019
Declaration of G. Reilly
EXHIBIT 125

Matthews, Holly

From: Staub, Ted L.
To: Williams, George (U.S.)
Cc: Heyse, Joseph F.; Matthews, Holly
Subject: RE: CDOC - MMRII Comments
Date: Friday, February 20, 1998 9:23AM
Priority: High

George,

This protocol endpoint and hypothesis was changed at 10pm the night before CDOC. I was informed by Scott Thaler of the changes at 11am the morning of CDOC. The hypothesis presented at CDOC was very general and had no testable criteria associated with it. I was told by Scott Thaler that this was agreed to by Jerry and Reynold during conversations the previous night. My apologies for not informing you right away, It happened at such a late hour that I simply forgot to say anything. Scott also said that this had all been agreed to by Jerry and Reynold the night before.

The reduction in power with this protocol is an issue with every equivalence (or non-inferiority) protocol that we write. In calculating the power for an equivalence test, the assumption under the alternative hypothesis is always that the two groups have the same expected response. In this protocol I gave an example in which IF the true expected rates were not equal but differed by 3 percentage points (96% vs 93%) then the power is reduced from 98% to 72%. This is a dramatic reduction in power BUT it is also a gross violation of the assumption of equality. I believe that the example is put in each protocol to alert upper management to a potential risk in the study. I do not believe that we should add to the sample size and thus over-power our studies. Rather, we need to evaluate our assumption of equality in the two groups and, if warranted, change that assumption to a one or two degree difference and calculate the power accordingly. In this particular protocol, there was no reason to think that the assumption would be incorrect and therefore power was calculated using the equality assumption with an example showing the inherent risk in that assumption.

I hope this is helpful. If you would like to discuss this further perhaps we could arrange a meeting.

Ted

From: Williams, George (U.S.)
To: Staub, Ted L.
Cc: Heyse, Joseph F.; Matthews, Holly
Subject: FW: CDOC - MMRII Comments
Date: Friday, February 20, 1998 8:24AM

Ted,

In the comparison of MMRII and Priorix, I am still somewhat concerned about the reduction in power if, in fact, the true rates differ slightly. (See pg. 20 of CDP.) I should have raised this concern at CDOC. However, do you think the sample size should be increased to improve power?

George

From: Chiacchierini, Lisa M.
To: Staub, Ted L.; Williams, George (U.S.); Schofield, Timothy L.
Cc: Heyse, Joseph F.; Matthews, Holly
Subject: RE: CDOC - MMRII Comments
Date: Tuesday, February 17, 1998 2:02PM

George,

I cannot speak for Ted, but I can answer for my protocols (the three expiry trials and the one concomitant use study). Since the assay for the neutralizing antibodies to mumps is currently under development, we are not sure what results to expect for mumps. We are basing the expected rate of 96% on the package circular, but we are not certain how the new assay will correlate with the one used 25 years ago. This is the reason for the statements about the power decreases if the true rates are lower than expected. I selected 94% as the alternative case because the clinical monitor and I feel that if the response to mumps in the control is lower than this, we should generally be concerned (given what is in our circular). The power for 94% is still above 80% for the expiry trials, and we were comfortable with that. However, I plan to bring the power calculations for larger sample sizes to CDOC with me tomorrow in case this issue is raised and others feel that 80% power is too low.

The two different clinically relevant differences in the concomitant use study were also used in the ARBI CDP that was presented to CDOC last month. They were approved by CDOC, but I do not think that the FDA has had the opportunity to review that document yet. I'll look into this further before tomorrow.

Thanks for your comments,
Lisa

From: Williams, George (U.S.)
To: Chiacchierini, Lisa M.; Staub, Ted L.; Schofield, Timothy L.
Cc: Heyse, Joseph F.; Matthews, Holly
Subject: CDOC - MMRII Comments
Date: Tuesday, February 17, 1998 7:55AM

I have a couple of comments/questions:

CDP

pg. 20,30, 38,, etc. - It is informative the reduction in power that results when the true rates differ slightly. Are you comfortable with the sample sizes given this observation?

pg. 49 - Are the two clinically relevant differences that are presented acceptable to FDA?

10/25/2019
Declaration of G. Reilly
EXHIBIT 126

MERCK
Research Laboratories

M E M O **DATE:** **September 29, 1999**

TO: **Keith Chirgwin, Jeff Hastings, David Krah, Barbara Kuter, William Long, Stephanie Olsen, Timothy Schofield, Alan Shaw, Joan Staub, Scott Thaler, Pete Kniskern, Peggy Fahnestock, Nick Spring, Joye Bramble, Len Rubinstein and Joe Antonello; Kati Abraham; John Lewis**

Cc: **David Blois, Emilio Emini, Jerald Sadoff, Dorothy Margolskee, Henrietta Ukwu; Barry Buckland**

FROM: **Manal Morsy**

SUBJECT: **Mumps Neutralization Assay Meeting Minutes.**
Attendees: Dorothy Margolskee (Video), Peter Kniskern, William Long, Joan Staub, Alan Shaw, Peggy Fahnestock, Jeff Hastings, Tim Schofeild, Stephanie Olsen, Nick Spring, Joye Bramble, Leonard Rubinstein, Joe Antonello , Keith Chigwin.

Agenda items for discussion were:

- Mumps End Expiry Trial
  - Impact on Manufacturing if Trial is Stopped
  - Choice of Neutralization Assays for Expiry Sera
    - Statistical Analysis of Both PRN and CPE
  - Concordance of Current Neutralization Assays and ELISA
    - Statistical Analysis of Existing Concordance Data
    - QPA -Possible alternative assay
    - Development of More Sensitive ELISA (Glycoprotein)
  - Effectiveness of M-M-R®II
    - Literature Search and Summary of Existing Trials
  - CBER Discussion
    - Arguments that Support Choice of Surrogate for MMRV

<u>Minutes</u>:

1-Choice of Neutralization Assays for MMRII End Expiry Sera

A) Statistical Analysis of Both PRN and CPE
1-There is no difference between the PRN and CPE assays, data are equivalent.
2-Thus, selection criteria would ultimately be based on greater through put capabilities.

B) Concordance of Current Neutralization Assays and ELISA
1-There is lack of concordance of current Neutralization Assays and ELISA
2- An alternative high throughput assay is required since there is lack of concordance of current Neut. assays and ELISA
3- Pete Kniskern's group is working on establishing PCR assay capabilities, and are also identifying antigens that may help in the development of more sensitive ELISA (Glycoprotein)

C) Implications of label changes:
1-Priorix-study results will be available within 4-6 weeks, which will help in addressing path forward
2-Current status Neut. assays support >90% SCR for JL and a range up ~ 70-75% for wild type virus.

2-Functional neutralization QPA -Possible alternative assay

Characteristics: a rapid, more sensitive and less variable assay
1- QPA is a PCR based viral DNA amplification assay that would measure % virus infection post incubation in serum from vaccinee relative to control potency
2- The % infection measured is theoretically independent or of limited dependency on the capacity of the un-neutralized virus to package, release, propagate and re-infect, unlike the case with a PRN or a CPE assay. This theoretically would enhance sensitivity.
3- A QPA based assay may allow for a broader range of wild type viral strains to be more likely tested overcoming limitations possibly due to suboptimal wild type virus culture conditions of interfering abortive infection issues.
4- As for JL for which culture conditions have been optimized it would be expected that a PRN assay which currently is giving us ~ 90% Neut. would then be more likely to correlate with a function Neut. QPA thus allowing for the bases of bridging between the two assays in which case the functional Neut. QPA would be a surrogate marker of high through put and one that may be acceptable to CBER based on their recommendation of a Neut. assay as surrogate or a correlate thereof.

Assignments:

1) Determine whether Manufacturing can support overfilling Mumps for at least the next two years and Biologics Licensing would support this strategy **Kati Abreham**
2) Submit Neutralization/ELISA Results to Tim Schofield for Analysis **Krah/Long**
3) Statistical Analysis of PRN and CPE Neutralization Assays **Schofield**
4) Possible Development of QPA pending Resources and Prioritization looking at LO1, JL and Swiss **Kniskern/ Lewis**
5) Literature Search on Effectiveness of M-M-R®II **Thaler**
   Post Meeting Note: Scott has already performed the literature search and will send the papers to the CAS (assignment from August meeting). He will be arranging a meeting with Joe Heyse and Paul Copeland to review the design of the trials within the next few weeks. A summary of the trials will then be issued.
6) Schedule meeting with CBER within the next few months after Head-to Head results are available. **Morsy/Chirgwin**

10/25/2019
Declaration of G. Reilly
EXHIBIT 127

MMR®II End Expiry Trial

- Status:
  - PRN and CPE : performance : 70-75% Neut. WT
  - PRN and CPE : no correlation with ELISA
  - Label change UNDESIRABLE at the present time
  - MMD - capacity to overfill ~ 2 years
  - Delay serum analysis of End Expiry trial so as to:
    - Delay label changes
    - Have time to develop a more sensitive functional Neut. assay (Especially as this would impact MMRV label)
    - Have time to re-focus efforts on developing a more stable MMRII

MRK-CHA00025315

MMR®II End Expiry Trial

- Develop a functional neutralization assay:
  - Characteristics:
    - high through put
    - rapid
    - lessor variability
    - greater sensitivity
- Proposal:
  - a modified QPA (fnQPA):
- Timing:
  - availability within 12-15 month help support MMRV filing (3Q01)
  - availability within the constrains of MMD's capacity to overfill MMRII and the acceptable delay in time for analysis of End Expiry trial sera

Thus we may not require a bridging back to ELISA

MMR®II End Expiry Trial

- fnQPA:
  - PCR based viral DNA amplification assay:
    - Measures reduction in:
      % virus infection post incubation in serum from vaccinee relative to control potency
    - % infection measured is theoretically independent or of limited dependency on:
      capacity of un-neutralized virus to package, release, propagate and re-infect, unlike a PRN or CPE assay.

MMR®II End Expiry Trial

- Thus, theoretically:
  - an enhancement in sensitivity is expected.
  - A broader range of wild type viral strains may be more likely tested in such an assay (overcoming limitations - possibly due to suboptimal culture conditions - of interfering abortive infection issues of wild type in vitro)
  - Where as for JL (for which culture conditions have been optimized) it would be expected that a PRN assay (~ 90%) would correlate to a fnQPA, thus allowing for the bases of bridging between the two assays.

MMR®II End Expiry Trial

- Current Status:
  - MMRII vs PRIORIX:
    - (the MMRII and Priorix vaccine lots used in the trial will be matched by age, in month, of vaccine lot)
  - JL5/JL2 (80:20%) vs JL5 (100%) in vaccine lot
    - potential outcome:
    - at or closer to release if JL2 provides broader protection:
      - » JL5/JL2 in MMRII vs JL5 in Priorix ---> MMRII superior - advantage
        or JL/JL2 in MMRII vs JL5 in Priorix ---> equivalent SCR in assay - no advantage
    - at or closer to expiry JL5/JL2 ratio unknown -
      - » If JL2 is lost & JL5 in MMRII < JL5 in Priorix ---> Priorix superior - disadvantage

MMR®II End Expiry Trial

- Plaque-reduction neutralization assay:
  - designed to quantify mumps antibody titers pre- and post-vaccination.
  - Specifically, the assay was developed to permit an evaluation of the capacity of sera obtained from recipients of MMR®II and PRIORIX vaccines to neutralize vaccine and wild-type viruses.
  - The over all goal is to identify qualitative differences in the antibody responses to these two vaccines that would relate to protection from disease.

Case: 23-2553 Document: 47-5 Page: 209 Date Filed: 11/16/2023

MMR®II End Expiry Trial

- CPE Mumps Neutralization Assay (cytopathic effect)
  - designed to quantify mumps antibody titers pre- and post-vaccination.
  - The over all goal is to identify qualitative differences in the antibody responses to these two vaccines that would relate to protection from disease.

10/25/2019
Declaration of G. Reilly
EXHIBIT 128

Draft/summary of meeting: 8/17/99 (M.Morsy) 0

Attendees: Arena, Deitra E.; Abraham, Katalin G.; Staub, Joan M.; Nalin, David R.; Schofield, Timothy L.; Burke, Carl J.; Bennett, Philip S.; Obara, Tim; Thaler, Scott; Hastings, Jeff; Morsy, Manal.
Subject: M-M-R®II CDTF

M-M-R®II Competitive Defense Task Force
Tuesday
August 17, 1999
8:30-9:30 AM
WP53-Maine/Montana

AGENDA

- Mumps Neut Results - Effect on Expiry Trial Thaler

Summary:

Mumps Neut. Assay results
Our label: 96% serum Neut. (per dose)
Virus and cell biology (VCB) & developmental human vaccine serology (DHVS – Pete's group) developed Neut → 100% dilute VHCS????
50% pfu
Antibodies to virus → engineer too wild
Different wild types example London 1 (Lo1), Tennessee isolate from CDC
sero conversation rate
Summary to date → 70% conversion rate
TCID50 preliminary data vs Neut. look similar
Pfu is favored by CBER
CBER requests 90% lower band limit
Problem for trial to have confidence in a 80% Neut conversation sample size has to increase from 500 patient to ~ 800 / group, assuming they would allow us to use 80% sero-conversion
Hillman assay used Haem-adsorption as end point
LO1 doesn't grow well on Vera
Recent publication: NEJM comparative study – our vaccine → 78% protection (small study size!)
Cathy Carbone (FDA) concern: wild type and vaccine are not doing as well
Arguments:
World wide efficacy / effectiveness seen: US / Finland
Merck issues (driven irrationally)
(1) Driven to increase dose??? Safety (not likely but a concern)
(2) have they looked at hotter places – Albequrki?? (? Efficacy vs vaccine expiry vs JL5/JL2 ratio???)
A paper will be put together to discuss "disconnect" to reconfigure assay
Assay discission would be made after Joe and Tim (assignment) gets results
CBER – September
If this is not resolved and doesn't change → label may have to be changed from 96% to 75% (concern if Smith Kline has better sensitivity and higher seroconversion rates – competition??
Dorothy's concern
J5/J2 (in accelerated aging – loose J2)
(SK – J5 pure)

Additional concerns:
1- If JL2 doesn't work – will be hit by SK

2- vaccine doesn't work – fails neut. assay????

- rHA Update — ~~Bramble~~ Thaler
  - Product Number for rHA containing MMR

Summary:
Presented new contract – approved
Begin looking for safety in humans as early as 10/2000 (release and start)
Adults (with virus) / ped. (without virus)
Look for similarity in adverse effects
(backup Centeon data – 65mg rHA / repeated administration
Japan – we have data with 25% AE (prompted)
August of 2001
Q: Are you going to exclude yeast sensitive or allergic history patients
Suggestion: exclude initially then include in a smaller trial
Q: primed with yeast containing vaccines – do you expect AE?
Suggestion: split patients to : allergic vs non-allergic (be pro-active for making Merck "safety"
REDACTED – OMP
[redacted]
so concern would be adding a new set of allogens.

- Potential Trial in China — Obara

Summary:
Potential trial in China:
Their interest: 1- when does M-M-R®II best fit in their schedule (0-6 or 6-18 etc)
2- effectiveness of M-M-R®II (particularly mumps) they have noticed outbreaks – no hard data!!
Need a controlled study to figure this out.
Our protocol : GOS ??
We need to review their intended publications for approval
Will – circulated email on what to do, marketing would pay for this, monitering would be done through CROPS

- Path Forward to "Stingless" M-M-R®II — Bramble

Summary:
PAC on Thursday
→ not interested in it unless they have it NOW before SK comes on market.
→ "stingless M-M-R
M-M-R-V 4°C 1Q/01 → clinical trial
M-M-R-V frozen 3Q/02 → launch

Major concern (especially in how we approach this)
Louisiana and California : Autism caused by multivalent vaccines!!

Vejay vs Nick & Tim
→ need agreement
4°C /frozen vs "stingless"

10/25/2019
Declaration of G. Reilly
EXHIBIT 129

MERCK
Research Laboratories

M E M O

DATE:

TO: **Dr. Henrietta Ukwu**

CC:

FROM: **Dr. Keith Chirgwin**

SUBJECT: **Options and proposed path forward for the Mumps Expiry Trial**

Issue:
CBER insistence on a WT neutralization assay will likely result in SCR of 70-80%

1) The feasibility of developing or identifying (outside investigator) a WT neutralization assay with a sufficiently higher SCR (>90%) is uncertain
2) Low SCR will require increased sample size and/or increased equivalence margin to maintain power; CBER is extremely resistant to increasing the equivalence margin
3) Implications of low SCR on the MMRII label are uncertain

Options:

1) Complete the Mumps Expiry Trial
   Benefits (if successful):
   a) Reduced product cost
   b) May be able to apply the new expiry dose to MMRV, permiting greater flexibility in setting the release/expiry specifications for MMRV
   Risks:
   a) Label may be adversely affected with perceived change in efficacy
   b) If the trial fails with the 4.0 dose this may conceivably raise questions about the adequacy of the 4.3 dose
   c) Success in convincing CBER to widen equivalence margin may possibly facilitate licensure of Priorix (CBER has repeatedly emphasized need to be consistent with other manufacturers in this area)
   d) The feasibility of extrapolating the mumps expiry data from MMRII to MMRV has not been confirmed with CBER

2) Stop the Mumps Expiry Trial
   Benefits:
   a) Allows team to focus efforts on WT ELISA for the MMRV program without the additional distraction of attempting to develop a more sensitive WT neut assay
   b) Avoids potential labeling implications of measured low SCR for mumps in MMRII
   c) Avoids the need for wider equivalence margin which might facilitate Priorix licensure

Risks:

a) Although mumps overfill to target of 5.2 to maintain an expiry of 4.3 is feasible for MMRII, this is less certain for MMRV due to outstanding questions about mumps suppression, assay validation and stability of the frozen and urea-based formulation. If the current expiry of 4.3 is not feasible in manufacturing with the current target of 5.2 for MMRV, then either a mumps expiry trial for MMRV to evaluate a lower expiry dose, or a safety evaluation of a higher mumps target will be needed. It should be noted that an MMRV expiry trial faces the same risks as the current MMRII expiry trial (i.e. need for WT neutralization assay) plus the additional complication of how to produce a clinical lot with an appropriate mumps expiry titer as well as a varicella titer within the anticipated licensed potency range.

Proposed path forward

1) Determine whether it is possible to have a higher SCR (i.e. >90% lower bound) with a WT neutralization assay (discussion with CBER, Dr. Forghone). If yes then proceed with trial using this enhanced assay. If no:
2) Determine CBER's position with regard to the impact of this study on label if the SCR is in the 70-80% range. If CBER indicates that a negative impact on the label is anticipated, then it may be prudent to defer completion of trial (complete trial but don't run assays?). If no negative impact on label then proceed with study, and:
3) Determine with CBER whether mumps expiry results in MMRII can be extrapolated to MMRV. If these results cannot be extrapolated to MMRV, then the utility of this trial is limited (at this juncture the questions about manufacturing feasibility apply primarily to MMRV, not MMRII). If results can be applied to MMRV then proceed with trial. If not then consider stopping trial.
4) Resolution of assay validation and definition of the mumps suppression are essential to determining whether the mumps expiry issue is a factor for MMRV. If, upon completion of these investigations, the 4.3 mumps expiry is determined to not be feasible for MMRV then consideration of either conducting an MMRV mumps expiry trial or increasing the mumps target may be necessary. The potency and sample size of the clinical safety evaluation of a higher mumps target need to be determined as well as the feasibility of incorporating this into the safety trial for the release potency of varicella..

KDC
UN-B121

cc: file, chron

10/25/2019
Declaration of G. Reilly
EXHIBIT 130

Forsythe, Colleen A.

From: Schodel, Florian P.
To: Forsythe, Colleen A.
Subject: FW: mumps issues
Date: Monday, July 07, 1997 7:07PM

From: West, David J.
Sent: Monday, July 07, 1997 8:49AM
To: Chirgwin, Keith D.; Schodel, Florian P.
Cc: Kuter, Barbara J.
Subject: RE: mumps issues

In three studies of COMVAX, the proportions of initially seronegative children who seroconverted for Ab to mumps after concurrent injections of COMVAX and M-M-R II were: 100% (39/39), 97% (72/74), and 100% (55/55).

David J. West

From: Schodel, Florian P.
To: Chirgwin, Keith D.
Cc: Kuter, Barbara J.; West, David J.
Subject: RE: mumps issues
Date: Thursday, July 03, 1997 6:46PM

From: Chirgwin, Keith D.
Sent: Monday, June 30, 1997 6:39PM
To: Fontaine, Joline; Schodel, Florian P.
Cc: Forsythe, Colleen A.; Sadoff, Jerald C.
Subject: RE: mumps issues

Dear Keith,

I do not have a complete answer to this question. We have to check data that were generated in other programs recently (Comvax and Varivax/MMRV). Collen will look into that and I'll forward this message to Barb and David West to get their feedback. The only data about a lower mumps dosage I have are in a message from David Nalin. I have never seen the original data and they are monovalent mumps vaccine data, therefore it is not clear whether they can be extrapolated to MMR. However we should be on the safe side with the mumps titres in MMR at expiry, regardless of what they are (and if we are not we have a problem that needs to be fixed differently). Setting the acceptable difference at 10% should be acceptable. What worries me is that there is no clearly defined standards and we may be waking up sleeping dogs 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).

Cheers

Florian

Florian,
I agree that titrating the virus may make things much more complicated in terms of varying degrees of viral interference. However, we should define acceptable historical seroconversion rate very carefully and also make certain that the regulatory agencies agree with this definition. The label currently indicates that a single dose of MMRII results in a mumps seroconversion rate of 96%; if we are held to this as the "acceptable historical standard" there is a chance that we may have a problem. We may need to consider the possibility that the SC rate at expiry may be lower and plan for this contingency now. If we had more confidence that there was little likelihood of a drop in SC rate at expiry, of course the whole discussion above becomes moot. Are there any clinical data that you are aware of that provide some reassurance that lower mumps potency will not be problem?
Keith

From: Schodel, Florian P.
To: Fontaine, Joline
Cc: Sadoff, Jerald C.; Chirgwin, Keith D.; Staub, Ted L.; Forsythe, Colleen A.
Subject: RE: mumps issues
Date: Monday, June 30, 1997 7:48AM

Dear Joline,

if we decide to address the at expiry mumps titre vs immunogenicity issue 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/rubella with possible ensuing changes in interference. The trial should only compare seroconversion rates to acceptable historical seroconversion data after immunization with lots at expiry, thus making sure that even lower titres meet the standards (the problem here is whether the assays our lab is willing to run are generally accepted by the agencies or the scientific public at large, short of publications I have my doubts). Let me know what your thoughts are.

Yours

Florian

From: Fontaine, Joline
Sent: vendredi 27 juin 1997 23:33
To: Schodel, Florian P.
Cc: Walter, Maureen V.
Subject: FW: mumps issues
Importance: High

Florian - what do you think of the studies proposed below?

Joline

From: Ukwu, Henrietta
Sent: Thursday, June 26, 1997 3:11 PM
To: Staub, Joan M.; Garfinkle, Barry D.
Cc: Forsythe, Colleen A.; Sadoff, Jerald C.; Sharrar, Robert G; Chirgwin, Keith D.; Guess, Harry; Heyse, Joseph F.; Blois, David W.; Fontaine, Joline; Nalin, David R.; Walter, Maureen V.; Abraham, Katalin G.; Wonnacott, David M.; Shaw, Alan R; Krah, David
Subject: FW: mumps issues
Importance: High

Joan and Barry

The study at expiry should evaluate minimum effective dose - so as Barry suggested should titrate as low as we

can get to if possible. I agree with the reasons to conduct this study.

Henrietta

From: Garfinkle, Barry D.
To: Ukwu, Henrietta; Staub, Joan M.
Cc: Forsythe, Colleen A.; 'Nalin, David R.'; Sadoff, Jerald C.; Sharrar, Robert G; Chirgwin, Keith D.; Guess, Harry; Heyse, Joseph F.; Blois, David W.; Fontaine, Joline; Shaw, Alan R; Walter, Maureen V.; Abraham, Katalin G.; Wonnacott, David M.; Krah, David; 'Lewis, John'
Subject: RE: mumps issues
Date: Monday, June 23, 1997 2:37PM
Priority: High

J,
Only the obvious downsides. One other consideration is that we should be sure we run it at the lowest we ever expect to get? I would almost prefer this to a real world situation. A titration in the clinic would be nice but I don't know if we could do this.
B

From: Staub, Joan M.
Sent: Thursday, June 19, 1997 2:10PM
To: Ukwu, Henrietta; Garfinkle, Barry D.
Cc: Forsythe, Colleen A.; Nalin, David R.; Sadoff, Jerald C.; Sharrar, Robert G; Chirgwin, Keith D.; Guess, Harry; Heyse, Joseph F.; Blois, David W.; Fontaine, Joline; Shaw, Alan R; Walter, Maureen V.; Abraham, Katalin G.; Wonnacott, David M.; Krah, David; Lewis, John
Subject: RE: mumps issues
Importance: High

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. If they meet the expiry critera and we don't we stand to loose a major market. Colleen Forsythe (MPC for MMR) brought that suggestion back to Jerry who thinks we should run the trial and do it in Germany. We would use MMR at release and at expiry and look at Mu seroconversions. Any downsides to this...other than the obvious? Joan

----

From: Ukwu, Henrietta
To: Sharrar, Robert G; Chirgwin, Keith D.; Nalin, David R.; Wonnacott, David M.
Cc: Sadoff, Jerald C.; Staub, Joan M.; White-Guay, Brian; Blois, David W.; Garfinkle, Barry D.; Beck Liane GER; Guenther Susanne GER; Gerdil Emmanuele HBO; Vose John HBO; Abraham, Katalin G.
Subject: FW: mumps issues
Date: Monday, June 16, 1997 4:19PM

Please review discussion below and determine best approach for providing clinical data to support the mumps titer discussion.

Keith, please contact Jerry .

Joan, the clinical write-up should be tracked rapidly since the need is quite urgent. Please keep me posted.

Thanks. Henrietta

From: Wonnacott, David M.
To: Beck Liane GER; Guenther Susanne GER; Gerdil Emmanuele HBO; Vose John HBO
Cc: Sadoff, Jerald C.; Ukwu, Henrietta; Garfinkle, Barry D.; Nalin, David R.; Abraham, Katalin G.; Fujii, Catharina

C.; Thompson, Barbara; Rosolowsky, Mark; Varilla, Mark F.
Subject: FW: mumps issues
Date: Thursday, June 12, 1997 4:13PM

All,
From the standpoint of clarification to the message from Susanne, we do not anticipate that the issue with Dr. von Wangenheim re. mumps shelf life titer will go away after we complete a more detailed investigation of real time stability data. If anything, the Mumps shelf life titre loss may actually be more than 0.5 Log.

Some clarification is also needed for the comment on clinical studies. M-M-R-II, with the current release specifications, has clearly demonstrated safety and efficacy in the United States beyond any early clinical study. It seems we should emphasize this. We do not release vaccine with mumps titers below 4.3. Therefore, we do not intend to provide clinical studies for vaccines with release titers below 4.3. We are not planning to include a clinical "expert report" with the package. However, we will seek input from clinical experts at Merck for this paper (by copy of this memo I suggest Kati follow up with H. Ukwu & clinical team).

This issue is obviously frustrating to us since we want to maintain manufacturing consistency. It is our position that we must provide the SAME product that has historically demonstrated such a high level of safety and efficacy. We cannot change the product based on a flawed premise, (i.e. Dr. von Wangenheim currently does not accept that the label was originally filed as release titer). Another complicating factor is that Dr. von Wangenheim's argument does not take into account assay variability when multiple laboratories test our product. (For example, RIVM EU batch release provides a shelf life titer for mumps significantly lower than ours.)

In conclusion, an issue came up in our teleconference today which we should address. Susanne has discussed M-M-RII issues with Dr. von Wangenheim without having copies of the background material we previously provided the JV and the EP. We will provide Germany, including Chiron Behring (if deemed appropriate by JV), with this information in the near future. However, it would have been better if Susanne had this information earlier.

We certainly appreciate your help on these issues. Hopefully we can reach a resolution with Dr. von Wangenheim in the near future. Thanks,
Dave

From: Vose John HBO
To: Guenther Susanne GER; Gerdil Emmanuele HBO
Cc: Beck Liane GER; Wonnacott David MRK
Subject: RE: mumps issues
Date: Thursday, June 12, 1997 11:38AM

Microsoft Mail v3.0 IPM.Microsoft Mail.Note
De: Vose John HBO
A: Guenther Susanne GER
Gerdil Emmanuele HBO
Cc: Beck Liane GER
Wonnacott David MRK
Objet: RE: mumps issues
Date: 1997-06-12 17:15
Niveau de priorité:
Identification du message: D449B389
ID de la conversation: D449B389

-- --

Thanks for the clear report of this recent conversation. We look forward to receipt from Merck of the mumps statement including the new data that we have not yet seen. I trust it will convince Germany (and Austria) to

accept our position .

De: Guenther Susanne GER
A: Gerdil Emmanuele HBO; Vose John HBO
Cc: Beck Liane GER; Wonnacott David MRK
Objet: mumps issues
Date: jeudi 12 juin 1997 17:09
Niveau de priorité: Haut

Microsoft Mail v3.0 IPM.Microsoft Mail.Note
Von: Guenther Susanne GER
An: Gerdil Emmanuele HBO
Vose John HBO
Cc: Beck Liane GER
Wonnacott David MRK
Betreff: mumps issues
Datum: 1997-06-12 17:08
Priorität: R
Nachrichten-ID: 11E7704D
Conversation ID: 11E7704D

--

A few minutes ago Merck (Dave Wonnacott, Kati Abraham, Barbara Thompson, Cathy Fujii) were discussing the PEI requirements for mumps containing vaccines with Dr. Enssle from Chiron Behring and myself on the phone.

I try to give you a short summary:

It was stated that Dr. von Wangenheim's main concern is, that she wants the shelf life titer to be 4,3 log for mumps (and not 3,7 log) because the clinical results were obtained with vaccines that had a titer of at least 4,3 log. The results of the downdosing studies, that were also presented at the Straßbourg OMCL - meeting did not convince her because they were not commented and explained with enough details. EP conformity is no argument for her.

The second problem is that she wants the release titer to be 4,8 log assuming a log loss of 0,5 log during the shelf life.

Dr. Enssele from Chiron Behring emphasized that the thermostability test could also become a problem in the future because his own results over several years showed that the log loss was increasing constantly. At the moment the batches fulfill the requirement only just. The resuts reach the acceptable limit. He will send his results to Merck.

Moreover it was mentionned that Dr. von Wangenheim is interested in the results as regards the stabilizer.

The conclusion was that Merck will prepare a paper containing all the arguments that may convince Dr. von Wangenheim by the end of July. This paper will be first sent to us. They will include the argument, that the clinical experience with the vaccine showed that it is effective even with titers lower than 4,3 log for mumps. An expert opinion will also be included

(probably after July). They will also include new results from stability tests that probably show that the log loss during shelf life is less than 0,5 log and that consequently a release specification of 4,8 log is not necessary to meet a shelf life specification of 4,3 log. Furthermore results

of the tests as regards the stabilizer will probably be included (results are available by the end of July).

In addition further information about thermostability results will be sent to us.

Best regards, Susanne

10/25/2019
Declaration of G. Reilly
EXHIBIT 131

Case 23-2553 Document: 35 Page: 224 Date Filed: 11/16/2023

MEMO August 23, 2000

TO: Alan Shaw

FROM: Dave Krah

SUBJECT: Monthly report for August, 2000.

REDACTED – OMP

[redacted]

II. Measles, Mumps and Rubella

A. Mumps serum neutralization (Nt) assay (plaque-reduction Nt).

1. Modification of the standard mumps Nt assay to include an incubation with anti-human IgG (anti-IgG enhanced mumps neutralization assay [mumps AIGENT]) has been evaluated to determine whether the sensitized assay is capable of detecting ≥95% seroconversion in vaccinees. This target has been established by CBER to demonstrate adequate immunogenicity of mumps vaccine in current use. Testing with the mumps AIGENT assay includes the "standard" mumps plaque-reduction neutralization assay using JL135 "low-passage" Jeryl Lynn™ mumps, an anti-human IgG treatment (30 min) after "primary" neutralization, and immunostaining to visualize plaques. Sera are typically tested at dilutions 1:32 through 1:4096 (due to a prozone effect at higher serum concentrations), and the Nt titer is assigned to highest tested dilution producing ≥50% Nt relative to a mock serum control. Preliminary studies have focused on identifying an optimum concentration of anti-human IgG that provides adequate sensitivity to detect post-vaccination responses, but does not provide excess pre-vaccination positive titers. Adult lab sera have also been used to evaluate effects of the anti-IgG concentration on assay sensitivity. The composite data suggest that this optimum concentration is between 1:4 and 1:8 (125 and 62.5 µg/mL antibody protein, respectively), and testing of two panels of pediatric sera was completed using one or both of these anti-IgG amounts to determine seroconversion rates and pre-positivity rates.

The first pediatric serum panel included a subset of sera from protocol 006, selected to include most of the non-responders to Jeryl Lynn™ in the "standard" Nt format to determine whether the enhanced Nt assay detects seroconversions in serum pairs that did not show seroconversion in the standard assay. The seroconversion rates for this set were 79.5% (31/39) to Jeryl Lynn™ mumps in the standard assay (historical values) and 91.7% (33/36) and 94.0% (32/34) in

the AIGENT assay using 1:4 and 1:8 anti-IgG dilutions, respectively. Pre-positivity rates were 9%, 5% and 3% in the standard assay and the AIGENT using 1:4 and 1:8 anti-IgG, respectively. These data demonstrated that the 1:4 and 1:8 anti-IgG dilutions provided enhanced sensitivity to detect seroconversions without producing excess pre-positive rates. The 1:4 anti-IgG dilution was then used to test another panel of 60 paired pediatric sera. Seroconversions for the second serum set were 100% (47/47), but also included an unexpectedly high pre-positive rate (13/60: 22%). The majority of the pre-positive sera were positive at only a single serum dilution, and did not repeat as positive on repeat assay, consistent with the weak Nt responses for these pre-positive samples.

The overall seroconversion rate in pediatric sera using 1:4 anti-IgG is 96% (80/83). Retesting of a subset of this serum block using 1:4, 1:6 and 1:8 anti-IgG dilutions is underway to identify the optimum concentration that provides ~10% or lower pre-positive rates.

Examples of titrations curves for pre-positive and pre-negative serum pairs are presented in Figures 1 and 2.

Figure 1

Example of Anti-IgG Enhanced Nt for Pre-Negative Serum Pairs

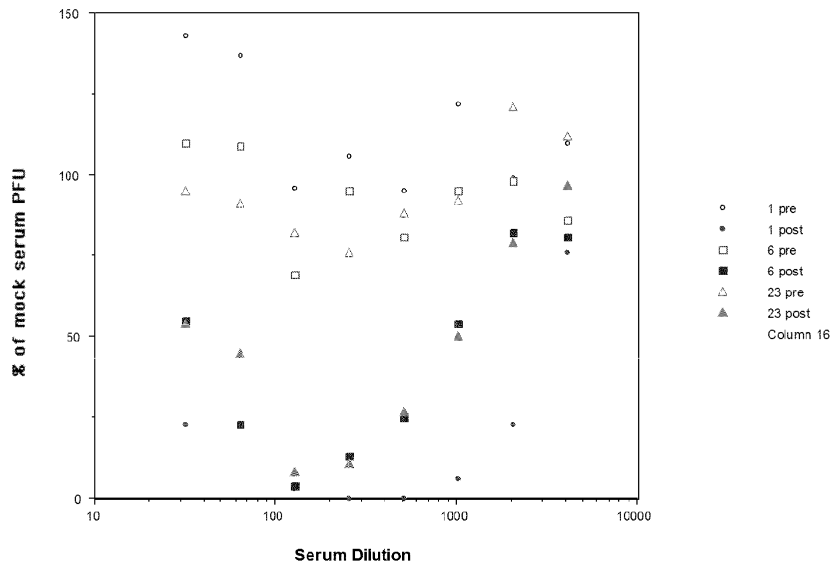
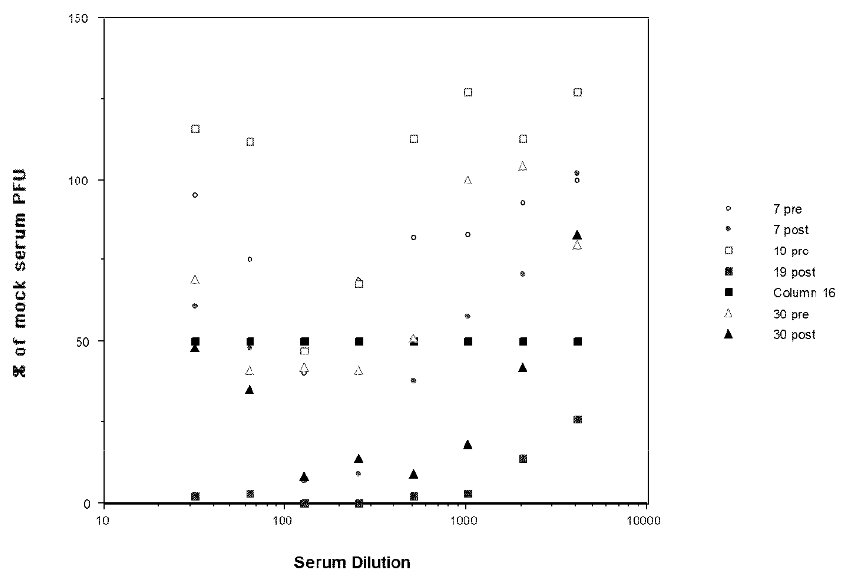


Figure 2

Example of Anti-IgG Enhanced Nt for Pre-Positive Serum Pairs



Further development and characterization of the mumps AIGENT assay (optimize the anti-IgG concentration and confirm seroconversion rate estimate and pre-positive rate, test a panel of 20 paired sera at 1:2 through 1:4096 dilutions to characterize % Nt in the 1:2 through 1:16 range that is not included in the typical dilutions of the assay, and characterize “weak” positive and negative Nt responses: targeted to be completed in 4-6 weeks) will continue is parallel with plans to transfer the assay to an outside testing lab (to start over the next few weeks).
Additionally, a subset of experiments is underway to evaluate the performance of alternative strains (Lo1, Barnes, TN) to establish whether another “wild-type” strain would provide comparable sensitivity in the anti-IgG enhanced Nt assay and to determine if the Nt sensitivity ranking observed in the standard assay is also found in the enhanced assay.

REDACTED – OMP

[redacted]

Dave

cc: Lab staff
Paul Keller

10/25/2019
Declaration of G. Reilly
EXHIBIT 132

VIRUS & CELL BIOLOGY RESEARCH PROCEDURE

SUBJECT: Anti-IgG Enhanced Mumps Plaque-Reduction Neutralization Assay

No.: 874.3489
Rev.: 00
Page: 1 of 10
Effective Date: 18-DEC-2000

Written By: David Krah/Mary Yagodich Date: 28-Nov-00
Approved By: Alan Shaw Date: 28-Nov-00
QCA: Denise A. Williams Date: 18-DEC-2000

I. Introduction

The Anti-IgG Enhanced Mumps Plaque-Reduction Neutralization Assay (AIGENT) was designed to provide a sensitive means to determine mumps antibody titers pre and post vaccination or in post infection sera. The general neutralization assay procedure is modeled after Virus and Cell Biology Research Procedure No. 874.3422: Mumps Plaque Reduction Neutralization Assay (rev. 00), and neutralization is enhanced by the addition of anti-human IgG following the incubation of virus and serum. Neutralization (Nt) is identified by the reduction in pfu (plaque forming unit) against negative controls (either seronegative patient sera or mock sera). The Nt endpoint is assigned to the highest tested serum dilution providing ≥ 50% plaque reduction. Sera are tested at serial 2-fold dilutions, typically ranging from 1:32 through 1:4096 in the enhanced neutralization assay, utilizing a constant virus dilution. This procedure describes virus and antibody attachment conditions and reagents. Following the virus/antibody attachment reactions virus plaques are measured using Virus and Cell Biology Research Procedure 874.3268 (following "Materials and Methods" steps 1 through 7; and "Protocol for the plaque assay" steps 2 through 8, using 62,500 cells/mL and 2 mL/well of 12-well plates). Reagent lot information, serum and virus identification numbers and dilutions, and conditions for the Nt assay and corresponding mumps plaque assay are recorded in the attached "AIGENT Assay Info Sheet".

II. Reagents, Supplies and Equipment

A. Reagents

1. Human serum: Serum from patients with wild type mumps infection or from vaccinees.

   Serum received frozen is stored at -20°C or colder and is routinely not thawed until needed. Sera are held in a 35°C (±1°C) or 37°C (±1°C) water bath for 5-10 minutes or until thawed and may be held at 2-8°C for up to one year after thawing. Sera should not be refrozen if further short-term Nt testing is planned. For longer term storage or after testing is completed, the serum samples are refrozen. If the serum samples are received thawed, and have never been frozen, they are aliquoted and frozen at -20°C or colder. If the serum samples previously frozen have been thawed and refrozen prior to testing, note this additional freeze/thaw in the documentation for the neutralization assay using these sera. Record the serum thawing and refreezing dates (if applicable) in either the experiment write-up for those sera or in a serum log. Once serum samples are thawed, the serum is

heat inactivated for 35±1 minutes at 56°C±1°C, then transferred to 2-8°C or held on ice for a minimum of 5 minutes and up to a one month prior to diluting in medium for assay of virus neutralizing activity. Sera are typically heat-inactivated on the day of assay. Record the serum heat-inactivation date in the experiment write up or in a serum log.

2. Hyperimmune serum: Polyclonal anti-mumps (MPS), anti-measles (MV) and anti-rubella sera (for example, goat polyclonal antisera, prepared by Hazleton Biotechnologies/Covance).
This anti-mumps serum may be used as a control to compare serum antibody titers, or used to characterize mumps strains which may be used in the Nt assay. Hyperimmune goat serum offers a polyclonal Nt activity and a higher Nt titer than sera from most human vaccinees. Additionally, these hyperimmune sera are utilized when combined vaccine is used an indicator virus (e.g.: combined MMR vaccine) to neutralize viruses not being assayed for neutralization activity . These hyperimmune sera are tested in the "standard" mumps Nt assay (Virus and Cell biology Research Procedure No. 874.3422: Mumps Plaque Reduction Neutralization Assay) format, without the addition of anti-human IgG.

3. Virus and Serum diluent and medium for use in overlays.
Used for diluting virus and serum and as overlay medium component for mumps plaque assay (Maintenance Medium: MM):
Medium 199 (GIBCO cat #11150-159 or equivalent), 2% heat-inactivated Fetal Bovine Serum (JRH cat #12-10378P or Merck Product # 38493-909, or equivalent); 2 mM L-Glutamine (from 200 mM Glutamine stock: GIBCO Cat # 25030-081 or BioWhittaker Cat #17-605B, or equivalent); 50 ug/mL Neomycin (from 10 mg/mL neomycin stock [for example, Sigma cat # N-1142] or 100 mg/mL stock [Merck CM274, or equivalent]).
Formulated MM can be held for up to one month after day of being made. Media can be aseptically formulated in the original Medium 199 bottles or may be optionally filtered prior to use using a sterile 0.22 um filter or filter unit.

4. Virus
Indicator viruses used in the neutralization assay may be lyophilized or frozen liquid virus preparations (which must be thawed prior to use), and are diluted in Maintenance Medium (MM) to the targeted virus concentration. Indicator viruses are deemed suitable by plaque morphology and neutralization capacity, and may

include vaccine viruses (and viruses derived from the vaccine) or wild-type (WT) viruses.
An example of an indicator virus is Mumps House Standard fill #0613945 (lyophilized) from MMD.
Indicator viruses may also include combined samples (e.g. M-M-R®II), lyophilized.

Lyophilized samples are reconstituted with 700 uL sterile distilled water (RCM66 or equivalent) or sterile diluent (provided by MMD), and can be held up to one hour on ice before diluting for use in the neutralization assay.

Liquid frozen virus preps are thawed in a 35°C±1°C water bath for 5-10 minutes, and held on ice for up to one hour before diluting.
Note that WT or other mumps preparations are prepared by a separate protocol (typically in Vero or chick cell cultures).
Virus dilution utilized is targeted to provide 20-30 plaques per well (predetermined by standard mumps plaque assay).

5. Buffers and solutions
RCM563 (sterile Phosphate buffered saline), or equivalent
RCM66 (sterile distilled water), or equivalent

6. Anti-human IgG
Rabbit IgG fraction to human IgG (whole molecule), ICN/Cappel catalog #55008, or equivalent (5 mg/mL antibody protein; formulation typically contains 0.05% sodium azide).

Note: lot 1943 of this anti-IgG was used in assay development studies, and is being used routinely at a 1:6 dilution for use in the AIGENT testing of pediatric sera. Additional dilutions may be used as needed to achieve the required neutralization sensitivity. A new lot of anti-IgG is qualified by comparing the anti-IgG dilution of lot 1943 to different dilutions (including 1:4, 1:6, 1:8) of the new lot against a panel of paired pediatric sera. The use level of the new lot is established as the dilution of the new lot that provides comparable Nt results (titers) to those obtained using the 1:6 dilution of lot 1943.

Reconstitute with RCM66 or equivalent (typically 5 mL/vial, allowing 2-30 min for reconstitution, aseptically pool replicate vials, if applicable, after reconstitution) and dilute in RCM563 or equivalent to the desired concentration.

Anti-IgG should be used only on the day of reconstitution (unless further studies confirm the acceptability of longer holding times after reconstitution).

B. Supplies and Equipment

1. Sample/Dilution tubes

Biorad Microtube 96-rack sterilized Titertubes; or other suitably sized sterile polypropylene microtubes. Apply sterile caps (or use tubes with caps) for heat-inactivation, storage at 2-8°C for periods longer than 24 hours, or for freezing.

2. Incubators

37°C±1°C + 5.0%±1.0% CO_2 incubator for Antibody (ab)/Antigen (ag) attachment.
35°C±1°C + 5.0%±1.0% CO_2 for virus attachment and plaque development.
2-8°C incubator (for medium and serum storage and for gelling of overlay media in the plaque assay).

3. Water baths

56°C ± 1°C
35°C ± 1°C and 37°C ±1°C

4. Pipettes

12-channel multichannel pipettor for serial dilutions: Costar or Eppendorf (or equivalent).
Sterile 100 uL-200 uL micropipet tips [for example, 96-rack Costar or Eppendorf (or equivalent)].
Micropipettors: Eppendorf, Gilson, (or equivalent), capable of dispensing 100 µL volumes for inoculating samples onto Vero monolayers.
Repeat pipettor (Eppendorf) (or equivalent) and sterile tips, capable of dispensing 100-200 µL volumes.

III. Sample Preparation

Heat-inactivated sera are diluted through serial 2-fold dilutions in titertube racks.

Note: The following dilution series is routinely used to determine an endpoint titer on a serum of unknown titer. Note: diluent = "dil".
Dilution schemes and the serum identification numbers are outlined in the experiment write-ups.

The serum dilution scheme for routine testing follows:

Serum dilutions and volumes

Dilution	Volumes
1:16	25 uL (undiluted serum) + 375 uL diluent
1:32	200 uL (1:16) + 200uL dil
1:64	200 uL (1:32) + 200 uL dil
1:128	200 uL (1:64) + 200 uL dil
1:256	200 uL (1:128) + 200 uL dil
1:512	200 uL (1:256) + 200 uL dil
1:1024	200 uL (1:512) + 200 uL dil
1:2048	200 uL (1:1024) + 200 uL dil

discard 200 µL from the final serum dilution to provide 200 µL serum/tube

The anti-IgG enhanced Nt assay shows a prozone effect at high serum concentrations, and the results of preliminary experiments have established an initial 1:16 serum dilution (1:32 dilution after the addition of virus and serum) as the starting dilution for routine testing.

Alternatively, additional serum dilutions may be tested, using the following serum dilution scheme starting with undiluted serum (not used for routine testing in the anti-IgG enhanced neutralization assay):

Serum dilutions and volumes

Dilution	Volumes
1:1	400 uL undiluted serum
1:2	200 uL (1:1) + 200 uL dil
1:4	200 uL (1:2) + 200 uL dil
1:8	200 uL (1:4) + 200 uL dil
1:16	200 uL (1:8) + 200 uL dil
1:32	200 uL (1:16) + 200uL dil
1:64	200 uL (1:32) + 200 uL dil
1:128	200 uL (1:64) + 200 uL dil
1:256	200 uL (1:128) + 200 uL dil
1:512	200 uL (1:256) + 200 uL dil
1:1024	200 uL (1:512) + 200 uL dil
1:2048	200 uL (1:1024) + 200 uL dil

discard 200 µL from the final serum dilution to provide 200 µL serum/tube

Additional serial 2-fold dilutions may be included for both dilution series, as needed, to obtain an endpoint titer.

Note: Pre-vaccination sera and post-vaccination sera are typically tested at eight serial 2-fold dilutions (typically starting with a 1:16 [initial dilution before adding virus and anti-IgG]). The initial serum dilution may be started at an intermediate dilution (for example, using 100 µL of serum + 300 µL of diluent to provide 400 µL of a 1:4 serum dilution) if the serum volume is limiting. The dilution series may also be started at higher dilutions to determine endpoint titers for high titered sera (sera providing positive Nt at the highest tested dilutionin initial testing). As an additional option for sera of known high titer (e.g., if the serum titer is 1:1024 [final dilution of serum and virus]), an initial dilution of 1:10 (for example 50 µL serum + 450 µL diluent) and then 1:12.8 (31 µL from 1:10 dilution + 369 µL diluent) may be made to provide serum dilutions of 1:128, 1:256, 1:512, 1:1024 (rather than start with lower serum dilutions).

Each assay includes 4 tubes containing diluent (no serum) to serve as the "no serum" ("mock serum") control. Additionally, positive control serum/sera (typically a low and a high-positive control) are included to monitor assay performance.

To each serum dilution tube or mock serum sample, add 100 µL of diluted virus. Shake the rack gently to ensure that the serum and virus solutions are mixed (avoid droplets of solutions remaining on the sides of the tubes above the liquid level).

Place the rack(s) of serum + virus samples at 37°C±1°C for 60 minutes ± 5 minutes.

At end of this incubation, remove the plates from the 37°C incubator and transfer to room temperature holding (15-30°C).

Add 100 µL of diluted anti-human IgG to each tube, manually shake 2-5 times to mix the solutions, and incubate at room temperature (15-30°C) for 30 minutes ± 5 minutes.

Note: The final reaction tube contains 200 µL of diluted serum + 100 µL of diluted indicator virus + 100 µL of diluted anti-IgG, thus providing an additional 2-fold dilution of serum and a 4-fold dilution of virus in the final reaction mixture.

Example: 200 uL (1:16) serum + 100 uL (1:250) virus + 100 µL anti-IgG = (1:32) final serum dilution and (1:1000) final virus dilution.

Samples are then inoculated onto Vero cell monolayers (within 2 h of the end of the incubation of virus + serum + anti-IgG) to measure virus pfu in the mumps plaque assay as described in section IV.

IV. Mumps plaque assay procedure

A. Virus inoculation and plaque development

Aliquots of 100 uL of the incubated virus + serum samples from section III are inoculated into Vero cell monolayers in triplicate wells of 12-well plate monolayers as described in Virus and Cell Biology Research Procedure No. 874.3268: "Plaque assay for the measurement of mumps infectivity titers", using a cell plant concentration of 62,500 ±10% cells/mL and 2 mL ± 0.5 mL/well of 12-well plates.

Note: details of the cell preparation and plaque assay are recorded in the attached "AIGENT Assay Info Sheet". Note that the measurement of Vero cell concentration is made using a 1:5 dilution of the harvested cell suspension (counting 5 squares), and cells are planted at 62,500 ±10% cells/mL and 2 mL ± 0.5 mL/well of 12-well plates. The cell passage information (passage level, date passaged), the date cell are harvested, reagent lot and expiration information, cell count and plate lot number are recorded in the experiment write up or in a worksheet..

Cultures are processed for virus attachment, overlay and incubation for plaque development as described in this procedure from steps 2 through 8 of "Protocol for the plaque assay". Note that the virus standard described in Virus and Cell Biology Res. Proc. No. 874.3268 is not required, since the neutralization assay includes an indicator virus which serves the same purpose. Plaques are typically stained following the immunostaining method described in step IV.B of this procedure (874.3489). For experimental or evaluation purposes, plaques may also be visualized by the methods described in Virus and Cell Biology Res. Proc. No. 874.3268. Following staining and counting of the plaques, plaque counts are entered into a Microsoft Excel spreadsheet (or a functionally equivalent calculation spreadsheet) and average plaque counts for each sample are determined.

B. Plaque detection by immunostaining

Three days (72 h ± 8 h) after infection, the overlay medium is decanted and the plates are processed for immunostaining, as described in Virus and Cell Biology Research Procedure No. 874.3488 ("Immunostaining of Plaque Assays").

Briefly, the overlays are decanted onto absorbent pads or into a waste container and cells are rinsed with RCM563. The rinsed monolayers are then fixed with 90% acetone, 10% water, rinsed with RCM563 and processed for immunostaining, using sequential incubation with goat anti-mumps antibody, rabbit anti-goat IgG peroxidase conjugate, and a diaminobenzidine substrate.

V. Calculation of serum neutralization titer

A. Calculation of neutralization

The replicate plaque counts for the "no serum" control are averaged (record results to the nearest 0.01 pfu or smaller [≥2 significant digits]) and the plaque counts for the test sera are divided by this "no serum" average plaque count to calculate the "% of no serum" or "% of mock" value (record calculated % value to the nearest 0.1 or smaller [≥1 significant digits]) for each serum dilution. Percent neutralization (Nt) is calculated as [100% - (% of mock) value] (rounded to the nearest whole number). For example, if a test serum provided 25% of the pfu of the mock serum control, the % Nt is 100%-25% = 75%. The data calculation spreadsheet may include a "% Nt column" in addition to the "% of mock" column.

Unless otherwise indicated, % Nt is calculated using the "no serum" control values. An additional % Nt calculation may be made using the averaged plaque counts for a negative control serum (if applicable) or the paired pre-vaccination serum. Indicate in the experiment write up if this additional calculation is made.

B. Serum neutralization titer determination

1. The serum titer is determined as the highest tested serum dilution which provides ≥50% neutralization of virus pfu relative to the mock serum control (or a corresponding value of ≤50% of the "mock serum" value).

An alternative titer measurement is by calculation of the serum dilution providing 50% plaque reduction using a data interpolation calculation such as Reed-Muench or Karber methods. Indicate in the experiment write up if this alternative titer calculation is used, and describe the calculation or reference the calculation procedure in the experiment write up.

2. Record the serum titer results in the experiment write up. If applicable, transcribe the titers and corresponding serum identification numbers into a spreadsheet or onto a report form for report submission.

3. Record the titers of the control sera in a control table to permit monitoring of the controls.

C. Requirements for a valid test

1. No plaques may be identified in uninfected control plates
2. At least two plaque counts must be available from the set of 3 inoculated wells for each sample.

SUBJECT: Anti-IgG Enhanced Mumps
Plaque-Reduction Neutralization Assay

No.: 874.3489
Rev.: 00
Page: 10 of 10
Effective Date: 18-DEC-2000

AIGENT ASSAY INFO SHEET

Date Planted:				% Confluency			
Serum samples are thawed at 35-37C for 5-10 minutes, then heat-inactivated at 56C for 35 minutes.							
Time begin heat-inactivation:			Waterbath Temp:				
Time end heat-inactivation:			Waterbath Temp:				
Serum samples+dilutions			Serum and Virus Diluent-Maintenance Medium (MM)				
1 to 16	25ul serum+375ul MM		Final Serum dilutions:		1 to 32		
1 to 32	200ul (1:1) + 200ul MM				1 to 64		
1 to 64	200ul (1:2) + 200ul MM				1 to 128		
1 to 128	200ul (1:4) + 200ul MM				1 to 256		
1 to 256	200ul (1:8) + 200ul MM				1 to 512		
1 to 512	200ul (1:16) + 200ul MM				1 to 1024		
1 to 1024	200ul (1:32) + 200ul MM				1 to 2048		
1 to 2048	200ul (1:64) + 200ul MM				1 to 4096		
	discard final 200ul 1:2048 diluted serum						
Prep Virus Dilutions at 4X final desired dilution: when mixed 1:4 with serum+-IgG gives final dilution							
Add virus to diluted sera with an eppendorf repeat pipettor: 100ul diluted virus per tube.							
Viruses dilution scheme used in assay:							
Serum + virus incubate at 37C + 5.0% CO2 for one hour							
Time begin incubation of Virus+serum:			Incubator Temp:				
Time end incubation of Virus+serum:			Incubator Temp:				
ICN/Cappel Laboratories Rabbit IgG fraction to Human IgG whole molecule, Catalog #55008							
Lot#							
Rehydrate Anti-IgG with RCM 66: or Sterile Distilled Water							
Lot#		Exp. Date					
When lyophilized product has fully dissolves, dilute 1:6 in RCM 563, or Phosphate Buffered Saline equivalent:							
Lot#		Exp. Date:					
Record volumes used to make a 1:6 dilution of Anti-IgG (ex: 1ml anti-IgG + 5mL PBS=1:6)							
Time begin incubation of Virus+serum+anti-IgG:			Room Temp:				
Time end incubation of Virus+serum+anti-IgG:			Room Temp:				
Serum+Virus+anti IgG inoculum/well=100ul: incubate inoculated plates at 1hr for 60 minutes; rock plates at 30 minutes							
on@		Rock@		overlay@			
Maintenance Medium: Med 199, 2% heat inactivated FCS, 50ug/mL Neomycin, 2mM L-Gln Date Prepared:							
Med 199 Gibco cat#11150-059					exp. date		
FCS JRH 12103-78P lot# 8B2043			date heat inactivated		exp. date		
Neomycin Sigma cat# N-1142					exp. date		
L-Glutamine Gibco cat#25030-016					exp. date		
Overlay volume: 2mL/well							
Overlay Medium-dilute agarose 1:9 in 35C+1C MM			4.5% LGT agarose date prepared:				
Comments:							

10/25/2019
Declaration of G. Reilly
EXHIBIT 133

BB-IND 7068: MMRV

November 5, 1999

CBER Letter

Arena, D.	UN-214
Blois, D.	BLA-22
Buckland, B.	RY 80Y-370
Carfagno, P.	BLA-10
Chirgwin, K.	UN-B121
Cohen, H.	UN-B121
Dray, M.	BLA-10
Henshall, R.	WP 53C-308
Herron, M.	BLA-10
Hostelley, L.	BLB-30
Huber, E.	BLA-22
Kuter, B.	UN-C151
Mahon, K.	UN-C151
Margolskee, D.	RY 7-200
Mathews, R.	WP 42-215
Morsy, M.	UN-B121
Oppenheimer, L.	RY 33-408
Orr, B.	UN-B121
Petroski, C.	WP 28B-100
Ralls-Morrison, D.	WP 53C-312
RI-BL	UN 101
RI-R	RY86-205
Ronio, K.	BLB-30
Russo, C.	UN-B121
Sadoff, J.	UN-C151
Salerno, R.	WP 36A-212
Slater, E.	RY 33-728
Staub, J.	UN-214
Ukwu, H.	UN-B121
Verhoeven, T.	RY 80M-113
Wetzler, J.	UN-C151
Wonnacott, D.	WP 36A-212
WORF-BL	BLA-11
Zeldin, R.	UN-B121

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

1401 Rockville Pike
Rockville MD 20852-1448

OCT 26 1999

Our Reference: BB-IND 7068

Division of Vaccines and
Related Products Applications
Telephone: 301-827-3070

Merck Research Laboratories
Attn: Keith D. Chirgwin, M.D.
Director, Regulatory Liaison
Sumneytown Pike
P.O. Box 4, BLA-34
West Point, PA 19486

Dear Dr. Chirgwin:

We have reviewed your submissions of August 9, 1999 and September 1, 1999, to your **Investigational New Drug Application (IND)** for "Measles (chick embryo cells), Mumps (chick embryo cells), Rubella (WI-38 cells) and Varicella (MRC-5 cells) Virus Vaccine, Live, Attenuated," and have the following questions and comments:

With regard to the August 9, 1999, submission:

1. Please clarify that the ELISA test is an appropriate test for assessing seroconversion rates and geometric mean antibody titers (GMT) to mumps virus. Please note that false positive and false negative results are frequently observed when ELISA assays using mumps virus are used to assess antibody responses. It is essential that ELISA testing methods be validated against a working neutralization assay to demonstrate the absence of such problems. In addition, the assignment of cut-off values for the ELISA needs to be justified. Please comment.

With regard to the September 9, 1999, submission describing a post-vaccination adverse event:

2. We note that although you describe a negative spinal tap result for the affected subject, the subject experienced symptoms such as fever and seizures and laboratory parameters such as elevated lymphocyte counts which suggest that infection did occur. Infection by a wild type virus or a vaccine virus could result in the presence of virus in the CSF. Please submit results of testing of the CSF (e.g., by culture, PCR or RT-PCR) to determine the presence or absence of vaccine viruses.

DR. MANAL A. MORSY

NOV 02 1999

If you have any questions please contact Dr. Herbert A. Smith of this office at the above telephone number.

Sincerely yours,

Karen L. Goldenthal, M.D.

Karen L. Goldenthal, M.D.
Director
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

10/25/2019
Declaration of G. Reilly
EXHIBIT 134

MERCK **MEMO**

DRAFT

DATE: 01/31/02

TO: Dr. Keith Chirgwin

FROM: Dr. Patrick Brill-Edwards

SUBJECT: Filing Strategy for ProQuad

1. Program Objectives:

- Development of a quadrivalent product with similar efficacy and safety compared to the licensed products (MMR and Varivax).
- Facilitate increased varicella coverage through incorporation into MMR, which has a high coverage rate.
- Development of a refrigerator stable quadrivalent product that would enhance global use.
-

2. Product Profile:

- Indication: simultaneous vaccination against measles, mumps, rubella, and varicella in persons 12-23 months of age.
- Shelf Life: Maximum of 18 months frozen at -15°C.
- Potency:

Antigen	End expiry dose	Maximum release dose
REDACTED – OMP		
Mumps	4.3 log TCID50	*
REDACTED – OMP		

*Maximum release doses for Measles, Mumps, and Rubella have not been finalized.

** Estimated

3. Clinical Data

The total registration database includes 5376 subjects (received Varicella expiry dose ≥ 5500 PFU_{PQ}), and the safety database includes 4974 subjects (received Varicella minimum release dose of > 14,000 PFU_{PQ}). Supporting trials include Protocols 009, 011, 012, and 013 in IND 7068 (see Table 1). Protocol 009 was a high dose study, and results indicate that subjects safely tolerate Varicella at 68,000 PFU. Protocol 011, the dose selection study, provides the evidence for the end expiry dose for the components of MMRV. Protocol 012 provides evidence of manufacturing consistency and the maximum release dose for Varicella in MMRV. Protocol 013 established the safety of concomitant use of MMRV with Tripedia (DTaP) and Comvax (Hib and Hep B).

Protocol	Objective	Claim Supported	Vaccine	Antigen Potency					N receiving doses ≥ proposed expiry dose (ProQuad® formulations with VZV dose ≥ 5500 PFU_{PQ})	N receiving doses ≥ proposed minimum release dose (ProQuad® formulations with VZV dose > 14,000 PFU_{PQ})
				$Log_{10}TCID_{50}$/0.5 ml dose			Log_{10} (PFU/PFU_{PQ})/0.5 ml dose			
				Measles	Mumps	Rubella	Varicella	N	N	N
009	High Dose Safety	Safety & immunogenicity at highest release dose of varicella	ProQuad® M-M-MR ® II + VARIVAX®	REDACTED – OMP	4.9 4.9	REDACTED – OMP		323 157	REDACTED – OMP	
011	Dose Selection	Safety & immunogenicity at expiry & release doses of varicella	ProQuad® ProQuad® ProQuad® M-M-R® II + Process Upgrade Varicella Vaccine (PUVV)		4.9 4.8 4.7 5.0			387 393 381 390		
012	Consistency Lots	Safety & immunogenicity of frozen vaccine made by final process @ release dose; clinical evaluation of manufacturing consistency	ProQuad® ProQuad® ProQuad® M-M-R® II + VARIVAX®		5.0 4.7 4.5 5.0			947 947 947 946		
013	Concomitant Use with TRIPEDIA® & COMVAX®	Safety & immunogenicity of frozen vaccine made by final process @ release dose; clinical evaluation of concomitant administration of TRIPEDIA & COMVAX®	ProQuad® + COMVAX® + TRIPEDIA® ProQuad® followed by COMVAX® & TRIPEDIA® 6 weeks later M-M-R® II + VARIVAX® followed by COMVAX® & TRIPEDIA® 6 weeks later		4.7 4.7 5.0			953 476 476		
TOTAL										

4. Key Regulatory Issues

Measles-like Rashes and Fever Rates: The combination of MMRV appears to enhance the immunogenicity of measles. This resulted in an increase in the rate of measles-like rash (Protocol 009 results) and fever (Protocol 012 results) in recipients of MMRV compared with MMR + V. *Strategy to address:* The following points will be emphasized in the file and during pre-filing meetings with regulatory agencies: a) fevers and rashes observed were transient, b) the rate of fever associated with use of MMRV is similar to historical rates observed with use of other MMR containing vaccines, c) the observed rate of febrile seizures does not appear different for recipients of MMRV. A postlicensure safety study is anticipated, and an epidemiologic study of febrile seizures under different prevalence assumptions had been prepared. However, recent published evidence demonstrates that febrile seizures have no long-term adverse outcomes. Lastly, preliminary results indicate no difference in the amount of circulating measles RNA when comparing MMRV with MMR + V recipients. CBER requested RT-PCR data from Protocol 012 subjects who developed a measles-like rash, but the results will not be available until late Q202 because the assay process requires validation.

Alternate cutoffs for measles and mumps assays: CBER had indicated at the End of Phase II/Pre-Phase III meeting that specific assay criteria would be necessary in Phase III studies The outstanding issues are:

REDACTED – OMP

[redacted]

b)Justification is required for the new mumps cutoff of 10 ELISA antibody units (10 ELISA antibody units versus >= 5 gpELISA units). CBER requested that the ELISA results be compared to the mumps Plaque Reduction Neutralization (PRN) assay. CBER would like the rationale for the new cutoff to be linked to a biologically relevant reference standard.
Strategy to address: A background document is being prepared that will provide comparisons of the modified Merck mumps ELISA assay with the PRN assay in paired serum samples. This comparison should provide the evidence that the ELISA cutoff correlates the PRN. This document should be ready for submission by the end of February, 2002, and CBER's concurrence for the use of a cutoff of 10 ELISA antibody units for mumps will be by teleconference.

REDACTED – OMP

[redacted]

REDACTED – OMP

[redacted]

Maximum release dose of the MMR components: There is currently no consensus at Merck concerning the maximum release dose of the MMR components of MMRV. This has not been required for MMR II, but it is highly likely this will be required for MMRV because it is a new product with a limited safety database. The assays used to assess the potency of MMR components are variable, and this assay variability contributes to the lack of commitment to a range of release potencies. Standardizing the assays to a House Standard (HS) assay for each of the four MMRV antigens has been suggested, but CBER has not concurred with this approach.
Strategies to address: The components of this strategy are: a) use HS adjustment for lots of MMR II used in previous WAES reports, b) provide adjusted values to WPSE in order for new safety reports to be generated so that the safety database for MMR II will be relevant to MMRV, and c) incorporate the adjusted data into a proposal for CBER's concurrence on the use of HS that Biometrics has been preparing.

Licensure of MMRV 4C°: Acceptance of a frozen MMRV vaccine will be limited, but a refrigerator stable MMRV is highly desirable.
Strategies to address: Propose, as a Manufacturing Supplement, a single lot comparison of MMRV 4C° to frozen MMRV that would reduce the size of the clinical trial compared with an Efficacy Supplement (N~1200 versus N~3400). At the pre-BLA meeting, seek CBER's concurrence with this Manufacturing Supplement to the frozen MMRV license for the 4C° product, under the assumption that the frozen product will be licensed. The Manufacturing Supplement also has a shorter review period than an Efficacy Supplement (6 versus 10-12 months).

5. Worldwide Filing Strategy

USA: The pre-BLA meeting will occur in March, 2002; file for license in 4Q02, anticipate license in 4Q03. Most important additional label claim will be MMRV 4C°, plan to file as manufacturing supplement when MMRV licensed, anticipate approval 3Q04 (allowing six months for review).

EU: Will apply to EMEA for license under Centralized Procedure because MMRV is a new (and unique) combination of antigens. Will request Germany as primary rapporteur, Co-Rapporteur to be determined. Plan to meet with PEI Q202 to review scientific issues. Will send "Intention to File" notification to EMEA Q302 and will have response from EMEA regarding Merck's meeting request by September 02. Start filing procedures in March 03. Will file frozen MMRV in Canada, Australia, and New Zealand in similar time frame using CTD format.

ROW: The strategy for ROW will require further discussions within WWRA. At issue is the most appropriate way to integrate the file because it would be complicated and inefficient to file frozen MMRV in smaller markets that are highly unlikely to adopt this product. Thus, for the smaller

ROW markets, the advantage of filing frozen MMRV to which supplemental claims for a 4°C formulation and incorporation of recombinant human albumin (r-HA) is lost for practical reasons. The problem then becomes how to optimally integrate the frozen MMRV data with either the r-HA or the formulation claim, or both.

An integrated frozen/4°C file for ROW countries, with an r-HA supplement to follow may be the best approach. The market for the product will be driven by 4ºC storage. Attempting to combine 2 supplemental claims (4°C and r-HA) with the frozen MMRV data for integrated submission would result in the most complicated document for a reviewer, and therefore would likely require longer review process.

Table 1. Estimated Filing Dates for Frozen ProQuad and Supplemental Claims

Agency	MMRV	4ºC MMRV	PREVNAR Concomittant Use	2nd Dose	rHA	HEXAVAC Concomittant Use
CBER	4Q02	1Q04	TBA	?2Q03	4Q03	TBA
EU/Can-Aus-NZ	1Q03	2Q04			4Q03	
ROW	**X**	3Q04*				

* As noted, ROW will be an integrated file (a combination of data from the frozen MMRV file and at least data for the 4ºC formulation)

10/25/2019

Declaration of G. Reilly

EXHIBIT 135

MERCK
Research Laboratories

MEMO

DATE: October 19, 2001

TO: Henrietta Ukwu

Cc: D Arena, J Antonello, D Blois, J Boslego, J Bramble, B Patrick, I Chan, N Chirmule, K Chirgwin, E Emini, D Greene, D Krah, J Hartzel, J Heyes, H Matthews, D Margolskee, M Morsy, S Olsen, C Osborne, M Severino, F Schodel, T Schofield A Shaw, B Thompson, C Wadsworth and H Winterbottom

FROM: Manal Morsy

SUBJECT: CBER teleconference (October 16, 2001): Measles, Mumps and Rubella ELISAs

---

CBER participants:
Dr. Kathryn Carbone, Dr. Steven Rubin, Dr. Henry Hsu and Ms. Luba Vujcic

Merck attendees:
*Dr. Joe Antonello, Dr. Brill-Edwards Patrick, Dr. Ivan Chan, *Dr. Narendra Chirmule, *Dr. Keith Chirgwin, *Dr. Jonathan Hartzel, Ms. Holly Matthews, *Dr. Manal Morsy, *Dr. Stephanie Olsen, *Dr. Mike Severino, *Dr. Florian Schodel, and *Dr. Tim Schofield
*participants

Executive Summary:

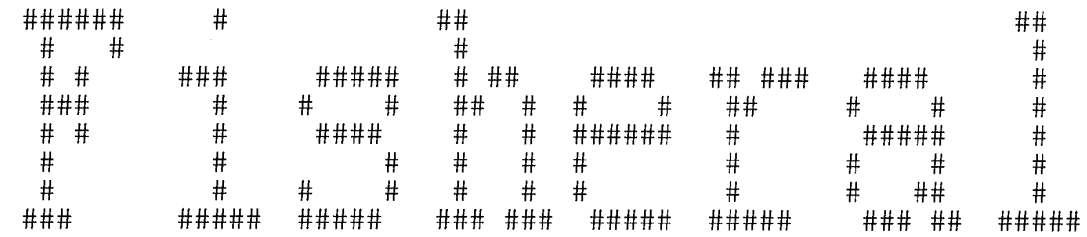
1. <u>Measles and Rubella ELISA assays</u>:
   - CBER accepted the new (modified) measles and rubella ELISA assays using WHO protective antibody cutoff and a single cutoff for sero-status evaluation. CBER concurred with the use of these modified assays in ongoing and future clinical studies.

2. <u>Mumps ELISA assay</u>:
   - CBER requests additional justification for the cutoff chosen for the mumps ELISA. The observation that the assay cutoff is sufficiently high to accurately classify pre-vaccination sera as negative is useful, but insufficient by itself as it does not relate to seroprotection.
   - Because neutralization assay results were correlated with seroprotection in early efficacy trials, CBER recommends that the ELISA cutoff be compared with the cutoff used in the PRN assay.
   - CBER requests that individual titers are identified in the relative range around cutoff in the PRN and ELISA in order to confirm that these two assays are categorizing sera in a comparable fashion.
   - CBER requests clarification regarding the reference sera used in the wild-type mumps ELISA assay as they relate to the PRN assay. Using the same reference sera in both assays will assist in the comparison of results between them.

3. <u>Statistics</u>:
   CBER will provide a list of specific clarifications requested by Dr. Hsu (CBER statistician) regarding some of the data analysis and equations used.

Assignments:
<u>A meeting is being set up for next week (week of October 22) to discuss draft responses and timeline for submission to CBER</u>

- Mumps ELISA assay and PRN assay comparison **(J Antonello)**



Job : 738
Date: 3/22/2005
Time: 2:08:17 PM

- Clarification regarding the reference sera used in the wild-type mumps ELISA assay as they relate to the PRN assay (the initials) **(D Krah - N Chirmule)**
- Individual titers are identified in the relative range around cutoff – PRN and ELISA (CBER is looking for reassurance that the controls are negative across assays) **(J Antonello)**.
- Statistics: CBER will provide a list of specific clarifications requested by Dr. Hsu (CBER statistician) regarding some of the data analysis and equations used. **(T Schofield - J Antonello)**
- Audited data prior to CBER submission **(Cathy Wadsworth)**
- Submission of summary of discussion and requested information to CBER **(M Morsy)**

Summary of discussion:

Overall CBER was satisfied with the information they had reviewed. I initiated the meeting by reviewing the highlights of the three assays in terms of the changes in each and the impact of the changes on assay performance and seroconversion rates.

The discussion was focused in the following main areas:

Wild type mumps ELISA cutoff:

CBER was generally satisfied with the assay, the following points were discussed:

- Biological relevance of the 10 Ab ELISA units cutoff:
  CBER pointed out that in the absence of a reference standard for a sero-protective level for mumps, the best we can do is try to relate the ELISA cutoff to a neutralization assay cutoff, an acceptable biologically relevant cutoff is that of the PRN assay. CBER requests a comparison between the PRN and the ELISA cutoff.
- Assay variability and true seroconversion around the cutoff:
  CBER requested clarification on how we would be able to distinguish 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. ≤ 1.25 pre to ≥ 5 post).

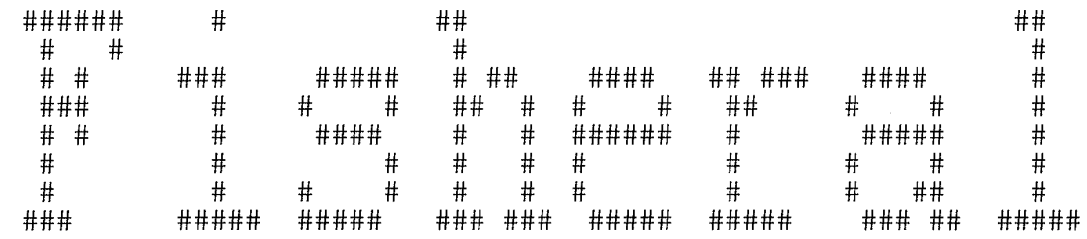
Merck response:

- Biological relevance of the 10 Ab ELISA units cutoff:
  The closest we can get to a biologically relevant evaluation is exactly what was used in defining the cutoff, which is the use of a large panel of samples at or close to pre-positivity. This evaluation - at the 10 Ab ELISA unit cutoff - provided data consistent with expected results (meeting expectations of pre-vaccination samples), and therefore the cutoff can reasonably distinguish between pre-vaccination negative and post-vaccination positive samples.

  CBER was not satisfied with the rationale as this does not relate the cutoff in any fashion to seroprotection but rather is circular in that Merck is verifying that Merck's historical experience with the legacy ELISA assay is consistent with the outcome of this new assay.

  We then reviewed with CBER data generated from a comparison performed between 600 PRN samples and the wild - type mumps ELISA data from the End Expiry study (protocol 007). The results suggest an overall 92% correlation, with 42 discrepancies of which 36 positive in PRN and negative in ELISA and 6 positive in ELISA and negative in PRN.

  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.



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Date: 3/22/2005
Time: 2:06:44 PM

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.

CBER requested that we provide them with the data for their review followed by further discussions to reach an agreement on the assay cutoff.

- Assay variability and true seroconversion around the cutoff:
  In terms of CBER's question regarding the ability to distinguish between assay variability and true titer differences around the cutoff threshold, Merck noted that misclassification due to variability around the cutoff should operate in both directions (i.e. negatives misclassified as positives and vice versa). Therefore, this should balance out in the context of the large clinical studies Merck conducts, with limited impact on overall results.

  Merck also noted that in case of the Varicella gpELISA, titer determination and discrimination can be done at low dilutions used in that assay, however, that is not possible in case of the wild type mumps ELISA due to the dilution effects seen below the 10 Ab ELISA unit cutoff.

It should be noted that if the questions about the 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 rise criterion, as that would be necessary to demonstrate 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 sero-protection.

Reference sera and controls:

- CBER requested clarification on the standards and reference sera used in the development of the wild-type mumps ELISA and whether they were the same standards and reference sera used in the development of the PRN assay.

  Information regarding the reference sera and the internal standards used will be provided to CBER.

Measles and Rubella ELISAs:

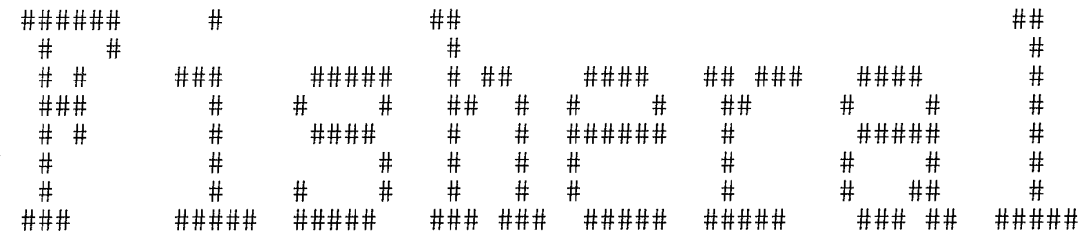
- CBER indicated that they were comfortable with established cutoffs such as in the case of measles and rubella were there is biological meaningfulness and accepted these two assays acknowledging that Merck is using them in ongoing studies and will be using them in future studies.

  CBER asked if the data provided in the background document was officially submitted to CBER. We advised them of the official submission (October 10, 2001, serial # 072) and Ms. Luba Vujcic confirmed that she had received the document submitted to BB IND 1016.

Post teleconference communication with CBER:
I contacted Luba Vujcic after the teleconference to inquire about the PRN evaluation that is ongoing in Dr. Carbone's laboratory. Specifically to ow weather CBER expects us to go ahead with the correlation studies requested between the PRN assay results and the wild type mumps ELISA results (End Expiry - Protocol 7) with the data at hand or if we should wait until we receive the results of their investigation. Luba indicated that Dr. Carbone suggests we conduct the correlation with the data on file - she has no real sense yet for when the investigation / evaluation in her lab will be completed.

M.Morsy
x3785

cc: file



Job : 734
Date: 3/22/2005
Time: 2:34:15 PM

10/25/2019
Declaration of G. Reilly
EXHIBIT 136

Dekleva, Michael L.

From: Fisher, Alison L
Sent: Tuesday, October 26, 2004 6:32 PM
To: Dekleva, Michael L.
Subject: RE: Mumps ELISA

Mike-

Thanks for the sending the slides.

In my opinion, I think we need to look at the points just below, at, and above the cut-off and else where there is disagreement between the assays.

PRN is functional assay--correlate of protection. ELISA is not a functional assay but an antibody assay.
We need to convince CBER that the ELISA will provide equivalent results to PRN and thus equate (bridge) to protection.

The ELISA assay may slightly overestimate seroconversion when compared to the AIGENT assay based on data from protocol 007 (94.8% seroconversion in the ELISA versus 92.8% seroconversion in the AIGENT assay). This could cause uncertainty if the seroconversion rate were by chance to approach 90% for a given clinical study. In this case, a conservative measure of seroconversion could possibly be defined as >8 fold rise for pre-vaccination positives. This could possibly lower the overestimate of seroconversion of the ELISA (this is last paragraph of attached doc below).

I have discussed this in the attached document. I will delve into further statistical details and add.

Preparation for CBER question ...

Alison

-----Original Message-----

From: Dekleva, Michael L.
Sent: Tuesday, October 19, 2004 10:52 AM
To: Fisher, Alison L
Subject: Mumps ELISA

O.K. Alison, here's a summary of the CBER memo and what I think they're looking for. Let me know if you agree. Seems like a subtle point, and they could have asked in a simpler way if it is (which is why I'm wondering if I'm off track!).

Mike

<< File: Mumps ELISA 19Oct2004.ppt >>

Michael L. Dekleva, Ph.D.
Director, World Wide Regulatory Affairs, Vaccines/Biologics
Phone: (484) 344-2789
FAX: (484) 344-2962
e-mail: michael_dekleva@merck.com

Correspondence with CBER regarding: 1) cut-off for Merck WT ELISA and 2) supporting documentation for equivalence between the AIGENT and ELISA assays.

In correspondence with CBER (June, 10, 2002: Morsy to Zoon, serial # 86) Merck conducted a comparison between standard and control sera used in the routine operation of the Mumps WT ELISA (Described in Feb 2, 2001: Morsy to Zoon, serial # 62, SOP 910-0096) and the AIGENT assay (Described in March 12, 2001: Morsy to Zoon, serial # 63, SOP # 874.3489). Also, AIGENT control samples were tested in the Mumps WT ELISA assay (serial #86).

Based on this data (all data submitted previously to CBER in serial #86), there is good agreement between the AIGENT and Mumps WT ELISA assays with regard to performance of controls and standards. The low positive controls, high positive controls, ELISA negative control, and ELISA standard performed similarly in both assays relative to the cutoff of 10 ab Units in the Mumps WT ELISA and a cutoff of 1:32 in the AIGENT assay.

In this same correspondence, CBER requested Merck to provide additional justification of the cut-off point (limit of assay) of the Mumps WT ELISA by providing identification of titers around the cut offs of both assays to confirm that both assays are categorizing sera in a comparable fashion. In this process, cut-off points were defined that simultaneously minimized the "false positive" and false negative rates observed in validation samples when comparing the two assays.

AIGENT and Mumps WT ELISA pre-vaccination and Day 42 post-vaccination titers from 1023 subjects in the Protocol 007 trial were compared using a serostatus cut off of 10 ab units in the ELISA and cut off of 32 in the AIGENT assay. There is good agreement between the mumps WT ELISA and the AIGENT assays in terms of serostatus classification when using these cut-offs (data submitted previously in serial # 86). Despite variability inherent in biological assays the overall agreement between the two assays based on data from the 007 trial is 90.4% (925/1023).

Despite good agreement, differences in the assays were observed depending on whether the sample was pre or post vaccination; a prevaccination sample was more likely to be classified as sero-positive in the AIGENT assay than in the ELISA assay and post-vaccination sample the reverse; higher likiehood of positives in the ELISA versus the AIGENT assay (93% positives in the AIGENT assay versus 95% positives in the ELISA and 92.8% seroconversion in the AIGENT assay versus 94.8% seroconversion in the ELISA assay).

Of discordant pairs of pre-vaccination samples, the pre positive rate was 12% (61/510) in the AIGENT assay and 2% (10/510) in the ELISA assay. Thus, for prevaccination samples, there is statistical evidence that a discordant pre vaccination pair is more likely to be positive in the AIGENT assay relative to the ELISA assay. It should be considered that a greater proportion of samples would be excluded from analysis using the AIGENT assay.

Conversely, for post-vaccination sera, the trend is reversed. Of 33 discordant pairs pairs, 22 were positive in the ELISA, but negative in the AIGENT assay, and 11 were negative in the ELISA but positive in the AIGENT assay. However, the test for imbalance approached but did not attain statistical significance (data presented in serial # 86). The trend was the same for sero-conversion; of 29 discordant pairs 19 seroconverted in the ELISA assay versus 10 in the AIGENT assay (pre-post vaccination rise $\geq$ to 4-fold). Again, the imbalance approached but did not reach statistical significance.

Possible reasons for imbalance at the cut-off between pre and post vaccination sera:

Although not specifically described in any report, the fact that a pre vaccine sample is more likely to be positive by AIGENT could be accounted for by a 12% pre-positive rate using titer of 1:32 as observed in the validation (data in serial #62).

That post-vaccination samples are slightly less likely to be classified as positive in the AIGENT versus the ELISA, could be accounted for by titers in the ELISA increasing with each 10-fold dilution, with the magnitude of the effect being sample specific (data in serial #62).

Also, the precision of the ELISA and AIGENT assay are not equivalent. Although precision appears to be constant across range of titer, intra and inter-assay variability precision estimates for the AIGENT assay (%RSD) are 38.7 and 42.9% respectively; ELISA, intra and inter-assay variability precision estimates (%RSD) are 18.9 and 25.3% respectively.

Thus, biological effects unique to each assay could contribute to the imbalance observed at the cut-off between pre-vaccination and post-vaccination sera.

Driver for use of the WT ELISA in place of the AIGENT Assay.

The WT Jeryl Lynn passage 8 virus is used in both assays. Both assays have an agreement rate of 90% between two assays (925/1023) with 469 samples classified as positive in both assays and 456 samples characterized as negative in both assays. Thus, both assays are categorizing sera in a comparable fashion and both are reliable detectors of protective antibody response. The driver for using the ELISA assay over the AIGENT assay is better precision in the ELISA than the AIGENT assay and higher throughput in the ELISA compared to the AIGENT assay.

Low risk issue: The ELISA assay may slightly overestimate seroconversion when compared to the AIGENT assay based on data from protocol 007 (94.8% seroconversion in the ELISA versus 92.8% seroconversion in the AIGENT assay). This could cause uncertainty if the seroconversion rate were by chance to approach 90% for a given clinical study. In this case, a conservative measure of seroconversion could possibly be defined as >8 fold rise for pre-vaccination positives. This could possibly lower the overestimate of the ELISA.

Comparison between the AIGENT and ELISA assays

	Antigen	Specificity	Precision	Ruggedness	Cut-off	Dilatability
ELISA	WT Jeryl Lynn passage 8 virus	Specific in presence of measles and rubella, specific for mumps antisera.	Constant across range of tier response. Overall intra and inter-assay variability precision estimates (%RSD) are 18.9 and 25.3% respectively.	No effect of operator.		Titers increased on average by 23.8% with each 10-fold dilution. The magnitude of the effect sample specific.
PRN	WT Jeryl Lynn passage 8 virus	Specific in presence of measles and rubella, specific for mumps antisera.	Constant across range of tier response. Overall intra and inter-assay variability precision estimates (%RSD) are 38.7 and 42.9% respectively.	Rugged for incubator. Not assessed for operator but is believed to be operator rugged.	12% pre-positive rate using titer of 1:32.	

10/25/2019

Declaration of G. Reilly

EXHIBIT 137

Alison L. Fisher, Ph. D.
Associate Director
Worldwide Regulatory Affairs
Vaccines/Biologics

Merck & Co., Inc.
P.O. Box 4, BLB-22
West Point PA 19486-0004
Tel 484 344 3761
Fax 484 344 2962
Email:alison_fisher@merck.com

April 13, 2005

MERCK
Research Laboratories

Norman Baylor, Ph.D.
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review (HFM-400)
Document Control Center (HFM-99)
Woodmont Office Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

Dear Dr. Baylor:

Measles, Mumps, and Rubella Virus Vaccine Live
(M-M-R®II)

STN 101069/5061

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to a letter from CBER on December 3, 2004 regarding the above supplement. In addition to Merck responses, the letter from CBER is attached for your convenience.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

We appreciate your time and consideration in this matter. Should you have any comments or questions regarding the responses provided, please address them directly to me at (484) 344-3761 or in my absence, Dr. Ercem Atillasoy at (484) 344-7811.

Sincerely yours,

MD ATILLASOY for Fisher

Alison Fisher, PhD.
Associate Director
Worldwide Regulatory Affairs
Vaccines and Biologics

Attachment
References on attached CDs
Federal Express

Q:\Winterbottom\Responses to CBER for MEE 2005

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2006
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck & Co., Inc.	April 13, 2005
TELEPHONE NO. *(include Area Code)*	FACSIMILE (FAX) *Number (include Area Code)*
(484) 344-3761	(484) 344-2962
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Sumneytown Pike, P.O. Box 4, BLB-22, West Point, PA 19486-0004	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* STN# 101069

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Measles, Mumps and Rubella Virus Vaccine Live	M-M-R® II

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*

CODE NAME *(If any)* V205C

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	Measles/1,000 TCID (50) per 0.5 mL Dose Mumps/20,000 TCID (50) per 0.5 mL Dose Rubella/1,000 TCID (50) per 0.5 mL Dose	S.C.

(PROPOSED) INDICATION(S) FOR USE:
MMR® II is indicated for simultaneous vaccination against measles, mumps and rubella in persons 15 months of age or older.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☒ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUALREPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT *(Rx)* ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 356h (9/02)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CIFIR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601-2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or 0)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
✓	20. OTHER (Specify) Responses to Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contra i nd ications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Alison L. Fisher	Alison L. Fisher, Ph.D. Associate Director Worldwide Reg. Affairs/Vaccines Biologics	April 13, 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Sumneytown Pike, P.O. Box 4, BLB-22 West Point, PA 19486-0004	(484) 344-3761

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Response 1

Response 1

1. Please describe the purpose and underlying rationale for proposing a reduction in potency of the mumps component of the approved product, MMRII.

Response:

The rationale for proposing a reduction in the potency of the mumps component of M-M-R®II has been discussed during a series of meetings, teleconferences and in correspondence between CBER and Merck since 1997.

Briefly, during discussions between CBER and Merck in 1997, it was recognized that the minimum release potency specification for mumps in M-M-R®II in place at the time (4.3 $\log_{10}$ $TCID_{50}$), did not provide assurance that the labeled mumps potency was maintained through the end of shelf life in all lots released to the market. It was also recognized that providing such assurance would require increasing the targeted mumps potency to levels substantially above the historical marketed experience. The rationale for initially proposing a reduction in the end expiry potency of the mumps component of M-M-R®II in 1997 was to align the mumps potency specifications (at release and end-expiry) with potencies actually reflective of the previous marketed experience with M-M-R®II (i.e. target release 4.9 $\log_{10}$ $TCID_{50}$).

Given the amount of time which has elapsed since some of these discussions took place and the change in personnel over this period, a brief recapitulation of the previous discussions and agreements may be helpful in understanding the rationale and the approaches taken in Protocol 007.

Previous discussions and correspondence:

- A face-to-face meeting between CBER and Merck was held on December 16, 1997 to discuss label claims for mumps potency in M-M-R®II. Slides presented by Merck at this meeting included a proposal for a clinical trial to investigate mumps immunogenicity at an end-expiry dose consistent with the EP mumps potency specification (3.7 $\log_{10}$ $TCID_{50}$). At this December 16, 1997 meeting CBER requested a draft of Merck's clinical trial protocol designed to support the end-of-shelf life titer for mumps.

- A letter from Dr. Garfinkle to Dr. Hardegree dated January 28, 1998 included a summary of the December 16, 1997 meeting. This correspondence included slides presented by Merck at the December 16, 1997 meeting.

- A letter to BB-IND 1016 (Dr. Chirgwin to Dr. Zoon, general correspondence, serial # 024) dated June 23, 1998 included as an attachment a draft protocol for a clinical trial to support a lower expiry potency for the mumps component of M-M-R®II which was submitted for CBER's assessment and concurrence.

- CBER provided comments on the End Expiry Protocol 007 in a letter to Merck dated September 8, 1998.

- A letter from Dr. McKee to Dr. Egan dated June 18, 1999 stated that Merck had undertaken a clinical study, initiated February 1999, to evaluate the immunogenicity of mumps at potencies lower than the existing expiry claim and that once these clinical studies were completed, the label claim would be re-evaluated and any proposed change would be submitted for CBER review and approval.

- A letter from Dr. McVittie to Dr. McKee dated August 20, 1999 summarized telephone conversations held on August 10, 1999 and August 16, 1999 between Merck and CBER (Dr. Baylor , Dr. S. Rastogi and Ms. Vujcic) to discuss increasing the minimum release titer for the mumps component to 5.0 $\log_{10}$ $TCID_{50}$.

- A prior approval supplement was filed October 20, 1999 and approved February 11, 2000 to increase the target mumps potency from 4.9 to 5.2 $\log_{10}$ $TCID_{50}$ with minimum release potency specification of 5.0 $\log_{10}$ $TCID_{50}$. In the context of discussions about this PAS, it was acknowledged by both Merck and CBER that when data from a mumps end expiry trial became available, the mumps end expiry potency claim would be reassessed. During a telephone conversation between Ms. K. Abraham and Dr. N. Baylor on February 9, 2000 (prior to approval of the mumps overfill PAS), CBER noted that the manufacturing change in terms of increased mumps potency was viewed as an interim measure pending completion of the mumps expiry trial.

<u>Summary</u>

The purpose and underlying rationale of this file is to provide clinical data supporting a reduction in expiry potency of the mumps component for M-M-R®II. This clinical data provides evidence that a mumps end expiry potency of 4.1 $\log_{10}$ $TCID_{50}$ dose in M-M-R® II at the end of its shelf life is not statistically different to that of the product at release [based on Mumps Plaque Reduction Neutralization (PRN) assay used as a surrogate marker for vaccine efficacy].

Response 2

Response 2

2. You state in module 2, page 7, that the mumps potency assay initially used primary green monkey kidney cells (BSC-1) and was later changed to Vero cells, resulting in higher mumps titers and revisions of the end-expiry potency from 3.7 to 4.3 log10 TCID50 per dose. You also state on page 7, section 2.5.1.4.3, Evolution of the Mumps End-Expiry Potency Value, of the same module; "Since the original end-expiry dose had been set conservatively, it was assumed that a mumps potency below 4.3 log10 TCID50 per dose would be equally immunogenic." Please provide the rationale and calculations used to determine the maximum acceptable reduction in mumps potency.

Response:

The clinical data used to guide selection of candidate end-expiry doses for evaluation in Protocol 007 were derived from two mumps vaccine dose response studies. These studies were conducted in 1967 and involved a total of 99 initially seronegative children, age 11 months to 12 years (average 4 years) who were immunized with mumps vaccine with potency ranging from 31,700 (4.5 log) to 10 (1.0 log) $TCID_{50}$/dose [Buynak, EB; Hilleman, MR; Leagus, BM; et al. Jeryl Lynn Strain Live Attenuated Mumps Virus Vaccine. JAMA 1968 Jan 1; 203(1): 9-12].

All 74 subjects who received mumps vaccines with titers ranging from 317 (2.5 log) to 31,700 (4.5 log) $TCID_{50}$/dose had detectable mumps-specific antibodies, while seroconversion was observed in 75% to 78% of subjects immunized with Mumps vaccine titers between 10 (1 log) and 100 (2.0 log) $TCID_{50}$/dose. Moreover, the latter group also exhibited lower GMTs in comparison to individuals immunized with higher Mumps vaccine titers (>317 $TCID_{50}$/dose).

Based on these clinical data, the minimum immunizing dose for mumps vaccine could be considered to be the lowest potency associated with 100% seroconversion rate, i.e. at 317 (2.5 log) $TCID_{50}$/dose, corresponding to 1,268 (3.1 log) $TCID_{50}$/dose in Vero cells (currently used cell substrate for the measurement of Mumps potency).

The mumps end expiry titer was conservatively set at 5000 (3.7 log) $TCID_{50}$/dose (this would be equivalent to 20,000 or 4.3 log $TCID_{50}$ in Vero cells), representing an approximate 15-fold increase above the potency determined as the minimum immunizing dose. We are not aware of specific calculations which support the need for a 15-fold margin above the minimum immunizing dose; it is our understanding that this margin was incorporated in part to address possible assay variability. The potency assay format and our understanding of assay variability have evolved since the 1960's when these mumps dose-ranging studies were conducted. The mumps doses of the expiry lots evaluated in Protocol 007 had assigned potencies which were 0.7 log and 1.0 log $TCID_{50}$/dose above the minimum immunizing dose of 3.1 log $TCID_{50}$/dose (in Vero cells).

Response 3

Response 3

3. You state that the oGOS stabilizer was developed in response to the European Pharmacopoeia requirement to demonstrate thermal stability of MMRII (module 5, page 30, last paragraph) and you have data on file, not provided in this BLA supplement, that supports the similarity in vaccine immunogenicity between MMRII manufactured GOS and MMRII manufactured with oGOS (module 2, pages 9-10). Please submit this data to the file.

Response:

A report comparing the immunogenicity immunogenicity between M-M-R®II Manufactured with GOS and M-M-R™II manufactured with oGOS was provided as part of the BLA supplement. Data from M-M-R™II manufactured with oGOS were derived from M-M-R™II Protocol 007 (Mumps End-Expiry clinical trial) and data from M-M-R®II manufactured with GOS were derived from several studies in which M-M-R®II was used as control during the development of ProQuad™ or VARIVAX™. Data from the latter studies that were not included in this BLA supplement are provided in this response in the attached CD as SAS transport files.

Response 4

Response 4

4. Please provide data demonstrating that the immunogenicity observed using the heat-aged oGOS-containing, live viral vaccine (oGOS reportedly added to enhance thermal stability), can be used to determine end-expiry of the non-heat-aged, non-oGOS containing licensed vaccine.

Response:

The rationale for demonstrating that the immunogenicity observed using the heat-aged oGOS-containing, live viral vaccine (oGOS reportedly added to enhance thermal stability) can be used to determine end-expiry of the non-heat-aged, non-oGOS containing licensed vaccine has been discussed during a series of meetings, teleconferences and correspondence between CBER and Merck since 1998. These communications are summarized (below).

Previous discussions and correspondence:

- CBER provided comments on End Expiry Protocol 007 in the letter to Merck dated September 8, 1998 that included the statement "if vaccine near expiry is unavailable, artificially aged vaccine would be acceptable".

- In a letter to BB-IND 1016 (Dr. Morsy to Dr. Goldenthal, Request to FDA Request for information, Serial # 052) dated December 30, 1999 Merck provided justification for using vaccine formulated with oGOS to set a release titer of vaccine formulated with GOS stabilizer.

- During a teleconference on November 29, 2000 (CBER participants K. Carbone, S. Rubin, H. Hsu, J. Beeler, C. Atreya, L. Vujcic) to discuss Protocol 007, CBER acknowledged that Merck did not plan to file oGOS. Dr. K. Carbone indicated that if antibody response data with the oGOS formulation were consistent with historical antibody response data with the GOS formulation, then this would support use of the clinical data from the expiry trial.

- In a letter to BB-IND 1016 (Dr. Morsy to Dr. Zoon, Response to FDA Request for information, Serial # 062) submitted February 2001, Merck responded to CBER's guidance provided during the November 29, 2000 teleconference regarding approach to bridging between the current GOS and the oGOS stabilizer formulations with historical serologic data. To enable this assessment, Merck proposed a descriptive analysis to link the oGOS clinical data with the historical GOS data.

Summary

Based on the above correspondence and the rationale summarized below (rationale communicated previously- BB-IND 1016 Serial # 052), immunogenicity data provided by this study can be used to support the end expiry mumps potency titer and can be applied to vaccine formulated with either stabilizer for the following reasons:

- The reconstituted vaccine has no new components and the same target potencies as current product.
- Differences between the two vaccine formulations are minor (different concentrations of sucrose and sorbitol), occur during manufacture of the final product, and are component concentration differences with out the deletion of an active component or the addition an active component.
- There is no difference between current formulation and oGOS product in the processing losses through filling and lyophilization.
- Subsequent to the aging at room temperature to achieve the targeted potencies to be tested, the vaccine used in this clinical trial was stored frozen at -20°C to ensure that that there was no change in the determined potency of the lots, thus, improvement in thermal stability achieved by the use of oGOS was not realized under conditions of the study.

To summarize, the changes in the stabilizer represented by the oGOS formulation are not deemed relevant to the design or outcome of this study.

Response 5

Response 5

5. **You have submitted an additional study report in Module 5, volume 5, section 5.3.5.4, to support the proposed change in mumps end expiry potency. We note these post hoc analyses compare ELISA data but not PRN data, and include populations receiving various concomitant vaccinations including MMRV (an earlier formulation of ProQuad™) and ProQuad™. Furthermore, you do not describe a specific statistical approach for performing this comparability bridging study, nor indicate the assay methods and standards used in each of the comparator groups. It does not appear that these data support the proposed change in mumps end expiry potency. Please comment.**

Response:

The approach for demonstrating that the immunogenicity observed using the heat-aged oGOS-containing, live viral vaccine can be used to determine end-expiry of the non-heat-aged, non-oGOS containing licensed vaccine was discussed and agreement on approach reached during teleconferences and correspondence between CBER and Merck since 1998. These communications are summarized below.

Previous discussions and correspondence:

- CBER provided comments on End Expiry Protocol 007 in the letter to Merck dated September 8, 1998 that included the statement "if vaccine near expiry is unavailable, artificially aged vaccine would be acceptable".

- In a letter to BB-IND 1016 (Dr. Morsy to Dr. Goldenthal, Request to FDA Request for information, Serial # 052) dated December 30, 1999 Merck provided justification for using vaccine formulated with oGOS to set a release titer of vaccine formulated with GOS stabilizer.

- During a teleconference on November 29, 2000 (CBER participants K. Carbone, S. Rubin, H. Hsu, J. Beeler, C. Atreya, L. Vujcic) to discuss Protocol 007, CBER acknowledged that Merck did not plan to file oGOS. Dr. K. Carbone indicated that if antibody response data with the oGOS formulation were consistent with historical antibody response data with the GOS formulation, then this would support use of the clinical data from the expiry trial.

- In a letter to BB-IND 1016 (Dr. Morsy to Dr. Zoon, Response to FDA Request for information, Serial # 062) submitted February 2001, Merck responded to CBER's guidance provided during the November 29, 2000 teleconference regarding approach to bridging between the current GOS and the oGOS stabilizer formulations with historical serologic data. To enable this assessment, Merck proposed a descriptive analysis to link the oGOS clinical data with the historical GOS data.

As discussed previously (Serial # 062) in the final bridging study report, the definition of seroconversion and the type of assays used were provided for each study.

This observational analysis was proposed prior to unblinding the clinical database for Protocol 007. The comparative analysis was conducted using ELISA data because the PRN assay had only been developed and used for the primary endpoint of the Mumps End-Expiry clinical trial as discussed with CBER. The ELISA remains the accepted method for the measurement of vaccine-induced immunity to mumps and was used for other endpoints. We agreed with CBER to perform only ELISA for the persistence (1-year) immunogenicity endpoint since a strong correlation had been demonstrated between mumps ELISA and PRN assays.

CBER requested the mumps ELISA seropositive cutoff be justified via use of known mumps neutralizing and non-neutralizing sera. Merck submitted these data (June 2002, serial # 86) and believes that they provide helpful supportive information on the clinical relevance of the chosen ELISA cutoff for seropositivity.

Response 6

Response 6

6. You propose to use accelerated stability data instead of real-time stability data to compare various subpotent lots to licensed product that meets release specifications in order to support a change in end-expiry potency specification.

a. Please describe the rationale and/or data to support the use of accelerated stability testing of test lots in lieu of real-time stability for this particular product and its components.

b. Please describe how the chosen temperature range and durations of exposure were validated as representative of real-time stability for this particular product and its components.

Response:

a. Please describe the rationale and/or data to support the use of accelerated stability testing of test lots in lieu of real-time stability for this particular product and its components.

The rationale to support the use of accelerated stability testing of test lots in lieu of real-time stability of this licensed product was based on the fact that no vaccine lots with potencies at or near the proposed expiry dose were available. In this context CBER provided comments on the End Expiry Protocol 007 in a letter to Merck (Dr. Hardegree to Dr. Chirgwin) dated Sept 8, 1998 that included statement "if vaccine near expiry is unavailable, artificially aged vaccine would be acceptable".

b. Please describe how the chosen temperature range and durations of exposure were validated as representative of real-time stability for this particular product and its components.

The rationale for accelerated aging was based the assumption that the decline in measured mumps potency over time (due to a biological loss of virus infectivity) was identical to the loss of infectivity observed at 2-8 °C, differing only in rate.

This can be demonstrated by graphing the observed potency for a stability lot of M-M-R®II over time at various temperature conditions (see Figure 1). Additionally, the mumps potency result for lot 0626290 (real time aged expiry time point) is comparable (within the range of assay variability) to the potency value of accelerated aged material used in the end-expiry clinical trial (Figure 2).

Figure 1: Arrhenius Plot of Mumps Stability: potency loss/time versus temperature for the mumps component in M-M-R®II.

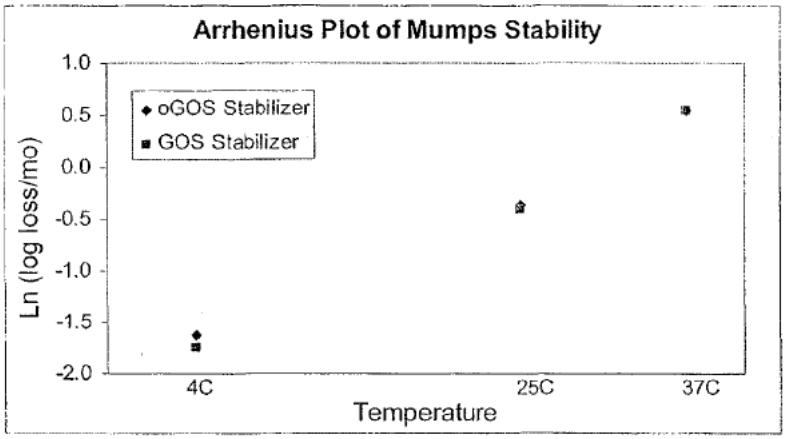


Figure 2: Mumps potency of clinical lot (accelerated aging) compared to same lot aged for two years at 5°C.

Lot 062690, Mumps potency	
Stability result 24 month, 5°C (Log $TCID_{50}$/dose)	Clinical lot 1579-W-E724 (Log $TCID_{50}$/dose)
4.12	4.1

Response 7

Response 7

7. In Module 5, pages 19 and 31, section 1.2.2.2, Minimum End-Expiry Potencies, you describe the recalculation of previously assigned potencies for each of the sublots of clinical material used in this study due to a reassignment of the mumps House Standard "based upon several studies performed at Merck & Co., Inc."

a. Please describe the purpose (s) of the referenced studies.

b. Please explain why a new house standard was created.

c. Please indicate the date the new standard was instituted with respect to the conduct of this study and data analysis.

d. Please describe the impact of the new standard on the study endpoints compared to the results that would have been obtained with the old standard.

Response:

a. Please describe the purpose(s) of the referenced studies.

In the mumps infectivity potency assay, historically, the mumps house standard served as a quality control and was assayed along with unknowns (M-M-R®II lots). If the house standard potency fell within the control limits for a particular assay run, that assay was deemed acceptable for reporting purposes. In general, preliminary control limits for each of the three house standards were calculated as the average and 95 percent confidence control limits (two standard deviations) of at least 30 valid assay runs. Mumps potencies (unknowns) were assigned based on their observed (uncalibrated) potencies in the assay. This method for reporting mumps potency did not account for the shifts and drifts in the assay on any particular day of analysis.

The mumps house standard potency was reassigned from 4.2 to 4.3 $\log_{10}$ $TCID_{50}$/0.1 mL based on 3064 thousand assay runs over about 8 years. The reassigned house standard serves both as an assay control and calibration standard that normalizes unknown potency values to compensate for the assay running high or low on any particular day. This was reported in a manufacturing PAS approved by CBER 18-May 2004 (*Measles Formulation and Potency Assay Format Changes to Support Potency Through Twenty-Four Month Expiry*, STN: BL 101068/5029, 101069/5034, 101078/5029).

b. Please explain why a new house standard was created.

A new mumps house standard was not created; its potency was reassigned from 4.2 to 4.3 $\log_{10}$ $TCID_{50}$/0.1 mL, as discussed in 7a (above). Implementation of the reassigned house

standard and calibration of measles, mumps and rubella potencies to house standards was reported in the manufacturing PAS referenced in 7a.

c. Please indicate the date the new standard was instituted with respect to the conduct of this study and data analysis.

There was no effect on the conduct or results of the study. After the study was completed, the previously assigned potencies for each of the sublots of clinical material were retrospectively reassigned based on reassignment of the mumps House Standard. The expiry specification for mumps as demonstrated in Protocol 007 ≤4.0 log10 TCID50/dose segment would be 4.1 log10 TCID50/dose using mumps house standard calibration with an assigned potency of 4.3 log10 TCID50/0.1 mL.

d. Please describe the impact of the new standard on the study endpoints compared to the results that would have been obtained with the old standard.

The change in assigned potency would raise all of the original calibrated data (calibrated using 4.2 $\log_{10}$ $TCID_{50}$/0.1 mL) by 0.1 $\log_{10}$ $TCID_{50}$/dose.

Response 8

Response 8

8. Regarding the mumps PRN assay, module 5, page 81, Clinical Study Report section 5.8.1.3, Changes to Seronegative and Seroconversion Definitions, states: "It was expected that ~ 75% of the samples would be titered to endpoint (1:4096), reported as titer of ≥ 1:4096, and assigned a value of 1:4096 for analysis...and median titers would be provided along with geometric mean titer (GMT) summaries."

Response:

The statement in module 5, page 81, Clinical Study Report section 5.8.1.3 was incorrect. It stated:

"In addition, since it was expected that ~75% of the samples would be titered to endpoint (1:4096), reported as titer of ≥1:4096, and assigned a value of 1:4096 for analysis, the amendment stated that median titers would be provided along with GMT summaries."

The upper limit of the mumps plaque reduction neutralization assay was 1:4096. It was expected that ~75% of the samples would be titered to endpoint (have a titer <1:4096). Samples that were not titered to endpoint were assigned a value ≥1:4096. The proportions of subjects that were not titered to endpoint were 33.8%, 34.4%, and 31.6% for the 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency groups, respectively.

The primary endpoint on which the primary hypotheses and conclusions were based was the percent of initially seronegative subjects who developed neutralizing antibodies to mumps (≥4-fold rise in antibody titer, i.e., 1:16 to 1:64 where 1:16 is assigned to titers below 1:32, the limit of detection) 6 weeks postvaccination. Thus, the upper endpoint titer of 1:4096 did not affect the evaluation of the primary endpoint for the study. The GMTs and median titers were summarized to provide additional descriptive statistics, but were not a part of the primary hypotheses.

Response 9

Response 9

9. In Module 5, Clinical Study Report, Page 20, the table indicates that there are differences in the assays of the accelerated stability sublots as compared to the product control lot.

a. Footnote "§" describes "estimated mumps virus potencies" for sublots 1 and 2 (accelerated stability lots) and "actual mumps virus potency" for sublot 3. Please explain why analysis of the accelerated stability lots differs from that of the licensed product and describe the rationale for comparing data that are derived differently.

b. Footnote "t t" indicates that the point estimates for the control group are listed, although the table header indicates the values are 95% Upper Confidence Bounds. Please explain this discrepancy.

c. Footnote "#" indicates that the licensed product control assays were conducted in a different format that the accelerated stability sublots assays, i.e., the parent lot was assayed as 3 replicates performed on 1 day, while accelerated stability product sublots were assayed once on 6 separate days; also the licensed control product result is reported out to 1 decimal place while the accelerated stability sublots are reported out to 2 decimal places. Please explain why all sublots were not assayed simultaneously using the same format.

Response

a. Footnote "§" describes "estimated mumps virus potencies" for sublots 1 and 2 (accelerated stability lots) and "actual mumps virus potency" for sublot 3. Please explain why analysis of the accelerated stability lots differs from that of the licensed product and describe the rationale for comparing data that are derived differently.

Sublots 1 and 2 were accelerated stability lots derived from a common parental lot (Sublot 3) and were assigned a mumps potency based on regression analysis of multiple assays across the aging process. Sublot 3 was assigned its potency using the conventional release practice for any manufactured lot. Both are legitimate approaches to defining the potency of lots of product (under each design), and thereby comparable. Merck is proposing the use of the upper 95% confidence bound on the potency estimate for sublots 1 and 2 in order to provide a conservative value for the expiry potency. In order to obtain more precise estimates of the accelerated aged sublots, the potency data obtained during aging of the lots were used. It should be noted that the potency assay did not differ, only the calculation method to reduce the error of the estimate.

b. Footnote "† †" indicates that the point estimates for the control group are listed, although the table header indicates the values are 95% Upper Confidence Bounds. Please explain this discrepancy.

Although the table header indicates the potency values are the "95% Upper Confidence Bound," for the control M-M-R®II lot, the listed potency was derived from the point estimate (as noted in footnote ††) using a 3 x 1 potency assay This potency was not derived from the "95% Upper Confidence Bound." The listed potencies for the two Candidate mumps end expiry sublots are indeed values obtained from the 95% Upper Confidence Bound.

c. Footnote "#" indicates that the licensed product control assays were conducted in a different format that the accelerated stability sublots assays, i.e., the parent lot was assayed as 3 replicates performed on 1 day, while accelerated stability product sublots were assayed once on 6 separate days; also the licensed control product result is reported out to 1 decimal place while the accelerated stability sublots are reported out to 2 decimal places. Please explain why all sublots were not assayed simultaneously using the same format.

This is very similar to question a), above.

Sublots 1 and 2 were accelerated stability lots derived from a common parental lot (Sublot 3) and were assigned a mumps potency based on regression analysis of multiple assays (assay x 6 days) across the aging process. Sublot 3 was assigned its potency (3 assays x 1 day) using the conventional release practice for any manufactured lot.

The additional testing on Sublot 1 and Sublot 2 were performed in order to obtain precise estimates of the potency for the sublots that were to be used for establishing a new expiry. It should be noted that the potency assay did not differ, only the calculation method to reduce the error of the estimate.

Additional testing of the parent lot was not performed as it was released according to the release practices in place at the time of manufacturing. The release potency of this lot was within the historically observed manufacturing potencies, and further precision in potency assignment would not change (improve) its use as a control comparator in the clinical study.

Response 10

Response 10

10. In Module 5, in the table on page 23, you show that the accelerated stability 3.8 log10 TCID50 lot failed both the acceptability criteria as well as the non-inferiority comparison to the control lot, while the accelerated stability 4.1 log10 TCID50 lot met acceptability (lower bound of 95% CI for observed SCRs > 90%, with actual value of 90.4) and the non-inferiority comparisons to the control lot. We note that the "estimated SCR" for the 4.1 log10 TCID50 lot is actually higher (93.4%) than the "estimated SCR" for the 4.8 log10 TCID 50 control lot (92.2%), thus it appears possible that the control lot actually failed the acceptability criteria. Please comment.

Response:

We acknowledge that the lower bound of the confidence interval for the group with M-M-R™II with 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency was below 90%. However, in order to demonstrate that M-M-R™II with 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency was an acceptable end-expiry potency, the primary study hypotheses required that:

- The mumps immune response in children who receive M-M-R™II with 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency group be no more than 5 percentage point lower than mumps immune response in M-M-R™II with 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency group in order to declare similarity. This corresponds to the 90% two-sided confidence interval for the difference in proportions excluding a decrease of 5.0 percentage points or more.

- M-M-R™II with 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency had to induce an acceptable mumps immune response with the lower bound of the 95% two-sided CI on the observed response being >90% in subjects who develop neutralizing antibodies.

These hypotheses were met in this study; therefore, 4.1 $\log_{10}$ $TCID_{50}$ mumps virus potency was declared an acceptable end-expiry titer for M-M-R™II. There was not an acceptability hypothesis for the 4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency.

Though the 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Group had a slightly lower observed mumps seroconversion rate than the 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Group (92.2% versus 93.3%) based on the mumps virus neutralization assay, this difference is not statistically significant (p-value=0.538). Given the observed mumps seroconversion rate of 92.2% (403/437) for the 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Group, the probability that the true rate is above 90% is ~84%. In the design of this study, it was assumed that ~502 subjects would be evaluable from each group for the immunogenicity hypotheses. Due to an unexpectedly higher pre-positive rate in the plaque-reduction neutralization assay (PRN) and a sample storage issue, only 437 subjects were evaluable in the 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Group. If the study had maintained the planned evaluable sample size of 502 subjects in the 4.8 $\log_{10}$

$TCID_{50}$ Mumps Virus Potency Group and the same seroconversion rate of 92.2% was observed, the probability that the true rate was above 90% would have been ~97%.

The current M-M-R™II label states that a single injection of the vaccine induced mumps neutralizing antibodies in 95.8% (95% CI [92.7%, 97.8%]) of susceptible persons. This was based on 284 triple seronegative (to measles, mumps, and rubella) children using an earlier version of mumps neutralization assay. Since the original mumps neutralization assay was no longer in operation, a new plaque-reduction neutralization assay (PRN) designed to quantitate mumps neutralizing antibody in prevaccination and postvaccination sera was developed for this study to evaluate a mumps end expiry potency. Despite the use of a different assay, the seroconversion rate of 92.2% (95% CI [89.3%, 94.6%]) for the 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Group was inline with that observed in the original clinical studies used in the licensure of M-M-R™II.

The PRN assay was developed and validated by the applicant specifically for this study, and is not the primary assay used by the applicant to evaluate the serologic response to a mumps virus-containing vaccine. Typically, the mumps ELISA is used to detect immunoglobulin gamma antibody (IgG) to mumps virus before and after vaccination. The observed seroconversion rates using the mumps ELISA for the 4.8 and 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Groups were 98.1% and 96.9%, respectively. Based on the applicant's broad experience since the late 1980's with this ELISA assay for evaluating the mumps serologic response to M-M-R™II, the observed rate in the 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Group is consistent with historical experience.

Response 11

11. In the table on page 24 of Module 5, you show that only 437 of the 672 immunized control group subjects (65%) contributed to the per-protocol analyses. Likewise, only 65% (433 out of 662) of the 4.1 log10 TCID50 group were included and 69% (449 out of 663) of the 3.8 log10 TCID50 group were included in the per-protocol analysis for the primary endpoint (mumps PRN assay) at Day 42. Please discuss how comparisons between datasets with a large amount of missing data at a relatively early time point can be used to support approval of this supplement.

Response:

In Protocol 007, the analyses of the primary and secondary immunogenicity hypotheses were based on a per-protocol approach. The per-protocol population was defined as subjects who had valid baseline and 6-week (day-range of 27 to 84 days postvaccination) serology results, were seronegative at baseline, had no violation of inclusion/exclusion criteria, and received correct study vaccine. A detailed description of the protocol violations can be found in the Protocol 007 Data Analysis Plan (DAP). A summary of subjects excluded from the per-protocol analyses can be found in the Protocol 007 CSR (Tables 11-14) {P007}.

For the mumps (PRN) per-protocol analyses, 204, 229, and 235 subjects were excluded from the 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency groups, respectively. As displayed in Table 11 of the Protocol 007 CSR, the majority of the subjects excluded (>55%) were excluded due to an unknown serostatus at baseline (117, 126, and 138 subjects, respectively). Subjects whose blood samples were stored at 4°C for >1 year prior to testing in the PRN assay (and hence declared invalid as discussed in the Protocol 007 CSR Section 5.8.4.1) were considered as having an unknown baseline mumps (PRN) serostatus. Thus, over half of the exclusions due to an unknown serostatus (64, 77, and 88 subjects, respectively) resulted from the improper storage of the blood samples. In addition, since baseline and 6-week blood samples were tested in pairs in the PRN assay, subjects who did not have both a baseline and a 6-week blood sample were not tested. These subjects accounted for the remaining number of subjects with an unknown baseline serostatus. The second largest reason for being excluded from the per protocol analyses was due to a positive prevaccination serostatus (75, 93, and 84 subjects, respectively). The occurrences of events warranting exclusion from the per-protocol analyses were unrelated to treatment. The distribution of the reasons for exclusion was comparable across the three treatment groups.

The demographic profiles of the subjects excluded from the mumps (PRN) per-protocol analyses were comparable between the treatment groups. As given in the Table 1, the mean ages were 12.5, 12.6, and 12.5 months in the 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency groups, respectively, with ~52% subjects being female in each group and greater than 60% being Caucasian. Of the 204, 229, and 235 subjects excluded from the mumps (PRN) per-protocol analyses in the 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency groups, respectively, greater than 60% (131, 161, and 163 subjects, respectively) were included in the mumps (ELISA) per-protocol analyses. The mumps (ELISA) seroconversion rates (SCRs) based on these subjects were 95.4% (95% CI: [90.3%,

98.3%]), 96.3% (95% CI: [92.1%, 98.6%]), and 98.2% (95% CI: [94.7%, 99.6%]) for the 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency groups, respectively, which were comparable to the mumps (ELISA) SCRs observed for the entire per-protocol population (Protocol 007 CSR Table 21).

An analysis of all subjects with serology, regardless of initial serostatus or protocol violations, was presented in Protocol 007 CSR Section 7.5.2 to assess the impact of excluding non-per-protocol subjects. Only subjects with both pre and postvaccination samples (excluding improperly stored samples) were included in this analysis. The results of the all subjects with serology analysis were consistent with the results of the per-protocol analysis, except for the analysis of Primary Hypothesis 2 (the acceptability of the mumps response [as measured by PRN) in the 4.1 $\log_{10}$ $TCID_{50}$ mumps virus potency group]. As discussed in Section 7.5.2, the reason for the differing results between the per-protocol analysis and the all subjects with serology analysis was the inclusion of the pre-positive subjects. Subjects with higher baseline mumps antibody titers were less likely to achieve a 4-fold rise in mumps antibody titer. Furthermore, since the upper limit of detection of the neutralization assay was 1:4096, it was not possible for subjects who had baseline mumps antibody titers >1024 to achieve a 4-fold rise in mumps antibody titer.

Both the mumps (PRN) per-protocol analyses and the mumps (PRN) all subjects with serology analyses excluded subjects whose blood samples had been improperly stored prior to testing (~300 paired samples). As discussed in Protocol 007 CSR Section 5.8.4.1, an experiment revealed a significant decrease in seroconversion rate as well as a ~3-fold lower GMT in samples stored at 4°C for greater than one year. Agreement was obtained from the CBER to invalidate the mumps PRN data obtained from those samples and to replace some of the invalidated data (87 paired samples) with data from field retained serum samples (stored frozen at the study sites) (letter to BB-IND, general correspondence, serial # 92, dated November 7, 2002). The improper storage of the blood samples was not related to treatment and occurred randomly across all three treatment groups. To assess the impact of excluding the invalidated data on the non-inferiority analyses, the per-protocol and all subjects with serology analyses based on the mumps PRN data were repeated (Table 2) using the data from the samples that had been invalidated (and did not have a replacement result). Since it was shown that the invalidated samples had significant decreases in GMTs and seroconversion rates, the hypothesis tests related to the acceptability of the mumps (PRN) responses were not repeated. With the inclusion of the invalidated data, the per-protocol analyses excluded less than 25% of the data whereas the all subjects with serology analysis excluded less than 10% of the data. As displayed in Table 2, the conclusions when the invalidated results were included in the analyses were the same as those observed without the invalidated data.

The summaries and analyses presented above suggest that the immunogenicity profiles of the subjects excluded from the per-protocol and all subject with serology analyses were comparable to those included in the analyses. Thus, the analyses presented in the Protocol 007 CSR support the approval of this supplement.

Table 1. Summary of Subject Characteristics by Treatment Group for Subjects Excluded
From the Per-Protocol Mumps (PRN) Analyses

	Treatment Groups of M-M-R™II			
	3.8 $\log_{10}$ $TCID_{50}$/Dose Mumps Virus Potency† (N=204)	4.1 $\log_{10}$ $TCID_{50}$/Dose Mumps Virus Potency† (N=229)	4.8 $\log_{10}$ $TCID_{50}$/Dose Mumps Virus Potency‡ (N=235)	Total (N=668)
	n (%)	n (%)	n (%)	n (%)
Gender				
Male	97 (47.5)	108 (47.2)	114 (48.5)	319 (48.8)
Female	107 (52.5)	121 (52.8)	121 (51.5)	349 (52.2)
Age (Months)				
Mean	12.5	12.6	12.5	12.5
SD	0.9	1.2	1.0	1.1
Median	12.0	12.0	12.0	12.0
Range	11 to 17	11 to 18	12 to 17	11 to 18
Male	11 to 17	12 to 17	12 to 17	11 to 17
Female	12 to 15	11 to 18	12 to 17	11 to 18
Race/Ethnicity				
Asian	1 (0.5)	3 (1.3)	2 (0.9)	6 (0.9)
Black	39 (19.1)	37 (16.2)	48 (20.4)	124 (18.6)
Caucasian	135 (66.2)	155 (67.7)	150 (63.8)	440 (65.9)
Hispanic	14 (6.9)	11 (4.8)	20 (8.5)	45 (6.7)
Native American	4 (2.0)	5 (2.2)	3 (1.3)	12 (1.8)
Other	11 (5.4)	18 (7.9)	12 (5.1)	41 (6.1)

† Two sublots of M-M-R™II derived from the same parent lot as the control lot of M-M-R™II were aged to target mumps virus potencies with a 95% upper confidence bound of no more than 3.7 and 4.0 $\log_{10}$ $TCID_{50}$/dose. After reassignment of the mumps house standard (HS) potency to 4.3 $\log_{10}$ $TCID_{50}$/0.1 mL, the 95% upper confidence bound values were no more than 3.8 and 4.1 $\log_{10}$ $TCID_{50}$, respectively. Final mumps virus potencies (95% upper confidence bound) were 3.76 (3.79) and 4.04 (4.08) $\log_{10}$ $TCID_{50}$, respectively.

‡ The mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$/dose is the point estimate for the control group and is representative of a mumps potency within the release range for M-M-R™II.

N = Number of subjects excluded from the per-protocol mumps (PRN) analyses.

Table 2. Statistical Analysis of Non-Inferiority of Mumps [PRN] Seroconversion Rates Including Invalidated Results from Blood Samples Stored Improperly

Mumps End Expiry Treatment Group[†]	Estimated SCR[‡]	Estimated SCR[‡] of M-M-R™II– 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (Control Group)[§] (N=672)	Estimated Differences[‡‖] (90% CI)[¶]	Non-Inferiority Conclusion[¶]
Per-Protocol Analysis				
M-M-R™II– 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (N=662, n=497)	90.5%	89.3% (n=506)	1.1 (-2.0,4.3)	Similar (p-value <0.001)
M-M-R™II– 3.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (N=663, n=511)	86.9%	89.3% (n=506)	-2.4 (-5.7,0.9)	Unable to Show Similarity (p-value = 0.096)
All Subjects With Serology Analysis				
M-M-R™II– 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (N=662, n=613)	84.8%	85.3% (n=621)	-0.5 (-3.8,2.9)	Similar (p-value = 0.013)
M-M-R™II– 3.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency (N=663, n=607)	83.2%	85.3% (n=621)	-2.0 (-5.4,1.4)	Unable to Show Similarity (p-value = 0.074)

[†] Two sublots of M-M-R™II derived from the same parent lot as the control lot of M-M-R™II were aged to target mumps virus potencies with a 95% upper confidence bound of no more than 3.7 and 4.0 $\log_{10}$ $TCID_{50}$/dose. After reassignment of the mumps house standard (HS) potency to 4.3 $\log_{10}$ $TCID_{50}$/0.1 mL, the 95% upper confidence bound values were no more than 3.8 and 4.1 $\log_{10}$ $TCID_{50}$, respectively. Final mumps virus potencies (95% upper confidence bound) were 3.76 (3.79) and 4.04 (4.08) $\log_{10}$ $TCID_{50}$, respectively.

[‡] Estimated SCRs and their differences were based on a statistical analysis model adjusting for study centers.

[§] The mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$/dose is the point estimate for the control group and is representative of a mumps potency within the release range for M-M-R™II.

[‖] [Treatment Group - Control Group].

[¶] A lower bound of 90% CI on the difference excluding -5.0 implies that the difference is statistically significantly less than the prespecified clinically relevant decrease of 5 percentage points and allows for a conclusion of similarity (non-inferiority). A one-sided p-value ≤0.05 implies that the difference is statistically significantly less than the prespecified difference of 5 percentage points.

N = Number of subjects vaccinated in each treatment group.

n = Number of subjects contributing to the respective analysis including subjects whose samples were stored improperly.

CI = Confidence interval.

SCR = Seroconversion rate.

Response 12

Response 12

12. The purpose of concomitant administration of VARIVAX with MMRII in this study is not clear, since no specific rationale, objectives, or endpoints were provided. It is unclear how concomitant administration of VARIVAX together with MMRII might impact on immunogencity data. Please discuss.

Response:

M-M-R®II Protocol 007 was conducted in the United States under IND 1016. It is a common practice to administer M-M-R®II and VARIVAX™ concomitantly in the United States and this practice can be regarded as the current standard of care. This routine practice has been approved by several bodies including the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) {MMWR, Jan 7, 2005:53(51); Q1-Q3}. Their recommendations are supported by results from several clinical studies which indicate that concomitant administration of VARIVAX™ with M-M-R®II does not interfere with responses to measles, mumps, and rubella. Each of the product circulars also allow for their concomitant administration. Based on the published literature and on the high SCRs for measles, mumps, and rubella in Protocol 007, there is no evidence to suggest that concomitant administration of VARIVAX™ has a negative influence on the response to M-M-R®II. Furthermore, these studies have also demonstrated that with the exception of the added local reactions associated with the administration of VARIVAX™, the safety profile of M-M-R®II is not impacted by the concomitant administration of VARIVAX™.

Response 13

Response 13

13. We note in your study that only the primary endpoint comparison appears to have been prospectively defined, making it difficult to draw conclusions from the remaining data and analyses. Please discuss.

Response:

All analyses in the Protocol 007 CSR and supportive analyses in the file were predefined and submitted to CBER prior to unblinding the clinical database.

- The additional historical comparison of M-M-R®II immunogenicity data presented in Module 5, volume 5, section 5.3.5.4, was discussed during the teleconference with CBER on November 29, 2000, and submitted in writing to CBER in February 2001 (see question 4).

- A detailed description of the strategy, rationale, and statistical techniques that were used for the analyses of Protocol 007 was submitted to the IND in an amended Data Analysis Plan (DAP) on July 11, 2002 prior to the unblinding of the study. The DAP fully detailed the immunogenicity and safety analyses that were presented in Protocol 007 CSR for both the primary and secondary endpoint comparisons.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Submission Tracking Number (STN): BL 101069/5061

Alison Fisher, Ph.D.
Merck & Co., Inc.
P.O. Box 4
Sumneytown Pike
West Point, PA 19486

DEC - 3 2004

Dear Dr. Fisher:

This letter is in regard to the Supplement to your License Application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research (CBER) has completed the review of your Supplement received on February 4, 2004, for Measles, Mumps, and Rubella Virus Vaccine Live (M-M-R® II), to include a change in the labeled potency of the mumps component of M-M-R® II from 20,000 $TCID_{50}$ to 12,500 $TCID_{50}$. Our review finds that the information and data submitted are inadequate for final approval at this time based on the deficiencies described below.

1. Please describe the purpose and underlying rationale for proposing a reduction in potency of the mumps component of the approved product, M-M-R® II.

2. You state in module 2, page 7, that the mumps potency assay initially used primary green monkey kidney cells (BSC-1) and was later changed to Vero cells, resulting in higher mumps titers and revision of the end-expiry potency from 3.7 to 4.3 $\log_{10}$ $TCID_{50}$ per dose. You also state on page 7, section 2.5.1.4.3, Evolution of the Mumps End-Expiry Potency Value, of the same module: "Since the original end-expiry dose had been set conservatively, it was assumed that a mumps potency below 4.3 $\log_{10}$ $TCID_{50}$ per dose would be equally immunogenic." Please provide the rationale and calculations used to determine the maximum acceptable reduction in mumps potency.

3. You state that the oGOS stabilizer was developed in response to the European Pharmacopoeia requirement to demonstrate thermal stability of M-M-R® II (module 5, page 30, last paragraph) and you have data on file, not provided

in this BLA supplement, that supports the similarity in vaccine immunogenicity between M-M-R® II manufactured with GOS and M-M-R® II manufactured with oGOS (module 2, pages 9-10). Please submit this data to the file.

4. Please provide data demonstrating that the immunogenicity observed using the heat-aged oGOS-containing, live viral vaccine (oGOS reportedly added to enhance thermal stability), can be used to determine end-expiry potency of the non-heat aged, non-oGOS containing licensed vaccine.

5. You have submitted an additional study report in Module 5, volume 5, section 5.3.5.4, to support the proposed change in mumps end expiry potency. We note that these *post hoc* analyses compare ELISA data but not PRN data, and include populations receiving various concomitant vaccinations including MMRV (an earlier formulation of ProQuad™) and ProQuad™. Furthermore, you do not describe a specific statistical approach for performing this comparability bridging study, nor indicate the assay methods and standards used in each of the comparator groups. It does not appear that these data support the proposed change in mumps end expiry potency. Please comment.

6. You propose to use accelerated stability data instead of real-time stability data to compare various subpotent lots to licensed product that meets release specifications in order to support a change in end-expiry potency specification.

   a. Please describe the rationale and/or data to support the use of accelerated stability testing of test lots in lieu of real-time stability of this licensed product.

   b. Please describe how the chosen temperature range and durations of exposure were validated as representative of real-time stability for this particular product and its components.

7. In Module 5, pages 19 and 31, section 1.2.2.2, Minimum End-Expiry Potencies, you describe the recalculation of previously assigned potencies for each of the sublots of clinical material used in this study due to a reassignment of the mumps House Standard "based upon several studies performed at Merck & Co., Inc."

a. Please describe the purpose(s) of the referenced studies.

b. Please explain why a new house standard was created.

c. Please indicate the date the new standard was instituted with respect to the conduct of this study and data analysis.

d. Please describe the impact of the new standard on the study endpoints compared to the results that would have been obtained with the old standard.

8. Regarding the mumps PRN assay, module 5, page 81, Clinical Study Report section 5.8.1.3, Changes to Seronegative and Seroconversion Definitions, states: "It was expected that ~ 75% of the samples would be titered to endpoint (1:4096), reported as titer of ≥ 1:4096, and assigned a value of 1:4096 for analysis... and median titers would be provided along with geometric mean titer (GMT) summaries."

If the seroconversion rate (SCR) is not considered a stand-alone criterion to determine potency, it is unclear how non-inferiority between 3 study lots can be determined based upon an assay in which ~ 75% of samples would be assigned the same maximal possible value, i.e., they are above the upper limit of detection of the assay. If characterization of immunogenicity requires comparison of GMTs, use of an assay that is anticipated to result in the overwhelming proportion of data points falling outside of the limits of assay detection is of concern as it would markedly decrease the possibility of observing actual differences between lots. Please comment.

9. In Module 5, Clinical Study Report, page 20, the table indicates that there are differences in the assays of the accelerated stability sublots as compared to the product control lot.

a. Footnote "§" describes "estimated mumps virus potencies" for sublots 1 and 2 (accelerated stability lots) and "actual mumps virus potency" for sublot 3. Please explain why analysis of the accelerated stability lots differs from that of the licensed product and describe the rationale for comparing data that are derived differently.

b. Footnote "††" indicates that the point estimates for the control group are listed, although the table header indicates the values are 95% Upper Confidence Bounds. Please explain this discrepancy.

c. Footnote "#" indicates that the licensed product control assays were conducted in a different format than the accelerated stability sublots assays, i.e., the parent lot was assayed as 3 replicates performed on 1 day, while accelerated stability product sublots were assayed once on 6 separate days; also the licensed control product result is reported out to 1 decimal place while the accelerated stability sublots are reported out to 2 decimal places. Please explain why all sublots were not assayed simultaneously using the same format.

10. In Module 5, in the table on page 23, you show that the accelerated stability 3.8 $\log_{10}$ $TCID_{50}$ lot failed both the acceptability criteria as well as the non-inferiority comparison to the control lot, while the accelerated stability 4.1 $\log_{10}$ $TCID_{50}$ lot met acceptability (lower bound of 95% CI for observed SCRs > 90%, with actual value of 90.5) and the non-inferiority comparison to the control lot. We note that the "estimated SCR" for the 4.1 $\log_{10}$ $TCID_{50}$ lot is actually higher (93.4%) than the "estimated SCR" for the 4.8 $\log_{10}$ $TCID_{50}$ control lot (92.2%), thus it appears possible that the control lot actually failed the acceptability criteria. Please comment.

11. In the table on page 24 of Module 5, you show that only 437 of the 672 immunized control group subjects (65%) contributed to the per-protocol analyses. Likewise, only 65% (433 out of 662) of the 4.1 $\log_{10}$ $TCID_{50}$ group were included and 69% (449 out of 663) of the 3.8 $\log_{10}$ $TCID_{50}$ group were included in the per-protocol analysis for the primary endpoint (mumps PRN assay) at Day 42. Please discuss how comparisons between datasets with a large amount of missing data at a relatively early time point can be used to support approval of this supplement.

12. The purpose of concomitant administration of VARIVAX™ with M-M-R® II in this study is not clear, since no specific rationale, objectives, or endpoints were provided. It is unclear how concomitant administration of VARIVAX™ together with M-M-R® II might impact on immunogenicity data. Please discuss.

13. We note in your study that only the primary endpoint comparison appears to have been prospectively defined, making it difficult to draw conclusions from the remaining data and analyses. Please discuss.

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the Supplement; (2) notify us of your intent to file amendments; (3) withdraw the Supplement; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the Supplement. In the absence of any of the above responses, CBER may initiate action to deny the Supplement.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact CAPT Gale Heavner at 301-827-3070.

Sincerely yours,

Karen L. Goldenthal, M.D.

Karen L. Goldenthal, M.D.
Director
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

10/25/2019
Declaration of G. Reilly
EXHIBIT 138

Alison L. Fisher, Ph.D
Associate Director
Worldwide Regulatory Affairs

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November 15, 2006

MERCK
Research Laboratories

Norman Baylor, Ph.D.
Office of Vaccines Research and Review (HFM-400)
c/o Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center (HFM-99)
Woodmont Office Center, Suite 400N
1401 Rockville Pike
Rockville, MD 20852-1448

Dear Dr. Baylor:

Measles, Mumps, and Rubella Virus Vaccine Live
(M-M-R®$_{II}$)
STN 101069/5061

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to a letter from CBER on October 17, 2005 regarding the above supplement. In addition to Merck responses, the letter from CBER is attached for your convenience.

This submission is formatted as required in Title 21 paragraph 312.23 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing *one Compact Disk (CD)/DVD* which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD/DVD and is not more than 100 MB/GB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate. We consider the filing of this supplemental Biologics License Application to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning the content of this submission should be directed to me at 267-305-6727 or, in my absence to Kenneth Surowitz, Ph.D. at 267-305-6764.

Sincerely,

Alison Fisher, Ph.D.
Associate Director
Worldwide Regulatory Affairs

Q:/Winterbottom/V205C/Response to Request for Information October 2005

Enclosure: *CD/DVD RAM*

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE** *(Title 21, Code of Federal Regulations, Parts 314 & 601)*	*Form Approved: OMB No. 0910-0338* *Expiration Date: September 30, 2008* *See OMB Statement on page 2.* FOR FDA USE ONLY APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Merck & Co., Inc.	DATE OF SUBMISSION November 15, 2006
TELEPHONE NO. *(include Area Code)* (267) 305-6727	FACSIMILE (FAX) *Number (include Area Code)* (267) 305-6407
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* UG2D-68 P.O. Box 1000 North Wales, PA 19454-1099	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* STN# 101069

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Measles, Mumps and Rubella Virus Vaccine Live	PROPRIETARY NAME *(trade name)* IF ANY M-M-R® II	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*		CODE NAME *(If any)* V205C
DOSAGE FORM: Injection	STRENGTHS: Measles/1,000 TCID (50) per 0.5 mL Dose Mumps/20,000 TCID (50) per 0.5 mL Dose Rubella/1,000 TCID (50) per 0.5 mL Dose	ROUTE OF ADMINISTRATION: S.C.

(PROPOSED) INDICATION(S) FOR USE:
MMR® II is indicated for simultaneous vaccination against measles, mumps and rubella in persons 15 months of age or older.

APPLICATION DESCRIPTION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☒ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT *(Rx)* ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED | THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 356h (10/05)

CONFIDENTIAL

Merck-EDPA-00364

MRK-KRA00000395
MRK-CHA00000395

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314 50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e g., 21 CFR 314.50(d)(1); 21 CFR 601 2)
☐	B. Samples (21 CIFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C Methods validation package (e g , 21 CFR 314.50(e)(2)(i); 21 CFR 601 2)
☐	5. Nonclinical pharmacology and toxicology section (e g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e g , 21 CFR 314 50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e g .. 21 CFR 314 50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e g , 21 CFR 314 50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10 Statistical section (e.g., 21 CFR 314 50(d)(6); 21 CFR 601 2)
☐	11 Case report tabulations (e g , 21 CFR 314 50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601-2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16 Debarment certification (FD&C Act 306 (k)(1))
☐	17 Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER (Specify) Response to Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contra i nd ications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved. I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314 71, 314.72, 314 97, 314.99, and 601 12
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600 80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Alison L. Fisher	Alison L. Fisher, Ph.D. Associate Director Worldwide Reg. Affairs/Vaccines Biologics	Nov. 15, 2006

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Submission Tracking Number (STN): BL 101069/5061

Alison Fisher, Ph.D.
Merck & Co., Inc.
P.O. Box 4
Sumneytown Pike
West Point, PA 19486

OCT 17 2005

Dear Dr. Fisher:

This letter is in regard to the Supplement to your License Application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research (CBER) has completed the review of your Supplement received on April 13, 2005, for Measles, Mumps, and Rubella Virus Vaccine Live (M-M-R® II), to include a change in the labeled potency of the mumps component of M-M-R® II from 20,000 $TCID_{50}$ to 12,500 $TCID_{50}$. Our review finds that the information and data submitted are inadequate for final approval at this time based on the deficiencies described below.

1. The clinical trial described in your supplement is inadequate to support this label change for the mumps component due to the following deficiencies:

   a. A substantial amount of sample data was excluded from the analyses. We note that only 437 out of 672 immunized control group subjects contributed to the per-protocol analysis. This large proportion of missing data precludes a conclusion of success.

   b. The accelerated-stability lots (Sublots 1 and 2) were assayed at a separate time and in a different assay format (1x6 vs. 3x1) from the product control lot (Sublot 3), which was the parental lot used to make accelerated-stability lots (Sublots 1 and 2).

   c. The control lot failed the acceptability criteria as you acknowledge in your April 13, 2005 response.

If you intend to pursue the proposed changes in labeled potency, we recommend that you support the proposed label change by

correlating these study data and/or other relevant mumps vaccine immunogenicity data with the immunogenicity data from the original efficacy studies. You could also consider shortening the end-expiry dating period based upon these data.

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the Supplement; (2) notify us of your intent to file amendments; (3) withdraw the Supplement; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the Supplement. In the absence of any of the above responses, CBER may initiate action to deny the Supplement.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact CAPT Gale Heavner at 301-827-3070.

Sincerely yours,

Karen L. Goldenthal, M.D.

Karen L. Goldenthal, M.D.
Director
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

1. **The clinical trial described in your supplement is inadequate to support this label change for the mumps component due to the following deficiencies:**

   a. **A substantial amount of sample data was excluded from the analyses. We note that only 437 out of 672 immunized control group subjects contributed to the per-protocol analysis. This large proportion of missing data precludes a conclusion of success.**

   Response:

   We acknowledge the deficiency concerning the mumps plaque reduction neutralization (PRN) assay data. However, we believe that the clinical trial described in our supplement, and further described in this response, is adequate to support the proposed M-M-R™II label change to revise the mumps end-expiry potency. The following summary presents data in support of our label claim.

   The total number of serum samples excluded in the per-protocol immunogenicity analysis for mumps PRN assay was 204, 229, and 235 for subjects immunized with M-M-R™II containing mumps virus potency of 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$/dose, respectively. The proportions of missing PRN data were comparable across the 3 treatment groups. The 4 major reasons for the exclusion of these data were as follows:

   - A seropositivity to mumps by PRN at baseline (75, 93, and 84, for subjects immunized with M-M-R™II containing mumps virus potency of 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$/dose, respectively)
   - An unknown serostatus at baseline (117, 126, and 138 subjects, respectively) which includes subjects with invalid baseline serum sample but also those with invalid 6-week serum sample since testing of study samples by PRN was only performed when both baseline and 6-week pair samples were available and fit for testing,
   - An extended storage of serum specimen at 4°C for >1 year prior to testing in the PRN assay (64, 77, and 88 subjects, respectively) [1],
   - A lost to follow-up or refusal from the parents to allow a blood draw or any further participation in the study.

   A detailed summary of subjects excluded at 6 weeks postvaccination from the per-protocol immunogenicity analyses for mumps PRN is included in **Exhibit A**.

   However, the absence of PRN data for approximately 30% of subjects enrolled in this clinical trial does not indicate that no mumps-specific antibodies were detected in these samples and thus imply lack of vaccine-induced mumps response. As per secondary study objectives, serum samples were also tested by an enzyme-linked immunosorbent assay (ELISA) for the presence of mumps-specific antibodies in all 3 treatment groups. The ELISA assay used by Merck utilizes mumps antigen derived from a low passage mumps virus (Jeryl Lynn strain) and is a very sensitive and specific assay for the evaluation of vaccine-induced mumps antibody response. The priority order for the testing of study serum samples were (1)Mumps PRN, (2)Mumps ELISA, (3)Measles ELISA, (4)Rubella ELISA, and (5)Varicella gpELISA.

[1] Merck Research Laboratories (MRL) obtained agreement from the Center for Biologics Evaluation and Research (CBER) to invalidate data from the PRN testing carried out in Jun- to Aug-2002 on ~300 pairs of serum samples stored over 1 year at 4°C across all 3 treatment groups (letter to BB-IND, general correspondence, serial #92, November 2002).

The testing of study samples for mumps-specific neutralizing antibodies by PRN was interrupted at the Center for Biologics Evaluation and Research's (CBER) request for an investigation (BB-IND 1016, serial #80, February 2002). While waiting for CBER's response, Merck Research Laboratories (MRL) continued to perform the other study-specified tests by ELISA and gpELISA. When testing for PRN resumed, some samples had been stored at 4^0C for 1 year or more which was later found to negatively impact the suitability of the samples for PRN testing. PRN assay results for these samples were invalidated but results of the testing by ELISA were deemed valid since ELISA testing was performed well before the storage duration would have impacted the quality of the clinical samples. Because of the difference in the sensitivities of the mumps PRN and ELISA assays, some samples were tested positive at baseline by PRN assay but were found negative by ELISA. Given all these reasons, a great proportion of samples were excluded from the PRN immunogenicity analysis but were found acceptable to be included in the per-protocol immunogenicity analysis by mumps ELISA.

Exhibit B documents the number of seropositive subjects (per mumps ELISA) within the non-evaluable mumps PRN sample pool for the 4.8 $\log_{10}$TCID$_{50}$ mumps virus potency group. Of the 235 subjects excluded from the mumps PRN per-protocol analysis in the control group, more than 80% (191 subjects) had valid mumps ELISA results with 188 demonstrating a seropositive result 6 weeks postvaccination in this assay. One hundred sixty-three (163) of the 191 subjects with valid mumps ELISA results were included in the per-protocol mumps ELISA analysis[2]. The mumps seroconversion rates (SCRs) by ELISA based on these subjects (163) was 98.2% (95% Confidence Interval (CI): [94.7%, 99.6%]) for the 4.8 $\log_{10}$ TCID$_{50}$ mumps virus potency group. The observed mumps ELISA SCR, 98.0% (95% CI: [96.5%, 98.9%]) in the control group based on all per-protocol subjects is in line with historical experience, and the estimated mumps ELISA response rate is comparable to the estimated mumps ELISA response rate in the 4.1 $\log_{10}$ TCID$_{50}$ mumps potency group (98.0% versus 97.4%; non-inferiority p-value= <0.001, δ=5%). Furthermore, additional analysis performed by MRL has shown a strong correlation (93.6%) between ELISA and PRN serology results suggesting that the majority of the non-evaluable samples would have tested positive by PRN (BB-IND 1016, serial #86, June 2002).

Given that we have mumps ELISA antibody titers for a substantial portion of the subjects with missing (or non-evaluable) PRN data, the observed ELISA results and the strong correlation between ELISA and PRN assay provide indirect evidence about the likely outcome for the missing data. As a supportive analysis, we performed an analysis of the primary hypothesis using multiple imputation techniques to account for the incomplete data from the PRN assay. Through the use of statistical modeling and multiple imputation techniques, sets of plausible values of the missing data can be simulated and combined with the observed data to produce multiple "complete" datasets. The multiple versions of the "complete" datasets are then analyzed by standard methods, and the results are combined using simple rules (Rubin, 1987) to yield estimates and standard errors that formally incorporate missing-data uncertainty. As described in **Exhibit C**, we used this approach to assess the impact of the missing data on the study conclusions.

The approach described in **Exhibit C** was replicated 1000 times, creating 1000 simulated "complete" datasets. For each dataset, the observed seroconversion rates (and standard

[2] Twenty-eight (28) subjects were excluded from the mumps ELISA per-protocol analysis due to: missing baseline or 6-week serology result; developed or exposed to disease; received wrong vaccine; day range violation; or initially seropositive.

errors) and the estimated (stratified) difference in seroconversion rates (and standard error, based on Miettinen and Nurminen, 1985) were calculated for the 4.1 and 4.8 log_{10} $TCID_{50}$ Mumps Virus Potency groups. The overall estimates and standard errors (accounting for both between and within imputation variability) were then calculated using the method of Rubin (1987). The per-protocol acceptability and non-inferiority hypotheses for the 4.1 log_{10} $TCID_{50}$ Mumps Virus Potency group were then assessed using the overall estimates and standard errors. These results can be found in **Table 1**.

On average across the 1000 simulations, 515 and 502 subjects in the 4.8 and 4.1 log_{10} $TCID_{50}$ Mumps Virus Potency groups, respectively, were included in the analyses, compared with 437 and 433, respectively, in the original analysis. This analysis excludes subjects who were initially seropositive at baseline, or subjects who were predicted to be initially seropositive based on Model 2. As seen in **Table 1**, conclusions consistent with the original analysis were obtained for both acceptability and non-inferiority with the inclusion of the imputed data. It is also noted that the lower bound of 95% confidence interval for the observed seroconversion rate for the 4.8 log_{10} $TCID_{50}$ Mumps Virus Potency group was 89.956% (rounded to 90.0%). Thus, the simulations predict that if the missing PRN data had been available, their inclusion in the analyses would have confirmed the original results of the study. In addition they suggest that the seroconversion rate in the 4.8 log_{10} $TCID_{50}$ Mumps Virus Potency group would have likely met the non-hypothesized 90% lower bound criterion.

Table 1
Statistical Analysis of Non-Inferiority and Acceptability of Mumps [PRN] Seroconversion Rates for the ≤ 4.1 $\log_{10}$ $TCID_{50}$ Mumps Potency Group Using Multiple Imputation (Per-Protocol Analysis)

4.1 $\log_{10}$ $TCID_{50}$ Mumps Potency (N=662)		4.8 $\log_{10}$ $TCID_{50}$ Mumps Potency (N=672)		Estimated Differences[‡§] (90% CI)[‖]	Acceptability Conclusion[†]	Non-inferiority Conclusion[‖]
n	Observed SCR (95% CI)[†]	n	Observed SCR (95% CI)			
502	93.3% (90.9%, 95.6%)	515	92.4% (90.0%, 94.8%)	0.9 (-2.0, 3.8)	Acceptable	Similar

[†] The lower bound of the 95% CI being >90% implies that the value of the parameter is statistically significantly greater than the prespecified acceptability criterion (90%) and allows for a conclusion of acceptability.

[‡] Estimated differences were based on a statistical analysis model adjusting for study centers.

[§] [Treatment Group - Control Group].

[‖] A lower bound of 90% CI on the difference greater than -5.0 implies that the difference is statistically significantly less than the pre-specified clinically relevant decrease of 5 percentage points and allows for a conclusion of similarity (non-inferiority).

N = Number of subjects vaccinated in each treatment group.

n = Average number of subjects (over the 1000 simulations) initially seronegative for mumps [PRN] contributing to the per-protocol analyses.

CI = Confidence interval.

SCR = Seroconversion rate.

b. The accelerated-stability lots (Sublots 1 and 2) were assayed at a separate time and in a different assay format (1x6 vs. 3x1) from the product control lot (Sublot 3), which was the parental lot used to make accelerated-stability lots (Sublots 1 and 2).

Response:

Unlike Sublots 1 and 2, Sublot 3 (product control lot) did not undergo any manipulation in order to achieve a specific virus potency but was rather kept frozen immediately after the parental lot has been split into 3 sublots. The product control lot (Sublot 3), underwent standard release testing at the time of manufacture like any other commercial lot of M-M-R™II. This included the 3x1 assay format for potency determination, which was the standard procedure at that time. This method has an estimated standard error of approximately 0.15 $\log_{10}$. Hence the 95% confidence interval around the reported value is estimated to be 4.5 to 5.1 $\log_{10}$ $TCID_{50}$/dose, values well above the current minimum end-expiry potency of 4.3 $\log_{10}$ $TCID_{50}$/dose. Sublots 1 and 2 were tested at a separate time, following incubation at room temperature which was used to decrease their potencies. The expanded assay format (1x6) was performed on Sublots 1 and 2 in order to obtain a more precise estimate of the more critical "expiry" potency. Indeed, multiple 1x6 assays were compiled on Sublots 1 and 2 in order to have an error on the estimated potencies near 0.02 $\log_{10}$. Since the use of the standard release testing provides a mumps virus potency for the product control lot well above the current minimum mumps end-expiry potency (4.3 $\log_{10}$ $TCID_{50}$/dose) and the proposed candidate expiry potencies (3.8 and 4.1 $\log_{10}$ $TCID_{50}$/dose), additional testing or the use of the 1x6 assay format would have added little value for the appropriateness of the selected lot as a suitable control for the clinical trial.

c. The control lot failed the acceptability criteria as you acknowledge in your April 13, 2005 response.

We acknowledge that the lower bound of the CI for the control group (i.e., 4.8 log_{10} $TCID_{50}$ mumps potency) was below 90% (89.3%) as measured by the mumps PRN assay, however an acceptability hypothesis was not postulated for the 4.8 log_{10} $TCID_{50}$ mumps potency group. No acceptability hypothesis was set for the control group because it was designed to serve as a suitable internal reference of the safety and immunogenicity profile of the vaccine. To be acceptable, the candidate mumps end-expiry potency (4.1 or 3.8 log_{10} $TCID_{50}$/dose) had to display safety and immunogenicity profiles comparable to the internal control group. Based on the study results, only subjects receiving M-M-R™II containing mumps virus potency of 4.1 log_{10} $TCID_{50}$/dose achieved the study pre-specified criteria for success. Moreover, the 4.8 log_{10} $TCID_{50}$ mumps potency group had only a slightly lower observed seroconversion rate by PRN assay compared with the 4.1 log_{10} $TCID_{50}$ mumps potency group (92.2% versus 93.3%), and this difference was not statistically significant (p-value=0.538).

As previously discussed, the proportions of non-evaluable samples by PRN assay were similar across the 3 treatment groups (M-M-R™II containing mumps virus potency of 3.8, 4.1, and 4.8 log_{10} $TCID_{50}$/dose, respectively), and mumps ELISA antibody titers are available for a substantial portion of the subjects with non-evaluable PRN data in all 3 groups, including the control group (subjects immunized with M-M-R™II containing mumps virus potency of 4.8 log_{10} $TCID_{50}$/dose). The observed mumps ELISA results (SCR 98.0%) and the strong correlation between ELISA and PRN assay provide indirect evidence about the likely outcome for the missing data in the 4.8 log_{10} $TCID_{50}$ mumps potency group.

Additionally, there are several factors relating to the use of a neutralization assay that should be considered:

- Although virus neutralization assays may be the most predictive method for assessing protective immunity, these assays are not standardized making them poorly suited to evaluate large numbers of human sera due to assay variability (Mauldin et al. 2005. Mumps Virus Specific Antibody Titers from Pre-Vaccine Era Sera: Comparison of the Plaque Reduction Neutralization Assay and Enzyme Immunoassays. J. Clin. Microbiol. 2005;9:4847-4851).

- Validation testing for the mumps PRN assay used in this study was performed using a sample size of 50. Unfortunately, this does not provide a definitive guarantee of assay performance when addressing significantly larger subject populations as was evaluated in this study.

- The use of 4.8 log_{10} $TCID_{50}$ mumps virus potency (60,000 $TCID_{50}$) rather than 4.3 log_{10} $TCID_{50}$ mumps virus potency (20,000 $TCID_{50}$) as a suitable mumps potency for the study control lot provides a high degree of assurance regarding the level of safety and immunogenicity that was to be achieved by any of the 2 candidate mumps end-expiry potencies (3.8 and 4.1 log_{10} $TCID_{50}$/dose) tested in the clinical trial. Hence the 95% confidence interval around the reported potency value is estimated to be 4.5 to 5.1 log_{10} $TCID_{50}$/dose, values well above the minimum end-expiry potency of 4.3 log_{10} $TCID_{50}$/dose currently in place.

- Given the suitability of the internal control group in this clinical trial (see explanation provided in the preceding bullet point), the true performance of the PRN assay used in this clinical trial should be assessed by responses observed in the control group rather than by the arbitrary acceptability criteria (lower bound of the observed response being equal or greater than 90%) set by the applicant.

- The PRN assay used in the study was developed solely for the purpose of this clinical trial. It was not used in any previous nor subsequent clinical trials. It is therefore difficult to ascertain the real performance of this assay other than in the context of this clinical trial.

Furthermore, as noted in **Table 1**, the supportive analysis based on multiple imputation techniques suggests that by accounting for the incomplete data in the PRN assay, the seroconversion rate in the 4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency group would have likely met the non-hypothesized 90% lower bound criterion and would have been similar to the rate observed in the 4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency group.

Since the data show that M-M-R™II containing a 4.1 $\log_{10}$ $TCID_{50}$ mumps potency induced an acceptable antibody response to mumps, as determined by the seroconversion rate for mumps neutralizing antibodies, which was also noninferior to M-M-R™II containing a release dose of mumps virus (4.8 $\log_{10}$ $TCID_{50}$), a mumps virus potency of 4.1 $\log_{10}$ $TCID_{50}$ was declared an acceptable end-expiry titer for M-M-R™II.

Exhibit A

Summary of Subjects Excluded at 6 Weeks Postvaccination From Per-Protocol Immunogenicity Analyses for Mumps (PRN)

	M-M-R™ II Containing		
	≤3.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency	≤4.1 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency	~4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency
Subjects Vaccinated at Day 0:	663	662	672
Subjects Included at Week 6:	459	433	437
With a retention baseline sample and a retention 6-week sample	16	18	22
Subjects Excluded from Week 6 [†]:	204	229	235
Mumps (PRN) seropositive[‡] at Baseline[§]	75	93	84
Initial serostatus unknown	117	126	138
Received M-M-R™ II or varicella prior to the study	1	0	0
Had febrile illness prior to vaccination	0	1	0
Received incorrect M-M-R ™II study vaccine lot/dose	1	1	1
Developed measles, mumps, rubella, varicella or zoster	4	4	3
Exposed to mumps during 42-day safety follow-up	0	0	1
Missing or not evaluable 6-week serology result	125	135	150
Sample outside of day range	8	11	16
Blood sample not sufficient	2	6	2
Blood sample difficult to obtain	3	4	14
Blood sample misplaced/not received/identity unknown	0	2	2
Blood sample contaminated	0	2	1
Blood sample too old (>1 year storage at 4°C)	64	77	88
Incomplete baseline/6-week serology pair	2	3	2
Parent refused blood draw	22	5	10
Lost to follow-up	27	27	22
Parent refused further participation	20	8	19

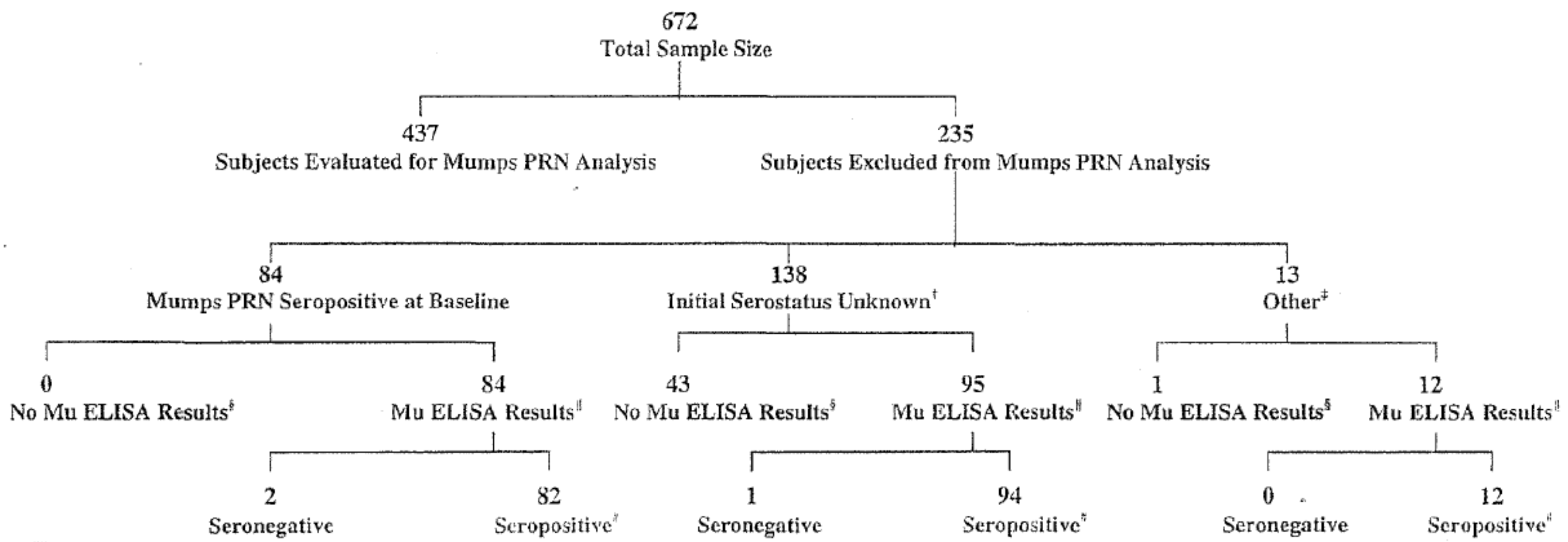
[†] Subjects can be counted more than once in any exclusion category

[‡] Mumps (PRN) seronegative at baseline corresponds to prevaccination samples with antibody titers <1:32
Mumps (PRN) seropositive at baseline corresponds to prevaccination samples with antibody titers ≥1:32

[§] Baseline is considered as the blood sampling before the vaccination.

Exhibit B

~4.8 $\log_{10}$ $TCID_{50}$ Mumps Virus Potency Treatment Group:
Flow Chart Documenting the Number of Seropositive Subjects (per Mumps ELISA)
Within the Non-Evaluable Mumps PRN Sample Pool



Key

† Initial Serostatus Unknown = Blood samples at baseline and/or at 6-week postvaccination were too old (stored at 4°C for >1 year prior to testing); no result due to refusing participation/bleed; quantity not sufficient (QNS); contamination; and/or missing sample.

‡ Other = Day range violation; missing 6-week result; exposed or developed disease.

§ No Mu ELISA Results: Refusing participation/bleed; quantity not sufficient (QNS); contamination; and/or missing sample.

|| Mu ELISA Results: 191 of 235 non-evaluable PRN samples have valid mumps ELISA results.

188/191 (98.4%) of subjects determined to be non-evaluable for the primary immunogenicity analysis (who had valid mumps ELISA data) were seropositive at 6-weeks postvaccination. Seropositive in the assay meant that subjects had an antibody titer ≥10 ELISA Ab units.

Mu = Mumps

Seronegative = Subjects demonstrating an antibody titer <10 ELISA Ab units

Seropositive = Subjects demonstrating an antibody titer ≥10 ELISA Ab units

Exhibit C

Statistical Method - Multiple Imputation

In order to predict if subjects with missing PRN data would have seroconverted, two logistic regression models were fit. In the first model, the probability of seroconverting (based on the PRN assay) was modeled as a function of treatment group and the natural logarithm of the fold-rise in mumps ELISA antibody titer (baseline to 6-weeks postvaccination). Subjects who were initially seropositive to mumps (based on the PRN assay) were excluded from this model. In the second model, the probability of being initially seropositive (based on the PRN assay) was modeled as a function of treatment group and the natural logarithm of the baseline mumps ELISA antibody titer. The estimates and standard errors for Models 1 and 2 are found in **Table 2**.

A "complete" dataset was obtained in the following manner. First, for each model the logistic regression parameters were assumed to follow multivariate normal distributions with means and covariance matrices equal to the parameter estimates and covariance matrix estimates obtained from the respective models. A random sample was then drawn from each multivariate normal distribution to define the estimated logistic regression models for calculating the probability of seroconverting and the probability of being initially seropositive (this introduces variability to account for the uncertainty in the model parameters estimates from Models 1 and 2). For those subjects who had missing PRN data but had baseline and 6-week mumps ELISA data, the probabilities of seroconverting and being initially seropositive were calculated and then used to randomly determine "success" or "failure" based on the binomial distribution. This procedure resulted in a "complete" dataset, with seroconversion status imputed for those subjects with missing PRN data.

Using the methods of Miettenen and Nurminen (Statistics in Medicine, 1985) for testing the non-inferiority of two binomial proportions with stratification by study center, the estimated difference ($\hat{Q}_i$) in seroconversion rates (based on PRN) between the 4.8 and 4.1 $\log_{10}$ $TCID_{50}$ potency groups and the associated variance (U_i) were calculated for each "complete" dataset. The multiple imputation (overall) estimate is given by

$$\overline{Q} = \frac{1}{m}\sum_{i=1}^{m}\hat{Q}_i .$$

The total variance for the estimate has two components that take into account variability within each dataset and across each dataset. The within-imputation variance is the average of the estimated variances

$$\overline{U} = \frac{1}{m}\sum_{i=1}^{m}U_i .$$

The between-imputation variance is the sample variance of the estimates

$$B = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{Q}_i - \overline{Q})^2 .$$

The total variance, T, is the sum of the two components with an additional correction factor to account for simulation error in $\overline{Q}$

$$T = \overline{U} + (1 + \frac{1}{m})B .$$

A $100\times(1-\alpha)\%$ confidence interval is obtain using

$$\overline{Q} \pm t_{df}\sqrt{T}$$

where t_{df} denotes a quantile of Student's t-distribution with degrees of freedom

$$df = (m-1)\left(1+\frac{m\overline{U}}{(m+1)B}\right)^2.$$

A similar approach was used for calculating the estimate and confidence interval for the observed seroconversion rate (by PRN) for the 4.8 and 4.1 $\log_{10}$ $TCID_{50}$ potency groups.

Table 2

Parameter Estimates and Standard Errors for Logistic Regression Models 1 and 2

	Model 1		Model 2	
Parameter[†]	Estimate	SE	Estimate	SE
Intercept	-0.35	0.23	3.71	0.57
4.8 Group Indicator	0.20	0.26	-0.17	0.17
4.1 Group Indicator	0.22	0.27	-0.30	0.17
Log (Fold-Rise)	5.12	0.42	NA	NA
Log (Baseline Titer)	NA	NA	-0.79	0.24

NA = Not applicable.
Model 1 = Logistic regression model which modeled the probability of seroconverting (based on PRN assay).
Model 2 = Logistic regression model which modeled the probability of being initially seronegative (based on PRN assay).
[†] The 3.8 Group was coded as the baseline category.

10/25/2019
Declaration of G. Reilly
EXHIBIT 139

BB-IND 1016: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine (M-M-R® II)

June 10, 2002/Serial No. 086

Response to FDA Request for Information (Mumps Cutoff Document)

Bagarazzi, M.	BLB-22
Barber, R.	BLA-22
Bramble, J.	WP 17-201
Brill-Edwards, P.	BLB-22
Buckland, B.	RY 80Y-370
Chirgwin, K.	BLB-22
Demol, G.	BLB-22
e-Worf	
Gutsch, D.	BLB-22
Hartzel, J./att	UN-102
Hastings, J./att	UN C-151
Hetrick, L.	Bethesda Office
Kuter B./att	UN-C141
Matthews, H./att	WP 36M-5
McKee, R.	WP 78-106
Morsy, M./att (2)	BLB-22
Musey, L./att	UN C-141
Nauman, B./att	UN C-141
Oppenheimer, L.	RY 33-408
Pineda, R.	UG 4A-42
RI-R/att	RY 86-205
Russo, C.	BLB-22
Shaw, A.	BL B-30
Simon, K.	WP 17-101
Ukwu, H.	BLB-22
Verhoeven, T.	RY 80M-113
Willison, B.	WP 28-70
Winterbottom, H.	BLA-10
WORF-BL/att	BL A-11

Manal A. Morsy, M.D., Ph.D.
Associate Director
Worldwide Regulatory Affairs
Vaccines/Biologics

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June 10, 2002

MERCK
Research Laboratories

Kathryn C. Zoon, Ph.D., Director
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research & Review
Division of Vaccines and Related Products Applications
Document Control Center (HFM-99)
Woodmont Office Center
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

Serial No. 086

Dear Dr. Zoon:

BB-IND 1016: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine (M-M-R®II)

RESPONSE TO CBER COMMENTS

Reference is made to the following CBER – Merck communications:

- CBER meeting minutes to Merck (Assay Development discussion April 11, 2000 – BB IND 1016).
- March 12, 2001 Merck submission to CBER (BB IND 1016, Serial # 063).
- Merck submission to CBER on October 10, 2001 (Bridging study – Mumps Wild Type ELISA (Mumps WT ELISA) and Legacy Mumps ELISA - BB IND 1016, serial # 072).
- Teleconference discussion between Merck and CBER on October 16, 2001 (summary of discussion outcome faxed to Ms. Luba Vujcic on October 19, 2001 and submitted to CBER on October 25, 2001 – BB IND 1016, serial # 075) regarding the Mumps WT ELISA assay.

This submission is in response to CBER's request for additional information regarding the cutoff chosen for the Mumps WT ELISA comparing the ELISA cutoff to the AIGENT assay cutoff and specifically to provide:

A) Clarification regarding reference sera used in the Mumps WT ELISA assay as they relate to the Anti-IgG Mumps Plaque Reduction Neutralization (AIGENT) assay – using the same reference sera to assist in the comparison of results between the two assays

B) Identification of individual titers in relative range around cutoffs of both assays in order to confirm that both assay are categorizing sera in a comparable fashion

Dr. Kathryn Zoon
BB-IND 1016: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, (M-M-R®II)

In addition Merck requests the use of the Mumps WT ELISA assay in place of the AIGENT assay for one year persistence sera analysis in the Mumps End Expiry Study (BB IND 1016, Protocol 007).

Merck is providing the following attachments with this package:

1. Mumps Wild Type ELISA cutoff, justification based on the Anti-IgG Mumps Plaque Reduction Neutralization (AIGENT) Assay standards and controls (Attachment 1).

2. Comparison Between the Mumps Wild Type (WT) ELISA (SOP 910.0096) and the Anti-IgG Enhanced Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489) Using the "Original" AIGENT Results (Attachment 2).

3. Expected Mismatch Classification Rates Due to Assay Variability (Attachment 3).

Protocol 007 and DAP amendments reflecting the change in assay to be used for one year persistence sera analysis (BB IND 1016, study titled "A Study of M-M-R®II at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age") are submitted separately but simultaneous with this document.

CBER concurrence is requested for the following:

1. Mumps WT ELISA cutoff of 10 Ab units.

2. Merck's request to use the Mumps WT ELISA only in place of using both the AIGENT assay and ELISA for measuring persistence of the mumps immune response at the one year time point (Protocol and DAP Amendments - BB IND 1016, protocol 007 – secondary objective – sent to CBER simultaneously with this submission).

If you need further information, please do not hesitate to contact me at (484) 344-3785, or in my absence, Henrietta Ukwu, M.D. at (484) 344-7176.

Sincerely,

Manal A. Morsy, M.D., Ph D.
Associate Director
Worldwide Regulatory Affairs
Vaccines / Biologics

Attachment
Federal Express

Desk copy to Dr. K. Carbone

Case 23-2553 Document: 74-5 Page: 332 Date Filed: 11/01/2023

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Merck & Co., Inc.

2. DATE OF SUBMISSION
June 10, 2002

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Sumneytown Pike
P.O. Box 4, BLB-22
West Point, PA 19486

4. TELEPHONE NUMBER *(Include Area Code)*
(484) 344-3785

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

6. IND NUMBER *(If previously assigned)*
1016

7. INDICATION(S) *(Covered by this submission)*
Prevention of measles-mumps and rubella virus infections

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☒ OTHER 5 *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
086

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☒ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER ____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [X] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [ ] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [ ] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [ ] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [ ] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [ ] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [X] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [ ] YES [X] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [ ] YES [ ] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Luwy K. Musey, M.D., Associate Director
Biologics Clinical Research

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Luwy K. Musey, M.D., Associate Director
Biologics Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Manal Morsy, M.D., Ph.D., Associate Director Worldwide Regulatory Affairs, Vaccines/Biologics	Manal Morsy	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Sumneytown Pike P.O. Box 4, BLB-22 West Point, PA 19486	(484) 344-3785	June 10, 2002

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

Information and data submitted herein contains trade secrets, or privileged or confidential information, the property of Merck & Co., Inc., and government agencies are not authorized to make it public without written permission from Merck.

Issues:

1. CBER requested additional information regarding the cutoff chosen for the Mumps WT ELISA comparing the ELISA cutoff to the AIGENT assay cutoff and specifically to provide:

   A) Clarification regarding reference sera used in the Mumps WT ELISA assay as they relate to the AIGENT assay – using the same reference sera to assist in the comparison of results between the two assays

   B) Identification of individual titers in relative range around cutoffs of both assays in order to confirm that both assay are categorizing sera in a comparable fashion.

2. Merck requests the use of the Mumps WT ELISA assay in place of the AIGENT assay for one year persistence sera analysis in the Mumps End Expiry Study (BB IND 1016, Protocol 007).

Merck Responses / Comments:

1. CBER requests additional information regarding the cutoff chosen for the Mumps WT ELISA comparing the ELISA cutoff to the AIGENT assay cutoff and specifically to provide:

   A) Clarification regarding reference sera used in the Mumps WT ELISA as they relate to the AIGENT assay – using the same reference sera to assist in the comparison of results between the two assays

In response this request, Merck conducted comparisons between the standard and control sera used in routine operation of the Mumps WT ELISA (SOP #910.0096) were tested in the AIGENT assay (V&CB Research Procedure #874.3489) in order to estimate their titers in the AIGENT assay. Although not requested by CBER, the AIGENT control samples were also tested in the Mumps WT ELISA to estimate their titers in that assay (Attachment 1).

The Mumps WT ELISA samples tested in the AIGENT assay were the standard, the high positive control, the low positive control, and the negative control, a pool of historically negative serum samples, mock serum and AIGENT control samples. Six assay runs were performed, with three independent preparations of each sample tested in each assay run. In a corresponding fashion, the AIGENT high and low positive controls were tested in the Mumps WT ELISA.

The precision (%RSD) for the AIGENT assay as reported in the validation is 43%. The precision for the Mumps WT ELISA as reported in the validation is 25%. In production runs the precision of the Mumps WT ELISA as measured on the control samples is 39%.

Results are shown in table 1 below:

Table 1:

Sample	AIGENT GMT reciprocal dil. [AIGENT Spec. Limit] or (95% CI)*	ELISA GMT Ab units [ELISA Spec. Limit] or (95% CI)*
AIGENT LPC	912 [256, 2048]	17 (15, 21)
AIGENT HPC	8192 [2048, 16384]	508 (425, 608)
ELISA HPC	4257 (3355, 5401)	490 [>279.4]
ELISA LPC	948 (747, 1203)	47 [16.3, 117.0]
ELISA Negative controls	<32	<5 [<10]
ELISA Standard	7298 (5753, 9259)	160**
* Confidence intervals based on overall estimates of intra- and inter-assay variability. **ELISA assigned potency; [Specification Limit]; (95% CI)		

Relative variability was comparable among AIGENT samples and between assay and within assay variance components on the natural logarithm transformed titers are 0.0229 and 0.0855, respectively. The corresponding between assay, within assay, and total %RSD's are 16.3%, 34.0%, and 39.0%, respectively, and the standard error of the GMT for each sample is 9.7%.

In a corresponding fashion, the AIGENT high and low positive controls were tested in the Mumps WT ELISA. Relative variability was comparable between AIGENT control samples. Between assay and within assay variance components on the natural logarithm transformed titers were 0.0206 and 0.0255, respectively. The corresponding between assay, within assay, and total %RSD's are 15.4%, 17.3%, and 23.9%, respectively, and the standard error of the GMT for each sample is 7.2%.

Conclusion:

There is good agreement between the AIGENT and Mumps WT ELISA assays with regard to performance of controls and Standards. The low positive controls, high positive controls, ELISA negative control and the ELISA standard, performed similarly in both assays relative to the cutoff of 10 Ab Units in the Mumps WT ELISA and a cutoff of 1:32 in the AIGENT assay.

Titer listings are in tables 2 and 3:

Table 2
AIGENT Assay Titer Listing

Sample	Rep	Assay Run					
		MMRV-26-02	MMRV-27-02	MMRV-28-02	MMRV-29-02	MMRV-52-02	MMRV-53-02
ELISA Std (FB)	1	4096	8192	8192	4096	8192	8192
	2	8192	4096	8192	8192	8192	8192
	3	8192	8192	8192	8192	8192	8192
ELISA High PC (PB)	1	2048	4096	8192	4096	8192	4096
	2	2048	4096	4096	8192	8192	4096
	3	4096	2048	4096	4096	4096	4096
ELISA Low PC (RK)	1	1024	512	1024	1024	1024	1024
	2	1024	512	1024	1024	1024	1024
	3	1024	1024	1024	1024	1024	1024
ELISA Neg. Control	1	<32	<32	<32	<32	<32	<32
	2	<32	<32	<32	<32	<32	<32
	3	<32	<32	<32	<32	<32	<32
AIGENT High PC (CMB)	1	8192	8192	8192	8192	8192	8192
AIGENT Low PC (MKY)	1	1024	1024	1024	1024	1024	512

Table 3
Mumps WT ELISA Titer Listing

Sample	Rep	Dilution	Assay Run					
			1130_X_03	1130_X_04	1204_X_07	1204_X_08	1205_X_02	1205_X_03
AIGENT High PC (CMB)	1	1000	423	362	392	339	518	LE
		10000	467	439	568	460	599	LE
	2	1000	508	458	633	408	>640	>640
		10000	510	460	544	419	616	576
	3	1000	>640	633	>640	481	>640	>640
		10000	535	500	628	456	659	586
AIGENT Low PC (MKY)	1	1000	16	16	25	16	27	19
		10000	<50	<50	<50	<50	67	<50
	2	1000	15	15	18	13	24	20
		10000	<50	<50	<50	<50	<50	<50
	3	1000	16	14	17	15	20	15
		10000	<50	<50	<50	<50	<50	<50
ELISA High PC (PB)	1	2000	440	430	529	509	471	574
ELISA Low PC (RK)	1	1000	45	43	53	45	51	45

LE - Lab Error
Per study protocol, only the highlighted results for AIGENT samples CMB and MKY are used in subsequent analyses.

1. CBER request that Merck provide additional justification for the cutoff chosen for the Mumps WT ELISA comparing the ELISA cutoff to the AIGENT assay cutoff and specifically to provide:

   B) Identification of individual titers in relative range around cutoffs of both assays in order to confirm that both assay are categorizing sera in a comparable fashion

In response to this request Merck conducted comparison between the Mumps WT ELISA (SOP 910.0096) and the AIGENT assay for Mumps (SOP 874.3489) Using the "Original" AIGENT Results (Attachment 2).

AIGENT and Mumps WT ELISA pre-vaccination and Day 42 post-vaccination titers from 565 subjects in the M-M-R®II 007 trial were compared in the Mumps WT ELISA assay using a serostatus cutoff of 10 Ab units relative to the AIGENT assay using a serostatus cutoff of 32 (1:32 dilution). AIGENT titers presented in this report were obtained using only the pre-specified SOP 874.3489 and validation rules.

The 2×2 cross-classification tables summarizing the sero-status assignments (Table 4-7).

Table 4
Sero-Status Cross-Classification for M-M-R®II 007 Pre- and Post-Vaccination Samples

		AIGENT		
		>=32	<32	Total
ELISA	>=10	469	29	498
	<10	69	456	525
	Total	538	485	1023

Table 5
Sero-Status Cross-Classification for M-M-R®II 007 Pre-Vaccination Samples

		AIGENT		
		>=32	<32	Total
ELISA	>=10	3	7	10
	<10	58	442	500
	Total	61	449	510

Table 6
Sero-Status Cross-Classification for M-M-R®II 007 Post-Vaccination Samples

		AIGENT		
		>=32	<32	Total
ELISA	>=10	466	22	488
	<10	11	14	25
	Total	477	36	513

Table 7
Sero-Conversion Cross-Classification for M-M-R®II 007

		AIGENT		
		>=32	<32	Total
ELISA	>=10	400	19	419
	<10	10	13	23
	Total	410	32	442

Despite that AIGENT titers are measured values and subject to the variabilities inherent in a biological assay, agreement between the ELISA and AIGENT assays was found to be quite good, exceeding 85% for each of the cross-classification measures evaluated (sensitivity, specificity, positive and negative predictive value, and overall percent agreement). The overall agreement rate between the two assays is 90.4% (925/1023) with 469 samples classified as positive in both assays and 456 samples classified as negative in both assays. Of the 98 discordant pairs, 29 were positive in the ELISA and negative in the AIGENT, and 69 were positive in the AIGENT and negative in the ELISA. Relative to the AIGENT assay, the sensitivity of the ELISA assay is 87.2% (469/538), the specificity of the ELISA assay is 94.0% (456/485), the predictive value of a negative ELISA is 86.9% (456/525), and the predictive value of a positive ELISA is 94.2% (469/498) (Table 4).

Separate cross-classification tables were also constructed for the pre- and post-vaccination samples (Tables 5 and 6). A pre-vaccination sample was more likely to be classified sero-positive in the AIGENT assay than in the ELISA (12.0% as compared to 2.0%), and a post-vaccination sample was only slightly less likely to be classified sero-positive in the AIGENT assay than in the ELISA (93.0% as compared to 95.1%). With respect to sero-conversion (Table 7), the overall agreement

rate between assays was 93.4% (413/442), with the ELISA being only slightly more likely than the AIGENT to classify a sample as a seroconverter. Among the set of

samples that were evaluable in both assays, the sero-conversion rate was 94.8% (419/442) in the ELISA and 92.8% (410/442) in the AIGENT assay.

Discrepancies between the AIGENT and Mumps WT ELISA:

In a comparison between the WT ELISA and AIGENT assays, discordant classifications were observed for 33 of 513 post-vaccination samples tested in both assays. The data were evaluated in an attempt to determine if the number and distribution of the discordant classifications differ from what might be expected given assay variability (Attachment 3). Acknowledging certain limitations of the assessment, the analysis indicates that for samples within two standard deviations of the cutoff, the observed number of mismatched sample classifications are within expectation. However, beyond two assay standard deviations (i.e., WT ELISA titer ≥20 Ab units), only one or two mismatches are expected to occur due to assay variability alone, and in this study there were 16 samples having a WT ELISA ≥20 Ab units that were AIGENT negative, and 8 samples having an AIGENT titer ≥512 that were WT ELISA negative.

Inferences from the resampling analysis are limited in that (1) the true titers for the samples are unknown; (2) the negative WT ELISA samples were not included in the resampling procedure as titers are not measured below 10 Ab units; and (3) a similar analysis could not be performed using the AIGENT titers since the proximity of a sample value to the cutoff is difficult to determine given the acknowledged pro-zone effect in the AIGENT assay. It is also noted that the mismatch rates obtained through the resampling procedure represent mismatches in both directions, whereas the observed rates presented in Table 8 are only in one direction (i.e., WT ELISA postive and AIGENT negative). It is likely that this comparison provides for a more appropriate assessment in light of item (2) above. That is, several of the samples that tested negative in the WT ELISA may have had titers close to the cutoff (e.g., 8-9 Ab units), and had they been included in the resampling procedure, would have resulted in an increase (perhaps a doubling) in the number of expected mismatched samples in the neighborhood of the cutoff.

The minor differences observed at the low end of the spectrum thus may be accounted for by the artificially truncated sensitivity of the AIGENT assay due to the choice of lowest dilution tested and/or the pro-zone effect inherent to this type of assay.

Conclusion:
There is good agreement between the Mumps WT ELISA and the AIGENT assays in terms of serostatus classification when using a cutoff of 10 Ab units in the Mumps WT ELISA and a cutoff of 1:32 in the AIGENT assay. Identification of individual titers in relative range around cutoffs of both assays confirms that both assay are categorizing sera in a comparable fashion.

Table 8
Observed and Expected Mismatch Rates as a Function of Distance from the Cutoff in the Context of the Comparison Between the AIGENT and WT ELISA Assays

		Resampling Procedure				Observed Results			
ELISA Titer Grouping	ELISA Titer Grouping	ELISA Titer Distribution	No. Mismatched Samples	95% CI on No. Mismatched Samples	Percent Mismatched Samples	ELISA Titer Distribution	No. Mismatched Samples	Percent Mismatched Samples of Subgroup	Percent Mismatched Samples of Total
10<=titer<1sd	10<=titer<14.1	12.62	5.10	(1,10)	40.40%	13	4	30.77%	0.82%
1sd<=titer<2sd	14.1<=titer<20	14.64	1.96	(0,5)	13.40%	12	2	16.67%	0.41%
2sd<=titer<3sd	20<=titer<28.3	29.71	0.41	(0,2)	1.40%	31	6	19.35%	1.23%
3sd<=titer<4sd	28.3<=titer<40	36.92	0.03	(0,1)	0.10%	37	2	5.41%	0.41%
4sd<=titer<5sd	40<=titer<56.6	65.74	0.00	(0,0)	0.00%	69	4	5.80%	0.82%
5sd<=titer<6sd	56.6<=titer<80	78.19	0.00	(0,0)	0.00%	77	1	1.30%	0.20%
6sd<=titer<7sd	80<=titer<113.1	81.75	0.00	(0,0)	0.00%	83	0	0.00%	0.00%
7sd<=titer<8sd	113.1<=titer<160	79.62	0.00	(0,0)	0.00%	78	2	2.56%	0.41%
8sd<=titer<9sd	160<=titer<226.2	51.68	0.00	(0,0)	0.00%	49	1	2.04%	0.20%
9sd<=titer<10sd	226.2<=titer<320	23.71	0.00	(0,0)	0.00%	25	0	0.00%	0.00%
11sd<=titer	320<=titer	13.43	0.00	(0,0)	0.00%	14	0	0.00%	0.00%
	Totals:	488	7.49			488	22		4.51%

Bridging to historical performance:

Comparison of the Mumps WT ELISA 10 Ab units cutoff to the Legacy Mumps ELISA cutoff using historical M-M-R®II data:

To assess the change to 10 ELISA Ab units on the historical mumps seroconversion rates (based on the definition of seronegative and seropositive in the Legacy Mumps ELISA), data from 10 Merck clinical trials in which M-M-R®II was administered were analyzed using both the old and new mumps cutoffs. The studies included were ProQuad™ protocols 004, 005, and 007, COMVAX™ protocol 009, M-M-R®II protocol 006, and VARIVAX™ protocols 010, 032, 033, 044, 045, and 051.

Per assay protocol for the Legacy Mumps ELISA, serostatus was assigned at the 1:100 dilution using a variable cutoff (~2 Ab units) in these studies. For the Wild Type mumps ELISA assay, samples are run at the 1:1000 dilution. Based on a bridging study between the Legacy Mumps ELISA assay and the Mumps WT ELISA assay [Merck submission to CBER on October 10, 2001: Bridging Study of the Legacy Mumps ELISA (SOP No. 910.0007) and Mumps "Wild Type" IgG ELISA (SOP No. 910.0096) BB IND 1016, serial #072], titers are approximately 1.5 times higher when tested in the Mumps WT ELISA when compared to the Legacy Mumps ELISA due to differences in dilution. Thus, the cutoff of 10 Ab units in the Mumps WT ELISA corresponds to approximately 6.67 Ab units (10 Ab units/1.5) in the Legacy Mumps ELISA.

Table 9 shows the mumps seroconversion rates from 10 Merck clinical trials using both the old and new mumps cutoffs. For each study, all treatment groups which received M-M-R®II were combined and a single seroconversion rate was reported. As explained above, pre and postvaccination titers from these studies were compared to 6.67 Ab units to estimated the seroconversion rate based on the Wild Type mumps cutoff of 10 Ab units. Though slightly lower, the Mumps WT ELISA cutoff provides consistent response rates when compared with the Legacy Mumps ELISA cutoff, with the overall mumps seroconversion rate differing by 1.1 percentage points between the two assays (99.1% based on the Legacy Mumps ELISA cutoff versus 98.0% based on the Mumps WT ELISA cutoff).

Conclusion:
High rate of agreement between the Mumps WT ELISA and the Legacy Mumps ELISA is observed when using a cutoff of 10 Ab units cutoff point on serostatus interpolation and assignments to historical data.

Table 9

Comparison of the Mumps WT ELISA 10 Ab units cutoff to the Legacy Mumps ELISA cutoff using historical M-M-R®II data

	Protocol											
Cutoff	004 (n=204)	005 (n=135)	006 (n=84)	007 (n=118)	009 (n=674)	010 (n=188)	032 (n=458)	033 (n=459)	044 (n=609)	045 (n=944)	051 (n=842)	All (n=4715)
Old[†]	99.5%	99.3%	100%	99.2%	98.8%	98.4%	99.3%	99.1%	99.0%	98.5%	99.6%	99.1%
New[‡]	98.5%	97.8%	100%	98.3%	97.7%	97.9%	98.5%	97.5%	97.7%	97.4%	98.7%	98.0%

[†]Cutoff Based on Legacy Mumps ELISA
[‡]Cutoff Based on Mumps WT ELISA

2. Merck requests the use of the Mumps WT ELISA assay in place of the AIGENT assay for one year persistence sera analysis in the Mumps End Expiry Study (BB IND 1016, Protocol 007).

   CBER previously agreed that the Mumps Wild Type ELISA assay can be used in place of the AIGENT assay for the remainder of the Mumps End Expiry Study (BB IND 1016, Protocol 007) if a comparison between the Mumps WT ELISA and the AIGENT assay shows acceptable agreement between the two assays.

   All pre-vaccination and post-vaccination second visit (day 42) sera are run in both the AIGENT assay and the Mumps WT ELISA for measurement of mumps immune response. Protocol 007 and the study DAP also specify that both assays are used for measurement of persistent immune response at 1 year post vaccination. Based on the following conclusions:

   1. Good agreement between the AIGENT and Mumps WT ELISA assays with regards to performance of controls and Standards. The low positive controls, high positive controls, ELISA negative control and the ELISA standard, performed similarly in both assays relative to the cutoff of 10 Ab Units in the Mumps WT ELISA and a cutoff of 1:32 in the AIGENT assay.

   2. Good agreement between the Mumps WT ELISA and the AIGENT assays in terms of serostatus classification when using a cutoff of 10 Ab units in the Mumps WT ELISA and a cutoff of 1:32 in the AIGENT assay. Confirmation both assays are categorizing sera identified of individual titers in relative range around cutoffs in a comparable fashion.

   3. High rate of agreement between the Mumps WT ELISA and the Legacy Mumps ELISA is observed when using a cutoff of 10 Ab units cutoff point on serostatus interpolation and assignments to historical data.

   Mumps End Expiry protocol and DAP have been amended (BB IND 1016, protocol 007) removing the requirement for using the AIGENT assay to measure mumps immune response persistence at 1 year post vaccination and maintained only the requirement to use the Mumps WT ELISA for measurement of mumps immune response persistence at one year.

CBER concurrence is requested for the following:

1. **Wild Type Mumps ELISA assay cutoff of 10 antibody units.**
2. **Use of Wild type Mumps ELISA assay only in place of both PRN Assay and Wild type Mumps ELISA for summarizing the one-year persistence of antibody data to mumps (Protocol and DAP Amendments - BB IND 1016, protocol 007 – secondary hypothesis).**

Attachment 1

ATTACHMENT #1

MERCK

SUBJECT: Testing the Mumps Wild Type ELISA Standard and Control Samples in the Mumps Anti-IgG Enhanced Plaque Reduction Neutralization Assay

Summary

Per CBER request, the standard and control sera used in routine operation of the Mumps Wild Type (WT) IgG ELISA (SOP #910.0096) were tested in the Mumps Anti-IgG Enhanced Plaque Reduction Neutralization (AIGENT) Assay (V&CB Research Procedure #874.3489) in order to estimate their titers in the AIGENT Assay. Although not requested by CBER, the Mumps AIGENT control samples were also tested in the WT ELISA to estimate their titers in that assay.

The Mumps WT ELISA samples tested in the AIGENT assay were the standard (FB), the high positive control (PB), the low positive control (RK), and the negative control (NC). Within each run of this experiment, samples were tested in an extended 2-fold dilution series from 1:32 to 1:65536. The AIGENT high and low positive control samples, CMB and MKY, respectively, were also included in each run per assay operating procedure. Six assay runs were performed, with three independent preparations of each sample tested in each assay run. Each assay run was valid based on the average number of plaque counts for the mock control and the titers of the AIGENT control samples. In a corresponding fashion, the AIGENT high and low positive control samples were tested in the WT ELISA. Six assay runs were performed, with three independent preparations of each sample tested in each assay run. Each WT ELISA run was valid per the assay validity criteria established for the Mumps WT ELISA.

The results of the experiment are summarized in the table below:

Geometric Mean Titers (GMT) for Assay Controls and Standard in the Mumps AIGENT and Mumps WT ELISA Assays

Sample	AIGENT GMT reciprocal dil. [AIGENT Spec. Limit] or (95% CI)*	ELISA GMT Ab units [ELISA Spec. Limit] or (95% CI)*
AIGENT Low PC (MKY)	912 [256, 2048]	17 (15, 21)
AIGENT High PC (CMB)	8192 [2048, 16384]	508 (425, 608)
ELISA High PC (PB)	4257 (3355, 5401)	490 [>279.4]
ELISA Low PC (RK)	948 (747, 1203)	47 [16.3, 117.0]
ELISA Neg. Control	<32	<5 [<10]
ELISA Standard (FB)	7298 (5753, 9259)	160**

* Confidence intervals based on overall estimates of intra- and inter-assay variability.
** ELISA assigned potency

Objective

Per CBER request, the purpose of this experiment was to test the standard and control sera used in routine operation of the Mumps Wild Type (WT) IgG ELISA (SOP #910.0096) in the Anti-IgG Enhanced Mumps Plaque Reduction Neutralization (AIGENT) Assay (V&CB Research Procedure #874.3489) in order to determine the titers of these samples in the AIGENT Assay. Although not requested by CBER, the AIGENT control samples were also evaluated in the WT ELISA to determine their titers in the WT ELISA.

Statistical Methods

Within and between variance components were estimated on the natural logarithm transformed titers using PROC MIXED in SAS. The model included terms for Sample and Run, with Sample specified as a fixed effect. Denoting the inter- and intra-assay variance component estimates by $\hat{\sigma}_b^2$ and $\hat{\sigma}_w^2$, respectively, the standard error of the geometric mean titer for an individual test sample was calculated as $\left(\exp\left(\sqrt{\frac{\hat{\sigma}_b^2}{n} + \frac{\hat{\sigma}_w^2}{r \times n}} \right) - 1 \right) \times 100\%$, where n and r denote the number of assay runs and the number of independent preparations within each run, respectively. Denoting the geometric mean titer by *GMT*, the 95% confidence limits about the geometric mean, are given by $\left(GMT \div \exp\left(t_{0.05,n-1} \times \sqrt{\frac{\hat{\sigma}_b^2}{n} + \frac{\hat{\sigma}_w^2}{r \times n}} \right), GMT \times \exp\left(t_{0.05,n-1} \times \sqrt{\frac{\hat{\sigma}_b^2}{n} + \frac{\hat{\sigma}_w^2}{r \times n}} \right) \right)$.

Study Design & Results

The Mumps WT ELISA samples tested in the AIGENT assay were the standard (FB), the high positive control (PB), the low positive control (RK), and the negative control (NC), a pool of historically negative serum samples. Acceptance ranges for these samples in the Mumps WT ELISA are indicated in Table 3. Within each run of this experiment, samples were tested in an extended 2-fold dilution series from 1:32 to 1:65536. The mock serum and AIGENT control samples were also included in each run per assay operating procedure. Six assay runs were performed, with three independent preparations of each sample tested in each assay run. Each assay run was valid based on the average number of plaque counts for the mock control (average count must be in the range of 10-40) and the titers of the AIGENT control samples (MKY control must be in the range of 256-2048, CMB control must be in the range of 2048-16384). The individual plaque counts are provided in the Attachment and the resulting AIGENT titers are listed in Table 1 and summarized in Table 3. Relative variability was comparable among AIGENT samples and therefore variability was estimated over the three positive samples, FB, PB, and RK. Between assay and within assay variance components on the natural logarithm transformed titers are 0.0229 and 0.0855, respectively. The corresponding between assay, within assay, and total %RSD's are 16.3%, 34.0%, and 39.0%, respectively, and the standard error of the GMT for each sample is 9.7%.

In a corresponding fashion, the Mumps AIGENT high and low positive controls, CMB and MKY, respectively, were tested in the Mumps WT ELISA. Acceptance ranges for these samples in the AIGENT assay are indicated in Table 3. Six assay runs were performed, with three independent preparations of each sample tested in each assay run. The resulting WT ELISA titers are listed in Table 2 and summarized in Table 3. Within each WT ELISA run, the AIGENT samples were tested at the 1:1000 and 1:10000 dilutions. Per the study protocol, the titer from the 1:10000 dilution was used only in cases where a more extreme dilution than 1:1000 was needed to obtain a determinate titer. Therefore, for the AIGENT samples, only the highlighted results in Table 2 were used in subsequent analyses. Relative variability was comparable between AIGENT control samples and therefore variability was estimated over the two samples. Between assay and within assay variance components on the natural logarithm transformed titers are 0.0206 and 0.0255, respectively. The corresponding between assay, within assay, and total %RSD's are 15.4%, 17.3%, and 23.9%, respectively, and the standard error of the GMT for each sample is 7.2%.

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Table 1
Mumps AIGENT Assay Titer Listing

Sample	Rep	Assay Run					
		MMRV-26-02	MMRV-27-02	MMRV-28-02	MMRV-29-02	MMRV-52-02	MMRV-53-02
ELISA Std (FB)	1	4096	8192	8192	4096	8192	8192
	2	8192	4096	8192	8192	8192	8192
	3	8192	8192	8192	8192	8192	8192
ELISA High PC (PB)	1	2048	4096	8192	4096	8192	4096
	2	2048	4096	4096	8192	8192	4096
	3	4096	2048	4096	4096	4096	4096
ELISA Low PC (RK)	1	1024	512	1024	1024	1024	1024
	2	1024	512	1024	1024	1024	1024
	3	1024	1024	1024	1024	1024	1024
ELISA Neg. Control	1	<32	<32	<32	<32	<32	<32
	2	<32	<32	<32	<32	<32	<32
	3	<32	<32	<32	<32	<32	<32
AIGENT High PC (CMB)	1	8192	8192	8192	8192	8192	8192
AIGENT Low PC (MKY)	1	1024	1024	1024	1024	1024	512

Table 2
Mumps ELISA Titer Listing

Sample	Rep	Dilution	Assay Run					
			1130_X_03	1130_X_04	1204_X_07	1204_X_08	1205_X_02	1205_X_03
AIGENT High PC (CMB)	1	1000	423	362	392	339	518	LE
		10000	467	439	568	460	599	LE
	2	1000	508	458	633	408	>640	>640
		10000	510	460	544	419	616	576
	3	1000	>640	633	>640	481	>640	>640
		10000	535	500	628	456	659	586
AIGENT Low PC (MKY)	1	1000	16	16	25	16	27	19
		10000	<50	<50	<50	<50	67	<50
	2	1000	15	15	18	13	24	20
		10000	<50	<50	<50	<50	<50	<50
	3	1000	16	14	17	15	20	15
		10000	<50	<50	<50	<50	<50	<50
ELISA High PC (PB)	1	2000	440	430	529	509	471	574
ELISA Low PC (RK)	1	1000	45	43	53	45	51	45

LE - Lab Error
Per study protocol, only the highlighted results for AIGENT samples CMB and MKY are used in subsequent analyses.

Table 3
Geometric Mean Titers (GMT) for Assay Controls and Standard in the Mumps AIGENT and Mumps WT ELISA Assays

Sample	AIGENT GMT reciprocal dil. [AIGENT Spec. Limit] or (95% CI)*	ELISA GMT Ab units [ELISA Spec. Limit] or (95% CI)*
AIGENT Low PC (MKY)	912 [256, 2048]	17 (15, 21)
AIGENT High PC (CMB)	8192 [2048, 16384]	508 (425, 608)
ELISA High PC (PB)	4257 (3355, 5401)	490 [>279.4]
ELISA Low PC (RK)	948 (747, 1203)	47 [16.3, 117.0]
ELISA Neg. Control	<32	<5 [<10]
ELISA Standard (FB)	7298 (5753, 9259)	160**

* Confidence intervals based on overall estimates of intra- and inter-assay variability.
** ELISA assigned potency

DATA FOR ATTACHMENT #1

Attachment
PRN Assay Run mmrv-26-02 Data Listing

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Whitehouse Station, NJ USA

AIGENT results		*Assay Controls*	Limits	Result	Validity
Assay:	mmrv-26-02	Mock:	[10, 40]	24.92	Valid Assay
		Control 1:	[256, 2048]	1024	Valid
		Control 2:	[2048, 16384]	8192	Valid

Named Range	
Ext6RepMultiplier	4.1
Ext12RepMultiplier	5.4
Control1TiterMaximum	2048
Control1TiterMinimum	256
Control2TiterMaximum	16384
Control2TiterMinimum	2048
MockPlaqueMaximum	40
MockPlaqueMinimum	10

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
1	FB	32	1	0	0	0.33	1	4096
1	FB	64	1	2	2	1.67	7	
1	FB	128	7	15	10	10.67	43	
1	FB	256	19	14	15	16.00	64	
2	FB	512	8	4	6	6.00	24	
2	FB	1024	1	0	2	1.00	4	
2	FB	2048	1	8	4	4.33	17	
2	FB	4096	5	7	3	5.00	20	
3	FB	8192	11	20	11	14.00	56	
3	FB	16384	19	22	22	21.00	84	
3	FB	32768	30	23	22	25.00	100	
3	FB	65536	24	32	30	28.67	115	
4	FB	32	0	2	1	1.00	4	8192
4	FB	64	0	0	1	0.33	1	
4	FB	128	7	9	6	7.33	29	
4	FB	256	16	6	10	10.67	43	
5	FB	512	3	6	7	5.33	21	
5	FB	1024	4	2	3	3.00	12	
5	FB	2048	5	3	4	4.00	16	
5	FB	4096	3	7	7	5.67	23	
6	FB	8192	9	12	tm	10.50	42	
6	FB	16384	30	24	18	24.00	96	
6	FB	32768	40	29	30	33.00	132	
6	FB	65536	43	33	23	33.00	132	
7	FB	32	0	0	0	0.00	0	8192
7	FB	64	3	0	3	2.00	8	
7	FB	128	2	6	7	5.00	20	
7	FB	256	17	10	12	13.00	52	
8	FB	512	4	6	5	5.00	20	
8	FB	1024	2	2	4	2.67	11	
8	FB	2048	3	4	1	2.67	11	
8	FB	4096	9	2	4	5.00	20	
9	FB	8192	12	9	16	12.33	49	
9	FB	16384	18	17	20	18.33	74	
9	FB	32768	26	34	30	30.00	120	
9	FB	65536	34	32	35	33.67	135	
10	PB	32	5	4	6	5.00	20	2048
10	PB	64	5	5	7	5.67	23	
10	PB	128	11	12	12	11.67	47	
10	PB	256	10	12	9	10.33	41	
11	PB	512	1	2	2	1.67	7	
11	PB	1024	5	4	3	4.00	16	
11	PB	2048	7	7	9	7.67	31	
11	PB	4096	11	18	9	12.67	51	
12	PB	8192	20	25	24	23.00	92	
12	PB	16384	35	31	30	32.00	128	
12	PB	32768	25	35	36	32.00	128	
12	PB	65536	19	32	35	28.67	115	
13	PB	32	5	3	2	3.33	13	2048
13	PB	64	8	3	4	5.00	20	
13	PB	128	12	14	12	12.67	51	
13	PB	256	6	4	6	5.33	21	
14	PB	512	1	3	3	2.33	9	
14	PB	1024	2	0	2	1.33	5	
14	PB	2048	4	10	5	6.33	25	
14	PB	4096	14	21	9	14.67	59	
15	PB	8192	18	19	11	16.00	64	
15	PB	16384	16	21	22	19.67	79	
15	PB	32768	26	26	36	29.33	118	
15	PB	65536	28	24	32	28.00	112	
16	PB	32	3	4	4	3.67	15	4096
16	PB	64	6	6	8	6.67	27	
16	PB	128	8	9	9	8.67	35	
16	PB	256	9	10	10	9.67	39	
17	PB	512	2	1	1	1.33	5	
17	PB	1024	3	1	3	2.33	9	
17	PB	2048	2	5	9	5.33	21	
17	PB	4096	9	6	10	8.33	33	
18	PB	8192	9	17	28	18.00	72	
18	PB	16384	26	28	28	27.33	110	
18	PB	32768	35	28	28	30.33	122	

Attachment
PRN Assay Run mmrv-26-02 Data Listing

AIGENT results			Assay Controls	Limits	Result	Validity	
Assay:	mmrv-26-02		Mock:	[10, 40]	24.92	Valid Assay	
			Control 1:	[256, 2048]	1024	Valid	
			Control 2:	[2048, 16384]	8192	Valid	

Named Range	
[redacted]	4.1
[redacted]	5.4
[redacted]	2048

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
18	PB	65536	24	21	28	23.67	95	
19	RK	32	11	22	33	22.00	88	1024
19	RK	64	17	19	18	18.00	72	
19	RK	128	18	35	32	28.33	114	
19	RK	256	27	27	27	27.00	108	
20	RK	512	13	15	16	14.67	59	
20	RK	1024	5	7	13	8.33	33	
20	RK	2048	9	20	11	13.33	53	
20	RK	4096	13	27	17	19.00	76	
21	RK	8192	11	31	31	24.33	98	
21	RK	16384	25	27	29	27.00	108	
21	RK	32768	20	32	36	29.33	118	
21	RK	65536	25	19	33	25.67	103	
22	RK	32	18	21	16	18.33	74	1024
22	RK	64	29	22	16	22.33	90	
22	RK	128	16	29	23	22.67	91	
22	RK	256	29	22	16	22.33	90	
23	RK	512	11	19	11	13.67	55	
23	RK	1024	13	11	12	12.00	48	
23	RK	2048	18	14	19	17.00	68	
23	RK	4096	21	21	19	20.33	82	
24	RK	8192	18	24	19	20.33	82	
24	RK	16384	22	23	18	21.00	84	
24	RK	32768	26	19	20	21.67	87	
24	RK	65536	13	21	22	18.67	75	
25	RK	32	17	19	21	19.00	76	1024
25	RK	64	22	22	25	23.00	92	
25	RK	128	30	23	16	23.00	92	
25	RK	256	23	20	30	24.33	98	
26	RK	512	12	15	17	14.67	59	
26	RK	1024	7	8	12	9.00	36	
26	RK	2048	17	21	33	23.67	95	
26	RK	4096	13	19	16	16.00	64	
27	RK	8192	18	18	19	18.33	74	
27	RK	16384	23	21	33	25.67	103	
27	RK	32768	33	28	30	30.33	122	
27	RK	65536	18	24	34	25.33	102	
28	Neg ctrl	32	32	27	25	28.00	112	<32
28	Neg ctrl	64	31	21	21	24.33	98	
28	Neg ctrl	128	23	19	25	22.33	90	
28	Neg ctrl	256	25	21	25	23.67	95	
29	Neg ctrl	512	15	24	21	20.00	80	
29	Neg ctrl	1024	16	32	25	24.33	98	
29	Neg ctrl	2048	23	32	24	26.33	106	
29	Neg ctrl	4096	27	31	32	30.00	120	
30	Neg ctrl	8192	22	32	29	27.67	111	
30	Neg ctrl	16384	31	21	30	27.33	110	
30	Neg ctrl	32768	24	30	25	26.33	106	
30	Neg ctrl	65536	19	26	19	21.33	86	
31	Neg ctrl	32	29	30	30	29.67	119	<32
31	Neg ctrl	64	19	20	19	19.33	78	
31	Neg ctrl	128	28	22	23	24.33	98	
31	Neg ctrl	256	26	21	27	24.67	99	
32	Neg ctrl	512	19	37	17	24.33	98	
32	Neg ctrl	1024	19	25	23	22.33	90	
32	Neg ctrl	2048	26	28	33	29.00	116	
32	Neg ctrl	4096	21	15	23	19.67	79	
33	Neg ctrl	8192	25	27	14	22.00	88	
33	Neg ctrl	16384	30	29	22	27.00	108	
33	Neg ctrl	32768	22	33	25	26.67	107	
33	Neg ctrl	65536	18	23	22	21.00	84	
34	Neg ctrl	32	22	35	15	24.00	96	<32
34	Neg ctrl	64	21	25	22	22.67	91	
34	Neg ctrl	128	16	30	24	23.33	94	
34	Neg ctrl	256	14	22	16	17.33	70	
35	Neg ctrl	512	16	32	26	24.67	99	
35	Neg ctrl	1024	17	30	15	20.67	83	
35	Neg ctrl	2048	26	19	37	27.33	110	
35	Neg ctrl	4096	25	18	26	23.00	92	
36	Neg ctrl	8192	28	32	28	29.33	118	
36	Neg ctrl	16384	29	21	27	25.67	103	

Attachment
PRN Assay Run mmrv-26-02 Data Listing

AIGENT results			Assay Controls	Limits	Result	Validity
Assay:	mmrv-26-02		Mock:	[10, 40]	24.92	Valid Assay
			Control 1:	[256, 2048]	1024	Valid
			Control 2:	[2048, 16384]	8192	Valid

Named Range	
[redacted]	4.1
[redacted]	5.4
[redacted]	2048

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
36	Neg ctrl	32768	29	22	32	27.67	111	
36	Neg ctrl	65536	19	18	17	18.00	72	
37	CMB	32	0	0	0	0.00	0	8192
37	CMB	64	2	1	0	1.00	4	
37	CMB	128	4	4	8	5.33	21	
37	CMB	256	5	8	4	5.67	23	
38	CMB	512	0	0	1	0.33	1	
38	CMB	1024	3	0	1	1.33	5	
38	CMB	2048	0	1	2	1.00	4	
38	CMB	4096	4	6	6	5.33	21	
39	CMB	8192	8	4	5	5.67	23	
39	CMB	16384	18	8	17	14.33	58	
39	CMB	32768	17	11	16	14.67	59	
39	CMB	65536	8	18	19	15.00	60	
40	MKY	32	5	13	6	8.00	32	1024
40	MKY	64	15	18	14	15.67	63	
40	MKY	128	26	18	22	22.00	88	
40	MKY	256	18	22	16	18.67	75	
41	MKY	512	16	12	9	12.33	49	
41	MKY	1024	7	15	12	11.33	45	
41	MKY	2048	20	17	18	18.33	74	
41	MKY	4096	12	31	21	21.33	86	
42			1	0	1			
42			2	2	2			
42			4	4	7			
42			11	8	11			
43			1	0	1			
43			1	0	3			
43			5	3	3			
43			2	4	3			
44			10	10	15			
44			11	17	20			
44			13	20	25			
44			22	23	18			
45			12	14	16			
45			18	17	16			
45			12	17	24			
45			14	23	18			
46			21	21	33			
46			7	15	14			
46			18	27	24			
46			20	29	30			
47			4	6	11			
47			9	9	20			
47			12	18	10			
47			17	20	17			
48			3	5	0			
48			3	5	3			
48			8	4	5			
48			11	8	7			
49	mock		21	22	16			
49	mock		20	19	32			
49	mock		34	32	25			
49	mock		32	26	20			
50			0	0	0			
50			0	0	0			
50			0	0	0			
50			0	0	0			

Attachment
PRN Assay Run mmrv-27-02 Data Listing

Business Confidential - Merck & Co., Inc.
Whitehouse Station, NJ USA

AIGENT results
Assay: mmrv-27-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	26.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
51	FB	32	0	0	1	0.33	1	8192
51	FB	64	2	1	4	2.33	9	
51	FB	128	9	11	10	10.00	38	
51	FB	256	12	18	14	14.67	55	
52	FB	512	4	2	0	2.00	8	
52	FB	1024	0	0	0	0.00	0	
52	FB	2048	2	1	1	1.33	5	
52	FB	4096	6	7	2	5.00	19	
53	FB	8192	9	16	11	12.00	45	
53	FB	16384	19	17	9	15.00	56	
53	FB	32768	30	31	36	32.33	122	
53	FB	65536	24	27	22	24.33	92	
54	FB	32	0	0	0	0.00	0	4096
54	FB	64	2	1	1	1.33	5	
54	FB	128	9	4	5	6.00	23	
54	FB	256	13	7	14	11.33	43	
55	FB	512	1	4	2	2.33	9	
55	FB	1024	1	0	1	0.67	3	
55	FB	2048	1	0	1	0.67	3	
55	FB	4096	4	4	4	4.00	15	
56	FB	8192	19	11	19	16.33	61	
56	FB	16384	31	19	28	26.00	98	
56	FB	32768	38	33	24	31.67	119	
56	FB	65536	26	34	32	30.67	115	
57	FB	32	0	2	0	0.67	3	8192
57	FB	64	0	0	1	0.33	1	
57	FB	128	5	8	9	7.33	28	
57	FB	256	8	7	9	8.00	30	
58	FB	512	0	4	2	2.00	8	
58	FB	1024	3	0	0	1.00	4	
58	FB	2048	1	3	2	2.00	8	
58	FB	4096	3	6	5	4.67	18	
59	FB	8192	14	11	12	12.33	46	
59	FB	16384	20	20	18	19.33	73	
59	FB	32768	29	31	28	29.33	110	
59	FB	65536	18	27	26	23.67	89	
60	PB	32	1	2	1	1.33	5	4096
60	PB	64	13	4	8	8.33	31	
60	PB	128	10	12	8	10.00	38	
60	PB	256	7	8	5	6.67	25	
61	PB	512	3	2	0	1.67	6	
61	PB	1024	3	2	4	3.00	11	
61	PB	2048	6	8	5	6.33	24	
61	PB	4096	7	10	14	10.33	39	
62	PB	8192	25	14	14	17.67	66	
62	PB	16384	22	22	26	23.33	88	
62	PB	32768	36	26	19	27.00	102	
62	PB	65536	29	36	32	32.33	122	
63	PB	32	2	1	0	1.00	4	4096
63	PB	64	5	7	7	6.33	24	
63	PB	128	11	14	10	11.67	44	
63	PB	256	6	1	4	3.67	14	
64	PB	512	1	1	2	1.33	5	
64	PB	1024	2	1	4	2.33	9	
64	PB	2048	5	6	5	5.33	20	
64	PB	4096	12	13	9	11.33	43	
65	PB	8192	11	19	14	14.67	55	
65	PB	16384	20	22	18	20.00	75	
65	PB	32768	35	35	24	31.33	118	
65	PB	65536	30	26	35	30.33	114	
66	PB	32	1	0	2	1.00	4	2048
66	PB	64	11	16	8	11.67	44	
66	PB	128	14	24	10	16.00	60	
66	PB	256	2	0	6	2.67	10	
67	PB	512	2	0	3	1.67	6	
67	PB	1024	2	2	5	3.00	11	
67	PB	2048	5	10	9	8.00	30	
67	PB	4096	18	13	11	14.00	53	
68	PB	8192	14	19	22	18.33	69	
68	PB	16384	33	28	30	30.33	114	
68	PB	32768	23	30	36	29.67	112	

Attachment
PRN Assay Run mmrv-27-02 Data Listing

AIGENT results
Assay: mmrv-27-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	26.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
68	PB	65536	30	26	25	27.00	102	
69	RK	32	22	13	12	15.67	59	512
69	RK	64	30	17	17	21.33	80	
69	RK	128	26	27	18	23.67	89	
69	RK	256	27	15	20	20.67	78	
70	RK	512	11	9	6	8.67	33	
70	RK	1024	10	13	18	13.67	51	
70	RK	2048	25	30	15	23.33	88	
70	RK	4096	27	27	33	29.00	109	
71	RK	8192	20	32	39	30.33	114	
71	RK	16384	27	40	32	33.00	124	
71	RK	32768	26	31	32	29.67	112	
71	RK	65536	23	49	31	34.33	129	
72	RK	32	17	15	25	19.00	71	512
72	RK	64	20	25	24	23.00	87	
72	RK	128	33	34	35	34.00	128	
72	RK	256	21	29	32	27.33	103	
73	RK	512	10	11	12	11.00	41	
73	RK	1024	13	17	14	14.67	55	
73	RK	2048	18	12	12	14.00	53	
73	RK	4096	17	25	26	22.67	85	
74	RK	8192	25	24	29	26.00	98	
74	RK	16384	25	32	40	32.33	122	
74	RK	32768	37	28	28	31.00	117	
74	RK	65536	31	22	34	29.00	109	
75	RK	32	15	17	22	18.00	68	1024
75	RK	64	26	16	20	20.67	78	
75	RK	128	34	24	20	26.00	98	
75	RK	256	12	22	12	15.33	58	
76	RK	512	10	13	13	12.00	45	
76	RK	1024	13	11	8	10.67	40	
76	RK	2048	17	17	13	15.67	59	
76	RK	4096	20	21	19	20.00	75	
77	RK	8192	21	26	22	23.00	87	
77	RK	16384	29	21	23	24.33	92	
77	RK	32768	27	36	20	27.67	104	
77	RK	65536	26	24	16	22.00	83	
78	Neg ctrl	32	13	25	24	20.67	78	<32
78	Neg ctrl	64	18	25	22	21.67	82	
78	Neg ctrl	128	28	23	28	26.33	99	
78	Neg ctrl	256	16	22	21	19.67	74	
79	Neg ctrl	512	20	19	18	19.00	71	
79	Neg ctrl	1024	28	23	31	27.33	103	
79	Neg ctrl	2048	23	19	28	23.33	88	
79	Neg ctrl	4096	25	26	23	24.67	93	
80	Neg ctrl	8192	17	23	28	22.67	85	
80	Neg ctrl	16384	31	19	19	23.00	87	
80	Neg ctrl	32768	18	21	21	20.00	75	
80	Neg ctrl	65536	19	25	14	19.33	73	
81	Neg ctrl	32	29	26	33	29.33	110	<32
81	Neg ctrl	64	28	39	31	32.67	123	
81	Neg ctrl	128	28	23	39	30.00	113	
81	Neg ctrl	256	26	34	29	29.67	112	
82	Neg ctrl	512	26	32	32	30.00	113	
82	Neg ctrl	1024	30	28	25	27.67	104	
82	Neg ctrl	2048	31	21	34	28.67	108	
82	Neg ctrl	4096	24	22	23	23.00	87	
83	Neg ctrl	8192	36	21	24	27.00	102	
83	Neg ctrl	16384	36	22	28	28.67	108	
83	Neg ctrl	32768	23	34	21	26.00	98	
83	Neg ctrl	65536	33	21	25	26.33	99	
84	Neg ctrl	32	34	34	21	29.67	112	<32
84	Neg ctrl	64	27	25	24	25.33	95	
84	Neg ctrl	128	27	29	25	27.00	102	
84	Neg ctrl	256	31	21	16	22.67	85	
85	Neg ctrl	512	34	29	25	29.33	110	
85	Neg ctrl	1024	20	32	28	26.67	100	
85	Neg ctrl	2048	26	34	32	30.67	115	
85	Neg ctrl	4096	27	32	22	27.00	102	
86	Neg ctrl	8192	32	27	31	30.00	113	
86	Neg ctrl	16384	35	28	26	29.67	112	

Attachment
PRN Assay Run mmrv-27-02 Data Listing

AIGENT results
Assay: mmrv-27-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	26.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
86	Neg ctrl	32768	30	32	29	30.33	114	
86	Neg ctrl	65536	34	34	31	33.00	124	
87	CMB	32	1	0	1	0.67	3	8192
87	CMB	64	2	2	1	1.67	6	
87	CMB	128	8	7	4	6.33	24	
87	CMB	256	4	2	4	3.33	13	
88	CMB	512	0	1	0	0.33	1	
88	CMB	1024	3	0	0	1.00	4	
88	CMB	2048	0	3	0	1.00	4	
88	CMB	4096	7	2	4	4.33	16	
89	CMB	8192	17	8	8	11.00	41	
89	CMB	16384	22	21	30	24.33	92	
89	CMB	32768	24	22	27	24.33	92	
89	CMB	65536	24	22	22	22.67	85	
90	MKY	32	D.O.	18	14	16.00	60	1024
90	MKY	64	21	19	23	21.00	79	
90	MKY	128	26	23	17	22.00	83	
90	MKY	256	29	18	21	22.67	85	
91	MKY	512	4	7	11	7.33	28	
91	MKY	1024	10	8	13	10.33	39	
91	MKY	2048	17	26	22	21.67	82	
91	MKY	4096	27	37	11	25.00	94	
92			1	0	1			
92			3	2	2			
92			3	11	6			
92			6	6	4			
93			0	0	0			
93			0	3	2			
93			1	3	5			
93			4	6	4			
94			6	19	10			
94			18	8	21			
94			20	23	20			
94			23	27	14			
95			7	13	11			
95			17	16	17			
95			24	25	19			
95			23	22	18			
96			15	12	24			
96			19	9	10			
96			15	18	20			
96			28	14	29			
97			5	12	8			
97			14	14	12			
97			16	18	16			
97			13	8	9			
98			5	1	5			
98			3	7	4			
98			9	10	6			
98			11	19	17			
99	mock		28	25	25			
99	mock		27	39	20			
99	mock		30	20	27			
99	mock		21	37	20			
100			0	0	0			
100			0	0	0			
100			0	0	0			
100			0	0	0			

Attachment
PRN Assay Run mmrv-28-02 Data Listing

Business Confidential - Merck & Co., Inc.
Whitehouse Station, NJ USA

AIGENT results
Assay: mmrv-28-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	26.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
1	FB	32	0	0	0	0.00	0	8192
1	FB	64	1	2	2	1.67	6	
1	FB	128	2	8	2	4.00	15	
1	FB	256	9	8	7	8.00	30	
2	FB	512	3	4	3	3.33	13	
2	FB	1024	0	0	0	0.00	0	
2	FB	2048	0	3	1	1.33	5	
2	FB	4096	3	5	4	4.00	15	
3	FB	8192	9	12	7	9.33	35	
3	FB	16384	25	21	18	21.33	80	
3	FB	32768	27	27	27	27.00	102	
3	FB	65536	21	27	28	25.33	95	
4	FB	32	0	0	0	0.00	0	8192
4	FB	64	1	1	2	1.33	5	
4	FB	128	7	11	9	9.00	34	
4	FB	256	1	8	9	6.00	23	
5	FB	512	1	1	0	0.67	3	
5	FB	1024	1	0	1	0.67	3	
5	FB	2048	1	1	0	0.67	3	
5	FB	4096	DO	3	6	4.50	17	
6	FB	8192	8	5	6	6.33	24	
6	FB	16384	23	34	13	23.33	88	
6	FB	32768	23	34	20	25.67	97	
6	FB	65536	31	30	15	25.33	95	
7	FB	32	0	0	0	0.00	0	8192
7	FB	64	3	1	2	2.00	8	
7	FB	128	7	2	4	4.33	16	
7	FB	256	5	10	12	9.00	34	
8	FB	512	1	4	4	3.00	11	
8	FB	1024	1	0	1	0.67	3	
8	FB	2048	4	1	4	3.00	11	
8	FB	4096	0	5	3	2.67	10	
9	FB	8192	11	12	11	11.33	43	
9	FB	16384	12	19	24	18.33	69	
9	FB	32768	26	33	30	29.67	112	
9	FB	65536	30	26	34	30.00	113	
10	PB	32	DO	DO	DO			8192
10	PB	64	DO	DO	DO			
10	PB	128	DO	DO	DO			
10	PB	256	DO	DO	DO			
11	PB	512	2	1	0	1.00	4	
11	PB	1024	3	6	1	3.33	13	
11	PB	2048	5	6	1	4.00	15	
11	PB	4096	5	10	8	7.67	29	
12	PB	8192	6	13	11	10.00	38	
12	PB	16384	27	29	26	27.33	103	
12	PB	32768	29	34	31	31.33	118	
12	PB	65536	17	27	23	22.33	84	
13	PB	32	1	2	2	1.67	6	4096
13	PB	64	5	7	8	6.67	25	
13	PB	128	7	8	9	8.00	30	
13	PB	256	5	4	3	4.00	15	
14	PB	512	0	2	1	1.00	4	
14	PB	1024	2	3	3	2.67	10	
14	PB	2048	2	8	2	4.00	15	
14	PB	4096	3	6	6	5.00	19	
15	PB	8192	DO	DO	DO			
15	PB	16384	DO	22	26	24.00	90	
15	PB	32768	DO	27	21	24.00	90	
15	PB	65536	DO	10	19	14.50	55	
16	PB	32	0	0	2	0.67	3	4096

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Attachment
PRN Assay Run mmrv-28-02 Data Listing

Business Confidential - Merck & Co., Inc.
Whitehouse Station, NJ USA

AIGENT results
Assay: mmrv-28-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	26.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
16	PB	64	3	6	5	4.67	18	
16	PB	128	4	9	12	8.33	31	
16	PB	256	2	4	2	2.67	10	
17	PB	512	1	1	1	1.00	4	
17	PB	1024	1	2	2	1.67	6	
17	PB	2048	4	0	7	3.67	14	
17	PB	4096	1	5	2	2.67	10	
18	PB	8192	17	18	19	18.00	68	
18	PB	16384	31	23	25	26.33	99	
18	PB	32768	16	20	26	20.67	78	
18	PB	65536	18	23	23	21.33	80	
19	RK	32	10	19	11	13.33	50	1024
19	RK	64	27	21	22	23.33	88	
19	RK	128	30	29	19	26.00	98	
19	RK	256	26	23	14	21.00	79	
20	RK	512	9	13	6	9.33	35	
20	RK	1024	15	8	10	11.00	41	
20	RK	2048	16	19	18	17.67	66	
20	RK	4096	16	19	10	15.00	56	
21	RK	8192	15	18	23	18.67	70	
21	RK	16384	18	35	30	27.67	104	
21	RK	32768	20	32	32	28.00	105	
21	RK	65536	12	32	25	23.00	87	
22	RK	32	11	31	25	22.33	84	1024
22	RK	64	27	26	31	28.00	105	
22	RK	128	30	34	28	30.67	115	
22	RK	256	17	17	18	17.33	65	
23	RK	512	11	16	11	12.67	48	
23	RK	1024	10	11	4	8.33	31	
23	RK	2048	13	19	13	15.00	56	
23	RK	4096	18	21	12	17.00	64	
24	RK	8192	26	21	9	18.67	70	
24	RK	16384	19	25	38	27.33	103	
24	RK	32768	19	36	37	30.67	115	
24	RK	65536	23	28	33	28.00	105	
25	RK	32	10	18	16	14.67	55	1024
25	RK	64	17	28	17	20.67	78	
25	RK	128	23	30	32	28.33	107	
25	RK	256	12	26	18	18.67	70	
26	RK	512	6	10	6	7.33	28	
26	RK	1024	15	9	9	11.00	41	
26	RK	2048	16	18	17	17.00	64	
26	RK	4096	14	24	14	17.33	65	
27	RK	8192	32	18	22	24.00	90	
27	RK	16384	40	35	40	38.33	144	
27	RK	32768	27	38	17	27.33	103	
27	RK	65536	24	16	19	19.67	74	
28	Neg ctrl	32	20	24	24	22.67	85	<32
28	Neg ctrl	64	29	24	23	25.33	95	
28	Neg ctrl	128	26	42	44	37.33	140	
28	Neg ctrl	256	25	14	23	20.67	78	
29	Neg ctrl	512	11	27	20	19.33	73	
29	Neg ctrl	1024	32	38	23	31.00	117	
29	Neg ctrl	2048	39	27	30	32.00	120	
29	Neg ctrl	4096	28	35	30	31.00	117	
30	Neg ctrl	8192	13	19	11	14.33	54	
30	Neg ctrl	16384	29	18	21	22.67	85	
30	Neg ctrl	32768	18	36	20	24.67	93	
30	Neg ctrl	65536	11	20	19	16.67	63	
31	Neg ctrl	32	32	50	23	35.00	132	<32
31	Neg ctrl	64	25	39	55	39.67	149	

Attachment
PRN Assay Run mmrv-28-02 Data Listing

Business Confidential - Merck & Co., Inc.
Whitehouse Station, NJ USA

AIGENT results
Assay: mmrv-28-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	26.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
31	Neg ctrl	128	31	49	44	41.33	155	
31	Neg ctrl	256	17	39	30	28.67	108	
32	Neg ctrl	512	19	35	32	28.67	108	
32	Neg ctrl	1024	36	32	28	32.00	120	
32	Neg ctrl	2048	21	39	31	30.33	114	
32	Neg ctrl	4096 DO		37	31	34.00	128	
33	Neg ctrl	8192	26	32	30	29.33	110	
33	Neg ctrl	16384	34	32	27	31.00	117	
33	Neg ctrl	32768	26	49	33	36.00	135	
33	Neg ctrl	65536	16	26	18	20.00	75	
34	Neg ctrl	32	28	36	26	30.00	113	<32
34	Neg ctrl	64	30	38	24	30.67	115	
34	Neg ctrl	128	34	40	28	34.00	128	
34	Neg ctrl	256 DO		29	25	27.00	102	
35	Neg ctrl	512	23	39	21	27.67	104	
35	Neg ctrl	1024	29	37	28	31.33	118	
35	Neg ctrl	2048	27	30	34	30.33	114	
35	Neg ctrl	4096	20	26	23	23.00	87	
36	Neg ctrl	8192	29	33	20	27.33	103	
36	Neg ctrl	16384	19	41	24	28.00	105	
36	Neg ctrl	32768	27	30	43	33.33	125	
36	Neg ctrl	65536	32	25	26	27.67	104	
37	CMB	32	0	0	1	0.33	1	8192
37	CMB	64	0	3	0	1.00	4	
37	CMB	128	6	7	8	7.00	26	
37	CMB	256	6	7	4	5.67	21	
38	CMB	512	0	0	0	0.00	0	
38	CMB	1024	1	0	0	0.33	1	
38	CMB	2048	3	0	4	2.33	9	
38	CMB	4096	4	7	2	4.33	16	
39	CMB	8192	9	9	12	10.00	38	
39	CMB	16384	24	23	19	22.00	83	
39	CMB	32768	34	22	34	30.00	113	
39	CMB	65536	26	20	19	21.67	82	
40	MKY	32 DO		13	14	13.50	51	1024
40	MKY	64	27	31	15	24.33	92	
40	MKY	128	30	28	23	27.00	102	
40	MKY	256	17	23	23	21.00	79	
41	MKY	512	8	6	5	6.33	24	
41	MKY	1024	12	14	6	10.67	40	
41	MKY	2048	23	24	29	25.33	95	
41	MKY	4096	24	30	21	25.00	94	
42	mock		21	23	26			
42	mock		30	30	26			
42	mock		29	38	26			
42	mock		28	25	17			
43			0	0	0			
43			0	0	0			
43			0	0	0			
43			0	0	0			

Attachment
PRN Assay Run mmrv-29-02 Data Listing

Business Confidential - Merck & Co., Inc.
Whitehouse Station, NJ USA

AIGENT results
Assay: mmrv-29-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	28.5	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
44	FB	32	0	0	0	0.00	0	4096
44	FB	64	5	6	4	5.00	18	
44	FB	128	11	6	11	9.33	33	
44	FB	256	11	10	14	11.67	41	
45	FB	512	2	2	3	2.33	8	
45	FB	1024	0	4	1	1.67	6	
45	FB	2048	0	1	1	0.67	2	
45	FB	4096	5	7	5	5.67	20	
46	FB	8192	14	14	16	14.67	51	
46	FB	16384	28	22	27	25.67	90	
46	FB	32768	31	32	28	30.33	106	
46	FB	65536	23	38	32	31.00	109	
47	FB	32	0	0	1	0.33	1	8192
47	FB	64	2	2	1	1.67	6	
47	FB	128	5	6	4	5.00	18	
47	FB	256	15	13	9	12.33	43	
48	FB	512	2	7	6	5.00	18	
48	FB	1024	0	3	2	1.67	6	
48	FB	2048	2	1	0	1.00	4	
48	FB	4096	7	7	4	6.00	21	
49	FB	8192	11	8	15	11.33	40	
49	FB	16384	18	17	18	17.67	62	
49	FB	32768	25	30	32	29.00	102	
49	FB	65536	45	41	42	42.67	150	
50	FB	32	2	0	0	0.67	2	8192
50	FB	64	2	2	1	1.67	6	
50	FB	128	6	5	5	5.33	19	
50	FB	256	15	13	9	12.33	43	
51	FB	512	8	5	4	5.67	20	
51	FB	1024	1	0	5	2.00	7	
51	FB	2048	3	3	4	3.33	12	
51	FB	4096	6	6	2	4.67	16	
52	FB	8192	14	8	8	10.00	35	
52	FB	16384	18	19	15	17.33	61	
52	FB	32768	12	30	21	21.00	74	
52	FB	65536	33	25	23	27.00	95	
53	PB	32	1	1	4	2.00	7	4096
53	PB	64	9	9	8	8.67	30	
53	PB	128	9	9	16	11.33	40	
53	PB	256	7	10	6	7.67	27	
54	PB	512	2	0	0	0.67	2	
54	PB	1024	1	2	4	2.33	8	
54	PB	2048	4	9	1	4.67	16	
54	PB	4096	11	18	8	12.33	43	
55	PB	8192	20	23	17	20.00	70	
55	PB	16384	24	28	23	25.00	88	
55	PB	32768	36	35	26	32.33	113	
55	PB	65536	34	25	26	28.33	99	
56	PB	32	5	2	0	2.33	8	8192
56	PB	64	4	6	12	7.33	26	
56	PB	128	12	9	16	12.33	43	
56	PB	256	5	13	4	7.33	26	
57	PB	512	2	2	2	2.00	7	
57	PB	1024	0	2	3	1.67	6	
57	PB	2048	5	4	2	3.67	13	
57	PB	4096	8	9	12	9.67	34	
58	PB	8192	11	21	9	13.67	48	
58	PB	16384	27	24	24	25.00	88	
58	PB	32768	17	39	31	29.00	102	
58	PB	65536	19	28	23	23.33	82	
59	PB	32	1	4	2	2.33	8	4096

Attachment
PRN Assay Run mmrv-29-02 Data Listing

Business Confidential - Merck & Co., Inc.
Whitehouse Station, NJ USA

AIGENT results
Assay: mmrv-29-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	28.5	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
59	PB	64	1	1	3	1.67	6	
59	PB	128	13	14	8	11.67	41	
59	PB	256	9	5	8	7.33	26	
60	PB	512	1	1	3	1.67	6	
60	PB	1024	0	1	1	0.67	2	
60	PB	2048	4	6	2	4.00	14	
60	PB	4096	8	11	10	9.67	34	
61	PB	8192	26	18	26	23.33	82	
61	PB	16384	41	19	37	32.33	113	
61	PB	32768	20	34	33	29.00	102	
61	PB	65536	36	20	32	29.33	103	
62	RK	32	35	26	34	31.67	111	1024
62	RK	64	26	26	30	27.33	96	
62	RK	128	24	29	19	24.00	84	
62	RK	256	29	19	24	24.00	84	
63	RK	512	14	15	12	13.67	48	
63	RK	1024	13	18	5	12.00	42	
63	RK	2048	18	17	15	16.67	58	
63	RK	4096	24	22	26	24.00	84	
64	RK	8192	28	31	35	31.33	110	
64	RK	16384	35	29	28	30.67	108	
64	RK	32768	30	28	44	34.00	119	
64	RK	65536	41	36	34	37.00	130	
65	RK	32	14	21	15	16.67	58	1024
65	RK	64	19	27	17	21.00	74	
65	RK	128	20	22	31	24.33	85	
65	RK	256	21	36	28	28.33	99	
66	RK	512	15	19	8	14.00	49	
66	RK	1024	6	8	14	9.33	33	
66	RK	2048	22	23	21	22.00	77	
66	RK	4096	21	22	32	25.00	88	
67	RK	8192	37	21	25	27.67	97	
67	RK	16384	28	30	27	28.33	99	
67	RK	32768	47	33	16	32.00	112	
67	RK	65536	21	28	21	23.33	82	
68	RK	32	19	22	20	20.33	71	1024
68	RK	64	16	26	22	21.33	75	
68	RK	128	28	26	28	27.33	96	
68	RK	256	32	28	15	25.00	88	
69	RK	512	7	19	17	14.33	50	
69	RK	1024	11	7	12	10.00	35	
69	RK	2048	14	21	20	18.33	64	
69	RK	4096	22	19	34	25.00	88	
70	RK	8192	27	25	22	24.67	87	
70	RK	16384	33	28	28	29.67	104	
70	RK	32768	24	27	28	26.33	92	
70	RK	65536	34	25	23	27.33	96	
71	Neg ctrl	32	28	33	24	28.33	99	<32
71	Neg ctrl	64	27	33	31	30.33	106	
71	Neg ctrl	128	21	26	19	22.00	77	
71	Neg ctrl	256	24	30	24	26.00	91	
72	Neg ctrl	512	20	26	25	23.67	83	
72	Neg ctrl	1024	36	26	22	28.00	98	
72	Neg ctrl	2048	30	34	17	27.00	95	
72	Neg ctrl	4096	18	30	26	24.67	87	
73	Neg ctrl	8192	20	24	29	24.33	85	
73	Neg ctrl	16384	29	45	21	31.67	111	
73	Neg ctrl	32768	19	22	31	24.00	84	
73	Neg ctrl	65536	26	26	12	21.33	75	
74	Neg ctrl	32	32	41	43	38.67	136	<32
74	Neg ctrl	64	30	33	36	33.00	116	

Attachment
PRN Assay Run mmrv-29-02 Data Listing

AIGENT results
Assay: mmrv-29-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	28.5	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
74	Neg ctrl	128	45	36	33	38.00	133	
74	Neg ctrl	256	26	27	41	31.33	110	
75	Neg ctrl	512	30	25	42	32.33	113	
75	Neg ctrl	1024	41	33	35	36.33	127	
75	Neg ctrl	2048	38	17	31	28.67	101	
75	Neg ctrl	4096	29	31	31	30.33	106	
76	Neg ctrl	8192	25	20	21	22.00	77	
76	Neg ctrl	16384	29	28	29	28.67	101	
76	Neg ctrl	32768	26	30	35	30.33	106	
76	Neg ctrl	65536	23	36	24	27.67	97	
77	Neg ctrl	32	44	30	39	37.67	132	<32
77	Neg ctrl	64	19	36	32	29.00	102	
77	Neg ctrl	128	26	28	26	26.67	94	
77	Neg ctrl	256	33	27	38	32.67	115	
78	Neg ctrl	512	29	34	33	32.00	112	
78	Neg ctrl	1024	35	55	30	40.00	140	
78	Neg ctrl	2048	34	31	27	30.67	108	
78	Neg ctrl	4096	32	28	31	30.33	106	
79	Neg ctrl	8192	18	28	38	28.00	98	
79	Neg ctrl	16384	38	42	50	43.33	152	
79	Neg ctrl	32768	42	37	42	40.33	142	
79	Neg ctrl	65536	38	39	48	41.67	146	
80	CMB	32	1	1	0	0.67	2	8192
80	CMB	64	0	1	5	2.00	7	
80	CMB	128	1	5	5	3.67	13	
80	CMB	256	4	12	6	7.33	26	
81	CMB	512	0	2	0	0.67	2	
81	CMB	1024	1	0	0	0.33	1	
81	CMB	2048	2	4	5	3.67	13	
81	CMB	4096	1	6	7	4.67	16	
82	CMB	8192	14	12	12	12.67	44	
82	CMB	16384	19	18	15	17.33	61	
82	CMB	32768	18	24	23	21.67	76	
82	CMB	65536	26	20	28	24.67	87	
83	MKY	32	19	22	12	17.67	62	1024
83	MKY	64	22	30	24	25.33	89	
83	MKY	128	21	24	20	21.67	76	
83	MKY	256	21	27	22	23.33	82	
84	MKY	512	9	6	13	9.33	33	
84	MKY	1024	12	11	10	11.00	39	
84	MKY	2048	16	21	16	17.67	62	
84	MKY	4096	25	35	29	29.67	104	
85	mock		20	38	19			
85	mock		29	36	24			
85	mock		33	29	31			
85	mock		29	31	23			
86			0	0	0			
86			0	0	0			
86			0	0	0			
86			0	0	0			

Attachment
PRN Assay Run mmrv-52-02 Data Listing

results
mmrv-52-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	34.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
FB	32	1	1	0	0.67	2	8192
FB	64	1	0	2	1.00	3	
FB	128	11	11	10	10.67	31	
FB	256	16	10	13	13.00	38	
FB	512	2	3	5	3.33	10	
FB	1024	2	1	3	2.00	6	
FB	2048	3	1	2	2.00	6	
FB	4096	3	5	6	4.67	14	
FB	8192	9	14	12	11.67	34	
FB	16384	24	26	27	25.67	74	
FB	32768	34	36	34	34.67	100	
FB	65536	23	31	28	27.33	79	
FB	32	0	1	0	0.33	1	8192
FB	64	3	1	1	1.67	5	
FB	128	7	5	8	6.67	19	
FB	256	9	10	6	8.33	24	
FB	512	5	4	10	6.33	18	
FB	1024	3	1	0	1.33	4	
FB	2048	4	3	6	4.33	13	
FB	4096	4	10	3	5.67	16	
FB	8192	14	16	9	13.00	38	
FB	16384	9	32	29	23.33	67	
FB	32768	33	58	36	42.33	122	
FB	65536	27	37	32	32.00	93	
FB	32	0	0	1	0.33	1	8192
FB	64	2	2	1	1.67	5	
FB	128	7	8	9	8.00	23	
FB	256	16	5	8	9.67	28	
FB	512	2	1	2	1.67	5	
FB	1024	1	1	2	1.33	4	
FB	2048	9	5	3	5.67	16	
FB	4096	8	7	4	6.33	18	
FB	8192	13	8	11	10.67	31	
FB	16384	30	31	26	29.00	84	
FB	32768	26	38	44	36.00	104	
FB	65536	36	38	30	34.67	100	
PB	32	1	3	1	1.67	5	8192
PB	64	4	6	7	5.67	16	
PB	128	11	8	10	9.67	28	
PB	256	8	8	7	7.67	22	
PB	512	0	0	3	1.00	3	
PB	1024	4	3	5	4.00	12	
PB	2048	5	11	7	7.67	22	
PB	4096	13	20	15	16.00	46	
PB	8192	15	18	12	15.00	43	
PB	16384	29	27	22	26.00	75	
PB	32768	36	39	31	35.33	102	
PB	65536	25	20	29	24.67	71	
PB	32	5	1	3	3.00	9	8192
PB	64	3	6	8	5.67	16	
PB	128	17	12	16	15.00	43	
PB	256	12	4	9	8.33	24	
PB	512	0	3	2	1.67	5	
PB	1024	2	6	4	4.00	12	
PB	2048	7	6	8	7.00	20	
PB	4096	16	8	8	10.67	31	
PB	8192	25	14	6	15.00	43	
PB	16384	18	31	19	22.67	66	
PB	32768	26	34	33	31.00	90	
PB	65536	25	32	47	34.67	100	
PB	32	1	1	1	1.00	3	4096
PB	64	9	6	3	6.00	17	
PB	128	7	8	16	10.33	30	
PB	256	5	4	5	4.67	14	
PB	512	0	0	2	0.67	2	
PB	1024	1	3	3	2.33	7	
PB	2048	8	10	0	6.00	17	
PB	4096	16	10	11	12.33	36	
PB	8192	25	36	16	25.67	74	
PB	16384	25	32	21	26.00	75	
PB	32768	45	42	42	43.00	124	

Attachment
PRN Assay Run mmrv-52-02 Data Listing

results
mmrv-52-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	34.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
PB	65536	33	32	45	36.67	106	
RK	32	29	27	36	30.67	89	1024
RK	64	38	29	36	34.33	99	
RK	128	44	24	47	38.33	111	
RK	256	46	40	32	39.33	114	
RK	512	19	19	14	17.33	50	
RK	1024	14	18	16	16.00	46	
RK	2048	29	21	19	23.00	67	
RK	4096	29	24	17	23.33	67	
RK	8192	35	36	41	37.33	108	
RK	16384	40	45	53	46.00	133	
RK	32768	46	50	28	41.33	120	
RK	65536	24	58	25	35.67	103	
RK	32	19	29	26	24.67	71	1024
RK	64	35	38	30	34.33	99	
RK	128	44	25	36	35.00	101	
RK	256	22	21	35	26.00	75	
RK	512	18	15	11	14.67	42	
RK	1024	13	11	10	11.33	33	
RK	2048	22	18	29	23.00	67	
RK	4096	18	18	29	21.67	63	
RK	8192	27	30	19	25.33	73	
RK	16384	40	33	45	39.33	114	
RK	32768	32	37	33	34.00	98	
RK	65536	31	35	20	28.67	83	
RK	32	17	24	30	23.67	68	1024
RK	64	36	34	34	34.67	100	
RK	128	33	38	42	37.67	109	
RK	256	19	28	36	27.67	80	
RK	512	10	16	11	12.33	36	
RK	1024	12	4	13	9.67	28	
RK	2048	16	21	16	17.67	51	
RK	4096	12	16	35	21.00	61	
RK	8192	50	26	29	35.00	101	
RK	16384	32	40	45	39.00	113	
RK	32768	44	30	34	36.00	104	
RK	65536	33	28	40	33.67	97	
Neg ctrl	32	29	24	38	30.33	88	<32
Neg ctrl	64	38	29	35	34.00	98	
Neg ctrl	128	20	26	22	22.67	66	
Neg ctrl	256	21	15	28	21.33	62	
Neg ctrl	512	23	33	20	25.33	73	
Neg ctrl	1024	37	28	30	31.67	92	
Neg ctrl	2048	36	41	34	37.00	107	
Neg ctrl	4096	29	27	30	28.67	83	
Neg ctrl	8192	23	39	23	28.33	82	
Neg ctrl	16384	32	29	40	33.67	97	
Neg ctrl	32768	40	30	35	35.00	101	
Neg ctrl	65536	24	41	30	31.67	92	
Neg ctrl	32	52	54	39	48.33	140	<32
Neg ctrl	64	57	40	54	50.33	146	
Neg ctrl	128	66	51	47	54.67	158	
Neg ctrl	256	40	49	44	44.33	128	
Neg ctrl	512	52	51	38	47.00	136	
Neg ctrl	1024	42	39	41	40.67	118	
Neg ctrl	2048	36	38	47	40.33	117	
Neg ctrl	4096	44	30	46	40.00	116	
Neg ctrl	8192	38	38	37	37.67	109	
Neg ctrl	16384	35	34	40	36.33	105	
Neg ctrl	32768	38	52	35	41.67	121	
Neg ctrl	65536	36	40	43	39.67	115	
Neg ctrl	32	41	49	46	45.33	131	<32
Neg ctrl	64	53	45	50	49.33	143	
Neg ctrl	128	32	39	49	40.00	116	
Neg ctrl	256	36	46	38	40.00	116	
Neg ctrl	512	40	35	43	39.33	114	
Neg ctrl	1024	27	37	35	33.00	95	
Neg ctrl	2048	36	25	45	35.33	102	
Neg ctrl	4096	32	37	33	34.00	98	
Neg ctrl	8192	45	39	41	41.67	121	
Neg ctrl	16384	40	42	43	41.67	121	

Attachment
PRN Assay Run mmrv-52-02 Data Listing

results
mmrv-52-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	34.58	Valid Assay
Control 1:	[256, 2048]	1024	Valid
Control 2:	[2048, 16384]	8192	Valid

serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
Neg ctrl	32768	51	50	38	46.33	134	
Neg ctrl	65536	35	57	28	40.00	116	
CMB	32	1	0	0	0.33	1	8192
CMB	64	1	1	2	1.33	4	
CMB	128	8	9	7	8.00	23	
CMB	256	7	9	4	6.67	19	
CMB	512	1	0	2	1.00	3	
CMB	1024	0	2	0	0.67	2	
CMB	2048	1	4	3	2.67	8	
CMB	4096	10	12	9	10.33	30	
CMB	8192	10	12	9	10.33	30	
CMB	16384	27	26	38	30.33	88	
CMB	32768	47	36	30	37.67	109	
CMB	65536	28	40	38	35.33	102	
MKY	32	22	25	22	23.00	67	1024
MKY	64	22	37	26	28.33	82	
MKY	128	39	41	40	40.00	116	
MKY	256	28	33	42	34.33	99	
MKY	512	17	18	22	19.00	55	
MKY	1024	14	19	12	15.00	43	
MKY	2048	25	30	27	27.33	79	
MKY	4096	31	26	34	30.33	88	
		0	0	0			
		1	1	1			
		5	8	13			
		6	3	7			
		1	1	2			
		0	2	1			
		1	0	1			
		7	5	7			
		16	13	13			
		19	20	26			
		18	45	36			
		30	32	32			
		11	18	17			
		20	16	18			
		29	26	47			
		35	29	24			
		14	16	21			
		17	18	15			
		26	24	35			
		34	32	32			
		14	9	10			
		17	16	13			
		15	27	26			
		13	8	14			
		0	3	5			
		7	5	10			
		11	12	19			
		20	12	18			
mock		29	37	47			
mock		24	30	36			
mock		27	29	40			
mock		48	33	35			
		0	0	0			
		0	0	0			
		0	0	0			
		0	0	0			

Attachment
PRN Assay Run mmrv-53-02 Data Listing

AIGENT results
Assay: mmrv-53-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	31.25	Valid Assay
Control 1:	[256, 2048]	512	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
51	FB	32	0	0	DO	0.00	0	8192
51	FB	64	1	0	8	3.00	10	
51	FB	128	3	6	13	7.33	23	
51	FB	256	13	9	DO	11.00	35	
52	FB	512	11	7	4	7.33	23	
52	FB	1024	3	0	0	1.00	3	
52	FB	2048	3	1	4	2.67	9	
52	FB	4096	6	6	3	5.00	16	
53	FB	8192	12	14	10	12.00	38	
53	FB	16384	21	26	30	25.67	82	
53	FB	32768	29	22	36	29.00	93	
53	FB	65536	35	38	32	35.00	112	
54	FB	32	0	0	1	0.33	1	8192
54	FB	64	2	4	3	3.00	10	
54	FB	128	7	9	4	6.67	21	
54	FB	256	9	15	5	9.67	31	
55	FB	512	7	9	4	6.67	21	
55	FB	1024	2	1	5	2.67	9	
55	FB	2048	1	2	1	1.33	4	
55	FB	4096	5	8	6	6.33	20	
56	FB	8192	12	18	14	14.67	47	
56	FB	16384	32	25	35	30.67	98	
56	FB	32768	27	24	33	28.00	90	
56	FB	65536	30	38	43	37.00	118	
57	FB	32	0	0	0	0.00	0	8192
57	FB	64	3	5	6	4.67	15	
57	FB	128	4	8	6	6.00	19	
57	FB	256	13	14	19	15.33	49	
58	FB	512	4	6	2	4.00	13	
58	FB	1024	1	1	1	1.00	3	
58	FB	2048	1	4	1	2.00	6	
58	FB	4096	4	6	8	6.00	19	
59	FB	8192	18	15	14	15.67	50	
59	FB	16384	24	20	19	21.00	67	
59	FB	32768	30	33	22	28.33	91	
59	FB	65536	30	35	23	29.33	94	
60	PB	32	2	1	2	1.67	5	4096
60	PB	64	7	4	6	5.67	18	
60	PB	128	12	10	9	10.33	33	
60	PB	256	12	7	5	8.00	26	
61	PB	512	0	1	3	1.33	4	
61	PB	1024	2	1	5	2.67	9	
61	PB	2048	4	4	6	4.67	15	
61	PB	4096	13	10	9	10.67	34	
62	PB	8192	17	19	21	19.00	61	
62	PB	16384	28	38	35	33.67	108	
62	PB	32768	35	39	42	38.67	124	
62	PB	65536	32	20	35	29.00	93	
63	PB	32	2	0	3	1.67	5	4096
63	PB	64	6	3	5	4.67	15	
63	PB	128	10	13	6	9.67	31	
63	PB	256	9	12	7	9.33	30	
64	PB	512	1	1	3	1.67	5	
64	PB	1024	2	3	2	2.33	7	
64	PB	2048	8	7	7	7.33	23	
64	PB	4096	10	8	11	9.67	31	
65	PB	8192	17	17	15	16.33	52	
65	PB	16384	21	32	18	23.67	76	
65	PB	32768	32	30	27	29.67	95	
65	PB	65536	35	30	20	28.33	91	
66	PB	32	2	1	5	2.67	9	4096
66	PB	64	5	5	9	6.33	20	
66	PB	128	12	17	15	14.67	47	
66	PB	256	7	7	11	8.33	27	
67	PB	512	0	0	2	0.67	2	
67	PB	1024	2	1	6	3.00	10	
67	PB	2048	10	4	7	7.00	22	
67	PB	4096	10	9	7	8.67	28	
68	PB	8192	20	27	28	25.00	80	
68	PB	16384	30	24	30	28.00	90	
68	PB	32768	26	34	48	36.00	115	

Attachment
PRN Assay Run mmrv-53-02 Data Listing

AIGENT results
Assay: mmrv-53-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	31.25	Valid Assay
Control 1:	[256, 2048]	512	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
68	PB	65536	26	29	24	26.33	84	
69	RK	32	31	21	17	23.00	74	1024
69	RK	64	27	16	25	22.67	73	
69	RK	128	30	35	39	34.67	111	
69	RK	256	28	31	28	29.00	93	
70	RK	512	17	6	16	13.00	42	
70	RK	1024	11	15	13	13.00	42	
70	RK	2048	23	15	16	18.00	58	
70	RK	4096	28	26	21	25.00	80	
71	RK	8192	36	25	39	33.33	107	
71	RK	16384	32	34	29	31.67	101	
71	RK	32768	32	44	50	42.00	134	
71	RK	65536	30	38	29	32.33	103	
72	RK	32	31	20	19	23.33	75	1024
72	RK	64	22	26	20	22.67	73	
72	RK	128	37	25	30	30.67	98	
72	RK	256	28	29	21	26.00	83	
73	RK	512	8	15	11	11.33	36	
73	RK	1024	14	13	12	13.00	42	
73	RK	2048	22	14	22	19.33	62	
73	RK	4096	27	26	25	26.00	83	
74	RK	8192	16	31	26	24.33	78	
74	RK	16384	23	31	23	25.67	82	
74	RK	32768	35	19	33	29.00	93	
74	RK	65536	22	27	24	24.33	78	
75	RK	32	19	21	32	24.00	77	1024
75	RK	64	17	24	21	20.67	66	
75	RK	128	27	22	33	27.33	87	
75	RK	256	26	23	29	26.00	83	
76	RK	512	12	26	18	18.67	60	
76	RK	1024	9	7	23	13.00	42	
76	RK	2048	14	27	24	21.67	69	
76	RK	4096	39	32	42	37.67	121	
77	RK	8192	37	39	30	35.33	113	
77	RK	16384	29	34	20	27.67	89	
77	RK	32768	28	26	40	31.33	100	
77	RK	65536	33	30	34	32.33	103	
78	Neg ctrl	32	32	28	48	36.00	115	<32
78	Neg ctrl	64	33	42	35	36.67	117	
78	Neg ctrl	128	38	33	30	33.67	108	
78	Neg ctrl	256	26	33	34	31.00	99	
79	Neg ctrl	512	29	21	24	24.67	79	
79	Neg ctrl	1024	31	18	30	26.33	84	
79	Neg ctrl	2048	30	34	41	35.00	112	
79	Neg ctrl	4096	34	26	21	27.00	86	
80	Neg ctrl	8192	36	11	18	21.67	69	
80	Neg ctrl	16384	21	23	30	24.67	79	
80	Neg ctrl	32768	33	35	24	30.67	98	
80	Neg ctrl	65536	12	26	37	25.00	80	
81	Neg ctrl	32	37	42	45	41.33	132	<32
81	Neg ctrl	64 DO		33	31	32.00	102	
81	Neg ctrl	128 DO		39	38	38.50	123	
81	Neg ctrl	256 DO	DO	DO				
82	Neg ctrl	512	25	26	41	30.67	98	
82	Neg ctrl	1024	35	46	50	43.67	140	
82	Neg ctrl	2048	45	42	38	41.67	133	
82	Neg ctrl	4096	39	38	36	37.67	121	
83	Neg ctrl	8192	28	33	28	29.67	95	
83	Neg ctrl	16384	38	37	36	37.00	118	
83	Neg ctrl	32768	36	46	32	38.00	122	
83	Neg ctrl	65536	35	39	39	37.67	121	
84	Neg ctrl	32	38	34	26	32.67	105	<32
84	Neg ctrl	64	39	33	27	33.00	106	
84	Neg ctrl	128	30	33	28	30.33	97	
84	Neg ctrl	256	30	26	24	26.67	85	
85	Neg ctrl	512	35	30	38	34.33	110	
85	Neg ctrl	1024	32	37	30	33.00	106	
85	Neg ctrl	2048	27	29	28	28.00	90	
85	Neg ctrl	4096	25	28	26	26.33	84	
86	Neg ctrl	8192	48	23 DO		35.50	114	
86	Neg ctrl	16384	40	46	33	39.67	127	

Attachment
PRN Assay Run mmrv-53-02 Data Listing

AIGENT results
Assay: mmrv-53-02

Assay Controls	Limits	Result	Validity
Mock:	[10, 40]	31.25	Valid Assay
Control 1:	[256, 2048]	512	Valid
Control 2:	[2048, 16384]	8192	Valid

plate#	serum	Dilution	#plaques	#plaques	#plaques	Average	% of Mock	Titer
86	Neg ctrl	32768	30	32	36	32.67	105	
86	Neg ctrl	65536	32	36	30	32.67	105	
87	CMB	32	0	0	2	0.67	2	8192
87	CMB	64	1	4	1	2.00	6	
87	CMB	128	7	8	6	7.00	22	
87	CMB	256	10	11	6	9.00	29	
88	CMB	512	0	0	0	0.00	0	
88	CMB	1024	0	0	0	0.00	0	
88	CMB	2048	4	4	7	5.00	16	
88	CMB	4096	7	9	10	8.67	28	
89	CMB	8192	12	14	13	13.00	42	
89	CMB	16384	18	20	31	23.00	74	
89	CMB	32768	20	37	43	33.33	107	
89	CMB	65536	40	39	28	35.67	114	
90	MKY	32	15	19	17	17.00	54	512
90	MKY	64	26	21	24	23.67	76	
90	MKY	128	38	22	28	29.33	94	
90	MKY	256	36	26	34	32.00	102	
91	MKY	512	14	15	14	14.33	46	
91	MKY	1024	27	16	24	22.33	71	
91	MKY	2048	27	28	34	29.67	95	
91	MKY	4096	40	27	26	31.00	99	
92			0	1	2			
92			3	3	2			
92			5	5	5			
92			16	1	6			
93			1	0	1			
93			0	0	0			
93			2	2	1			
93			11	5	7			
94			13	14	12			
94			28	20	29			
94			29	21	40			
94			24	35	25			
95			8	17	14			
95			20	27	13			
95			25	42	25			
95			41	41	33			
96			13	19	20			
96			6	10	17			
96			26	18	19			
96			31	35	22			
97			13	12	12			
97			13	16	14			
97			26	20	24			
97			16	12	13			
98			2	7	5			
98			5	2	4			
98			8	8	13			
98			10	12	17			
99	mock		35	29	39			
99	mock		40	35	33			
99	mock		30	33	22			
99	mock		24	27	28			
100			0	0	0			
100			0	0	0			
100			0	0	0			
100			0	0	0			

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Attachment 2

ATTACHMENT #2

MERCK

SUBJECT: Comparison Between the Mumps Wild Type (WT) ELISA (SOP 910.0096) and the Anti-IgG Enhanced Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489) Using the "Original" AIGENT Results

Executive Summary

Mumps Anti-IgG Enhanced Plaque Reduction Neutralization (AIGENT) and Wild Type (WT) ELISA pre-vaccination and Day 42 post-vaccination titers from 565 subjects in the M-M-R®II 007 trial were compared to assess the accuracy of the WT ELISA assay using a serostatus cutoff of 10 Ab units relative to the AIGENT assay using a serostatus cutoff of 32 (1:32 dilution). AIGENT titers presented in this report were obtained using only the pre-specified SOP 874.3489 and validation rules.

Despite that AIGENT titers are measured values and subject to the variabilities inherent in a biological assay, agreement between the ELISA and AIGENT assays was found to be quite good, exceeding 85% for each of the cross-classification measures evaluated (sensitivity, specificity, positive and negative predictive value, and overall percent agreement). The overall agreement rate between the two assays is 90.4% (925/1023) with 469 samples classified as positive in both assays and 456 samples classified as negative in both assays. A pre-vaccination sample was more likely to be classified sero-positive in the AIGENT assay than in the ELISA (12.0% as compared to 2.0%), and a post-vaccination sample was only slightly less likely to be classified sero-positive in the AIGENT assay than in the ELISA (93.0% as compared to 95.1%). The data also demonstrates a positive association between the two assays even within the set of discordant post-vaccination results. With respect to sero-conversion, the overall agreement rate between assays was 93.4% (413/442), with the ELISA being only slightly more likely than the AIGENT to classify a sample as a seroconverter. Among the set of samples that were evaluable in both assays, the sero-conversion rate was 94.8% (419/442) in the ELISA and 92.8% (410/442) in the AIGENT assay.

Background & Objectives

This analysis is based on data from the M-M-R®II 007 trial. The paired pre- and post-vaccination samples from 565 subjects participating in the M-M-R®II 007 trial were tested in the Anti-IgG Enhanced Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489). The same samples were also tested in the Mumps WT ELISA (SOP 910.0096). The purpose of this analysis is to assess the accuracy of the ELISA assay using a serostatus cutoff of 10 Ab relative to the AIGENT assay using a serostatus cutoff of 32 (1:32 dilution). AIGENT titers presented in this report were obtained using only the pre-specified SOP 874.3489 and validation rules [1].

Results

Assay Comparison Using Both Pre- and Post-Vaccination Samples

Sample titers obtained in the AIGENT and ELISA assays are listed for the 565 subjects in the Attachment. Of the 565 subjects tested in the AIGENT assay, 510 had a reportable pre-vaccination titer and 513 had a reportable post-vaccination titer. All 565 subjects had reportable pre- and post-vaccination titers in the Mumps WT ELISA. AIGENT and ELISA titer results for the 1023 samples are presented in Figure 1. To prevent test sample results from overlaying one another in the figure, ELISA titers reported as <10 Ab were replaced by a randomly assigned value of between 1 and 10 Ab, and AIGENT titers were replaced by a randomly assigned value within either 2-fold (<32 or ≥4096) or 1.4-fold (all other titers) of the actual titer. Within Figure 1, the pre- and post-vaccination samples are differentiated by symbol and color. As indicated by the figure, the majority of pre-vaccination samples are in the AIGENT-negative and ELISA-negative quadrant, and the majority of post-vaccination samples are in the AIGENT-positive and ELISA-positive quadrant.

A 2×2 cross-classification table summarizing the sero-status assignments for the 1023 samples is provided in Table 1. Summary measures for assessing the accuracy of the ELISA relative to the AIGENT follow those defined in [2]. The **overall agreement rate between the two assays is 90.4%** (925/1023) with 469 samples classified as positive in both assays and 456 samples classified as negative in both assays. Of the 98 discordant pairs, 29 were positive in the ELISA and negative in the AIGENT, and 69 were positive in the AIGENT and negative in the ELISA. Relative to the AIGENT assay, the **sensitivity of the ELISA assay is 87.2%** (469/538), the **specificity of the ELISA assay is 94.0%** (456/485), the **predictive value of a negative ELISA is 86.9%** (456/525), and the **predictive value of a positive ELISA is 94.2%** (469/498).

Assay Comparison Using Only Pre-Vaccination Samples

To more thoroughly assess the nature of the discrepant pairs, separate 2×2 tables were constructed for the pre- and post-vaccination samples. The sero-status cross-tabulation for the 510 pre-vaccination samples is presented in Table 2. The pre-positive rate was 2.0% (10/510)

in the ELISA and 12.0% (61/510) in the AIGENT assay. The overall agreement rate was 87.3% (445/510) with 442 samples classified as negative in both assays and 3 samples classified as positive in both assays. Of the 65 discrepant pairs, 7 were positive in the ELISA and negative in the AIGENT, and 58 were positive in the AIGENT and negative in the ELISA, providing statistical evidence that a discordant pre-vaccination pair is more likely to be AIGENT positive and ELISA negative than AIGENT negative and ELISA positive (McNemar Exact Two-Sided P-value<0.0001). The pre-vaccination discordant pairs are highlighted in the attachment and listed separately in Tables 5a and 5b.

Assay Comparison Using Only Post-Vaccination Samples

The sero-status cross-tabulation for the 513 post-vaccination samples is presented in Table 3. The post-vaccination positive rate was 95.1% (488/513) in the ELISA and 93.0% (477/513) in the AIGENT assay. The overall agreement rate was 93.6% (480/513) with 466 samples classified as positive in both assays and 14 samples classified as negative in both assays. Of the 33 discordant pairs, 22 were positive in the ELISA and negative in the AIGENT, and 11 were positive in the AIGENT and negative in the ELISA. The test for imbalance approached but did not attain statistical significance (McNemar Exact Two-Sided P-value=0.080). The post-vaccination discordant pairs are highlighted in the Attachment and listed separately in Tables 6a and 6b.

Assay Comparison Based on Sero-Conversion

A 2×2 cross-classification table based on the definitions of sero-conversion for each assay is presented in Table 4. Subjects that are pre-vaccination positive in either the ELISA or AIGENT assay (ELISA titer ≥10 Ab units, AIGENT titer ≥32) are dropped from the assessment of sero-conversion. For the WT ELISA, a subject is defined to respond to vaccine if they are pre-vaccination negative and have a post-vaccination titer ≥10 Ab units. For the AIGENT assay, a subject is defined to respond to vaccine if they are pre-vaccination negative and have a post-vaccination titer that is ≥64 (corresponds to pre- to post-vaccination rise in titer of ≥4-fold). With the exception of the exclusion of 123 samples (samples either did not have one of their AIGENT titers or were pre-vaccination positive in one or both assays), the results mirror those of the post-vaccination titers. The sero-conversion rate was 94.8% (419/442) in the ELISA and 92.8% (410/442) in the AIGENT assay. The overall agreement rate was 93.4% (413/442) with 400 samples classified as converters in both assays and 13 samples classified as non-converters in both assays. Of the 29 discrepant pairs, 19 sero-converted in the ELISA but not in the AIGENT, and 10 sero-converted in the AIGENT but not in the ELISA. The test for imbalance approached but did not attain statistical significance (McNemar Exact Two-Sided P-value=0.136). The discordant pairs are highlighted in the Attachment and listed separately in Tables 7a and 7b. As indicated in Table 4, only 4.3% (19/442) of the evaluable samples were AIGENT negative and ELISA positive, and 2.3% (10/442) were classified in the other direction (i.e., AIGENT positive and ELISA negative).

Discussion & Conclusion

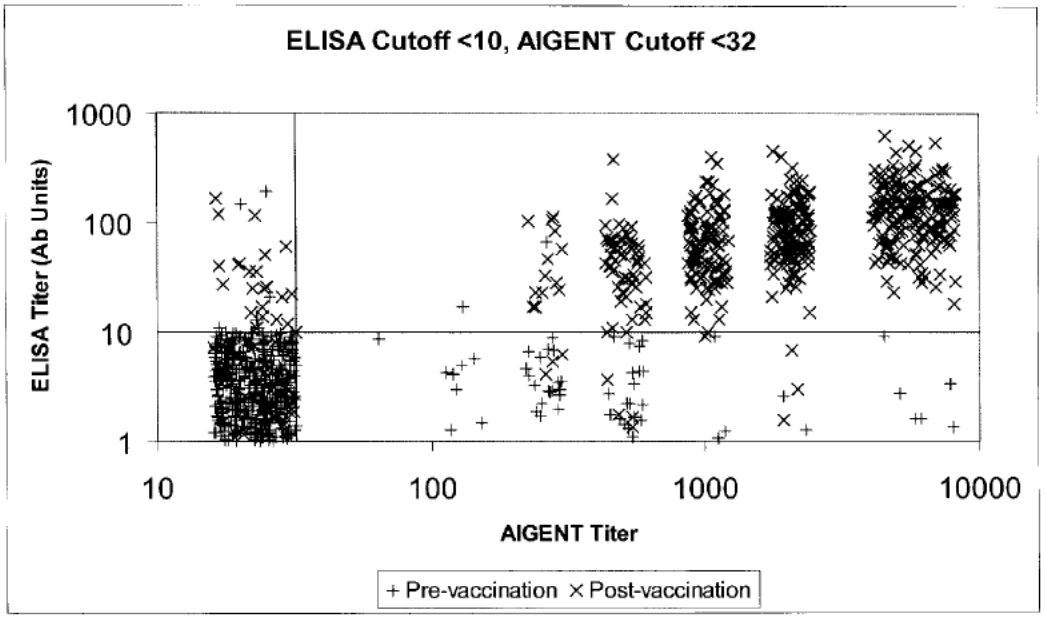
Agreement between the ELISA and AIGENT assays exceeded 85% for each of several cross-classification measures (sensitivity, specificity, positive and negative predictive value, and overall percent agreement). The overall agreement rate between the two assays is 90.4% (925/1023) with 469 samples classified as positive in both assays and 456 samples classified as negative in both assays. Recognizing that the AIGENT titers are measured values and as such are subject to the variabilities inherent in a biological assay, the agreement between assays is considered quite good. Differences between assays were observed depending upon whether the sample was pre-vaccination or post-vaccination. A pre-vaccination sample was more likely to be classified sero-positive in the AIGENT assay than in the ELISA (12.0% as compared to 2.0%), and a post-vaccination sample was slightly less likely to be classified sero-positive in the AIGENT assay than in the ELISA (93.0% as compared to 95.1%). It is noteworthy that, even within the set of discordant post-vaccination results, the data demonstrate a positive association between the two assays. The sero-conversion rate was 94.8% (419/442) in the ELISA and 92.8% (410/442) in the AIGENT assay. With respect to sero-conversion, the overall agreement rate between assays was 93.4% (413/442), with the ELISA being slightly, though not statistically significantly more likely than the AIGENT to classify a sample as positive, as 4.3% (19/442) of the evaluable samples were positive in the ELISA and negative in the AIGENT compared to 2.3% (10/442) that were negative in the ELISA and positive in the AIGENT.

Reference

[1] BB-IND 1016: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, General Correspondence: Response to December 7, 2001 Teleconference Issues, February 4, 2002.

[2] Ingelfinger JA, Mosteller F, Thibodeau LA, Ware JH. Biostatistics in Clinical Medicine. 2nd ed. Macmillan Publishing Co. 1989:1-22.

Figure 1
Titer Comparison Between the Mumps WT ELISA and the AIGENT Assay on Pre- and Post-Vaccination Samples from M-M-R®II 007



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limited access

Table 1
Sero-Status Cross-Classification for M-M-R®II 007 Pre- and Post-Vaccination Samples

		AIGENT		
		>=32	<32	Total
ELISA	>=10	469	29	498
	<10	69	456	525
	Total	538	485	1023

Table 2
Sero-Status Cross-Classification for M-M-R®II 007 Pre-Vaccination Samples

		AIGENT		
		>=32	<32	Total
ELISA	>=10	3	7	10
	<10	58	442	500
	Total	61	449	510

Table 3
Sero-Status Cross-Classification for M-M-R®II 007 Post-Vaccination Samples

		AIGENT		
		>=32	<32	Total
ELISA	>=10	466	22	488
	<10	11	14	25
	Total	477	36	513

Table 4
Sero-Conversion Cross-Classification for M-M-R®II 007

		AIGENT		
		>=32	<32	Total
ELISA	>=10	400	19	419
	<10	10	13	23
	Total	410	32	442

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Table 5a
M-M-R®II 007 Pre-Vaccination Discordant Pairs
AIGENT Negative and WT ELISA Positive Samples (n=7)

				Pre Titer		Post Titer	
AIGENT	**ELISA**	**Genstudy**	**Case**	**AIGENT**	**ELISA**	**AIGENT**	**ELISA**
<32	≥10	7003	00915	<32	21	>4096	153
		7005	01094	<32	191	>4096	156
		7007	02460	<32	11	1024	126
		7010	00503	<32	146	1024	101
		7014	01598	<32	10	512	381
		7015	01837	<32	11	2048	164
		7016	01698	<32	13	>4096	203

Table 5b
M-M-R®II 007 Pre-Vaccination Discordant Pairs
AIGENT Positive and WT ELISA Negative Samples (n=58)

				Pre Titer		Post Titer	
AIGENT	**ELISA**	**Genstudy**	**Case**	**AIGENT**	**ELISA**	**AIGENT**	**ELISA**
≥32	<10	7001	00013	>4096	<10	>4096	44
		7001	00066	512	<10	1024	<10
		7001	00071	128	<10	1024	89
		7001	02532	256	<10	512	58
		7001	02554	512	<10	>4096	157
		7001	02555	>4096	<10	512	42
		7001	02556	512	<10	>4096	142
		7001	02569	256	<10	2048	42
		7001	02576	256	<10	2048	184
		7001	02706	2048	<10	>4096	41
		7001	02732	512	<10	>4096	111
		7001	02766	512	<10	2048	56
		7001	03370	512	<10	512	50
		7001	03388	>4096	<10	1024	30
		7001	03422	256	<10	1024	60
		7001	03426	128	<10	2048	161
		7001	03452	2048	<10	1024	13
		7003	00867	256	<10	512	63
		7003	00932	512	<10	>4096	26
		7004	00966	256	<10	<32	61
		7005	01085	1024	<10	>4096	164
		7005	01097	512	<10	>4096	149
		7005	01124	32	<10	512	166
		7005	01130	512	<10	1024	20
		7006	00268	512	<10	1024	43
		7006	00270	512	<10	>4096	133
		7006	00273	256	<10	2048	79
		7006	00292	512	<10	>4096	71
		7006	00297	512	<10	1024	91
		7007	00195	>4096	<10	2048	194
		7007	00210	256	<10	>4096	288
		7007	02404	256	<10	<32	<10
		7007	02409	512	<10	>4096	70
		7007	02411	512	<10	>4096	315
		7007	02440	512	<10	512	11
		7007	02446	1024	<10	>4096	168

Table 5b (continued)
M-M-R®II 007 Pre-Vaccination Discordant Pairs
AIGENT Positive and WT ELISA Negative Samples (n=58)

				Pre Titer		Post Titer	
AIGENT	**ELISA**	**Genstudy**	**Case**	**AIGENT**	**ELISA**	**AIGENT**	**ELISA**
≥32	<10	7007	02458	256	<10	2048	109
		7007	02463	1024	<10	>4096	97
		7007	02464	256	<10	>4096	95
		7007	02465	>4096	<10	>4096	256
		7007	02478	64	<10	2048	41
		7007	02481	256	<10	>4096	129
		7008	01211	256	<10	2048	140
		7008	01228	128	<10	>4096	332
		7009	00384	512	<10	1024	49
		7009	00392	128	<10	256	84
		7009	00410	512	<10	>4096	152
		7011	01325	128	<10	1024	94
		7011	01358	128	<10	>4096	4085
		7011	01371	128	<10	>4096	168
		7011	01374	256	<10	>4096	72
		7011	01400	256	<10	>4096	112
		7012	00681	512	<10	<32	119
		7014	01472	256	<10	>4096	117
		7014	01578	>4096	<10	2048	41
		7014	01634	256	<10	2048	21
		7016	01709	256	<10	1024	63
		7019	02612	256	<10	>4096	278

Table 6a
M-M-R®II 007 Post-Vaccination Discordant Pairs
AIGENT Negative and WT ELISA Positive Samples (n=22)

				Pre Titer		Post Titer	
AIGENT	**ELISA**	**Genstudy**	**Case**	**AIGENT**	**ELISA**	**AIGENT**	**ELISA**
<32	≥10	7001	02540	<32	<10	<32	15
		7001	02699	<32	<10	<32	36
		7001	02717	<32	<10	<32	51
		7001	02804	<32	<10	<32	12
		7003	00859	<32	<10	<32	11
		7003	00933	<32	<10	<32	17
		7004	00966	256	<10	<32	61
		7007	00133	<32	<10	<32	115
		7007	00166	<32	<10	<32	166
		7007	00223	Deleted	<10	<32	40
		7012	00678	<32	<10	<32	41
		7012	00681	512	<10	<32	119
		7014	01480	<32	<10	<32	14
		7014	01487	<32	<10	<32	25
		7014	01647	<32	<10	<32	21
		7015	01839	<32	<10	<32	36
		7015	01840	<32	<10	<32	25
		7016	01712	<32	<10	<32	13
		7016	01715	<32	<10	<32	26
		7016	01716	<32	<10	<32	42
		7018	02068	<32	<10	<32	27
		7019	02602	<32	<10	<32	22

Table 6b
M-M-R®II 007 Post-Vaccination Discordant Pairs
AIGENT Positive and WT ELISA Negative Samples (n=11)

				Pre Titer		Post Titer	
AIGENT	**ELISA**	**Genstudy**	**Case**	**AIGENT**	**ELISA**	**AIGENT**	**ELISA**
≥32	<10	7001	00031	<32	<10	256	<10
		7001	00066	512	<10	1024	<10
		7001	03371	<32	<10	512	<10
		7003	00874	<32	<10	512	<10
		7005	01092	<32	<10	2048	<10
		7006	00250	<32	<10	512	<10
		7007	00174	<32	<10	256	<10
		7007	02425	<32	<10	512	<10
		7016	01714	<32	<10	256	<10
		7017	01935	<32	<10	2048	<10
		7020	02285	<32	<10	2048	<10

Table 7a
M-M-R®II 007 Sero-Conversion Discordant Pairs
AIGENT Converters and WT ELISA Non-converters (n=10)

		Pre Titer		Post Titer	
Genstudy	Case	AIGENT	ELISA	AIGENT	ELISA
7001	00031	<32	<10	256	<10
7001	03371	<32	<10	512	<10
7003	00874	<32	<10	512	<10
7005	01092	<32	<10	2048	<10
7006	00250	<32	<10	512	<10
7007	00174	<32	<10	256	<10
7007	02425	<32	<10	512	<10
7016	01714	<32	<10	256	<10
7017	01935	<32	<10	2048	<10
7020	02285	<32	<10	2048	<10

Table 7b
M-M-R®II 007 Sero-Conversion Discordant Pairs
WT ELISA Converters and AIGENT Non-converters (n=19)

		Pre Titer		Post Titer	
Genstudy	Case	AIGENT	ELISA	AIGENT	ELISA
7001	02540	<32	<10	<32	15
7001	02699	<32	<10	<32	36
7001	02717	<32	<10	<32	51
7001	02804	<32	<10	<32	12
7003	00859	<32	<10	<32	11
7003	00933	<32	<10	<32	17
7007	00133	<32	<10	<32	115
7007	00166	<32	<10	<32	166
7012	00678	<32	<10	<32	41
7014	01480	<32	<10	<32	14
7014	01487	<32	<10	<32	25
7014	01647	<32	<10	<32	21
7015	01839	<32	<10	<32	36
7015	01840	<32	<10	<32	25
7016	01712	<32	<10	<32	13
7016	01715	<32	<10	<32	26
7016	01716	<32	<10	<32	42
7018	02068	<32	<10	<32	27
7019	02602	<32	<10	<32	22

DATA FOR ATTACHMENT #2

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7001	00002	<32	<10	<32	<10
7001	00004	<32	<10	1024	32
7001	00007	<32	<10	1024	51
7001	00009	<32	<10	1024	36
7001	00011	<32	<10	>4096	120
7001	00013	[redacted]		>4096	44
7001	00019	<32	<10	>4096	1117
7001	00021	<32	<10	2048	52
7001	00022	<32	<10	1024	33
7001	00031	<32	<10	[redacted]	
7001	00032	<32	<10	>4096	72
7001	00035	<32	<10	>4096	46
7001	00061	<32	<10	2048	42
7001	00062	<32	<10	>4096	63
7001	00066	[redacted]			
7001	00071			1024	89
7001	00073	<32	<10	>4096	43
7001	00074	<32	<10	2048	77
7001	00078	<32	<10	2048	128
7001	00090	<32	<10	2048	131
7001	00093	<32	<10	>4096	509
7001	00102	<32	<10	>4096	77
7001	00103	<32	<10	2048	48
7001	00105	<32	<10	512	10
7007	00121	<32	<10	>4096	28
7007	00124	<32	<10	512	76
7007	00125	<32	<10	2048	83
7007	00130	<32	<10	512	59
7007	00133	<32	<10	<32	115
7007	00135	<32	<10	>4096	139
7007	00139	<32	<10	>4096	48
7007	00143	<32	<10	512	58
7007	00151	<32	<10	2048	121
7007	00161	<32	<10	>4096	153
7007	00166	<32	<10	<32	166
7007	00167	<32	<10	>4096	126
7007	00170	<32	<10	512	34
7007	00174	<32	<10	[redacted]	
7007	00176	<32	<10	1024	42
7007	00181	<32	<10	>4096	122
7007	00182	<32	<10	1024	38
7007	00183	<32	<10	>4096	132
7007	00195	[redacted]		2048	194
7007	00202	<32	<10	1024	76
7007	00205	<32	<10	512	31
7007	00210	[redacted]		>4096	288
7007	00211	<32	<10	2048	134
7007	00213	<32	<10	2048	124
7007	00218	<32	<10	1024	100
7007	00223	Deleted	<10	<32	40
7007	00224	<32	<10	1024	42
7006	00243	<32	<10	>4096	99

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

Genstudy	Case	Pre-vaccination Titer PRN	Pre-vaccination Titer ELISA	Post-vaccination Titer PRN	Post-vaccination Titer ELISA
7006	00249	<32	<10	1024	69
7006	00250	<32	<10	[redacted]	
7006	00251	<32	<10	512	23
7006	00258	<32	<10	>4096	91
7006	00267	<32	<10	>4096	122
7006	00268	[redacted]		1024	43
7006	00270			>4096	133
7006	00273			2048	79
7006	00274	<32	<10	2048	59
7006	00281	<32	<10	>4096	206
7006	00287	<32	<10	2048	88
7006	00288	<32	<10	256	17
7006	00290	<32	<10	1024	64
7006	00292	[redacted]		>4096	71
7006	00296	<32	<10	1024	35
7006	00297	[redacted]		1024	91
7006	00298	<32	<10	2048	86
7006	00302	<32	<10	1024	129
7006	00303	<32	<10	>4096	100
7006	00304	<32	<10	1024	25
7006	00305	<32	<10	>4096	100
7006	00307	<32	<10	512	27
7006	00310	<32	<10	512	52
7006	00311	<32	<10	2048	453
7009	00366	<32	<10	256	33
7009	00367	<32	<10	>4096	132
7009	00368	<32	<10	>4096	172
7009	00369	<32	<10	512	68
7009	00370	<32	<10	2048	82
7009	00371	<32	<10	>4096	150
7009	00378	<32	<10	1024	25
7009	00383	<32	<10	<32	<10
7009	00384	[redacted]		1024	49
7009	00385	<32	<10	2048	34
7009	00386	<32	<10	>4096	43
7009	00390	<32	<10	2048	71
7009	00391	<32	<10	2048	59
7009	00392	[redacted]		256	84
7009	00399	<32	<10	>4096	228
7009	00402	<32	<10	1024	237
7009	00404	<32	<10	>4096	71
7009	00406	<32	<10	2048	227
7009	00408	<32	<10	>4096	18
7009	00410	[redacted]		>4096	152
7010	00482	<32	<10	1024	395
7010	00486	<32	<10	256	57
7010	00502	<32	<10	>4096	274
7010	00503	<32	146	1024	101
7010	00504	<32	<10	256	28
7012	00604	Deleted	<10	Deleted	17
7012	00605	<32	<10	2048	41
7012	00606	<32	<10	1024	34

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7012	00607	<32	<10	2048	80
7012	00608	<32	<10	2048	108
7012	00609	<32	<10	>4096	87
7012	00610	<32	<10	>4096	131
7012	00621	<32	<10	>4096	29
7012	00625	<32	<10	2048	94
7012	00629	<32	<10	>4096	111
7012	00630	<32	<10	1024	220
7012	00634	<32	<10	2048	129
7012	00645	<32	<10	>4096	70
7012	00655	<32	<10	2048	397
7012	00656	<32	<10	512	51
7012	00657	Deleted	<10	Deleted	260
7012	00660	Deleted	<10	Deleted	129
7012	00663	Deleted	<10	Deleted	78
7012	00664	<32	<10	512	73
7012	00666	Deleted	<10	Deleted	133
7012	00667	Deleted	<10	Deleted	101
7012	00672	Deleted	<10	Deleted	51
7012	00677	Deleted	<10	Deleted	74
7012	00678	<32	<10	<32	41
7012	00679	Deleted	<10	Deleted	49
7012	00680	Deleted	<10	Deleted	112
7012	00681	[redacted]		<32	119
7002	00721	<32	<10	1024	84
7002	00724	<32	<10	>4096	187
7002	00728	<32	<10	512	72
7002	00736	<32	<10	2048	105
7002	00737	<32	<10	>4096	98
7002	00738	<32	<10	1024	155
7003	00853	<32	<10	>4096	151
7003	00854	<32	<10	2048	49
7003	00858	<32	<10	1024	13
7003	00859	<32	<10	<32	11
7003	00867	[redacted]		512	63
7003	00868	<32	<10	>4096	298
7003	00869	<32	<10	>4096	35
7003	00873	<32	<10	1024	17
7003	00874	<32	<10	[redacted]	
7003	00877	<32	<10	2048	65
7003	00879	<32	<10	1024	44
7003	00896	<32	<10	2048	60
7003	00897	<32	<10	>4096	173
7003	00898	<32	<10	>4096	109
7003	00900	<32	<10	2048	60
7003	00903	<32	<10	>4096	82
7003	00915	<32	21	>4096	153
7003	00917	<32	<10	1024	61
7003	00918	<32	<10	<32	<10
7003	00922	<32	<10	>4096	213
7003	00923	<32	<10	2048	83
7003	00925	<32	<10	>4096	154

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7003	00929	<32	<10	>4096	223
7003	00931	<32	<10	1024	43
7003	00932	[redacted]		>4096	26
7003	00933	<32	<10	<32	17
7003	00937	<32	<10	>4096	195
7003	00940	<32	<10	1024	10
7003	00943	<32	<10	>4096	186
7004	00961	<32	<10	2048	117
7004	00962	<32	<10	256	103
7004	00965	<32	<10	2048	191
7004	00966	[redacted]		<32	61
7004	00968	<32	<10	1024	69
7004	00969	<32	<10	1024	117
7004	00971	<32	<10	512	42
7004	00974	<32	<10	512	48
7004	00979	<32	<10	>4096	88
7004	00983	<32	<10	2048	131
7005	01082	<32	<10	>4096	291
7005	01084	<32	<10	>4096	145
7005	01085	[redacted]		>4096	164
7005	01086	<32	<10	>4096	210
7005	01089	<32	<10	1024	44
7005	01092	<32	<10	[redacted]	
7005	01094	<32	191	>4096	156
7005	01097	[redacted]		>4096	149
7005	01099	<32	<10	1024	165
7005	01108	<32	<10	2048	173
7005	01113	<32	<10	1024	145
7005	01114	<32	<10	>4096	113
7005	01120	<32	<10	>4096	314
7005	01124	[redacted]		512	166
7005	01127	<32	<10	>4096	108
7005	01129	<32	<10	2048	192
7005	01130	[redacted]		1024	20
7005	01136	<32	<10	>4096	123
7005	01137	<32	<10	1024	51
7005	01141	<32	<10	512	49
7005	01143	<32	<10	>4096	158
7005	01144	<32	<10	2048	182
7005	01147	<32	<10	512	22
7005	01150	<32	<10	2048	113
7008	01204	<32	<10	>4096	90
7008	01205	<32	<10	>4096	96
7008	01210	<32	<10	2048	31
7008	01211	[redacted]		2048	140
7008	01219	<32	<10	2048	106
7008	01222	128	17	1024	15
7008	01223	<32	<10	>4096	48
7008	01227	<32	<10	>4096	180
7008	01228	[redacted]		>4096	332
7008	01229	<32	<10	>4096	113
7008	01230	<32	<10	>4096	339

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7008	01233	<32	<10	>4096	311
7008	01236	<32	<10	1024	48
7008	01237	<32	<10	1024	28
7011	01325	[redacted]		1024	94
7011	01327	<32	<10	>4096	239
7011	01340	<32	<10	1024	119
7011	01341	<32	<10	512	93
7011	01345	<32	<10	512	45
7011	01350	<32	<10	<32	<10
7011	01352	<32	<10	1024	174
7011	01354	2048	115	1024	63
7011	01355	<32	<10	1024	80
7011	01358	[redacted]		>4096	4085
7011	01361	<32	<10	2048	71
7011	01365	<32	<10	>4096	449
7011	01368	<32	<10	512	71
7011	01371	[redacted]		>4096	168
7011	01374	[redacted]		>4096	72
7011	01386	<32	<10	512	18
7011	01388	<32	<10	>4096	90
7011	01395	<32	<10	512	45
7011	01396	<32	<10	>4096	155
7011	01400	[redacted]		>4096	112
7011	01402	<32	<10	>4096	116
7011	01403	<32	<10	>4096	104
7011	01406	<32	<10	2048	26
7011	01419	Deleted	<10	Deleted	20
7011	01423	Deleted	<10	Deleted	141
7011	01424	Deleted	<10	Deleted	64
7014	01443	Deleted	<10	Deleted	22
7014	01445	Deleted	<10	Deleted	61
7014	01448	Deleted	<10	Deleted	213
7014	01451	Deleted	<10	Deleted	107
7014	01454	<32	<10	2048	120
7014	01459	<32	<10	2048	116
7014	01460	<32	<10	512	42
7014	01463	<32	<10	1024	49
7014	01467	<32	<10	1024	188
7014	01469	<32	<10	512	92
7014	01471	<32	<10	1024	84
7014	01472	[redacted]		>4096	117
7014	01475	<32	<10	2048	199
7014	01477	<32	<10	1024	51
7014	01480	<32	<10	<32	14
7014	01487	<32	<10	<32	25
7014	01491	<32	<10	2048	46
7014	01497	<32	<10	2048	146
7014	01498	<32	<10	1024	39
7014	01501	<32	<10	2048	59
7014	01505	<32	<10	1024	97
7014	01511	<32	<10	2048	54
7014	01513	<32	<10	512	32

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7014	01519	<32	<10	2048	15
7014	01521	<32	<10	<32	<10
7014	01523	<32	<10	512	70
7014	01530	<32	<10	1024	33
7014	01534	<32	<10	2048	63
7014	01561	<32	<10	512	13
7014	01564	<32	<10	>4096	85
7014	01572	<32	<10	2048	58
7014	01577	<32	<10	512	31
7014	01578	[redacted]		2048	41
7014	01580	<32	<10	1024	66
7014	01582	<32	<10	1024	28
7014	01586	<32	<10	1024	38
7014	01587	<32	<10	>4096	94
7014	01594	<32	<10	1024	160
7014	01597	<32	<10	512	60
7014	01598	<32	10	512	381
7014	01603	<32	<10	2048	107
7014	01608	256	66	512	65
7014	01609	<32	<10	2048	77
7014	01610	<32	<10	1024	52
7014	01615	<32	<10	>4096	295
7014	01623	<32	<10	1024	30
7014	01624	<32	<10	>4096	32
7014	01625	<32	<10	>4096	96
7014	01627	<32	<10	1024	74
7014	01628	<32	<10	<32	<10
7014	01633	<32	<10	<32	<10
7014	01634	[redacted]		2048	21
7014	01636	<32	<10	2048	47
7014	01638	<32	<10	2048	74
7014	01639	<32	<10	>4096	145
7014	01642	<32	<10	2048	63
7014	01647	<32	<10	<32	21
7014	01650	<32	<10	>4096	76
7014	01651	<32	<10	2048	177
7014	01655	<32	<10	1024	182
7014	01656	<32	<10	2048	88
7014	01658	<32	<10	1024	111
7014	01659	<32	<10	1024	86
7016	01698	<32	13	>4096	203
7016	01699	<32	<10	1024	88
7016	01704	<32	<10	<32	<10
7016	01705	<32	<10	>4096	64
7016	01709	[redacted]		1024	63
7016	01712	<32	<10	<32	13
7016	01714	<32	<10	[redacted]	
7016	01715	<32	<10	<32	26
7016	01716	<32	<10	<32	42
7016	01717	<32	<10	1024	29
7016	01721	<32	<10	2048	54
7016	01722	<32	<10	2048	118

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7016	01723	<32	<10	>4096	81
7016	01724	<32	<10	<32	<10
7016	01731	<32	<10	2048	60
7016	01733	<32	<10	>4096	81
7015	01802	Deleted	<10	Deleted	118
7015	01803	Deleted	<10	Deleted	138
7015	01804	Deleted	<10	Deleted	34
7015	01809	Deleted	<10	Deleted	35
7015	01810	Deleted	12	Deleted	205
7015	01811	<32	<10	2048	150
7015	01814	<32	<10	2048	62
7015	01816	Deleted	<10	Deleted	69
7015	01829	Deleted	<10	Deleted	135
7015	01830	Deleted	<10	Deleted	58
7015	01837	<32	11	2048	164
7015	01839	<32	<10	<32	36
7015	01840	<32	<10	<32	25
7015	01841	<32	<10	1024	237
7015	01853	<32	<10	512	55
7015	01856	<32	<10	256	113
7015	01859	<32	<10	2048	49
7015	01860	<32	<10	>4096	216
7015	01862	<32	<10	1024	80
7017	01922	<32	<10	>4096	67
7017	01924	<32	<10	>4096	150
7017	01925	<32	<10	>4096	134
7017	01928	<32	<10	>4096	256
7017	01930	<32	<10	>4096	58
7017	01935	<32	<10	[redacted]	
7017	01936	<32	<10	>4096	97
7017	01942	<32	<10	>4096	132
7017	01943	<32	<10	2048	108
7017	01947	<32	<10	>4096	32
7017	01948	<32	<10	>4096	86
7017	01950	<32	<10	>4096	157
7017	01953	<32	<10	2048	112
7017	01959	<32	<10	>4096	543
7017	01962	<32	<10	>4096	124
7018	02042	<32	<10	1024	41
7018	02043	<32	<10	2048	246
7018	02046	<32	<10	512	15
7018	02047	<32	<10	512	71
7018	02049	<32	<10	512	90
7018	02056	<32	<10	>4096	202
7018	02064	<32	<10	>4096	235
7018	02066	<32	<10	>4096	58
7018	02067	<32	<10	2048	112
7018	02068	<32	<10	<32	27
7022	02162	<32	<10	>4096	134
7022	02165	<32	<10	<32	<10
7022	02168	<32	<10	1024	70
7022	02170	<32	<10	>4096	630

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

Genstudy	Case	Pre-vaccination Titer PRN	Pre-vaccination Titer ELISA	Post-vaccination Titer PRN	Post-vaccination Titer ELISA
7022	02173	<32	<10	>4096	125
7022	02180	<32	<10	256	105
7022	02189	<32	<10	2048	105
7022	02221	<32	<10	2048	87
7022	02225	<32	<10	2048	101
7022	02226	<32	<10	1024	48
7022	02227	<32	<10	1024	91
7022	02229	<32	<10	>4096	96
7022	02237	<32	<10	>4096	134
7022	02240	<32	<10	>4096	203
7022	02242	<32	<10	>4096	286
7022	02243	<32	<10	>4096	76
7022	02244	<32	<10	2048	82
7022	02248	<32	<10	>4096	287
7022	02253	<32	<10	2048	33
7022	02255	<32	<10	>4096	51
7022	02256	<32	<10	>4096	208
7022	02258	<32	<10	>4096	62
7020	02283	<32	<10	2048	62
7020	02285	<32	<10	[redacted]	
7020	02290	<32	<10	512	32
7020	02292	<32	<10	1024	126
7020	02293	<32	<10	1024	63
7020	02294	<32	<10	2048	54
7020	02297	<32	<10	512	40
7020	02308	<32	<10	256	23
7020	02311	<32	<10	>4096	153
7020	02312	<32	<10	512	17
7020	02342	<32	<10	256	24
7020	02349	<32	<10	>4096	304
7020	02350	<32	<10	2048	79
7020	02353	<32	<10	512	31
7020	02355	<32	<10	>4096	34
7020	02358	<32	<10	1024	78
7007	02401	<32	<10	>4096	170
7007	02403	<32	<10	512	19
7007	02404	[redacted]		<32	<10
7007	02405	<32	<10	512	36
7007	02408	<32	<10	2048	84
7007	02409	[redacted]		>4096	70
7007	02411	[redacted]		>4096	315
7007	02412	<32	<10	1024	91
7007	02423	<32	<10	2048	127
7007	02424	<32	<10	512	68
7007	02425	<32	<10	[redacted]	
7007	02427	<32	<10	1024	24
7007	02437	<32	<10	>4096	67
7007	02440	[redacted]		512	11
7007	02441	<32	<10	2048	50
7007	02444	<32	<10	>4096	157
7007	02446	[redacted]		>4096	168
7007	02448	<32	<10	2048	35

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

Genstudy	Case	Pre-vaccination Titer PRN	Pre-vaccination Titer ELISA	Post-vaccination Titer PRN	Post-vaccination Titer ELISA
7007	02449	<32	<10	>4096	145
7007	02452	<32	<10	512	21
7007	02456	<32	<10	>4096	218
7007	02458	[redacted]		2048	109
7007	02460	<32	11	1024	126
7007	02461	<32	<10	512	98
7007	02462	<32	<10	2048	76
7007	02463	[redacted]		>4096	97
7007	02464			>4096	95
7007	02465			>4096	256
7007	02471	<32	<10	1024	120
7007	02475	<32	<10	2048	25
7007	02478	[redacted]		2048	41
7007	02481			>4096	129
7007	02486	<32	<10	>4096	210
7007	02488	<32	<10	256	23
7007	02498	<32	<10	1024	88
7007	02503	<32	<10	>4096	73
7007	02505	<32	<10	1024	342
7001	02529	<32	<10	2048	33
7001	02532	[redacted]		512	58
7001	02540	<32	<10	<32	15
7001	02550	<32	<10	>4096	152
7001	02553	<32	<10	>4096	154
7001	02554	[redacted]		>4096	157
7001	02555			512	42
7001	02556			>4096	142
7001	02558	<32	<10	256	17
7001	02560	<32	<10	2048	41
7001	02561	<32	<10	>4096	69
7001	02565	<32	<10	256	46
7001	02569	[redacted]		2048	42
7001	02572	<32	<10	1024	32
7001	02576	[redacted]		2048	184
7001	02581	<32	<10	2048	68
7001	02584	<32	<10	2048	46
7001	02585	Deleted	<10	Deleted	83
7001	02586	Deleted	<10	Deleted	46
7001	02587	Deleted	<10	Deleted	122
7019	02596	<32	<10	2048	249
7019	02599	<32	<10	1024	140
7019	02600	<32	<10	>4096	174
7019	02601	<32	<10	2048	317
7019	02602	<32	<10	<32	22
7019	02603	<32	<10	512	10
7019	02605	<32	<10	512	26
7019	02607	<32	<10	>4096	208
7019	02611	<32	<10	<32	<10
7019	02612	[redacted]		>4096	278
7001	02657	Deleted	<10	Deleted	16
7001	02658	Deleted	<10	Deleted	149
7001	02667	Deleted	<10	Deleted	19

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

Genstudy	Case	Pre-vaccination Titer PRN	Pre-vaccination Titer ELISA	Post-vaccination Titer PRN	Post-vaccination Titer ELISA
7001	02668	Deleted	<10	Deleted	198
7001	02672	Deleted	<10	Deleted	16
7001	02682	Deleted	<10	Deleted	49
7001	02684	Deleted	<10	Deleted	103
7001	02690	Deleted	<10	Deleted	88
7001	02694	Deleted	<10	Deleted	69
7001	02697	Deleted	<10	Deleted	65
7001	02699	<32	<10	<32	36
7001	02702	<32	<10	2048	192
7001	02704	<32	<10	1024	28
7001	02706	[redacted]		>4096	41
7001	02707	<32	<10	512	40
7001	02710	<32	<10	2048	243
7001	02711	<32	<10	1024	47
7001	02713	<32	<10	2048	83
7001	02714	<32	<10	2048	124
7001	02717	<32	<10	<32	51
7001	02720	<32	<10	1024	31
7001	02724	<32	<10	>4096	216
7001	02725	<32	<10	2048	137
7001	02729	<32	<10	>4096	65
7001	02732	[redacted]		>4096	111
7001	02733	<32	<10	2048	189
7001	02735	<32	<10	2048	127
7001	02744	<32	<10	>4096	155
7001	02747	<32	<10	>4096	47
7001	02749	<32	<10	>4096	53
7001	02754	<32	<10	>4096	180
7001	02759	<32	<10	512	26
7001	02765	<32	<10	>4096	126
7001	02766	[redacted]		2048	56
7001	02770	<32	<10	>4096	141
7001	02773	<32	<10	2048	103
7001	02774	<32	<10	2048	134
7001	02780	<32	<10	1024	69
7001	02784	<32	<10	2048	40
7001	02788	<32	<10	1024	125
7001	02790	<32	<10	>4096	77
7001	02794	<32	<10	>4096	141
7001	02795	<32	<10	2048	66
7001	02797	<32	<10	>4096	150
7001	02799	<32	<10	2048	68
7001	02802	<32	<10	2048	56
7001	02804	<32	<10	<32	12
7001	02816	<32	<10	>4096	23
7001	03363	<32	<10	2048	83
7001	03364	<32	<10	2048	87
7001	03367	<32	<10	>4096	201
7001	03369	Deleted	<10	>4096	63
7001	03370	[redacted]		512	50
7001	03371	<32	<10	[redacted]	
7001	03374	Deleted	<10	32	10

Attachment
M-M-R II Trial 007 Data Listing
Comparison Between Mumps' WT ELISA and AIGENT Assays

		Pre-vaccination Titer		Post-vaccination Titer	
Genstudy	Case	PRN	ELISA	PRN	ELISA
7001	03377	<32	<10	>4096	53
7001	03388	[redacted]		1024	30
7001	03391	<32	<10	>4096	41
7001	03393	<32	<10	2048	46
7001	03422	[redacted]		1024	60
7001	03424	<32	<10	1024	39
7001	03426	[redacted]		2048	161
7001	03427	<32	<10	<32	<10
7001	03430	<32	<10	1024	25
7001	03434	<32	<10	2048	172
7001	03435	<32	<10	512	13
7001	03436	<32	<10	>4096	29
7001	03437	<32	<10	>4096	62
7001	03438	<32	<10	1024	61
7001	03443	<32	<10	2048	47
7001	03450	<32	<10	>4096	132
7001	03452	[redacted]		1024	13
7001	03456	<32	<10	2048	108
7001	03466	<32	<10	2048	182
7001	03467	<32	<10	2048	28
7001	03479	<32	<10	>4096	94
7001	03480	<32	<10	1024	39
7014	03664	<32	<10	2048	90
7014	03665	<32	<10	2048	60
7014	03667	<32	<10	>4096	432
7014	03674	<32	<10	>4096	230
7014	03676	<32	<10	1024	53
7014	03683	<32	<10	>4096	180
7014	03687	<32	<10	2048	89
7014	03690	<32	<10	>4096	144
7014	03693	Deleted	<10	Deleted	34
7014	03702	Deleted	<10	Deleted	210
7014	03704	Deleted	<10	Deleted	218
7014	03707	Deleted	<10	Deleted	82
7014	03709	Deleted	<10	Deleted	176
7011	03723	Deleted	<10	Deleted	30
7011	03728	Deleted	<10	Deleted	71
7011	03731	Deleted	<10	Deleted	162
7011	03733	Deleted	<10	Deleted	174
7011	03736	Deleted	<10	Deleted	140
7011	03737	Deleted	<10	Deleted	14
7011	03738	<32	<10	<32	<10
7011	03739	Deleted	<10	Deleted	333
7011	03741	Deleted	<10	Deleted	102
7011	03745	Deleted	<10	Deleted	158

Shaded results indicate AIGENT-ELISA mismatches.

Attachment 3

ATTACHMENT #3

MERCK

SUBJECT: Expected Mismatch Classification Rates Due to Assay Variability

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SUMMARY

In a comparison between the WT ELISA and AIGENT assays, discordant classifications were observed for 33 of 513 post-vaccination samples tested in both assays. The data were evaluated in an attempt to determine if the number and distribution of the discordant classifications differ from what might be expected given assay variability. Acknowledging certain limitations of the assessment, the analysis indicates that for samples within two standard deviations of the cutoff, the observed number of mismatched sample classifications are within expectation. However, beyond two assay standard deviations (i.e., WT ELISA titer ≥20 Ab units), only one or two mismatches are expected to occur due to assay variability alone, and in this study there were 16 samples having a WT ELISA ≥20 Ab units that were AIGENT negative, and 8 samples having an AIGENT titer ≥512 that were WT ELISA negative. These minor differences at the low end of the spectrum may be accounted for by artificially truncating the sensitivity of the AIGENT assay due to the choice of lowest dilution tested and/or the pro-zone effect inherent to this type of assay.

INTRODUCTION

For many clinical assays, a cutoff is assigned and samples are classified as positive or negative depending upon where their measured result falls in relation to the cutoff. In comparing two assays, it is often of interest to measure the agreement rate between assays in terms of their ability to similarly classify a matching set of samples. In this report we assess how sample proximity to the cutoff affects the likelihood of obtaining a mismatch in classification. This information is then applied to a data set comparing the Mumps AIGENT and WT ELISA assays [1].

STATISTICAL ASSESSMENT

For simplicity, we consider the case in which an assay is compared to itself, meaning that the two assays have the same assay precision, and the distance between a true sample titer and the cutoff is the same for both assays. Table 1 provides expected mismatch classification rates based strictly on assay variability for alternative distances between the true sample titer and the cutoff. The distance is reported in terms of assay standard deviations. For example, if a sample is one standard deviation from the cutoff, and that sample is tested in the same assay on two different occasions, then there is a 26.7% percent chance that the pair of serostatus assignments for that sample will be discordant. The table also provides approximate 95% confidence limits on the number of mismatched pairs for samples of size 100, 50 and 25, assuming the samples are tested in independent assay runs. For example, given 50 samples in which the true titer for each sample is exactly one assay standard deviation from the cutoff, then one would expect to observe between 6 and 20 discordant pairs with 13 being the expected outcome. In general, the relative width of the interval increases as the sample size decreases.

To assess whether the absolute number and distribution of the discordant samples in the comparison between the AIGENT and WT ELISA assays differs from what we would expect to see based strictly on assay variability, the set of 540 positive WT ELISA titers was randomly sampled with replacement 488,000 times (1000 sets of 488). In so doing, the 540 samples are taken to represent the distribution of positive samples in the WT ELISA. This procedure is commonly referred to as "bootstrapping" [2]. The WT ELISA negative samples were not included in the assessment since titers are not measured below 10 Ab units. To include the negative samples would require that some response distribution be imposed on the titers that are <10 Ab units, and the expected number of mismatches would depend heavily on the response distribution chosen. For each sampled titer, two pseudo-responses were created by adding a random error meant to reflect assay variability. The assay %RSD was taken to be 41%, which is a reasonable estimate for both the AIGENT and WT ELISA assays [3, 4]. The first pseudo-response represents a measurement on the sample within the first assay and the second pseudo-response represents a measurement on the same sample within the second assay. The two matching sets of 488,000 results were compared with respect to serostatus assignment using a cutoff of 10 Ab units. The agreement rate was assessed separately for alternative sample groupings according to the distance between the original sampled titer and the cutoff. Essentially, the mismatch rates obtained through the resampling procedure are what we would expect to

observe if the ELISA were compared to itself given the distribution of samples observed in the study. The results of the resampling analysis are provided in Table 2. The 95% confidence interval on the number of mismatched samples was determined using the percentile method [2] and is given by the 2.5^{th} and 97.5^{th} percentiles among the 1000 sample sets. The expected results presented in Table 2 are entirely consistent with the results of Table 1. The actual study results are also provided in Table 2. Relative to the expected rates, it would appear that for samples whose measured values are within two assay standard deviations of the cutoff, the observed number of mismatched sample classifications (e.g., ELISA titers between 10 and 20 Ab units) are within the range of expectation. However, beyond 2 assay standard deviations (i.e., ≥20 Ab units), only one or two mismatches are expected to occur due to assay variability alone, and in this study there were 16 samples having a WT ELISA ≥20 Ab units that were AIGENT negative, and 8 samples having an AIGENT titer ≥512 that were WT ELISA negative.

Inferences from the resampling analysis are limited in that (1) the true titers for the samples are unknown; (2) the negative WT ELISA samples were not included in the resampling procedure as titers are not measured below 10 Ab units; and (3) a similar analysis could not be performed using the AIGENT titers since the proximity of a sample value to the cutoff is difficult to determine given the acknowledged pro-zone effect in the AIGENT assay. It is also noted that the mismatch rates obtained through the resampling procedure represent mismatches in both directions, whereas the observed rates presented in Table 2 are only in one direction (i.e., WT ELISA postive and AIGENT negative). It is likely that this comparison provides for a more appropriate assessment in light of item (2) above. That is, several of the samples that tested negative in the WT ELISA may have had titers close to the cutoff (e.g., 8-9 Ab units), and had they been included in the resampling procedure, would have resulted in an increase (perhaps a doubling) in the number of expected mismatched samples in the neighborhood of the cutoff.

STATISTICAL METHODS

Given a sample is k standard deviations from the cutoff, the probability of obtaining a discordant serostatus assignment between two independent assay runs is given by

$$p_k = P[X < C - k\sigma] \times P[Y \geq C - k\sigma] + P[X \geq C - k\sigma] \times P[Y < C - k\sigma] = 2\Phi(-k)(1 - \Phi(-k))$$

where C denotes the cutoff, σ denotes one assay standard deviation, X and Y are independent $N(k\sigma, \sigma^2)$ random variables, and $\Phi(\cdot)$ denotes the distribution function for a standard normal variable.

In testing a panel of n samples that are each k standard deviations from the cutoff, the expected number of discordant assignments is given by np_k. Approximate $(1-\alpha)100\%$ lower and upper bounds on np_k are based on the binomial distribution and are given by given by

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$$\left(\max j \ni \sum_{x=0}^{j} \binom{n}{x} (p_k)^x (1-p_k)^{n-x} \le \alpha/2, \ \min j \ni \sum_{x=0}^{j} \binom{n}{x} (p_k)^x (1-p_k)^{n-x} \ge 1-\alpha/2 \right).$$

REFERENCES

[1] Internal Memo from J.M. Antonello to A. Shaw: Comparison Between the Mumps Wild Type (WT) ELISA (SOP 910.0096) and the Anti-IgG Enhanced Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489) Using the "Original" AIGENT Results, 8APR2002.

[2] Manly, BFJ. Randomization, Bootstrap and Monte Carlo Methodology in Biology. 2nd ed. London: Chapman & Hall, 1997; 34-41.

[3] Internal Memo from R. Wolchko and J.M. Antonello to D. Krah: Validation of the Anti-IgG Enhanced Mumps Wild Type Plaque Reduction Neutralization Assay (Virus and Cell Biology Research Procedure #874.3489), 27FEB2001.

[4] Internal Memo from R. Mogg to L. Mallette and P. Burke: Assessing the Extravariability Rule and the Specification Limits on the Control Parameters of the Standard Curve Fit and Control Samples in the Mumps "Wild Type" IgG ELISA (SOP No. 910.0096), 5FEB2002.

Table 1
Expected Mismatch Rates Due to Assay Variability as a Function of Distance from the Cutoff

Number of Assay Standard Deviations from the Cutoff	Expected Percentage of Discordant Classifications	No. Samples	Expected No. of Discordant Classifications	Approximate 95% Confidence Bounds	
				Lower	Upper
0	50.0%	100	50	39	60
0.5	42.7%	100	43	32	52
1	26.7%	100	27	17	36
1.5	12.5%	100	12	5	19
2	4.4%	100	4	0	9
2.5	1.2%	100	1	0	4
3	0.3%	100	0	0	2
0	50.0%	50	25	17	32
0.5	42.7%	50	21	14	28
1	26.7%	50	13	6	20
1.5	12.5%	50	6	1	11
2	4.4%	50	2	0	5
2.5	1.2%	50	1	0	2
3	0.3%	50	0	0	1
0	50.0%	25	13	7	17
0.5	42.7%	25	11	5	16
1	26.7%	25	7	2	11
1.5	12.5%	25	3	0	7
2	4.4%	25	1	0	3
2.5	1.2%	25	0	0	2
3	0.3%	25	0	0	1

Table 2
Observed and Expected Mismatch Rates as a Function of Distance from the Cutoff in the Context of the Comparison Between the AIGENT and WT ELISA Assays

		Resampling Procedure				Observed Results			
ELISA Titer Grouping	ELISA Titer Grouping	ELISA Titer Distribution	No. Mismatched Samples	95% CI on No. Mismatched Samples	Percent Mismatched Samples	ELISA Titer Distribution	No. Mismatched Samples	Percent Mismatched Samples of Subgroup	Percent Mismatched Samples of Total
10<=titer<1sd	10<=titer<14.1	12.62	5.10	(1,10)	40.40%	13	4	30.77%	0.82%
1sd<=titer<2sd	14.1<=titer<20	14.64	1.96	(0,5)	13.40%	12	2	16.67%	0.41%
2sd<=titer<3sd	20<=titer<28.3	29.71	0.41	(0,2)	1.40%	31	6	19.35%	1.23%
3sd<=titer<4sd	28.3<=titer<40	36.92	0.03	(0,1)	0.10%	37	2	5.41%	0.41%
4sd<=titer<5sd	40<=titer<56.6	65.74	0.00	(0,0)	0.00%	69	4	5.80%	0.82%
5sd<=titer<6sd	56.6<=titer<80	78.19	0.00	(0,0)	0.00%	77	1	1.30%	0.20%
6sd<=titer<7sd	80<=titer<113.1	81.75	0.00	(0,0)	0.00%	83	0	0.00%	0.00%
7sd<=titer<8sd	113.1<=titer<160	79.62	0.00	(0,0)	0.00%	78	2	2.56%	0.41%
8sd<=titer<9sd	160<=titer<226.2	51.68	0.00	(0,0)	0.00%	49	1	2.04%	0.20%
9sd<=titer<10sd	226.2<=titer<320	23.71	0.00	(0,0)	0.00%	25	0	0.00%	0.00%
11sd<=titer	320<=titer	13.43	0.00	(0,0)	0.00%	14	0	0.00%	0.00%
	Totals:	488	7.49			488	22		4.51%

10/25/2019
Declaration of G. Reilly
EXHIBIT 140

Restricted
Confidential
limited access

Regulatory Liaison FDA Conversation Record

To:	Dr. Keith Chirgwin
Vaccine/Project:	ProQuad™ Vaccine Program
Date of Conversation(s):	October 5, 2004
FDA Contact:	Dr. Herb Smith
Title / Affiliation:	Microbiologist, CBER

Merck Participant: Michael Dekleva

Discussion

Dr. Herb Smith called this morning and informed me that he was FAXing a memo that he had received as a request from Steven Rubin and Lev Sirota (the memo was dated 27 July 2004). The request is to provide additional data to support the appropriateness of the cutoff employed in the mumps ELISA for seropositivity, relative to the plaque reduction neutralization assay.

Attached you will find PDF file of Memo.

:robat Docume

Assignment

M. Dekleva will work with the ProQuad™ team to develop a response.

10/05/04 08:14 FAX 301 827 3532 FDA CBER OVR&R DVRPA ☑002

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: July 27, 2004

From: Steven A. Rubin, OVRR, DVP, HFM-460
Lev Sirota, OBE/DB/VEB, HFM-217

Subject: Review of Merck's 7068-214

To: Herbert Smith, Ph.D., OVRR, DVRPA, HFM-478

Cc: Judy Beeler, MD, OVRR, DVP, HFM-460
Philip Krause, MD, OVRR, DVP, HFM-460
Konstantin Chumakov, Ph.D., DVP, HFM-470
The File: 7068-187

Regulatory Affairs
OCT 05 2004
Dr. Michael Dekleva

Summary:
CBER had recommended use of a wild type mumps virus strain as the target antigen in the ELISA for assessing mumps virus immune responses under this IND. Such an assay was developed and the validation protocol for this assay is the subject of the present IND amendment. This validation protocol was previously reviewed by CBER under IND 1016-114 (serial 62) on February 2, 2001. At that time, a statistical review found the assay's operational characteristics to be acceptable, however, CBER requested that the mumps ELISA seropositive cutoff be justified via use of known mumps neutralizing and non-neutralizing sera. As the sponsor had not yet submitted this data, Herbert Smith and Steven Rubin (CBER) initiated a teleconference with Keith Chirgwin (Merck) on July 06, 2004. Dr. Chirgwin informed CBER that the overall agreement between the ELISA and a CBER approved plaque reduction neutralization assay (used in IND 1016) was 93%. Lev Sirota (CBER) and Steven Rubin met on July 27, 2004 to discuss the relevance of this new information to the ELISA used in IND-7068.

The purpose of IND 7068 is to demonstrate similarity between MMRV and MMR + V induced immune responses. Similarity has been defined as allowing no more than a 5% difference in seroconversion for M, M, and R and no more than a 10% difference for varicella and that GMT's do not differ by more than 1.5 fold. Because MMRV is essentially composed of licensed products and the efficacy of those products has already been demonstrated, there does not exist the need to conduct IND-7068 as an efficacy study. Thus, assays other than virus neutralization, such as the proposed ELISA, can be used to measure mumps virus immunogenicity for this study. Nonetheless, the appropriateness of the cutoff employed in the ELISA for seropositivity should be supported by data demonstrating some relevance with protective levels of antibody (e.g., neutralizing antibody). The sponsor's information that the overall agreement between the ELISA

and the plaque reduction neutralization assay is 93% is encouraging, but it is only a point estimate and does not support the chosen ELISA cutoff per se.

Comments to relay to the sponsor:
While it is not necessary for the ELISA used in this IND to be validated against a virus neutralization assay, some information as to the overall agreement between the ELISA and the plaque reduction neutralization assay would be helpful in providing information on the clinical relevance of the chosen ELISA cutoff for seropositivity. One recommendation would be to use data obtained under IND-1016 to estimate the upper and lower 95% confidence interval for the overall agreement between these two assays. Alternatively, analysis of the ELISA's predictive value in identifying sera that tested positive in a neutralization assay may also be acceptable.

10/05/04 08:14 FAX 301 827 3532 FDA CBER OVR&R DVRPA 001

UNITED STATES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

Number of Pages Faxed (inclusive of cover sheet): _____

Date: _____ Time: _____

To: Dr. DeKlerk

FAX Number: 484-344-2962 Phone Number: _____

MESSAGE: _____

From: _____

Facsimile Numbers: 301-827-3532 (Main) or 301-827-3075 (2nd)
Telephone Number: 301-827-3070

Address: Woodmont Office Center I
1401 Rockville Pike
HFM-475 Suite 370 North
Rockville, MD 20852-1448

KMH:Desktop:C:\DVRPA\Forms\Fax.wpd (07/06/01)

Michael L. Dekleva, Ph.D.
Director
Worldwide Regulatory Affairs
Vaccines/Biologics

Merck & Co., Inc.
P.O. Box 4, BLB-22
West Point PA 19486-0004
Tel 484 344 2789
Fax 484 344 2962
Email: michael_dekleva@merck.com

November 12, 2004

MERCK
Research Laboratories

Jesse Goodman, M.D., MPH, Director
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and Related Products Applications
Document Control Center (HFM-99)
Woodmont Office Center
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1448

Serial No. 221

Dear Dr. Goodman:

BB-IND 7068: Measles (chick embryo cells), Mumps (chick embryo cells), Rubella (WI-38 cells) and Varicella (MRC-5 cells) Virus Vaccine, Live, Attenuated

RESPONSE TO FDA REQUEST FOR INFORMATION

Per the July 27, 2004 CBER memo (Steven A Rubin and Lev Sirota to Herbert Smith; "Review of Merck's 7068-214"; received by Merck & Co., Inc. on October 5, 2004), CBER requested the mumps ELISA seropositive cutoff be justified via use of known mumps neutralizing and non-neutralizing sera. Furthermore, CBER recommended an analysis of the ELISA predictive value in identifying sera that tested positive in the neutralization assay. The sponsor submitted these data in an information package dated June 10, 2002 (BB-IND 1016 serial number 86) which we believe provided information on the clinical relevance of the chosen ELISA cutoff for seropositivity. The following attachment is a summary of key points from Merck's June 10, 2002 information package that we believe are relevant to your most recent information request. However, please refer to that original June 10, 2002 submission for additional details.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to me (484-344-2789) or, in my absence, to Keith Chirgwin, M.D. (484-344-2558).

Sincerely yours,

Michael L. Dekleva, Ph.D.
Director
Worldwide Regulatory Affairs
Vaccines/Biologics

Attachment: Response to FDA for Information

FedEx

Q:\Franklin\Vaccines\Feiler\Letters\MumpsCutoffNov04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Merck & Co., Inc.

2. DATE OF SUBMISSION
NOV 12, 2004

3. ADDRESS (Number, Street, City, State and Zip Code)
Sumneytown Pike
P.O. Box 4, BLB-22
West Point, PA 19486

4. TELEPHONE NUMBER *(Include Area Code)*
(484) 344-2789

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Measles [chick embryo cells] Mumps [chick embryo cells] Rubella [WI-38 cells] and Varicella [MRC-5 cells] Virus Vaccine, Live, Attenuated

6. IND NUMBER *(If previously assigned)*
7068

7. INDICATION(S) *(Covered by this submission)*

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
221

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☒ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.
☐ **TREATMENT IND 21 CFR 312.35 (b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35 (a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT
		IND NUMBER ASSIGNED

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14 NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Jacqueline O. Gress
Senior Medical Program Coordinator
Infectious Diseases/Vacine Clinical Research

Barbara J. Kuter, Ph.D., M.P.H., Director
Laura Digilio, M.D., Associate Director
Luwy Musey, M.D., Associate Director

15 NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Florian Schodel M.D., Executive Director
Infectious Diseases/Vaccine Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16 NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17 SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Michael L. Dekleva, Ph.D., Director **Worldwide Regulatory Affairs, Vaccines/Biologics**		
18 ADDRESS *(Number, Street, City, State and Zip Code)* **Sumneytown Pike** **P.O. Box 4, BLB-22** **West Point, PA 19486**	19. TELEPHONE NUMBER *(Include Area Code)* **(484) 344-2789**	20. DATE NOV 12, 2004

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

FORM FDA 1571 (1/03) **PAGE 2 OF 2**

ATTACHMENT

ATTACHMENT

RESPONSE TO CBER COMMENTS

Introduction:

Per the July 27, 2004 CBER memo (Steven A Rubin and Lev Sirota to Herbert Smith; "Review of Merck's 7068-214"; received by Merck & Co., Inc. on October 5, 2004), CBER requested the mumps ELISA seropositive cutoff be justified via use of known mumps neutralizing and non-neutralizing sera. Furthermore, CBER recommended an analysis of the ELISA predictive value in identifying sera that tested positive in the neutralization assay. The sponsor submitted these data in an information package dated June 10, 2002 (BB-IND 1016 serial number 86) which we believe provided information on the clinical relevance of the chosen ELISA cutoff for seropositivity. The following is a summary of key points from Merck's June 10, 2002 information package that we believe are relevant to your most recent information request. However, please refer to that original June 10, 2002 submission for additional details.

Predictive Value of a Positive ELISA (vs. AIGENT):

The agreement between the mumps Wild Type (WT) ELISA (SOP 910.0096) and the Anti-IgG Enhanced Plaque Reduction Neutralization Assay (AIGENT, SOP 874.3489) assays was assessed through an evaluation of the pre-vaccination and day 42 post-vaccination titers from 565 subjects in the M-M-R®II 007 Trial. For this comparison, serostatus cutoffs for the WT ELISA assay and AIGENT assay were selected as 10 Ab units and 32 (1:32 dilution), respectively.

Of the 565 subjects for which pre-vaccination and post-vaccination titers that were determined using the AIGENT assay, 510 and 513 (N=1023) had reportable pre-vaccination and post-vaccination titers, respectively. Pre-vaccination and post-vaccination titers were reported for all subjects in the ELISA assay. **Table 1** provides the sero-status cross-classification for M-M-R®II for Protocol 007 pre-vaccination and post-vaccination samples.

The overall agreement between the two assays for determining positives or negatives is 90.4% (925/1023) with 469 samples classified as positive in both assays. Of 98 discordant pairs, 29 were positive in the ELISA and negative in the AIGENT assay.
The predictive value of a positive ELISA is 94.2% (469/498*) from the data generated in protocol 007 and analyzed in both the validated WT ELISA and AIGENT assays.

498* = 469 positive in both assays + 29 positive in the ELISA only.

Assay Comparison Based on Sero-Conversion:

With respect to sero-conversion, the overall agreement rate between the assays was 93.4% (413*/442**; **Table 2).** For this data set, subjects that were pre-vaccination positive in either the ELISA or AIGENT assay (ELISA titer ≥10 Ab units, AIGENT titer ≥32) were dropped from the assessment of sero-conversion. For the ELISA, a subject is defined to respond to vaccine if they are pre-vaccination negative and have a post-vaccination titer of ≥10 Ab units. For the AIGENT assay, a subject is defined to respond

to vaccine if they are pre-vaccination negative and have a post-vaccination titer that is ≥64 (corresponds to pre- to post-vaccination rise in titer of ≥4 fold).

*400 samples classified as converters in both assays and 13 samples classified as non-converters in both assays.

** 442 = 400 converters +13 non converters + 29 discordant pairs

Table 1
Sero-status Cross-Classification for M-M-R®II 007
Pre- and Post-Vaccination Samples

		AIGENT		
		≥ 32 cut-off	<32 cut-off	Total
ELISA	≥ 10 cut-off	469	29	498
	< 10 cut-off	69	456	525
	Total	538	485	1023

Table 2
Sero-Conversion Cross-Classification for M-M-R® 007

		AIGENT		
		≥ 64 cut-off	<64 cut-off	Total
ELISA	≥ 10 cut-off	400	19	419
	< 10 cut-off	10	13	23
	Total	410	32	442

10/25/2019
Declaration of G. Reilly
EXHIBIT 141

Case: 23-2553 Document: 45 Page: 417 Date Filed: 12/06/2023

To: Dekleva, Michael L.[michael_dekleva@merck.com]
From: Schodel, Florian
Sent: Sat 7/3/2004 2:39:12 AM
Importance: Normal
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

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 at the time - hope this was captured. Agree with Joe - could not overemphasize the weakness of the PRN (50% specificity!!!!!!).
The roadshows went very well - no surprises really, other than that we should have considered the UK and not even bothered with Belgium.

Florian

-----Original Message-----
From: Dekleva, Michael L.
Sent: Friday, July 02, 2004 8:41 AM
To: Schodel, Florian
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

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 <10 Ab unit cutoff. We requested their concurrence, but never received a response.

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 PRN and WT ELISA, although around the cutoff (<10 Ab units) there's a greater chance of seeing positive results with the PRN rather than ELISA. Perhaps because of that there were slightly higher seroprotection rates reported with WT ELISA vs. PRN in the 007 study (something like 94 vs. 92% - significant?). Nonetheless, we opted for use of WT ELISA for future studies. The main reason for that comfort is described to be because of the assay's greater precision (and though not explicitly stated, greater ease of use and higher throughput).

SO… we are pulling the information together, including all prior CBER communiciations. 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. I spoke with Joe Antonella yesterday, and he re-emphasized that the precision with the PRN assay was very poor, and felt that the 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 data.

How did the "roadshows" go? Any surprises?

Mike

Michael L. Dekleva, Ph.D.
Director, World Wide Regulatory Affairs, Vaccines/Biologics
Phone: (484) 344-2789
FAX: (484) 344-2962
e-mail: michael_dekleva@merck.com

-----Original Message-----

From: Schodel, Florian
Sent: Thursday, July 01, 2004 5:19 PM
To: Dekleva, Michael L.
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Any chance we have enough documentation of the conversations with Kathy?

Florian

-----Original Message-----
From: Dekleva, Michael L.
Sent: Thursday, July 01, 2004 12:21 PM
To: Schodel, Florian
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Florian,
My understanding from Keith is that Steve Rubin is inheriting this program from Kathy so he may be looking for references to information (that we'd already sent CBER and agreed upon) to enhance his understanding. Hopefully it's as simple as that.

Mike

Michael L. Dekleva, Ph.D.
Director, World Wide Regulatory Affairs, Vaccines/Biologics
Phone: (484) 344-2789
FAX: (484) 344-2962
e-mail: michael_dekleva@merck.com

-----Original Message-----
From: Schodel, Florian
Sent: Wednesday, June 30, 2004 3:45 PM
To: Dekleva, Michael L.
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Thanks Mike,

This is a big surprise I thought we had it all squared away with Kathy Carbone…..

Florian

-----Original Message-----
From: Dekleva, Michael L.
Sent: Wednesday, June 30, 2004 3:38 PM
To: Shay, Charlotte
Cc: Antonello, Joseph M; Schodel, Florian
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Charlotte,

Alison and I will get together tomorrow to sort out details of what information had already been sent to CBER and go from there. I'll keep Florian posted, particularly if there's a planned teleconference to Dr. Krause.

Mike

Michael L. Dekleva, Ph.D.
Director, World Wide Regulatory Affairs, Vaccines/Biologics
Phone: (484) 344-2789
FAX: (484) 344-2962
e-mail: michael_dekleva@merck.com

-----Original Message-----
From: Shay, Charlotte **On Behalf Of** Schodel, Florian
Sent: Wednesday, June 30, 2004 11:38 AM
To: Dekleva, Michael L.
Cc: Antonello, Joseph M
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Mike - if Florian needs to be involved in this teleconference, let me know. Florian would want to participate. He's in Europe through 7/06 but I can get the info to him.

Charlotte Shay
Assistant to Florian Schodel, M.D.
Executive Director Vaccines Clinical Research 976
Phone: 484-344-3434
Fax: 484-344-7458
UN271
Email: charlotte_shay@merck.com

-----Original Message-----
From: Dekleva, Michael L.
Sent: Wednesday, June 30, 2004 10:59 AM
To: Morsy, Manal A.; Chirgwin, Keith D.; Antonello, Joseph M
Cc: Fisher, Alison L; Schodel, Florian
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Manal/Alison,
Peggy is seeting up some time for us to discuss exactly what information was sent and when, so I know how best to respond to Dr. Krause's request. Thanks!

Mike

Michael L. Dekleva, Ph.D.
Director, World Wide Regulatory Affairs, Vaccines/Biologics
Phone: (484) 344-2789

FAX: (484) 344-2962
e-mail: michael_dekleva@merck.com

-----Original Message-----
From: Morsy, Manal A.
Sent: Wednesday, June 30, 2004 1:13 AM
To: Chirgwin, Keith D.; Antonello, Joseph M
Cc: Dekleva, Michael L.; Fisher, Alison L; Schodel, Florian
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

Keith - all the information Joe refers to was submitted to CBER and was pulled once again at my request by Alison and used as references in response to questions about this topic received from CBER regarding the rHA IND - all these references are with Alison and I believe the responses have been submitted to CBER just the past week or two - so I think Alison can easily reassemble this information.

mm

Manal Morsy, MD, PhD, MBA
Director
Worldwide Regulatory Affairs
Vaccines/Biologics
manal_morsy@merck.com
tel: 484-344-3785
fax: 484-344-2962

-----Original Message-----
From: Chirgwin, Keith D.
Sent: Tuesday, June 29, 2004 10:13 PM
To: Antonello, Joseph M
Cc: Dekleva, Michael L.; Fisher, Alison L; Schodel, Florian; Morsy, Manal A.
Subject: RE: Comparing Mumps WT ELISA and AIGENT Assay

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. He was suggesting specific criteria for concordance which I am not sure we could meet. 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% of such ELISA low positive sera score negative in the PRN. I do not recall whether we ever did such a subset analysis with low positives - this seems like a problematic approach as the % "false-positive" would depend on which specific sera are selected for inclusion in such an analysis.

Alison and Mike - I believe that Manal organized a series of discussions

with CBER on this topic during 2001-2002 but do not recall whether or when there was any f/u with CBER following that submission that Joe is referring to which was probably late 2001 or early 2002. It would be useful to have the details of what was in that submission as well as any f/u when CBER calls back - please f/u with Manal.

Keith

-----Original Message-----
From: Antonello, Joseph M
Sent: Tuesday, June 29, 2004 6:27 PM
To: Chirgwin, Keith D.
Cc: Dekleva, Michael L.; Fisher, Alison L; Schodel, Florian
Subject: Comparing Mumps WT ELISA and AIGENT Assay

Keith,

In response to your MVX, I know that we prepared, and I assume that we sent an extensive response to CBER (Zoon/Carbone). Manal was involved in assembling that response and it should be in the regulatory files. That response contained:
(1) Results of testing the Mumps WT ELISA standard and controls in the AIGENT assay (this was requested by CBER).
(2) Comparison between the Mumps WT ELISA and the AIGENT assay for 565 subjects from the MMRII 007 trial.
(3) An assessment of the observed mismatch rates for post-vaccination samples as a function of the distance from the cutoff.

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 WT ELISA and a cutoff of 1:32 in the AIGENT assay, so I'm 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 an acceptable substitute for the neutralization assay.

I do agree with your key points that:
(1) We don't really know what a clinically protective level is in either assay; and
(2) The Mumps WT ELISA titers are useful for comparing response distributions/assessing equivalence between treatment groups.

Joe

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EXHIBIT 142

Proposal for Immunogenicity Analyses

The database for the Mumps End Expiry Study is still blinded. All of the safety data and approximately 95% of the serology data (measles, mumps, and rubella) for the baseline, 6-week, and 1-year visits have been screened and cleaned. The only unblinded summary of the mumps Plaque Reduction Neutralization (PRN) data occurred at the time of the interim analysis (February 2001, approximately 600 subjects).

As described in Protocol 007-02 and in the Data Analysis Plan 007-01, the primary immunogenicity analyses for the Mumps End Expiry Study will be based on a per-protocol approach, excluding subjects identified as protocol violators. In addition, for the primary and secondary hypotheses, the per-protocol analysis will be based on subjects who are seronegative at baseline for the assay being summarized. Given the proposal (outlined above) to declare the approximately 300 mumps PRN samples tested during 2002 invalid, Merck proposes that these results be excluded from the per-protocol analysis for the mumps PRN assay. That is, Merck proposes that the primary immunogenicity analyses for the mumps PRN assay be based on a per-protocol approach, excluding subjects identified as protocol violators and excluding subjects whose mumps PRN samples were tested during 2002. In the event that frozen retention samples are obtained from the study sites for some of the invalid mumps PRN samples, and that these retention samples are tested in the mumps PRN assay, Merck proposes that these results be included in the clinical study database and that a separate mumps PRN immunogenicity analysis be performed which includes these results.

As stated in Protocol 007-02 and in the Data Analysis Plan 007-01, all subjects with safety follow-up will be included in the safety analyses.

Risk of Study Failure

The Mumps End Expiry Study was originally powered (overall power of 92.4%, 96.1% power for a single Expiry Group) on a total sample size of 1770 subjects (Protocol Amendment 007-01). It was assumed that approximately 5% wold be seropositive at baseline to mumps (based on the PRN assay – the assay had not been developed at the time, thus there was no data to support this assumption) and that 10% would be lost to follow-up (or for other violations). Thus it was assumed that approximately 1506 subjects (502 per group) would be available for the primary mumps PRN analyses.

The final enrollment for the study was 1997 subjects. Upon CBER's concurrence, it is known that approximately 300 subjects will be excluded from the primary mumps PRN immunogenicity analyses due to the invalidation of the 2002 samples. In addition, based on a preliminary review of the serology data still blinded to treatment group, approximately 14% of the subjects tested positive to mumps at baseline based on the mumps PRN assay and approximately 10% of the subjects were lost to follow-up. Thus Merck projects that only 1290 subjects (430 per group) will be available for the primary mumps PRN analyses.

The goal throughout the development of the mumps PRN assay was to create an assay that achieved a 95% seroconversion rate. Utilizing input from CBER, Merck was able to obtain a seroconversion estimate of 100% (50/50) in the validation of the assay, with a 95% confidence interval of (94.2%, 100%). Based on the lower bound of the confidence interval being less than 95% and the supporting evidence from the interim analysis (the seroconversion estimate of the release group was 94.6%), the true assay performance may be less than 95%. Even with only slight deviations from 95%, the overall power for the study, especially for the lower bound of 90% criterion, is greatly impacted.

Given the stringent criteria set forth by CBER for the study which included both a 5 percentage point equivalence margin and a lower bound criterion of 90%, Merck is concerned that the study may fail on either one or both of the criteria due to the decrease in evaluable sample size and the uncertainty in the mumps PRN assay performance. In the table below (similar to the table found in Protocol 007-01 which did not include the lower bound criterion) are power estimates for the comparison of an Expiry Group to the Release Group based on the expected evaluable sample size of 430 per group. These estimates are calculated based on various hypothetical response rates for the two groups. The power estimates incorporate both the equivalence hypothesis and the lower bound hypothesis.

Table 1
Power to Rule Out a Difference of 5.0 Percentage Points and a Lower Bound of 90%
430 Evaluable Subjects Per Group
Equivalence α=0.05 (One-sided), Lower Bound α=0.025 (One-sided)

Expected True Rate in Control Group	True Decrease Between Control and Mumps Expiry Group		
	0.0 Percentage Points	1.0 Percentage Points	2.0 Percentage Points
96%	97.1%	83.6%	51.9%
95%	**92.5%**[1]	67.5%	30.9%
94%	77.0%	41.4%	13.5%
93%	48.5%	18.4%	4.4%
92%	22.0%	6.1%	1.1%

[1] Based on 502 evaluable subjects in the original protocol, the power was 96.1%.

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EXHIBIT 143

Krah, David

From: Krah, David
Sent: Monday, October 09, 2000 11:12 PM
To: Emini, Emilio A; Shaw, Alan; Margolskee, Dorothy; Washabaugh, Michael W
Cc: Yagodich, Mary
Subject: Update on anti-IgG enhanced mumps neutralization assay

All,
As an update, the SOP for the anti-IgG enhanced mumps Nt assay and training documents for transfer of the assay to Dick Ward's group have been prepared and are being circulated. Training is scheduled to start next Wednesday and should be completed by the follwoing Tuesday. Validation protocols are being prepared. The following attachments provide an update to the status of optimization of the anti-IgG dilution, and a 1:6 dilution appears to provide an "ideal" sensitivity.

Thanks,
Dave

MPS anti-IgG Nt update, Oct 8, 2000.doc

MPS Nt summary anti-IgG titrations, for

Anti-IgG Enhanced Mumps Neutralization Assay-Update: October 8, 2000

Objective: Identify a mumps neutralization assay format using a "wild-type" mumps strain that permits measurement of a ≥95% seroconversion rate in M-M-R®II vaccinees

Assay format:

•"Standard" mumps plaque-reduction neutralization assay using **JL135** "low-passage" Jeryl Lynn™ mumps
+ **anti-human IgG** treatment (30 min) after "primary" neutralization
+ **immunostaining** to visualize plaques

• Sera tested typically @ dilutions 1:32 through 1:4096
  - titer assigned to highest tested dilution producing Nt
  - negative results @ 1:32 dilution
    = negative, <32 titer

Data presented at August 18, 2000 CAS meeting:

Evaluation of seroconversion rates achievable in the Anti-IgG Enhanced Nt

- results from subset of protocol 006 and another set of 60 paired pediatric sera
- 1:4 or 1:8 anti-IgG used
- Seroconversion rate calculated from pre-negative sera (≥4-fold boost)

- **<u>Serum set #1</u>**:
  Subset of sera from protocol 006
  (includes set of 12 sera biased toward non-responders to Jeryl Lynn™ by "standard" Nt)

Seroconversion rates for this set:

Jeryl Lynn™ "standard" Nt: 31/39 =<u>79.5%</u>
JL135 1:4 Anti-IgG Nt: 33/36 = <u>91.7%</u>
JL135 1:8 Anti-IgG Nt: 32/34 = <u>94.0%</u>

Pre-positive rate:

"Standard" Nt:	4/43 = 9%
1:4 Anti-IgG Nt:	2/38 = 5%
1:8 Anti-IgG Nt:	1/35 = 3%

- **Serum set #2:**
  Panel of 60 paired pediatric sera

  Seroconversion rate for this set:
  JL135 + 1:4 Anti-IgG: 47/47 = 100%

  Pre-positive rate:
  1:4 Anti-IgG Nt: 13/60 = 22%
  (7 of these positive at 1 dilution)

- **Overall seroconversion rate observed for 1:4 anti-IgG and JL135**
  = 33/36 + 47/47 = 80/83 = 96%

Conclusions from previous testing with 1:4 anti-IgG

- Measurement of ≥95% seroconversion in vaccinees is achievable
- Pre-positive rate is higher than desirable.
- Continue evaluation of results using optimized anti-IgG amount (target ≤10% pre-positive rate and ≥ 95% seroconversions)

Results of Additional Anti-IgG Titrations Studies Performed Since the August 18 CAS meeting

- Compare Nt titers using 1:4, 1:6 and 1:8 anti-IgG on a panel of pediatric sera

- Results available for approximately 20 paired sera
  - -results from another set of 30 sera available within 1-2 weeks

- Results summary

Serum Classification	No. of sera/total for anti-IgG dilution 1:4	1:6	1:8
Pre-positives	7/29 24%	3/27 11%	2/26 8%
Seroconversions	21/22 95%	21/21 100%	22/23 96%

A summary of the serum titers and number of dilutions that are positive (values in parentheses) is presented in the attached Excel worksheet. The 1:4 anti-IgG dilution continues to provide excess pre-positive results, whereas the lower anti-IgG dilutions provide pre-positive rates within the targeted range (~10%). The 1:8 dilution of anti-IgG provides reduced titers and fewer positive serum dilutions than the 1:6 anti-IgG dilution. The overall recommendation from the current data is to use the 1:6 anti-IgG dilution of anti-IgG lot 01943 for expanded testing to support the

Expiry Trial. Subsequent lots of anti-IgG will need to be calibrated to the current lot to confirm appropriate assay enhancement.

Sheet1

Experiment	Serum #		MPS Nt titer @ anti-IgG dilution (# of dilutions scoring as positive for NT)								
			undil	1:2	1:3	1:4	1:5	1:6	1:7	1:8	
x502-00	Pre pool #1		32 (1)	64 (1)	<32	<32	<32	<32	<32	<32	
	Pre pool #2		64 (2)	<32	<32	<32	<32	<32	<32	<32	
	DK serum			512 (3)		512 (2)				<32	
x520-00	8-30 pre					not tested	<64	<64	<64	<64	
	8-30 post					=512 (4)	=512 (4)	=512 (3)	=512 (3)	=512 (2)	
	8-52 pre					<64	<64	<64	<64	<64	
	8-52 post					=512 (4)	=512 (4)	=512 (3)	=512 (3)	=512 (3)	
	8-55 pre					=512 (2)	256 (1)	<64	=512 (1)	<64	
	8-55 post					=512 (4)	=512 (4)	=512 (3)	=512 (2)	=512 (2)	
	8-59 pre					<64	<64	<64	<64	<64	
	8-59 post					=512 (4)	=512 (4)	=512 (4)	=512 (4)	=512 (4)	
	DK serum					256 (2)					
x530-00	8-19 pre					<32		<32		<32	
	8-19 post					2048 (7)		=4096 (8)		=4096 (8)	
	8-28 pre					<32		<32		<32	
	8-28 post					1024 (6)		1024 (6)		1024 (6)	
	8-32 pre					<32		<32		<32	
	8-32 post					1024 (6)		512 (3)		1024 (4)	
	8-43 pre					<32		<32		<32	
	8-43 post					128 (1)		256 (1)		<32	
	8-41 pre					64 (1)		<32		<32	
	8-41 post					1024 (6)		1024 (6)		1024 (6)	
	DK serum					<32		<32		512 (1)	
x532-00	8-1 pre					<32		<32		<32	
	8-1 post					2048 (7)		2048 (7)		2048 (6)	
	8-2 pre					<32		<32		<32	
	8-2 post					1024 (6)		1024 (6)		2048 (7)	
	8-6 pre					<32		<32		<32	
	8-6 post					256 (2)		256 (1)		256 (1)	
	8-7 pre					<32		not tested		<32	
	8-34 pre					256 (1)		<32		<32	
	8-8 pre					<32		<32		<32	
	8-8 post					1024 (5)		1024 (5)		1024 (4)	
	8-30 pre					256 (2)		256 (1)		<32	
	8-30 post					2048 (6)		2048 (5)		2048 (4)	
	8-38 pre					<32		<32		not tested	

Sheet1

	8-38 post					<32		256 (1)		not tested	
	DK serum					512 (2)		512 (1)		<32	
x535-00	8-21 pre					<32		<32		<32	
	8-21 post					1024 (6)		2048 (6)		2048 (5)	
	8-22 pre					<32		<32		<32	
	8-22 post					1024 (6)		1024 (6)		1024 (6)	
	8-24 pre					<32		<32		<32	
	8-24 post					=4096 (8)		=4096 (8)		=4096 (8)	
	8-26 pre					128 (1)		<32		256 (1)	
	8-26 post					1024 (5)		1024 (4)		512 (2)	
	8-27 pre					<32		<32		<32	
	8-27 post					=4096 (8)		=4096 (8)		=4096 (8)	
	DK serum					256 (1)		<32		<32	
x533-00	8-45 pre					<32		<32		<32	
	8-45 post					1024 (4)		1024 (3)		1024 (3)	
	8-55 pre					512 (3)		256 (1)		<32	
	8-55 post					1024 (5)		1024 (4)		1024 (3)	
	8-10 pre					<32		<32		<32	
	8-10 post					1024 (4)		1024 (3)		1024 (3)	
	8-11 pre					<32		<32		<32	
	8-11 post					=4096 (8)		=4096 (8)		=4096 (8)	
	DK serum					1024 (3)		<32		<32	
x534-00	8-14 pre					<32		<32		<32	
	8-14 post					512 (3)		1024 (4)		512 (2)	
	8-15 pre					<32		<32		<32	
	8-15 post					2048 (7)		=4096 (8)		=4096 (8)	
	8-57 pre					<32		<32		<32	
	8-57 post					1024 (7)		512 (4)		1024 (4)	
	8-59 pre					<32		<32		<32	
	8-59 post					=4096 (8)		=4096 (8)		=4096 (8)	
	8-20 pre					256 (3)		256 (3)		1024 (3)?/4096 (4)?	
	8-20 post					=4096 (8)		=4096 (8)		=4096 (8)	
	DK serum					256 (1)		512 (3)		512 (1)	

10/25/2019
Declaration of G. Reilly
EXHIBIT 144

Anti-IgG Enhanced Mumps Neutralization Assay-Update: October 24, 2000

Objective: Identify a mumps neutralization assay format using a "wild-type" mumps strain that permits measurement of a ≥95% seroconversion rate in M-M-R®II vaccinees

Assay format:

•"Standard" mumps plaque-reduction neutralization assay using **JL135** "low-passage" Jeryl Lynn™ mumps
+ **anti-human IgG** treatment (30 min) after "primary" neutralization
+ **immunostaining** to visualize plaques

• Sera tested typically @ dilutions 1:32 through 1:4096
- titer assigned to highest tested dilution producing Nt
- negative results @ 1:32 dilution
  = negative, <32 titer

Data presented at August 18, 2000 CAS meeting:

Evaluation of seroconversion rates achievable in the Anti-IgG Enhanced Nt

- results from subset of protocol 006 and another set of 60 paired pediatric sera
- 1:4 or 1:8 anti-IgG used
- Seroconversion rate calculated from pre-negative sera (≥4-fold boost)

- **Serum set #1**:

  Subset of sera from protocol 006 (includes set of 12 sera biased toward non-responders to Jeryl Lynn™ by "standard" Nt)

Seroconversion rates for this set:

Jeryl Lynn™ "standard" Nt: 31/39 = 79.5%
JL135 1:4 Anti-IgG Nt: 33/36 = 91.7%
JL135 1:8 Anti-IgG Nt: 32/34 = 94.0%

Pre-positive rate:

"Standard" Nt:	4/43 = 9%
1:4 Anti-IgG Nt:	2/38 = 5%
1:8 Anti-IgG Nt:	1/35 = 3%

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- **<u>Serum set #2:</u>**
  Panel of 60 paired pediatric sera

  Seroconversion rate for this set:
  JL135 + 1:4 Anti-IgG: 47/47 = <u>100%</u>

  Pre-positive rate:
  1:4 Anti-IgG Nt: 13/60 = 22%
  (7 of these positive at 1 dilution)

- **Overall seroconversion rate observed for 1:4 anti-IgG and JL135**
  = 33/36 + 47/47 = 80/83 = <u>96%</u>

Conclusions from previous testing with 1:4 anti-IgG

- Measurement of ≥95% seroconversion in vaccinees is achievable
- Pre-positive rate is higher than desirable.
- Continue evaluation of results using optimized anti-IgG amount (target ≤10% pre-positive rate and ≥ 95% seroconversions)

Results of Additional Anti-IgG Titrations Studies

- Compare Nt titers using 1:4, 1:6 and 1:8 anti-IgG and a panel of pediatric sera

- Results summary

Serum Classification	No. of sera/total for anti-IgG dilution 1:4	1:6	1:8
Pre-positives	7/29 24%	7/58 12%	2/26 8%
Seroconversions	21/22 95%	48/48 100%	22/23 96%

Proposal for Testing a Subset of Samples from the End-Expiry Study (Protocol 007)

- Test ~600 paired sera in AIGENT assay
  - ~200 from each of the three treatment groups (randomized)
  - 1:32 through 1:4096 dilutions
  - 1:6 anti-IgG to enhance neutralization

- Validation runs concurrent with clinical serum testing

Timing:

Assays for subset of 600 paired sera	5 weeks
Validation runs	1-2 weeks
Data analysis and auditing (partly concurrent with assays)	6 weeks
Total	**~10 weeks**

Plans for Transfer of the Anti-IgG Enhanced Neutralization Assay

- SOPs provided, reviewed and demonstrated for the AIGENT assay and immunostaining

- Training workplan prepared to document training

- Assay demonstrated to and performed by two representatives from D. Ward's lab (October 18 through 24)

- Status of assay transfer
  - -Outstanding issues:
    - Contract for testing
    - Reagent transfer
    - Demonstration of assay in D. Ward's lab
    - Validation studies
    - Run assay to confirm assay performance (pre-positive rate, seroconversion rate)
    - Others?

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Declaration of G. Reilly
EXHIBIT 145

To: Krah, David[Krahda@NorthAmerica.msx.merck.com]
Cc: Yagodich, Mary[Yagodicm@NorthAmerica.msx.merck.com]; Schofield, Timothy L.[SCHOFIEL@NorthAmerica.msx.merck.com]; Wolchko, Robin[Wolchkor@NorthAmerica.msx.merck.com]; Washabaugh, Michael W[WashabaM@NorthAmerica.msx.merck.com]; Shaw, Alan[Shawal@NorthAmerica.msx.merck.com]; Sadoff, Jerald C.[sadoff@NorthAmerica.msx.merck.com]; Chirgwin, Keith D.[chirgwik@NorthAmerica.msx.merck.com]; Morsy, Manal A.[Morsyma@NorthAmerica.msx.merck.com]
From: Antonello, Joseph
Sent: Mon 10/30/2000 8:38:29 AM
Importance: Normal
Subject: RE: Validation protocol for the anti-IgG enhanced mumps Nt assay
OPK Validation protocol v.03.doc
mumps JL135 validation 08222000.doc

Dave,

To help in preparing a Mumps PRN Validation Protocol, two recently completed validation protocols are attached. Per our meeting on Friday, I've also listed some of the items to be addressed in the protocol. If you think it useful, I would be happy to review your initial draft prior to circulating for approval.

Intra- and Inter-Assay Precision
Perform six assay runs. Across each of the six runs, test sera from 6 adults (chosen to span a range in titer response). Each run will contain three independent preparations of each of the six samples. The test sample data will be evaluated to (1) Estimate the inter- and intra-assay variability; and (2) Determine a statistically meaningful fold increase in titer when comparing pre and post-vaccination results.

Sero-Status Cutoff (Information on Pre- and Post-Vaccination Rates)
Test ~100 pediatric pre- and post-vaccination samples (since approximately half of these samples have already been tested, the remaining samples can be divided among the six runs used to assess precision). The test sample data will be used to establish a "sero-positivity" cutoff and provide estimates of pre- and post-vaccination sero-positivity rates.

Assay Quality Control Measures
- The mock control and test sample data will be used to establish (1) control criteria on the number of plaques for the mock control; and (2) replicate variability criteria for the mock control and test samples.
- In routine operation, two of the adult samples (one low titer and one high titer) will be included in each assay run as positive controls. Tentative control ranges for these samples will be determined from the validation data.
- The pre- and post-vaccination pediatric sample results will be used to evaluate a retest scheme for "equivocal" samples. The proposed scheme is to retest equivocal samples, where equivocal is defined as neutralizing at only one dilution. Samples will be tested a maximum of three times with a 2 out of 3 rule applied.

Specificity
The study will include an assessment of specificity per your suggestions.

Other Comments/Questions:
- If possible, it would be good to divide the six runs between two analysts. Aside from "analyst" are there any other ruggedness factors that we should be studying?
- The validation will not address ruggedness to IgG lot as only one anti-IgG lot is available for testing. Also because you have data which establishes that the assay is sensitive to anti-IgG concentration, the SOP should address anti-IgG qualification requirements for introducing a new lot of anti-IgG into the assay.

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- In routine operation, should the assay include a negative control comprised of a pool of pre-vaccinated pediatric sera or are the low and high positive controls sufficient?

As always, thank you for your patience and helpfulness.

Joe

From: Krah, David
Sent: Tuesday, October 17, 2000 1:13 AM
To: Schofield, Timothy L.
Cc: Antonello, Joseph; Yagodich, Mary
Subject: RE: Validation protocol for the anti-IgG enhanced mumps Nt assay

Tim,
The seroconversion required to demonstrate that the vaccine appropriately boosted titers requires a pre/post pair comparison. This need to demonstrate the variability and establish what titer for a post is required to show a significant boost from a pre-negative (primarily for pre-negative to be a true seroconversion, although a boost could be shown still with a pre-positive serum) is demonstrated in all of the Nt data (regardless of virus) that has come from from our lab.

Regarding the removal of heterologous antibodies, this is theoretically possible, but not yet proven to be achievable. We are doing experiments to address this, but the removal process may not be effective.

Thanks,
Dave

From: Schofield, Timothy L.
Sent: Thursday, October 12, 2000 11:16 AM
To: Antonello, Joseph; Long, William; Washabaugh, Michael W; Krah, David
Cc: Kriss, Jennifer A.; Barr, Colleen M; Yagodich, Mary; Shaw, Alan; Yancoskie, Elizabeth A.; Haas, Kristin; Olsen, Stephanie P.
Subject: RE: Validation protocol for the anti-IgG enhanced mumps Nt assay

Some comments highlighted below.

From: Krah, David
Sent: Tuesday, October 10, 2000 1:45 PM
To: Schofield, Timothy L.; Antonello, Joseph; Long, William; Washabaugh, Michael W
Cc: Kriss, Jennifer A.; Milliken, Colleen; Yagodich, Mary; Shaw, Alan; Yancoskie, Elizabeth A.; Haas, Kristin
Subject: Validation protocol for the anti-IgG enhanced mumps Nt assay

All,
The following are some thoughts on the validation protocol for the mumps Nt assay to be transferred to Dick Ward's group. The general items include some of those described in the rotavirus Nt assay validation protocol that James Drummond prepared.

I am providing these to get the ball rolling on developing the validation protocol. Dick Ward's group is to be trained next week. We are compiling some additional data on

the anti-IgG Nt responses (pre-positive rate and seroconversions) so that we will have results from ~55 paired sera to help in determining how many sera Dick Ward's group will need to run to show that they are getting comparable data. Also, I would like to factor in to this validation a qualification/calibration of a new lot of anti-IgG. We do not have enough of the current lot to support the entire trial, and my recommendation would be for Dick to obtain a sufficiently large lot and calibrate/qualify for the program.

Test samples: to be provided by CARD (paired pediatric sera) + adult lab volunteer sera (intiially provided by V&CB?)

Sera will be tested following Virus and Cell Biology Res. Proc. No. 874.3489, and results will be reported as the highest serum dilution providing >=50% Nt.

Sera will be run at 8 dilutions (initial 1:16 followed by 7 serial 2-fold dilutions).

Assay validation parameters:

Intra- and inter-assay variability.
This will establish the fold titer difference that is significant between pre and post-vaccination sera run in the same assay.

Will this be the clinical criterion. As I've commented before, traditionally seropositivity/negativity has been used to rate pre- and post-vaccination samples for measles, mumps, and rubella. Fold rise has been used only in the case of pre-positive pairs.

How many sera and how many replicates/assay?
How many replicate assays?

You'll work this out with Joe. Since you're testing another factor in this protocol (IgG source), there is "hidden replication" with that arm - ie., the variability characteristics of the testing of the new IgG source can be pooled with that of you're source. This highlights the fact that the IgG qualification should be performed over several runs, perhaps all the validation runs.

Qualification of anti-IgG lot
Lot 01943 will be used as the reference lot (1:6 dilution optimum)
A new lot of anti-IgG will be tested at 1:4, 1:6 and 1:8 dilutions vs the 1:4, 1:6 and 1:8 dilutions of lot 01943, against a panel of (10-20?) paired pediatric sera. The use level of the new lot will be the dilution that provides Nt titers "most comparable" to those achieved using the 1:6 dilution of lot 01943.

What happens if the dilution level that yields titers "most comparable" to the current lot, nevertheless yield significantly different results from the old lot. It seems like you need some "tolerable difference" criterion, so that the sensitivity is not grossly perturbed (different from that established during your development).

Should the validation also include a requirement for up-front testing to evaluate pre-positive rates (~10% target?) and sroconversion rates (>=95%) for a panel of 50-60? paired pediatric sera?

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.

Specificity is difficult to assess, since this would ideally include paired acute/convalescent sera to each of the viruses in MMR, or pre and post-vaccination sera (for monovalent vaccines). Animla sera would not be applicable for htis assay (since it uses anti-human IgG to enhance Nt).

Is there a way to neutralize the heterologous antibodies?

The above-listed items should address the validation of the assay.
Are there any items that I missed or any other suggestions?

Thanks,
Dave

10/25/2019
Declaration of G. Reilly
EXHIBIT 146

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, vs. MERCK & CO., INC., Defendant.	: CIVIL ACTION : NO. 2:10-04374(CDJ)
IN RE: MERCK MUMPS VACCINE ANTITRUST LITIGATION THIS DOCUMENT RELATES TO: ALL ACTIONS	: Master File No. : 2:12-cv-03555(CDJ)

HIGHLY CONFIDENTIAL - ATTORNEYS' EYES ONLY
February 9, 2018

Videotaped 30(b)(6) deposition of Merck & Co., Inc., through BARBARA KUTER, taken at the offices of Spector Roseman & Kodroff, 1818 Market Street, Suite 2500, Philadelphia, Pennsylvania 19103, beginning at 10:39 a.m., before LINDA ROSSI-RIOS, a Federally Approved RPR, CCR and Notary Public.

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A P P E A R A N C E S :

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A P P E A R A N C E S (cont'd):

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VIDEOGRAPHER: We are going on the record at 10:39 a.m. on February 9, 2018. This is media unit one of the video recorded deposition of Barbara Kuter taken in the matter of United States of America, et al. versus Merck, et al., filed in the United States District Court for the Eastern District of Pennsylvania, Case Number 201 -- 2:10-04374. This deposition is being held at Spector Roseman, located at 1818 Market Street, Suite 2500, Philadelphia, Pennsylvania.

My name is Philip Leaf from the firm Veritext. I am the videographer.

The court reporter is Linda Rossi, also from the firm Veritext.

Would counsel, please, put their appearances on the record?

MS. MAHENDRANATHAN: Hamsa Mahendranathan from Constantine Cannon, for the Relators.

MR. MACORETTA: John Macoretta from Spector Roseman & Kodroff, for the private plaintiffs.

MR. SANGIAMO: Dino Sangiamo from Venable for Merck.

MS. BRYAN: Sally Bryan from Venable for Merck.

MS. DYKSTRA: Lisa Dykstra, Morgan Lewis for Merck.

MR. HOWARD: Tim Howard, in-house counsel at Merck.

VIDEOGRAPHER: Will the court reporter, please, swear in the witness.

- - -

BARBARA KUTER, after having been duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

BY MS. MAHENDRANATHAN:

Q. Good morning.

A. Good morning.

Q. Could you say and spell your

name for the record, please?

A. Sure. It's Barbara Kuter, B-A-R-B-A-R-A, K-U-T-E-R.

Q. Thank you. So I know that you have taken a deposition before. Have you taken a deposition since the last time we met on December 2016?

A. No, I have not.

Q. Have you testified before at a trial or at a hearing?

A. No.

Q. So, as you know, I'm representing the Relators in a case against Merck. I just want to kind of explain some of, like, the rules that will help us, you know, get through this easier. I ask that you do your best to wait for me to finish a question before you try to answer it, and I will do my best to wait for you to finish answering before I ask the next question.

If you could verbalize your questions [sic] as opposed to nodding, that will help the court reporter out. If you don't understand a question, please let me know and I will try to rephrase it in a way

that you can understand.
Is there any reason that you cannot give truthful testimony today?
A. No.
Q. Could you confirm your business address at Merck?
A. It's Post Office Box 4, West Point, Pennsylvania 19486.
Q. You also have a street address?
A. 770 Sumneytown Pike.
Q. What is your position at Merck?
A. I'm an executive director in global medical affairs, responsible for pediatric and adolescent vaccines.
Q. And do you know what a 30(b)(6) deposition is?
A. Yes.
Q. And you have been designated as a 30(b)(6) deponent on behalf of Merck?
A. Yes, I have.
Q. And do you know what topics you have been selected to be the 30(b)(6) deponent on?
A. Yes, I do.

Q. What topics are those?
A. The eight topics on the list.
Q. I am going to get this document --
MS. MAHENDRANATHAN: Mark this as Exhibit 1.
- - -
(Exhibit 30(b)(6)(4)-1, Notice of Rule 30(b)(6) Deposition, was marked for identification.)
- - -
MR. MACORETTA: This can't be Kuter-1.
MS. DYKSTRA: It's 30(b)(6) Number 4.
MR. MACORETTA: 30(b)(6)(4) Number 1.
MS. DYKSTRA: 30(b)(6).
MR. MACORETTA: Okay. 30(b)(6)(4) Number 1. Got it.
BY MS. MAHENDRANATHAN:
Q. Do you know what this document is?
A. Yes, I do.
Q. Is this a 30(b)(6) notice that

we issued to Merck?
A. Correct.
Q. And if you see on page 4 there's a number of topics listed?
A. Yes, I do.
Q. Are you speaking to Topics 1 through 9?
A. No, I'm not. Sorry. Excuse me. 1 through 9, yes. Without information regarding to potency and shelf life.
Q. Understood.
MR. SANGIAMO: This afternoon's witness will also be testifying to some of the activities that Merck undertook in response to outbreaks. And Dr. Krah also testified as a 30(b)(6) witness on the same day as his deposition regarding work he undertook with the CDC and FDA. So Dr. Kuter will not be covering those topics.
MS. MAHENDRANATHAN: Okay.
THE WITNESS: And I believe there's one more clarification, which is on number 4, I'm not addressing

the composition or the manufacture of the mumps vaccine.
MR. SANGIAMO: Correct.
BY MS. MAHENDRANATHAN:
Q. Okay. So excluding the other topics, do you have knowledge on the subjects 1 through 9 as we had just discussed?
A. Yes, I do. Minus the others that we mentioned.
Q. Right.
A. Yes.
Q. Are you prepared to testify on that?
A. Yes, I am.
Q. Who decided that you would testify on these topics?
MR. SANGIAMO: Objection. Calls for speculation. It's a decision made by counsel.
BY MS. MAHENDRANATHAN:
Q. How did you prepare for this 30(b)(6) deposition?
A. I met with counsel in several meetings to discuss the topics.

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Q. When did you meet with counsel?
A. Over the last few weeks.
Q. Who specifically did you meet with?
A. Dino Sangiamo and Sally Bryan. Lisa was present some of the time. Lisa Dykstra. Tim Howard was present some of the time.
Q. Did you meet with anybody else at Merck to prepare for this deposition?
A. I asked one individual to clarify a particular item. Other than that, no.
Q. Who is that individual?
A. Her name is Beth Freer.
Q. Did you review any documents in preparation for this deposition?
MR. SANGIAMO: Just answer that very precisely. Did you review any documents?
THE WITNESS: Yes.
BY MS. MAHENDRANATHAN:
Q. Did any of those documents refresh your recollection?
A. Yes.

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Q. Did you -- have you brought any documents with you today?
A. Yes, this black binder.
Q. And what are these documents?
A. Would you like me to go through the specific table of contents with you?
Q. Sure.
A. Okay. There are 17 items in this book, referred to by respective tabs. The first document describes the CDC statements and the organizational chart including specifically the mission statement for the National Center for Infectious Diseases and Respiratory Diseases.
Number 2 is a list of publications from the CDC on mumps outbreaks. It's noncomprehensive.
Number 3 is information from the CDC "Pink Book" which describes the impact of Merck's mumps vaccine since 1968 in the United States.
Items 4 through 7 deal with information about the outbreaks.
Item 4 is the table

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summarizing outbreaks and Merck's response to each outbreak.
Item 5 discusses the possible causes of US mumps outbreaks.
Item 6 discusses the size and duration of the outbreaks as well as severity of disease experienced by vaccines.
Item 7 is an example from a presentation made at the National Vaccine Advisory Committee meeting in February 2017 by Dr. Ruth Lynfield, which talks about the fact that most outbreaks do, in fact, involve vaccinated persons.
Items 8, 9 and 10 are the ACIP presentations made on mumps specifically by several of the key individuals from CDC on this topic, Dr. Mona Marin and Dr. Marie Marlow. Those are from February, June and October of 2017.
Item 11 is a summary of the mumps vaccine effectiveness rates as reported by the CDC, the WHO and from The Vaccine Textbook.
Item 12 is a publication on the safety and immunogenicity of MMR II

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prepared by myself and some of my colleagues at Merck.
Item 13 is a summary of the Merck seroconversion rates as reported in the "Pink Book," the MMWR and by WHO.
Item 14 is a copy of the response to Interrogatory Number 2 which describes the range of mumps antibody responses.
Item 15 is a table of the studies of the third dose of MMR, studies that were conducted. And that's been adapted from presentations from ACIP as well as from the literature.
Item 16 describes a program called the Merck Investigator Initiated Studies Program and lists specifically the areas of interest. This is direct from the MISP, as its referred to, website.
Item 17, the last item, is a table that summarizes the mumps outbreak related research that involved Merck. And it was created from internal documents.
MS. MAHENDRANATHAN: I'm going to mark this document as Exhibit 2.

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Dino, do you have a copy to mark?
MR. SANGIAMO: Yes. Actually just mark Dr. Kuter's.
- - -
(Exhibit 30(b)(6)(4)-2, Table of contents Exhibits for Dr. Barb Kuter's 30(b)(6) Deposition Feb 9, 2017, was marked for identification.)
- - -
BY MS. MAHENDRANATHAN:
Q. Have you reviewed all of these documents in this binder?
A. Yes, I have.
Q. And you are familiar with them?
A. I am.
Q. I just want to go through them quickly. Tab 1, this is a document from the CDC's website?
A. That's correct.
Q. And then there's a yellow page, I think. Yeah. There's two yellow pages. And then it has a document with the title "National Center for Immunization and Respiratory Diseases"?

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A. Yes.
Q. Is this also from the CDC website?
A. Yes, it is. Yes. Just to clarify, the first page is simply the introduction to the specific mission statement. And behind the yellow page is, in fact, the mission statement itself.
Q. Great. There's a second yellow page in here. What is -- is this document also from the CDC?
A. Yes, it is.
Q. What is this document?
A. Specifically a Q&A document, question and answer document for patients regarding the outbreaks.
Q. And is this -- does this come from the same mission statement website or a different website?
A. It comes from the website that's shown at the very bottom of the page, the link is there.
Q. Going on to Tab 2, is this a document from the CDC website?
A. Yes, it is.

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Q. Now, going to Tab 3, what is this document?
A. This is a summary of the information that's presented in the "Pink Book." The "Pink Book" is formally known as the Epidemiology and Prevention of Vaccine-Preventable Diseases book as noted under the first footnote. It's produced by CDC, and it provides basically comprehensive information about specific vaccines.
Q. So who created this document?
A. I created this with counsel.
Q. The next tab, Tab 4, who created this document?
A. Again, created with counsel.
Q. And then what -- where did the information in this document come from?
A. If you take a look at the very first row, you'll see a source to the publication. And all the publications are then specified at the end of the document on pages 4 and 5. So that's where the information came from.
Q. I'm going to Tab 5. What is this document?

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A. This is an abstract from Merck's August 2017 response to Interrogatory Number 8.
Q. Who created this document?
A. Again, this is the response from the Interrogatory.
Q. This excerpt, who created this excerpt?
A. Again, created with counsel.
Q. So the next page, page 2, has a table?
A. Correct.
Q. Is this also from the -- excerpted from the Interrogatory?
A. No, this is information that we pulled from the respective sources that are listed here to talk about the various factors that have been identified that perhaps may be at play in regards to the outbreaks.
Q. And, again, this table or the following tables through page 19, they were created by you with counsel?
A. That's correct.
Q. Tab 6 is also a table. Who

created this document?
A. Again, created with counsel.
Q. And where did this information come from?
A. From the respective sources that are listed here.
Q. Going to Tab 7, what is this document?
A. So this is a slide, an adaption from a presentation that was made by Dr. -- sorry, Ruth Lynfield at the National Vaccine Advisory Committee meeting in February of 2017.
Q. Is this a publicly available document?
A. Yes, it is.
Q. What is the National Vaccine Advisory Committee?
A. It's a national committee that was put together by Health and Human Services to address vaccine issues.
Q. Is it affiliated with the CDC or any --
A. It's a separate committee.
Q. Is it underneath or anywhere --

any relationship?
A. No. No.
Q. Tab 8 is a PDF, it looks like, of a PowerPoint presentation?
A. Correct.
Q. Who created this document?
A. Again, it's abstracted from the direct ACIP website.
Q. And who made the abstraction? Who took out the slides?
A. It's literally cut and paste from the PDF.
Q. So it's the whole PDF?
A. Yes, exactly. Yes.
Q. Tab 9?
A. Same thing.
Q. Same thing?
A. Yes.
Q. Created by the CDC?
A. Correct.
Q. And Tab 10?
A. Same thing.
Q. Also this document was also created about the CDC?
A. Yes.

Q. So Tab 11 is a table. Who created this document?
A. Again, myself in coordination with counsel.
Q. Where did this information come from?
A. The sources are listed under Column B.
Q. And you and counsel decided which information to include in this table?
A. Yes, this is a summary of information from CDC and WHO publications and The Vaccine Textbook.
Q. How did you decide which sources to include in this table?
A. We limited them to the CDC, the WHO and The Vaccine Textbook.
Q. So this should be -- is an exhaustive listing?
A. It should be.
Q. What is this document in Tab 12 again?
A. Tab 12 is a publication that was -- publication we together and published in the Pediatric Infectious Disease Journal

in September 2016, talking about the safety and immunogenicity of MMR II over the time period from 1998 to 2009.
Q. And then going to Tab 13, this is another table. Who created this table?
A. Again, myself with counsel.
Q. And what are the sources of the information in this table?
A. The same. Look at -- I'm sorry, Column B please, the sources are listed.
Q. Tab 14. We're almost done. What is this document?
A. So this is information that was extracted from the December 2016 response to Interrogatory Number 2.
Q. And who compiled this information?
A. Again, myself with counsel.
Q. What is the document in Tab 15?
A. Tab 15 is a summary of the studies of the third dose of MMR.
Q. Who created this table?
A. Again, myself with counsel.

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Q. Where was this information compiled from?
A. It's adapted from the ACIP presentation by Dr. Marlow in October 2005 as well as the referenced publications that you will find at the very end.
Q. What is the -- moving to Tab 16. What is this document in Tab 16?
A. This is a direct copy of the information that sits on Merck's website called EngageZone. It describes the mission statement for our Investigator Studies Program known as the MISP program.
Q. Are these two different website pages?
A. They're the same website. The second page describes the specific areas of interest for research for measles, mumps, rubella, and varicella.
Q. I see the website at the bottom, engagezone msd.com/varicella. That encompasses the measles, mumps, and varicella issues?
A. Yes, it does.
Q. Finally Tab 17, this is a

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table. Who created this table?
A. I did with counsel.
Q. And what does it show?
A. These are the studies specifically that Merck was involved in with regards to mumps outbreaks.
Q. Where does this information come from?
A. It comes from the protocols that we received for these studies. It comes from the reports that were prepared by the investigators who did the research.
Q. Thank you.
A. You're welcome.
Q. I have a system here. I'm going to ask you some questions, and I'm going to use the phrase "Merck's mumps vaccine." When I say that, I mean any vaccine that Merck manufactures that has a mumps component that contains its mumps vaccine. So that would include ProQuad, MMR II, at one point Mumpsvax. Does that make sense?
A. Yes.
Q. I'm going to be talking

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about -- well, let me ask you this: How would you -- what would you call somebody who has been inoculated with a vaccine?
A. Vaccine recipient.
Q. Recipient, that's the phrase I will use, then, when I talk about them.
So in these -- any of these questions I'm asking about Merck's mumps vaccine, if your answer would depend on which particular vaccine, for example, if it's specific to ProQuad, please feel free to clarify that in your answer.
How well does Merck's -- the mumps component of Merck's mumps vaccine protect vaccine recipients from mumps today?
A. It protects very well.
Q. Very well. Can you quantify that?
A. I'd be happy to. If you look at the CDC website, you will see that the median response to a single dose is 78 percent and the median response to two doses is 88 percent. If you'll turn to Tab 11, you will see multiple sources showing both the one dose and the two dose effectiveness,

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this will be Columns C and D with the appropriate references next to them, ranging from 1998 up until the time period of 2018. Basically there's been very little change in that effectiveness over that time period. Again, with the last notation here directly from the CDC website showing 78 percent for a single dose and 88 percent for two doses.
Q. So this effectiveness information listed in this table, it comes from what sources?
A. The multiple sources that are shown in Column E.
Q. So in Column B as in boy?
A. Sorry. The reference is in Column E as in Edward.
Q. Okay. Are these sources -- strike that.
Do any of these sources include Merck studies?
A. In these, no.
Q. No. So all of these studies are CDC studies or other organization studies?
A. Yes.

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Q. What organizations have studied -- strike that.
Who has conducted these studies?
A. So the majority of these studies have been conducted by the CDC. You'll also see some references here to publications outside the US, specifically Canada, for example. A few publications in Spain where the Jeryl Lynn strain has been used.
Q. And Merck relies on these studies for its understanding of how well the mumps component of Merck's mump vaccine works?
A. Yes, we do.
Q. Does Merck conduct its own studies to assess how well the mumps component of Merck's mumps vaccine works?
A. Of effectiveness, no.
Q. Not effectiveness. Does Merck conduct any other studies to assess how well the mumps component of Merck's mumps vaccine works?
A. If you want to take a look at -- if you want to take a look at Tab 12, the publication. This is a summary of, again,

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our studies of the safety and immunogenicity in clinical trials conducted between 1998 and 2009. And basically if you want to turn to page 1015, in the paragraph in the right-hand column that says, "Immunogenicity," "Dose 1," you'll see that this is a summary of the data from 20 different studies. In regards to mumps, it specifically says the seroconversion rates by study were remarkably consistent over time ranging from -- I'll move to mumps, 97.7 percent to 100 percent for mumps. The analysis of the immunogenicity over time indicated there was no change in the performance of the measles, mumps, and rubella components of the vaccine over the 21 years in which immunogenicity was assessed.
Q. I actually brought my own copy of this document. I'm going to -- if you give me a minute, I'm going to pull it out.
So if we look at page 1013, what is this table here?
A. This is the table of the 23 studies that were included in this analysis.
Q. And are all of these studies --

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strike that.
Did all of these studies collect immunogenicity data?
A. Yes.
Q. I just want to point you to -- I tricked you -- I'm sorry.
I want to point you to row 21 and 23. I don't thing they collected -- they note that they did not collect the immunogenicity data.
A. I appreciate the correction. Thank you.
Q. No problem. Based on what it says, if we go back to page 1015, under "Dose 1," it notes that 20 percent -- "Across the 20 studies with immunogenicity data after a first dose of MMR II...." So does that indicate to you that 20 of these studies had first dose immunogenicity data?
A. Correct.
Q. And if you look at row 19, in the comments column it notes that "373 of the 1279 subjects received a second dose of MMR II in the same study. No immunogenicity data were collected after the second dose."

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I'm not sure if this is the one that's excluded such that the remaining are the list of 20 studies. Are you familiar with which 20 studies are the first dose studies?
A. Yes, I am. I'll take you to row 18, please.
Q. Okay.
A. Row 18 is four- to six-year-olds, so they had already received the first dose of MMR.
Q. Thank you.
A. And then the others are row 21 and 22. So that gives you 20.
Q. Thank you. Okay. The study in row 18 has immunogenicity data for the second dose?
A. Correct.
Q. Thank you. Do you know what kinds of immunogenicity tests were used in this study?
A. If you would --
MR. SANGIAMO: Object to the form. You said "this study," do you mean the --
MS. MAHENDRANATHAN: Oh, thank

you.
BY MS. MAHENDRANATHAN:
Q. Do you know what types of immunogenicity tests were used in these 21 immunogenicity studies?
A. Yes.
Q. And which -- what types?
A. If you'll turn to page 1012, please. Under "Assessment of Immunogenicity," under the third full paragraph you'll see that it says, "Appropriately sensitive enzyme-linked immunoabsorbent assays are used for the measure of the immune response to measles, mumps and rubella."
Q. Enzyme-linked immunoabsorbent assays, can I call that an ELISA assay?
A. Yes.
Q. Is that how it's referenced?
A. Yes.
Q. Do you know what the serostatus cutoff was for the 21 immunogenicity studies?
A. It was the cutoff that was established in the studies by the lab. I don't remember the cutoff.
Q. You don't remember the cutoff.

Staying on page 1012, just further down in the paragraph, it says -- so right after appropriately linked -- "...enzyme-linked immunoabsorbent assays were used for the measure of the immune response to measles, mumps and rubella," it then says, "The antigens used were representative of wild-type (low passage) or vaccine-type viruses."
Do you know which antigens were used in these 21 immunogenicity studies?
A. The same antigen for all of them.
Q. The same for all of them?
A. Yes.
Q. Do you know which one it was?
A. I believe it's the Jeryl Lynn strain.
Q. Was it a low passage Jeryl Lynn strain?
A. I'm not an expert on the assays.
Q. Understood. The next sentence says, "For measles and rubella, the assay

cut-offs for determining seroconversion were correlated with levels considered protective in terms of the World Health Organization (WHO) standards."
Does mumps have a level that's considered protective under the WHO standards?
A. Not that I'm aware of.
Q. So looking back to the table of the studies, on page 1013, you don't know -- just to confirm, you don't know what the serostatus cutoff was for each of these studies?
A. It's the same for all of them.
Q. It's the same for all of them?
A. Yes, it is.
Q. Could it be 10 Ab units?
A. I honestly don't remember, I'm sorry.
Q. You don't remember.
Do you know where that serostatus cutoff came from?
A. From the evaluations done in our own laboratory.
Q. What evaluations were those?
A. To determine a cutoff as they

do for these assays. Again, I'm not an expert in this area.
Q. So there was one methodology of ELISA used for all of these studies?
A. Yes, that's correct.
Q. And they used the serostatus cutoff that was established in Merck's lab?
A. Yes.
Q. Do you know when that was?
A. I don't recall.
Q. Do you know if that serostatus cutoff came out of Protocol 007?
A. It was before that.
Q. It was before that. Did it come out of Protocol 006?
A. Again, before that. These studies go back to 1988.
Q. Is there an average level of protection that Merck understands is what the mumps component of Merck's mumps vaccines affords to vaccine recipients?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. You can answer if you

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understand my question.
A. I am not able to answer that question. Again, I don't have that expertise.
Q. Does Merck know, does anyone at Merck know the answer to that question?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't know.
BY MS. MAHENDRANATHAN:
Q. Has the level of protection afforded by the mumps component of Merck's mumps vaccines changed over time?
MR. SANGIAMO: Object to the form. You can answer if you understand the question.
THE WITNESS: Again, I just went through Tab 11 with you and told you that based on the significant information that's presented here, we don't see any real change in the effectiveness over time.
BY MS. MAHENDRANATHAN:
Q. And that is based on studies outside of Merck?
A. Yes.

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Q. Has Merck done any studies of its own to establish whether the level of protection afforded by the mumps component of Merck's mumps vaccine has changed over time?
MR. SANGIAMO: Objection to the form.
THE WITNESS: Not that I'm aware of.
BY MS. MAHENDRANATHAN:
Q. Has Merck done any studies to approximate -- strike that.
Merck has conducted serology studies. Is that correct?
A. That's correct.
Q. And immunogenicity is -- an immunogenicity study would be a serology study?
A. Yes, it would.
Q. What is the relationship between serology results and protection from disease?
A. Again, there's no absolute direct correlate of protection that's been established.

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Q. So do Merck's immunogenicity studies in any way reflect protection from disease?
A. I think what matters here is the fact that you have a vaccine effectiveness that is quite high, and anyone would tell you that in the vaccine world we rely much more on effectiveness or efficacy data than immunogenicity because it represents the real world use of the vaccine.
Q. So do Merck's serology results reflect protection from the vaccine in any way -- strike that.
Do Merck's serology results reflect the protection afforded by the mumps component of Merck's mumps vaccines in any way?
A. It's not a direct correlate.
Q. Does it have any relationship to protection from disease?
A. I really can't answer that.
Q. How well did Merck's mumps vaccine protect vaccine recipients in 2006?
A. If you will go to -- I believe it's here. If you'll go to Tab 2. Sorry,

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wait a minute. Make that 3. If you go to Tab 3, you can take a look at the impact of Merck's vaccine since 1968, and overall year on year the CDC has reported that the percent decrease of the vaccine is more than 98 percent.
Q. Do you -- there is no row for 2006 in this table. Correct?
A. That's correct. Yes.
Q. Why is that?
A. I don't know. The CDC did not make a calculation. I can tell you that if you do the calculation, if you use the formula at the bottom, you'll come up with approximately 96 percent. That's a highly effective vaccine.
Q. So where do these calculations come from?
A. They from the "Pink Book." If you'd like, I can just explain what these really mean. So they compare the pre-vaccine era annual morbidity which ranges anywhere from about 150,000 cases per year to a high of 212,000 cases per year. Then you look at the percent reduction based

on the number of cases that are actually reported in any given year. So if you'd like, I can give you -- if you want to take row 9, for example, row 9 would have been the number of pre-vaccine era cases, 162,000 roughly, minus the number of cases in a given year, 2,528, and then you divide that by the number in the pre-vaccine era, the same number, 162,344. That gives you a 98 percent reduction.

Q. What chapter of the "Pink Book" is this calculation in?

A. These are actually in the appendices in the "Pink Book." The reference should be here for you.

Q. Do you know why from row number 8 to row number 9 the pre-vaccine era annual morbidity went up?

A. I only know that they change the number. And if you take a look here again at the footnote at the bottom, it's based on a publication by Roush in JAMA, November of 2007. The difference, as I understand it, is that the 152,000 number represents the number of cases reported in

1968; whereas the 162,000 number represents an average of 1963 to 1968.

Q. So I have a document here that I'm going to mark as Exhibit 3.

\- - -

(Exhibit 30(b)(6)(4)-3, Reported Cases and Deaths from Vaccine Preventable Diseases, United States, 1950-2013, was marked for identification.)

\- - -

BY MS. MAHENDRANATHAN:

Q. So I got this document from the CDC website, the "Pink Book" section. Do you know what this document is?

A. It's from the "Pink Book," yes.

Q. So if you go to page -- well, it says, "Appendix E-3," and it has, it lists mumps incidents starting from 1968.

A. Correct.

Q. And then on E-4 it goes through 2013. Do you see for 2006 it lists that there were 6,584 cases of mumps reported to the CDC?

A. Yes, I do.

Q. We don't have the calculation on the table in Tab 3, but is it your understanding that if we did this calculation, the percent decrease would be greater than 96 percent?

A. It's approximately 96 percent.

Q. Approximately 96 percent.

A. Yes.

Q. Would -- but would the percent decrease change depending on which years you used as your pre-vaccine era reference year?

A. Yes, it would. But recognize that the numbers that are here, most of them are based on the lower number, the 152,000. So, if anything, if I go to the 212,000 that's footnoted in asterisk number two, the rate would be even higher.

Q. Where did the pre-vaccine era annual morbidity data came from?

A. It came from the CDC, recognizing that the 162,000 number comes from a publication by Roush in JAMA, November 14, 2007.

Q. And the 152,209 number, do you

know where it came from?

A. It appears to be right here.

Q. Do you know why there's no data in this column before 1967?

A. My understanding is it's not a reportable disease, but obviously there's a -- for some of this information. I don't know the specifics.

Q. Do you know what appendix this percent decrease information comes from?

A. As I recall, it varies from year to year. It's in the appendices. I can't tell you the specific appendix for each one of these.

Q. In your opinion, does this information tell you how well the mumps component of Merck's mumps vaccine protects vaccine recipients from mumps in 2006?

A. I'm sorry, I'm not following.

Q. I'm sorry. Let me ask that again.

Your Tab 3, the table in Tab 3 --

A. Yes.

Q. -- that you created with

counsel compiled from information from the "Pink Book," does this table indicate your -- Merck's understanding of how well the mumps component of Merck's mumps vaccine protects vaccine recipients from mumps?
A. Not this table specifically, but the table that references these specific reductions does.
Q. So your table is with the reductions?
A. Correct.
Q. Does this reflect Merck's understanding of how well the mumps component of Merck's mumps vaccines protected vaccine recipients in 2006?
A. Again, it's not on here for 2006.
Q. So how well did Merck's mumps vaccine protect vaccine recipients in 2006?
A. Based on the numbers that I just described for you and doing the math, using the numbers that are here, for the 6,000 plus cases, you get about a 96 percent reduction. That's an excellent reduction in disease.

Q. Is there anything else that forms the basis of Merck's understanding for how well the mumps component of its mumps vaccine protects vaccine recipients from Merck -- strike that. Let me try it again.
Is there anything else that forms the basis of Merck's understanding of how well the mumps component of Merck's mumps vaccine protected vaccine recipients from mumps in 2006?
MR. SANGIAMO: Object to the form.
THE WITNESS: Again, I would refer you to the document I referenced already which is the vaccine effectiveness over time, Tab 11. That, to me, is the best representations based on the multiple studies that have been done that says a single dose is about 78 percent effective and a two dose is about 88 percent effective.
BY MS. MAHENDRANATHAN:
Q. So the effectiveness studies conducted outside of Merck and the disease

reduction forms the universe of information that is the basis for Merck's understanding of how well the mumps component of its mumps vaccines have protected vaccine recipients over time?
A. Yes.
Q. Do immunogenicity results inform Merck's understanding of how well the mumps component of its vaccines has worked over time?
A. Yes.
Q. Which immunogenicity results?
A. The ELISA assay.
Q. And how does an ELISA assay determine whether someone is protected?
A. Again, I'm really not an expert on assays.
Q. You have an understanding of what a serostatus cutoff is?
A. Yes.
Q. If a person's post-vaccination serum is measured above the serostatus cutoff in a particular ELISA, does that indicate that person is protected from mumps?

A. It means they seroconverted.
Q. Does that have any relationship to protection from mumps?
A. Again, it's a surrogate. That's all it is.
Q. Does it parallel protection from mumps?
A. I believe it does, yes. Not as a direct one-to-one. But if you get a positive, you should be generally positive.
Q. Would serology results from Merck's ELISA tests have clinical relevance if they indicated that a person seroconverted?
A. Yes.
Q. Even though they are not a correlate of protection?
A. Correct.
Q. Why is that?
A. Immunogenicity has been used with the agreement with regulatory agencies as a means by which to look at bridging between products, for example. So we look at comparison of immunogenicity for MMR versus MMR/V, for example, it's routinely accepted by regulatory agencies as an

appropriate endpoint when you can't do an efficacy study.

Q. So would the results of an ELISA assay in any way reflect protection from mumps?

A. Again, there's a parallel that is not an absolute.

Q. Are three doses of Merck's mumps vaccine more effective at preventing mumps than two doses?

A. If you'd like to turn to Tab 15, on the first page are three different studies that looked at the vaccine effectiveness of a third dose. These were studies done between -- or published between 2012 and 2017. What you can see is that the vaccine effectiveness of a third dose, which is shown in the far right column, ranges from 61 to 88 percent.

Q. Is this range of effectiveness greater than the effectiveness range associated with two doses of Merck's mumps vaccine?

A. The two dose is, again, about 88 percent. That's based on a large number

of studies. This is based on a small number of studies. It's probably comparable.

Q. Does Merck know whether three doses of the mumps vaccine is more effective at preventing mumps than two doses?

A. Based on the data that's shown here.

Q. What is its understanding?

A. That we have a 78 percent efficacy of three doses.

Q. How does that compare to two doses?

A. Again, the number seems to be comparable. This is a very small and, again, so far not a long-term follow up.

Q. What is Merck's position on whether -- strike that.

What is Merck's position on whether to implement a third dose of its mumps vaccine?

MR. SANGIAMO: Object to the form.

BY MS. MAHENDRANATHAN:

Q. You can answer if you understand my question.

A. We support the recommendations of the ACIP.

Q. What is ACIP's recommendation?

A. Currently the recommendation is to use a third dose in outbreak situations.

Q. Do you support -- strike that.

Is it Merck's position that there should be widespread third dose vaccination?

A. Again --

MR. SANGIAMO: Object to the form.

THE WITNESS: I really can't speculate on that.

BY MS. MAHENDRANATHAN:

Q. What's Merck's position?

MR. SANGIAMO: Is that in the notice?

MS. MAHENDRANATHAN: In Topic 4, "Merck's consideration of possible solutions for or responses to the mumps outbreaks...."

MR. SANGIAMO: Your question is whether -- what Merck's position

is on the use of a third dose to prevent outbreak, is that your question? I think she already testified it was reported that Merck supports the ACIP position on there.

BY MS. MAHENDRANATHAN:

Q. My question is whether Merck supports widespread third dose vaccination, not limited solely to the outbreak setting in an effort to prevent mumps outbreaks?

A. Again, I said before, we support the ACIP recommendation which at the present time is for outbreaks only.

Q. So Merck's position is not that it is necessary to have widespread third dose vaccination in an effort to prevent mumps outbreaks?

A. I really can't answer that.

Q. I'm trying to ask you is Merck for a third dose or it's against a third dose widespread vaccination?

MR. SANGIAMO: To prevent outbreaks.

BY MS. MAHENDRANATHAN:

Q. To prevent outbreaks.

A. Again, we support the recommendation of the ACIP. If they make a recommendation for use of the vaccine in a certain way, we follow it.
Q. So Merck has no opinion on whether it should be used, it will only follow the ACIP's recommendation?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Does Merck produce a monovalent mumps vaccine?
A. No.
Q. Why not?
A. We stopped production in 2009 based on the recommendations actually from the ACIP that the trivalent vaccine was the most important vaccine to be used.
Q. So when vaccine recipients get a third dose of Merck's mumps vaccine, they're receiving also a third dose of measles and rubella vaccine?
A. Yes.
Q. How does -- strike that.
What is Merck's understanding

of how well the mumps component of Merck's mumps vaccine protects vaccine recipients from mumps as compared to how well the measles component works?
A. As I said before, the numbers are there, 78 percent for one dose and 88 percent for two doses. I don't think you can really make a comparison between mumps and measles. They're very different diseases.
Q. Why is that?
A. They're different viruses. They have different modes of transmission. They have different complications. They have different incubation periods.
Q. How does that impact the vaccine's ability to protect from disease?
A. I'm sorry, I don't understand your question.
Q. You were describing differences between measles disease and mumps disease. How do those disease differences impact the vaccine's ability to protect vaccine recipients from disease?
A. Every virus is different.

Q. And so the effectiveness of the vaccine is somehow hinged to the characteristics of the virus?
A. Yes.
Q. What characteristics of mumps virus distinction issue it from measles such that the measles vaccine has a different protectiveness than the mumps vaccine?
MR. SANGIAMO: I'm going to object that this is outside the scope of this notice. She was not asked to be prepared to make comparisons between mumps vaccine and measles vaccine.
BY MS. MAHENDRANATHAN:
Q. But Merck has an understanding of how well its mumps vaccine works?
A. Yes, as I just said before.
Q. But Merck is unable to compare how well its mumps vaccine works to other vaccines?
MR. SANGIAMO: I'm going to instruct her not to answer that. That's beyond the scope of this notice. If you can show me how it's

in the scope of the notice, then I'll let her answer.
You're asking her to make comparisons to other vaccines. She's not called upon to do that. She's called upon to talk about the effectiveness of this vaccine.
MS. MAHENDRANATHAN: But her understanding of how well this vaccine works is colored by her vast experience with other vaccines. It's fair to ask her to compare if that reflects her understanding and Merck's understanding of a vaccine.
MR. SANGIAMO: She's not answering that question.
MS. MAHENDRANATHAN: Is it your position that her understanding of the vaccine has nothing to do with her understanding of other vaccines, her vast vaccine experience?
MR. SANGIAMO: She's testifying on behalf of Merck. She was asked to come prepared to testify about the effectiveness of the mumps component

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of Merck's mumps-containing vaccines. She's doing that. If you're asking for a comparison between one virus and another virus and why one vaccine might work better than another vaccine when they involved in viruses, those are complicated issues requiring studies, and she's not been called upon to be prepared to testify about that.

MS. MAHENDRANATHAN: I'm asking about Merck's own vaccines. I'm asking about the vaccine in the same, you know, trivalent. Merck doesn't have an understanding, she's not prepared to speak to her understanding of how measles work compared to the other vaccines in the same trivalent?

MR. SANGIAMO: That's correct. She was not asked to be prepared to speak to that.

THE WITNESS: Could we take a break, please?

MS. MAHENDRANATHAN: Sure.

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THE WITNESS: Thank you.

VIDEOGRAPHER: The time is now 11:36. We're going off the video record.

\- - -

(A recess was taken.)

\- - -

VIDEOGRAPHER: The time is now 11:48. This begins media unit number two.

BY MS. MAHENDRANATHAN:

Q. So earlier when I asked you about Merck's understanding of how well its vaccine works, you pointed me to a tab of effectiveness information. What tab is that again?

A. That would be Tab 11.

Q. Thank you. So does Merck's understanding of vaccine effectiveness come solely from these studies?

A. Yes.

Q. Merck doesn't do any of its own effectiveness studies?

A. No. Let me perhaps add here the importance of the role of the Centers

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for Disease Control. If I could take you back to Tab 1 if I may for a minute.

Again, recalling what's here, the mission statement, if you turn to particularly the page after the first yellow sheet labeled, National Center for Immunization and Respiratory Diseases.

Q. I'm here.

A. Okay. Good. CDC is a world-renowned organization that does this type of research. And importantly, if you look at what's highlighted in yellow here on the first page, they respond to these outbreaks domestically and aboard.

If you want to go further back with me, please, to the other highlights. Page 8, specifically the division of viral disease, they conduct surveillance under Item 1, estimate vaccine effectiveness. They provide consultation and support and participate in investigations and national and international outbreaks.

The point here is that the CDC has the absolute expertise in looking at outbreaks. They work very well with the

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state and local health departments. They are oftentimes called in by states to help them with outbreak investigations. Importantly is that the CDC also has a group called the Epidemic Intelligence Service, EIS. Individuals are trained in investigating outbreaks, emergence of new diseases. The CDC also has diagnostic laboratories to support all of this work. The CDC is clearly recognized as the global expert in evaluation of outbreaks.

Q. And so is Merck's understanding of how well its own mumps vaccine works reliant on information from the CDC?

MR. SANGIAMO: Object to the form.

THE WITNESS: Yes.

BY MS. MAHENDRANATHAN:

Q. And Merck's understanding of how well its own Merck's mumps vaccine works is based solely on information from the CDC?

MR. SANGIAMO: Object to the form.

BY MS. MAHENDRANATHAN:

Q. If you understand that question,

you can answer.
A. Again, it's the CDC, it's the WHO, it's all of these publications that are here, the majority of which do come from the CDC.
Q. Solely an outside organization?
A. Yes.
Q. And Merck does not conduct its own studies to ensure the effectiveness of its mumps vaccine?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. If you understand, you can answer my question.
MR. SANGIAMO: Would you just read back that question, please?
- - -
(The court reporter read the pertinent part of the record.)
- - -
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Did you understand my question?

A. I understand your question. Again, evaluation of effectiveness is a role that's been given to state, local health departments as well as the CDC. We do not have that basic jurisdiction, if you will.
Q. So expanding that a little broader, does Merck conduct its own studies to ensure how well its vaccine protects vaccine recipients from mumps?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Does that make sense?
MR. SANGIAMO: To ensure how well?
MS. MAHENDRANATHAN: Let me reask that. Let me reask that.
BY MS. MAHENDRANATHAN:
Q. Does Merck conduct its own studies to assess how well its mumps vaccine protects recipients from mumps?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Do you understand my question?

A. Not really.
Q. Do you understand what it means to assess protection from mumps disease?
A. Again, the best way to understand how a vaccine works is in the real world setting and do vaccine effectiveness studies, which is exactly what the CDC and others have done.
Q. So Merck's understanding of how well its mumps vaccine works is based only on effectiveness?
A. That's the most important endpoint that anyone can use to look at how a vaccine works. Effectiveness is more important than any other endpoint, describes the real world use of a vaccine.
Q. So is Merck's understanding of how well its vaccine works based on anything else?
A. We obviously use our additional immunogenicity data to look at trends over time. We use it to make comparisons to other vaccines. Effectiveness is a very important endpoint.

Q. So Merck's understanding of how well its mumps vaccine works is based partially on its own immunogenicity studies?
A. Yes.
Q. Are these studies all ELISA studies?
A. There was a small number of studies using the neutralization assay.
Q. Are you familiar with those studies?
A. Not in great detail, no.
Q. Are any of those studies from Protocol 007?
A. Yes.
Q. And does Merck rely on the results of that neutralization in part to form its understanding of how well its mumps vaccine protects vaccine recipients from mumps?
A. Let me take you to, if I may, I think it's here, the Interrogatory Number 2, Tab 14, please. Again, this shows the information from the ELISA results in Table 1. There's a small paragraph on page 1 that describes the neutralization results that

were performed. Please recognize that they range from 89 to 92 percent in Protocol 002 -- sorry, in Protocol 007. Excuse me.
Q. So this is on page 1 at Tab 14 in the narrative?
A. Yes.
Q. In the narrative it notes, 53 percent to 96.3 percent (MMR II Protocol 006). Does that reflect the PRN results from Protocol 006?
A. Yes, it does. Please recognize the note at the bottom which is that this was tested a bunch of different strains. And importantly, if you look at the one that says Merck Jeryl Lynn wild type, it's 96 percent.
Q. Why does the strain tested matter?
A. Because the strain that happens in the field may not be exactly the same strain as we have in the vaccine.
Q. Is the strain that is reflected in the field in the current outbreaks the same as the strain in the vaccine?

A. No.
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Why did Merck test against a number of different vaccine strains?
MR. SANGIAMO: That's outside of the scope.
BY MS. MAHENDRANATHAN:
Q. Did Merck test against a number of different vaccine strains in Protocol 006 to understand how well its mumps vaccine protects recipients from mumps?
MR. SANGIAMO: That's outside the scope. She was not asked to be prepared to testify on Protocol 006.
MS. MAHENDRANATHAN: I'm interested in Merck's understanding if that's based at all on Protocol 006. If you're not prepared to answer, then that's what it is.
THE WITNESS: I'm really not prepared to answer.
BY MS. MAHENDRANATHAN:

Q. Later in that same line, it notes 89.3 percent to 92.2 percent (MMR II Protocol 007). Does this reflect the plaque reduction neutralization PRN assay results from Protocol 007?
A. Yes.
Q. And this -- does this form part of the basis of Merck's understanding of how well its mumps vaccine works?
A. The study was done to look at the neutralization results to determine what the end expiry of the product was going to be.
Q. So we came to this tab because I asked you if Merck had done its own studies to assess how well the vaccine works, and you had pointed me to immunogenicity studies?
A. Yes.
Q. So would you say that the results from this PRN formed the basis of Merck's understanding, at least in part, of how well its mumps vaccine works?
MR. SANGIAMO: Object to the form.

BY MS. MAHENDRANATHAN:
Q. Did you understand my question?
A. Not really.
Q. Is Merck's understanding of how well its mumps vaccine works to protect recipients from disease based in part on these immunogenicity studies?
MR. SANGIAMO: Object to the form.
THE WITNESS: Understanding of the vaccine's effectiveness is what matters. And that's the data that I've said before, again, 78 percent for a single dose and 88 percent for --
BY MS. MAHENDRANATHAN:
Q. I understand --
A. -- two doses.
Q. Sorry to interrupt.
I understand what matters, but I'm interested to know if these PRN results in any way inform Merck's understanding of how well its vaccine protects recipients from mumps?
MR. SANGIAMO: Object to the form.

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BY MS. MAHENDRANATHAN:
Q. Did you understand my question?
A. I really can't answer that.
Q. So just to confirm, you cannot tell me whether Merck's understanding of how well its mumps vaccine protects vaccine recipients from Merck -- from mumps -- strike that. Let me start over.
I just want to confirm that you cannot tell me whether the mumps component of Merck's mumps vaccine -- strike that.
I'm going to try again. Can you tell me whether Merck's understanding of how well the mumps component of Merck's mumps vaccine protects recipients from mumps is based at least in part in the results from the PRN study in Protocol 007?
A. Understanding of how this vaccine works is based on aggregate data, both the effectiveness, the efficacy and the immunogenicity of data.
Q. Is this PRN data included in that aggregate?
MR. SANGIAMO: Object to the

form. Are you talking about 007 PRN data?
MS. MAHENDRANATHAN: Yes.
THE WITNESS: Yes, it's part of our database.
BY MS. MAHENDRANATHAN:
Q. So I'm just going clean that up because you fixed my question for me.
So to conform, the PRN results from Protocol 007 are part of your database of information that inform your understanding of how well the mumps component of Merck's mumps vaccine works?
A. Yes.
Q. Would it impact your understanding of how well the vaccine works to know that the results of this study were in any way falsified?
A. I have no reason to believe that these results were falsified.
Q. If they were, would it impact your understanding of how well the mumps component of Merck's mumps vaccine works?
A. If they're inadequate results or inappropriate results, we would exclude

them from our understanding.
Q. If there were inadequate results or inappropriate results, would it be proper for Merck to use those results in any way?
MR. SANGIAMO: What topic is this related to right now?
MS. MAHENDRANATHAN: I'm just following up --
MR. SANGIAMO: Sounds like you're asking questions about Protocol 007.
MS. MAHENDRANATHAN: Okay.
MR. SANGIAMO: So what are you asking or direct me to the topics that you're asking?
MS. MAHENDRANATHAN: I'll reframe.
BY MS. MAHENDRANATHAN:
Q. So if the results, the PRN results from Protocol 007 were improper in any way, they should not be included in Merck's understanding of how well its vaccine works?
MR. SANGIAMO: Objection. It also calls for speculation, and it's

an imprecise hypothetical question.
BY MS. MAHENDRANATHAN:
Q. Okay. Let's try again.
Does Merck make representations about how well its vaccine works based on its own understanding of how well the vaccine works?
A. Information on our product is what's shown in our package circular.
Q. Is there any other information that Merck represents based on its own understanding of how well its vaccine works?
MR. SANGIAMO: On the package circular?
MS. MAHENDRANATHAN: Anywhere.
MR. SANGIAMO: Well, where is that?
MS. MAHENDRANATHAN: So my question is, if Merck makes representations based on its understanding. So I'm just trying to get to if the representations that Merck makes are related to their understanding or separate from their understanding.

MR. SANGIAMO: What representations? Marketing representations?
MS. MAHENDRANATHAN: Sure.
MR. SANGIAMO: That's not on here.
MS. MAHENDRANATHAN: No, but I'm asking about Merck's understanding and how it represents its understanding.
MR. SANGIAMO: You can ask her about Merck's understanding. I'm objecting to your questions about representations Merck makes -- Merck makes other than on the labels.
BY MS. MAHENDRANATHAN:
Q. Okay. All right. So I'm going to get to the labels, but really quickly before I do, there is a number of PowerPoints in this binder that you've given us.
A. Uh-huh.
Q. There's one in Tab 7. There's one in Tab 8. There's one in Tab 9. There's one in Tab 10. I think that's all of them. Were any of these PowerPoints

created by Merck?
A. No. No.
Q. I just have one more document on this topic. I'm going to mark this as Exhibit 4.
\- - -
(Exhibit 30(b)(6)(4)-4, Effectiveness of a Third Dose of MMR Vaccine for Mumps Outbreak Control, was marked for identification.)
\- - -
BY MS. MAHENDRANATHAN:
Q. Do you know what this document is?
A. I do.
Q. What is it?
A. A recent publication on the "Effectiveness of a Third Dose of MMR.. for Mumps Outbreak Control."
Q. Who wrote this article?
A. Dr. Cardemil from the CDC.
Q. Does this reflect the results of a CDC study?
A. As I understand it, yes.
Q. I'm going to look at some of

the vaccine effectiveness results, they're on page 950 and 951.
Let me know if you need time to read it.
A. Specific paragraphs that you'd like me to look at?
Q. I'm looking in particular on -- in the second paragraph of the "VACCINE EFFECTIVENESS" section on page 951 which is right above the "DISCUSSION" section?
A. Correct. Yes.
Q. I'm looking at the latter part of that paragraph where it says -- it indicates that the effectiveness amongst students in the study who have received the second dose of MMR more than 13 years or before the outbreak was 31.8 percent. Do you see where that is?
A. Yes, I do.
Q. Is it Merck's understanding that the effectiveness of the mumps component of its mumps vaccine can be as low as 31.8 percent?
MR. SANGIAMO: Object to the

form.
THE WITNESS: These are the results from one study. I'll take you back to Tab 11, if I may, again, to remind you that even with the study included, if you go to the last page of Tab 11, page 9 specifically, this particular result is acknowledged, but you still end up with an effectiveness of 88 percent as a median with a range between 31 and 95 percent. So, again, this is one study you would look at the aggregate data rather than the results of any one particular study.
BY MS. MAHENDRANATHAN:
Q. So the range of effectiveness that Merck is aware of goes anywhere from 31 to 95 percent?
A. Correct.
Q. What is Merck's understanding regarding, on average, how well someone is protected from mumps by vaccination by the mumps vaccine?
A. So, again, refer you right

back to this. This is directly from the CDC. They're saying that the median is 88 percent. They basically say on their website that nine out of ten people are protected against -- protected over the use of this vaccine. It's a highly effective vaccine.
Q. So Merck's understanding is that nine out of ten people --
A. Yes.
Q. -- are protected with vaccination?
A. Yes.
Q. And that understanding comes from the CDC?
A. It comes from the information they've compiled, yes.
- - -
(Exhibit 30(b)(6)(4)-5, Package Circular for MMR II, was marked for identification.)
- - -
BY MS. MAHENDRANATHAN:
Q. So I'm going to mark this document as Exhibit 5.

A. Yes.
Q. Do you know what this document is?
A. Package circular for MMR II.
Q. And do you know if this is the current circular for MMR II?
A. I'm guessing it is based on the data on the last page, shows it was revised in May of 2017.
Q. So I want to point you to, under the "CLINICAL PHARMACOLOGY" section, page 1, your first sentence of the third paragraph it says, "Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that MMR II is highly immunogenic and generally well tolerated."
Do you see that?
A. Yes, I do.
Q. In Merck's opinion, is it true that MMR II is highly immunogenic?
A. Yes.
Q. So this is an accurate statement?
A. Yes, it is.

Q. Is it a complete statement reflecting Merck's understanding?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Do you understand my question?
A. It's a complete --
MR. SANGIAMO: Could you repeat your question, please?
BY MS. MAHENDRANATHAN:
Q. Sure. Is this statement, MMR II is highly immunogenic -- strike that.
Is this statement, MMR II is highly immunogenic, is that a complete statement?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. So do you agree with the statement that MMR II is highly immunogenic?
A. Yes, based on the data that's shown here.
Q. What does highly immunogenic mean?
A. It's probably -- it's an

arbitrary term but it probably means that it has an immunogenicity rate greater than 90 percent.
Q. Is it true that MMR II is still highly immunogenetic today?
A. Yes, it is.
Q. And it's true with respect to the mumps component of MMR II, that it is highly immunogenic today?
A. Yes.
Q. What is Merck's basis for its understanding that the mumps component of MMR II is highly immunogenic today?
A. Take you back to the publication as well as the documents under -- start with Tab 12 again. That same publication. If you go back to those same 20 studies referred to on page 1015, these are studies that were done over a 21-year period. You can see that the immunogenicity of mumps range from 97.7 to 100 percent for mumps over that time period. Again, the analysis of immunogenicity over time indicated there was no change in the performance of the measles, mumps or rubella

components in the vaccine.
Q. So the clinical -- strike that.
In the circular, does it cite these 20, 21 ELISA studies?
A. No, it does not.
Q. What does it cite?
A. The original studies that were done with the product prior to licensure.
Q. When were those studies conducted?
A. In the mid '70s I want to guess.
Q. What kind of studies were those?
A. Clinical trials prior to licensure.
Q. Were they ELISA studies?
A. As it's indicated here in this particular case, they were done with the neutralization assay.
Q. Merck relies on these initial clinical studies and the results of the 20 studies listed in the article in Tab 12 --
A. Yes.
Q. -- to form its understanding

that MMR II is highly immunogenic?
A. Yes.
Q. Does Merck rely on any PRN results since the early clinical studies to inform its opinion that MMR II is highly immunogenic?
A. Again, supporting information. The neutralization results are clearly shown here, it was 96 percent.
Q. So the supporting information is the clinical studies referenced at the beginning of the sentence?
A. Yes.
Q. And did you say when those studies were conducted?
A. Somewhere in the mid '70s. I don't know exactly.
Q. Mid '70s. Thank you.
So the next sentence says, In these studies, a single injection of the vaccine-induced measles hemoagglutination-inhibition (HI) antibodies in 95 percent, mumps neutralizing antibodies in 96 percent, and rubella HI antibodies in 99 percent of susceptible persons.

Is it true that a single injection of the MMR vaccine induces mumps neutralizing antibodies in 96 percent of susceptible persons?
A. Based on the results of this trial, yes.
Q. So this is an accurate representation of PRN results induced by a single injection of MMR II?
A. Based on the study that's presented here, yes.
Q. So is this still true today?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Is it still true today that a single injection of MMR II will induce mumps neutralizing antibodies in 96 percent of susceptible persons?
A. Again, if I go back to the tab where we showed you the results, if I can put my hands on it one more time, Interrogatory 2 under Tab 14, you see from Protocol 007 that the range was between 89 and 92 percent by a PRN assay.

Q. So --
A. I would like to make one caveat. What you have to understand that range actually represents, as it says in the footnote, it also contains where the mumps potency was lower than the expiry. So this is a range.
Q. It also contained mumps vaccine where the potency is higher than the expiry?
A. Yes.
Q. So you don't know if this 89.3 percent comes from mumps tested at potency lower than the expiry or higher than the expiry?
A. It's both.
Q. Both. But -- so the mumps vaccine tested above expiry did not test higher than 92.2 percent?
A. Correct.
Q. And this is lower than the 96 percent represented on the circular?
A. You can't make that comparison. There's no statistical evaluation being made. The assays may be somewhat different. So I would never make that comparison.

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Q. So you cannot compare PRN results from one assay to PRN results from another assay?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not an expert in that area.
BY MS. MAHENDRANATHAN:
Q. Is it important for Merck to ensure that this representation on its circular that a single injection of MMR II vaccine induces mumps neutralizing antibodies in 96 percent of susceptible persons is accurate?
A. Yes.
Q. How has Merck ensured that this representation is accurate?
A. By the data that I just showed you. By the ELISA results that I just showed you.
Q. And these are the ELISA results listed in the study you authored, Safety and Immunogenicity of MMR II in Clinical Trials of Healthy Children in Tab 12?

A. Correct.
Q. So these are ELISA studies, and I'm representing -- I'm referring to the mumps neutralization antibodies representation in the circular. So does Merck rely on these ELISA studies to ensure that this representation that a single injection of the mumps vaccine induces mumps neutralizing antibodies in 96 percent of susceptible persons?
MR. SANGIAMO: Object to the form. You misquoted the circular. It says induced in reference to the clinical trials that are referenced there. You quoted it as inducing, it says induced.
MS. MAHENDRANATHAN: Thank you.
MR. SANGIAMO: Your question is what does Merck do to ensure that that is a correct representation of what was found in the clinical trials.
BY MS. MAHENDRANATHAN:
Q. My question is, is it

important that Merck ensures that this representation about these PRN results reflect how well the mumps vaccine works today?
MR. SANGIAMO: Object to the form.
THE WITNESS: We have no reason to believe it's any different. We have a recent neutralization result that's 90-plus which is in the same range of this number. We also have ELISA results that are very confirmatory of this.
BY MS. MAHENDRANATHAN:
Q. So you have no reason to question this representation because of the results of Protocol 007 plus the results in the ELISA studies?
MR. SANGIAMO: Object to the form.
THE WITNESS: Correct.
BY MS. MAHENDRANATHAN:
Q. So I'm going to go to the next sentence. It says, However, a small percentage (1 to 5 percent) of vaccinees may

fail to seroconvert after the primary dose....
Is this a true statement?
A. Based on the results that were shown here, yes.
Q. And this is true with respect to the mumps component of MMR II, that a small percentage, 1 to 5 percent of vaccinees may fail to seroconvert after the primary dose?
A. Based on the assay shown here, yes.
Q. Does this sentence reflect the percentage of vaccinees that may fail to seroconvert -- strike that.
Does this sentence, a small percentage, 1 to 5 percent of vaccinees may fail to seroconvert after the primary dose reflect Merck's understanding of how well its vaccine works?
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Do you understand my question?
A. Again, the numbers shown here

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are reflective of this very study. The 1 to 5 percent comes directly from the numbers shown here. You have a 99 percent seroconversion for rubella conformance, so that's your 1 percent that don't seroconvert. You have 5 percent for measles, so that's where you get the 5. Yes, this is what it represents.

Q. So would Merck put this on its circular to reflect its understanding of how well the vaccine works?

MR. SANGIAMO: Object to the form.

THE WITNESS: This is the circular.

BY MS. MAHENDRANATHAN:

Q. Would you put this information on the circular today as it reflects Merck's understanding of PRN results associated with immunization from mumps?

MR. SANGIAMO: Objection. Calls for speculation.

MS. MAHENDRANATHAN: Could we take a short break?

VIDEOGRAPHER: The time is now

12:24. We're going off the video record.

- - -

(A recess was taken.)

- - -

VIDEOGRAPHER: The time is now 1:34. We're back on the video record.

BY MS. MAHENDRANATHAN:

Q. So I want to go back to what we were looking at on the label, the statements about neutralization. Do you see where I'm talking about?

A. One minute, please.

Q. Sure.

A. Paragraph 3.

Q. Paragraph 3 under "CLINICAL PHARMACOLOGY."

A. Yes.

Q. In the second sentence that we've gone over before about mumps neutralization antibodies and 96 percent, that's a true statement?

A. Yes, it is.

MR. SANGIAMO: Object to the form.

BY MS. MAHENDRANATHAN:

Q. Does a single dose of MMR II induce mumps neutralizing antibodies in 96 percent of people today?

MR. SANGIAMO: Object to the form.

BY MS. MAHENDRANATHAN:

Q. Is it true today, this statement?

MR. SANGIAMO: Is the statement in the package circular that in that clinical trial, is that true today in that clinical trial?

BY MS. MAHENDRANATHAN:

Q. My question is, today, is it true that a single dose of MMR II would induce mumps neutralizing antibodies in 96 percent of people?

MR. SANGIAMO: Object to the form.

THE WITNESS: Again, back to the same data I showed you previously. We have one other set of data and those results show between what, 89 and 92 percent, if I remember

correctly. I'm not sure.

BY MS. MAHENDRANATHAN:

Q. So what tab is that again?

A. Let's look for one second. 14, please.

Q. So this is below 96 percent?

A. Yes, it is below 96 percent, but those numbers are very comparable, they're very high. If you take the two numbers from that study for the doses that were above the expiry, it would be over 90 percent. 90 and 96 percent are in the same ballpark.

Q. So can Merck today replicate a study that shows that one dose of MMR II induces mumps neutralizing antibodies at 96 percent?

MR. SANGIAMO: Object to the form. Calls for speculation.

THE WITNESS: I can't speculate.

BY MS. MAHENDRANATHAN:

Q. So the only study you can point to is a study that shows a less than 96 percent PRN rate?

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MR. SANGIAMO: Object to the form.
THE WITNESS: It's numerically lower. It is probably not statistically lower.
BY MS. MAHENDRANATHAN:
Q. Why doesn't the label have the results from this PRN study included?
MR. SANGIAMO: Object to the form. Dr. Kuter is not a labeling expert. She's here to talk about what's on the label. She's not here to talk about what all goes into the regulatory assessment of what does and does not go into a label.
BY MS. MAHENDRANATHAN:
Q. But you're here to speak as to the representations on the label?
MR. SANGIAMO: Correct, which she's doing.
BY MS. MAHENDRANATHAN:
Q. Is this a complete representation with respect to PRN results if it does not include the results of this lower -- the lower PRN results from the Protocol 007?

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MR. SANGIAMO: Object to the form. Object to your use of the word "complete" here in the context of trying to interpret the regulatory issue of what belongs on the label.
BY MS. MAHENDRANATHAN:
Q. So can you tell me whether this is a complete statement or not?
MR. SANGIAMO: Object to the form.
THE WITNESS: It's the data from that study. That's what's here.
BY MS. MAHENDRANATHAN:
Q. So this data is from before 1990?
A. Yes.
Q. Is it from before 1980?
A. I don't know the exact year, I'm sorry.
Q. But does it reflect the results -- does it reflect what Merck knows about PRN results today?
MR. SANGIAMO: Object to the form.
THE WITNESS: Again, the

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numbers are within the range of what we have from Protocol 007.
BY MS. MAHENDRANATHAN:
Q. But they're lower?
A. I don't think they're lower. You're making an assumption. I cannot make that same assumption.
Q. Why are they not lower?
A. You need a statistician to say that they're lower. To me above 96 percent is excellent immunogenicity.
Q. But it is the same as 96 percent mumps neutralizing antibodies in 96 percent of people?
MR. SANGIAMO: You're getting pretty close to asked and answered too many times here.
MS. MAHENDRANATHAN: Are you going to let her answer this question?
MR. SANGIAMO: I'm going to let her answer this question if she understands it, if it makes sense to her.
BY MS. MAHENDRANATHAN:

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Q. Can you answer the question?
MR. SANGIAMO: The question is, is the rate from Protocol 007 above 96 percent mumps neutralizing. I think that's the question. Maybe ask the question again.
BY MS. MAHENDRANATHAN:
Q. You said the Protocol 007 results are above 90 percent?
A. Yes.
Q. But they are below 96 percent. Correct?
A. Numerically, I don't know if it's statistically different. I have no reason to believe that.
Q. So does Merck know that a single dose of MMR II would induce neutralizing antibodies in 96 percent of people today?
A. I can't tell you. We haven't tested it today.
Q. So you can't ensure that today the vaccine still induces mumps neutralizing antibodies in 96 percent of people?
MR. SANGIAMO: You mean today,

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you're asking if Merck right now is running neutralization studies?
BY MS. MAHENDRANATHAN:
Q. How about since 2010?
MR. SANGIAMO: Has Merck run a neutralization?
BY MS. MAHENDRANATHAN:
Q. Can Merck ensure that a single dose of MMR II will induce mumps neutralizing antibodies in 96 percent of people since 2010?
MR. SANGIAMO: Object to the form. Makes no sense.
BY MS. MAHENDRANATHAN:
Q. Does Merck know what PRN results it would expect from a test of its mumps vaccine today?
MR. SANGIAMO: Object to the form. Calls for speculation.
THE WITNESS: I can't speculate.
BY MS. MAHENDRANATHAN:
Q. So it does not know?
MR. SANGIAMO: Calls for speculation. Object to the form of

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that question.
BY MS. MAHENDRANATHAN:
Q. If you would have to speculate, it's because Merck does not have an understanding as to that. Is that correct?
A. I don't understand your question, I'm sorry. I can't speculate on what Merck thinks.
Q. Are you here to -- as a corporate designee of Merck?
A. Yes, I am.
Q. Are you here to speak to Merck -- what Merck knows?
A. Yes.
Q. Does Merck know whether a single dose of MMR II would induce Merck's neutralizing antibodies in 96 percent of people today?
MR. SANGIAMO: She's here to speak on the immunogenicity of the vaccine. She's not here to speculate about what might have happened if a particular assay was designed and a test was run on that assay.
MS. MAHENDRANATHAN: So she

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doesn't know about that?
MR. SANGIAMO: She's not going to speculate about that.
MS. MAHENDRANATHAN: Okay.
BY MS. MAHENDRANATHAN:
Q. I'm going to go to page 2. You see in the second full paragraph it says, "Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy...."
A. Yes.
Q. Is it true that the mumps vaccine demonstrates a high degree of protective efficacy?
A. Based on the studies reported here, yes, the results were about 96 percent efficacy based on two different trials.
Q. Do you know if that's true today, that the mumps vaccine still demonstrates a high degree of protective efficacy?
A. Efficacy studies are done in pre-licensure environment. They're not done

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in the post-licensure environment. Again, I refer you back to the same document that I presented before which is in regards to what the effectiveness of the vaccine is, and that's what matters here, much more so than any indication of an immunogenicity result.
So if I can take you back to the effectiveness table, which would be Tab 11, one more time, this is what matters. What matters is how the vaccine works in the real world. If I take you one more time to line 28 on page 9, 78 percent with one dose and 88 percent with two doses.
Q. Is this information anywhere in the package circular for MMR II?
A. No, it's not. Effectiveness data cannot be included in the circular.
Q. Why is that?
A. FDA regulations. You're not allowed such data in a label.
Q. So does Merck know whether its mumps vaccine still demonstrates a high degree of protective efficacy?
A. Again, what we know is the effectiveness which I've said several times

here. I don't know if I can say it any more time. 78 percent with one dose and 88 percent with two doses. That's what we are very comfortable with based on work that has been done by the CDC in some very well done studies particularly in the outbreak situation.

Q. Sure. So what you're saying is Merck cannot know what the efficacy is today because it cannot do efficacy studies?

A. That's correct. They would be deemed unethical.

MR. SANGIAMO: Object to the form of that last question.

BY MS. MAHENDRANATHAN:

Q. The next sentence it says, "These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases." Is it true that seroconversion rates to mumps parallel protection from disease -- from mumps disease?

A. Again, let's go to the source of the data here, please. These studies are

referring to the two efficacy studies that were done. In those particular studies there was a general parallel between people who seroconverted and people who were protected. As I recall for mumps, the numbers were 96 for one and 95 for the other. I don't remember the order. That's what's meant here by parallel protection. Parallel and protection I should say.

Q. So could you say that seroconversion rates generally parallel protection from disease?

MR. SANGIAMO: Object to the form.

THE WITNESS: It would depend on the assay. It would depend on the situation. It would depend on the laboratory running the tests. Those are all important variables when you look at assays.

BY MS. MAHENDRANATHAN:

Q. So you cannot be sure that seroconversion rates from a test studying mumps vaccine would necessarily parallel protection from disease?

A. You would have to define protection for me here because, again, are we talking the efficacy trial or are we talking the effectiveness trials? They're different situations.

Q. Let's talk about mumps. Does seroconversion to mumps necessarily parallel protection from disease?

A. In these efficacy studies it did.

Q. Does Merck know if generally seroconversion rates reflect parallel protection from mumps?

MR. SANGIAMO: Object to the form.

THE WITNESS: I would be speculating on that, I'm sorry.

BY MS. MAHENDRANATHAN:

Q. Merck does not know?

A. I didn't say that.

MR. SANGIAMO: She said she would be speculating to answer that question.

THE WITNESS: I didn't say that.

BY MS. MAHENDRANATHAN:

Q. I don't want to mischaracterize what you're saying.

Is it important for Merck to ensure that this statement is accurate?

A. This statement is accurate. It talks about the studies that were conducted.

Q. And how would Merck ensure that this statement is accurate?

A. Again, based on the clinical trials that were conducted which showed this information.

Q. So this information is only limited to these two studies from before 1990 and does not reflect current information?

MR. SANGIAMO: Object to the form.

THE WITNESS: The data that are here are from the two studies.

BY MS. MAHENDRANATHAN:

Q. When were those two studies conducted?

A. I don't remember the exact dates. Prior to licensure.

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Q. So were these studies from probably before 1975?
A. I would guess, yes. I'd have to look them up. I don't remember.
Q. I think we can -- this is referencing study 7 through 12 on page 9, and these studies were conducted in 1968, 1967, 1967. Measles unrelated or not relating to mumps 1991 but then mumps study in 1967. And then rubella. So it looks like all of these studies are from 1967 to 1968?
A. As published.
Q. As published?
A. Uh-huh.
Q. So this information about seroconversion parallel protection from diseases all comes from studies from 1967 or 1968?
A. Yes.
Q. Does Merck have more current information as to whether seroconversion from the mumps vaccine parallels protection from mumps?
A. Again, we have no ability to

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conduct efficacy studies of this nature, so no.
Q. So no.
I want to go to the next sentence. "Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests." Is that a true statement?
A. Yes.
Q. Is it true that antibodies associated with protection from mumps can be measured by ELISA?
A. Yes.
Q. What is the basis for that, your understanding?
A. I don't have the reference for this, I'm sorry.
Q. Do you know how Merck knows that antibodies associated with protection from mumps can be measured by ELISA?
A. Again, look at the next sentence, it says that both "Neutralizing and ELISA antibodies to measles, mumps, and rubella are still detectible in most

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individuals 11 to 13 years after primary vaccination."
Q. So is that your basis for Merck's understanding, that antibodies associated with protection from mumps can be measured by ELISA?
MR. SANGIAMO: I'm going to object or -- just to make clear what the scope of this is. She's here to testify about what's on the label. She's doing that. She's not here to testify to the entirety of the body of literature that could pertain to this that's in Merck's possession, or even the body of literature that went into this for that label and statement.
MS. MAHENDRANATHAN: So I just want to clarify. You have limited the license to the circular to exclude representations of potency and shelf life.
MR. SANGIAMO: About what?
MS. MAHENDRANATHAN: Potency and shelf life.

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MR. SANGIAMO: Correct.
MS. MAHENDRANATHAN: And we agree.
MR. SANGIAMO: Yes.
MS. MAHENDRANATHAN: However, we have questions about Merck's compliance with the remaining label specifications.
MR. SANGIAMO: We object to that. There's no such thing as compliance with -- those are not specifications. We objected to that. That's not part of this deposition.
MS. MAHENDRANATHAN: You didn't object at the beginning of this deposition.
MR. SANGIAMO: We defined in a letter to you folks on November 17th of 2017 what the scope was, and it excluded questions about compliance with label specifications as it applies to immunogenicity, efficacy, effectiveness, and seroconversion rates.
MS. MAHENDRANATHAN: So you're

not going to let her speak to what Merck does to ensure that these representations on the circular are accurate?

MR. SANGIAMO: Well, she has told you, where she can, what the source of the data on the circular is. But, no, this is not going to be a deposition about what goes into the FDA and Merck dialogue about what does and does not need to go into a label.

MS. MAHENDRANATHAN: So I'm intending to ask questions about what Merck does to ensure that these statements on the label are accurate. If we do not agree, then we need to figure it out, and if I need to call the magistrate, we'll call the magistrate.

MR. SANGIAMO: You can do that if you'd like. She's already testified to where she can about what the source of the data is. She's explained to you that it comes from

clinical trials. Told you several times that the statements come from clinical trials. She's told you what's there. She's done that.

MS. MAHENDRANATHAN: I understand. And if she doesn't know the answer, she can say she doesn't know the answer and that's fine. But I'm going to continue asking these questions. If you continue to have an objection, you can bring it up and if we have to call the magistrate, we will.

MR. SANGIAMO: You can do what you'd like.

BY MS. MAHENDRANATHAN:

Q. Does Merck have any current information that indicates that seroconversion in response to -- strike that.

Does Merck have any current information that indicates that seroconversion parallels protection from mumps?

A. Again, we don't have the ability to do that. Those are the types of things that are done in original efficacy

studies.

Q. So Merck does not have current information?

MR. SANGIAMO: Object to the form. Object to the use of current. She's answered your question.

MS. MAHENDRANATHAN: Are you instructing her not to answer?

MR. SANGIAMO: No, I'm not going to that stage right now.

MS. MAHENDRANATHAN: Okay.

MR. SANGIAMO: You've asked her the question multiple times. You just asked it twice in a row. So I'm not yet, but I'm getting there.

MS. MAHENDRANATHAN: We'll move on after this.

BY MS. MAHENDRANATHAN:

Q. If you would, please, answer my question.

A. Could you, please, repeat the question?

Q. I said, so Merck does not have current information?

MR. SANGIAMO: Current

information for what?

BY MS. MAHENDRANATHAN:

Q. My prior question was --

MS. MAHENDRANATHAN: Linda, could you read back my last few sets of questions on that?

\- - -

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

\- - -

THE WITNESS: I'm unaware of any information. There could have been data that came from effectiveness studies.

MS. MAHENDRANATHAN: So I'm going to mark this document as Exhibit 6.

\- - -

(Exhibit 30(b)(6)(4)-6, Package circular for ProQuad, was marked for identification.)

\- - -

BY MS. MAHENDRANATHAN:

Q. Do you know what this document is?

A. It's the package circular for ProQuad.
Q. Do you know if there's more than one package circular for ProQuad?
A. There could be a circular for a frozen formulation and one for refrigerator stable product. The content, I believe, is similar.
Q. Do you know if this is the current circular?
A. Again, based on the date of 5/2017 I would guess it is.
Q. So I'm on page 16. So right at the top under "Mechanism of Action," it says, ProQuad has been shown to induce measles-, mumps-, and rubella -- rubella, and varicella-specific immunity, which is thought to be the mechanism by which it protects against these four childhood diseases.
Do you see where it says that?
A. Yes.
Q. Is this a true statement?
A. Again, we believe that antibody is important in the development of

immune response but it may not be the only mechanism.
Q. Okay. So is it true that ProQuad induces mumps specific immunity?
A. You're going to have to define mumps specific immunity for me, please.
Q. As it is used in the circular.
A. I take that to mean that it's the measurement -- the detection of antibody, and the answer would be yes.
Q. And does the antibody induced protect against mumps?
A. Again, we're back to the same, which is that the efficacy -- if you go to the next paragraph, it says that the -- basically the efficacy results come from the original trials of the monovalent components.
Q. So this statement is based on the original efficacy studies?
A. Yes, it is.
Q. When were those efficacy studies?
A. Again, back to the late '60s.
Q. Then does Merck have any more current studies that reflect that ProQuad

induces mumps specific immunity which protects against mumps?
A. Again, the basis of the licensure of ProQuad was based on the immunologic endpoint only.
Q. So only the studies from the 1960s?
A. Yes.
Q. The next sentence which you have kind of already spoken about or you referenced, "...efficacy of ProQuad was established through the use of immunological correlates for protection against measles, mumps, rubella, and varicella." What does this mean?
A. It's basically the same as what we were talking about before, which is that for measles, mumps, and rubella in those early studies, that there was a parallelism between the presence of antibody and the efficacy results seems fairly similar. The text goes on to further elucidate the information with regard to varicella in which the endpoint was actually discussed with regulatory agencies and a

titer greater than five and gpELISA was considered to be indicative of protection based on some long-term follow-up studies.
Q. Do you know what the endpoint was for mumps?
A. The same as what we discussed earlier.
Q. Which was?
A. I assume it was the neutralization assays from the late '60s.
Q. So your understanding is that this information comes from the neutralization assays from the late '60s?
MR. SANGIAMO: Object to the form.
THE WITNESS: Yes.
BY MS. MAHENDRANATHAN:
Q. Were the studies referenced in the immunological correlate of protection, are those studies from the late 1960s?
A. The measles, mumps, and rubella are from the '60s. The varicella is from sometime in the '80s or '90s. I don't remember the exact year.
Q. Is that the original efficacy

studies or the studies doing the correlating of protection?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not understanding what you're asking me, I'm sorry.
BY MS. MAHENDRANATHAN:
Q. Sure. Let me try again. The sentence says efficacy was established for ProQuad through using immunological correlates of protection to mumps.
A. Yes.
Q. So is this sentence referencing the original efficacy studies for mumps or these immunological correlate of protection studies for ProQuad?
A. It's the original studies for mumps.
Q. Has Merck done any bridging studies to compare the original efficacy studies to the efficacy of ProQuad?
MR. SANGIAMO: Object to the form.
THE WITNESS: Efficacy studies

were not done for ProQuad. That was the agreement with regulatory agencies. The product was licensed on the basis of immunologic bridging between the component products, MMR and Varilrix.
BY MS. MAHENDRANATHAN:
Q. When were those bridging studies conducted?
A. I'd have to go back and look. I'm guessing 1990s, early 2000s.
Q. Does Merck have any current information that -- strike that.
Does Merck have any current studies on the immunological correlates of protection for ProQuad?
MR. SANGIAMO: Object to the form.
THE WITNESS: No.
BY MS. MAHENDRANATHAN:
Q. No. Okay. I'm going to move on to a different document.
How does Merck define mumps outbreak?
A. Merck doesn't define Merck

mumps outbreak. That's defined by the CDC.
Q. What is that definition?
A. It's usually somewhere between three or more cases in a particular geographic area in a particular time.
Q. Would you consider three cases of mumps in a -- you know, located within a particular location in time to be a significant mumps outbreak?
A. Not at all.
Q. What would you consider to be a significant mumps outbreak?
A. Probably thousands, if not tens of thousands of cases.
Q. Have you heard reference to a resurgence in mumps?
A. Yes, I've heard the term.
Q. What does it mean?
A. It means that there have been a few outbreaks. But, again, they're intermittent, they haven't continued over the years. They happen in very discrete environments, colleges, religious communities, churches.
Q. How many cases do you think

would constitute a resurgence in mumps?
A. That's speculating on my part.
Q. Does Merck have an understanding of how many cases per year of mumps would be a significant outbreak?
A. No, not really.
Q. Has there been a resurgence of mumps since 2006?
A. I don't know your definition of resurgence, I'm sorry.
Q. Okay. Has there been a significant increase in mumps since the last outbreak in 2006?
A. Frankly, no. Let's go back to Tab 3. Frankly, you can even -- let's go to Tab 3. So remember in the pre-vaccine era there were anywhere between 152 and 212,000 cases per year. Having 600, 300, whatever, is literally a drop in the bucket to put it simply. Even in the outbreaks that have occurred would have been -- there's been 200 cases on a college campus out of 20,000 individuals, that's a 1 percent attack rate. That means this vaccine is highly effective and these

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numbers here are really quite small when you compare them to the numbers that occurred in the pre-vaccine area. Think about the UK where there have been over 70,000 cases. We don't have anywhere near 70,000 cases.

Q. Does this table contain data from 2014 or 2015 or 2016 or 2017?

A. No. No, it does not.

Q. Do you know --

A. That's as far as the reference has gone.

Q. Do you know how many cases of mumps there were in 2015?

A. Is it on your sheet?

Q. I can bring a document that will help.

A. I don't see it.

Q. I have a document.

MS. MAHENDRANATHAN: Mark this as Exhibit 7.

- - -

(Exhibit 30(b)(6)(4)-7, Summary of Notifiable Infectious Diseases and Conditions - United States, 2015, was marked for identification.)

- - -

BY MS. MAHENDRANATHAN:

Q. Do you know what this document is?

A. It's the summary of notifiable diseases from 2015. It looks like it's published in 2017.

Q. Who publishes this document?

A. The CDC.

Q. And I'm just going to -- if it helps you, I think the easiest place to look for this information is on page 53.

A. Okay.

Q. So does this state how many cases of mumps there were in 2015?

A. Total says 1,329.

Q. And would you -- is this a reliable source of number of mumps cases in 2015?

A. Yes, I believe so. I don't know if this is the final numbers.

Q. Well, this is -- this document, this was published in August 11, 2017. It's the official MMWR summary of notifiable infectious diseases and conditions for 2015.

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A. Okay.

Q. I have another document.

MS. MAHENDRANATHAN: Can I mark this as Exhibit 8 now.

- - -

(Exhibit 30(b)(6)(4)-8, National Notifiable Diseases: Infectious Weekly Tables, was marked for identification.)

- - -

BY MS. MAHENDRANATHAN:

Q. Do you know what this document is?

A. I'm reading the title, "National Notifiable Diseases: Infectious Weekly Tables."

Q. So this is a document from the CDC WONDER website. It has provisional data for notifiable diseases. This is the page for meningococcal mumps and pertussis. Are you familiar with this document?

A. I'm not actually familiar with the WONDER website, no.

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Q. Do you see where it has mumps information cumulative for 2016?

A. Yes.

Q. How many cases does it list?

A. 6,369.

Q. Is it your understanding that this is the mumps incidents for 2016?

A. I assume based on what's reported here.

Q. And then what were the mumps incidents for 2017?

A. 5,629.

Q. These are thousands of mumps cases?

A. Yes.

Q. Several thousands?

A. Yes.

Q. Would you consider in these two years there was a relative resurgence in mumps as compared to 2000 when there was 270 cases?

A. Again, I don't know how you're using the word resurgence.

Q. How would you use that word?

A. A few more cases.

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Q. It's a few more cases?
A. Yes.
Q. It's several thousand more cases?
A. Again, the number of cases vary from year to year. That's the difference. Go back to what I showed you previously. Some years it's 600, some years it's 200, some years it's 2,000. When you consider it a resurgence, when you consider the effective of the vaccine has been remarkable over this time period. Even with these cases, as I think I gave you the math earlier, you still would have over 96 percent reduction in disease. This is a very small number of cases when you consider the total number of individual -- the impact of this vaccine.
Let me if I may, please, take you to another document. I'd like you to go to Tab 8, please. If you can just go to -- how is this described, page 7, it's on the top, the graph, the half-page graph. Just take a look at that. Look at the remarkable reduction in this disease. I'm talking over

40 -- sorry, make that 50 years. This is a remarkably effective vaccine. There will be a few cases here and there that differ by year, but you don't even need a statistician to tell you that's a remarkable reduction. This is a true public health story. This is a public health success.
Q. I just want to go back to my question. Would you say there is a significant increase in mumps from 2002 to 2016?
MR. SANGIAMO: Could you just direct me to where this relates to the notice?
BY MS. MAHENDRANATHAN:
Q. We just want to make sure we are on the same page with an understanding of what constitutes outbreaks, what's a significant -- what Merck is investigating with respect to outbreaks, and so I want to make sure that these thousands of cases fall under your understanding of what is a significant amount of mumps.
MR. SANGIAMO: You were asking her about whether something

constitutes a resurgence.
BY MS. MAHENDRANATHAN:
Q. So --
MR. SANGIAMO: Where is that?
BY MS. MAHENDRANATHAN:
Q. -- is it a significant increase in mumps?
A. Take a look at this graph. No, it's not.
Q. So 270 cases to 6,000 cases is not a significant increase in mumps?
A. No. Again, think about what this means. The attack rate in most of these outbreaks in vaccinated individuals is perhaps 1 or 2 percent. The normal attack rate in an outbreak is between 30 and 40 percent. We have a nine to tenfold reduction because of the value of this vaccine in cases. Again, it's a highly effective vaccine. It's also a very safe vaccine.
Q. Just to go back to my question, so you would not say 270 to 6,000 cases is a significant increase in mumps?

A. No.
MR. SANGIAMO: Object to the form. You can answer.
BY MS. MAHENDRANATHAN:
Q. Could you identify the mumps outbreak that Merck is aware of?
MR. SANGIAMO: Wait a minute. We defined what the scope of the outbreaks is that's going to be covered by this deposition.
MS. MAHENDRANATHAN: That's fine.
MR. SANGIAMO: So why don't you ask you about those outbreaks?
BY MS. MAHENDRANATHAN:
Q. Can you identify all mumps outbreaks that Merck has taken some formal response or action with respect to?
MR. SANGIAMO: Formal evaluation.
BY MS. MAHENDRANATHAN:
Q. Formal evaluation.
A. Again, it's not our role to formally evaluate outbreaks. We have been a cooperative partner in the evaluations where

appropriate.
Q. So Merck has not conducted any formal evaluation of any mumps outbreak?
A. As I said earlier, this is the job of the CDC.
Q. It is not Merck's job?
A. It is not Merck's job.
Q. So Merck does not formally evaluate mumps outbreaks?
A. No, we do not. CDC are the experts. We rely on their findings.
Q. Can you identify all the mumps outbreaks you're prepared to speak about today?
A. Yes, I can.
Q. Sure.
A. Can you turn to Tab 4, please. There's nine different outbreaks shown here that we were asked to discuss. I think I counted correctly.
Q. With respect to these nine outbreaks, Merck hasn't taken any formal evaluation of these outbreaks?
A. No. Again, we've cooperated with CDC. We have provided samples. We

have provided reagents.
Q. Could you describe the 2006 mumps outbreak?
A. Certainly. It was -- as described here, it's the first large mumps outbreak that was among two of those recipients, lasted between December 2005 and 2006. Started out in Iowa among college campuses. Moved on to eight different states. About 6,500 individuals in the primary group affected were 18 to 24-year-olds.
Q. Are there any other relevant demographic information related to the 2006 mumps outbreak?
A. Again, the fact that it was very much clustered in college campuses in very focal settings.
Q. Could you describe the 2009 to 2010 Northeast outbreak?
A. Sure. So this is a multi-state outbreak, actually it began in Orthodox Jewish boys camp and then it spread to other parts of New York, New Jersey and Canada, mostly within, again, a Jewish

community with about 3,500 individuals involved, primarily 13 to 17-year-old boys. And based on the religious practices in these communities, boys have very intensive study, literally sitting across the table from each other for 12 and 14 hours a day with extremely close contact.
Q. Did you mention whether the individuals who had mumps had been vaccinated?
A. Yeah, if you turn to the next page. So the vaccination status is that -- in the first one, that the Midwest outbreak at about 63 percent overall and 84 percent between 18 and 24-year-olds received two doses, and in the 2009, 2010, two dose recipients were about 76 percent, one dose recipients 14 percent.
Q. Can you describe the 2009, 2010 Guam outbreak?
A. Sure. So this is an outbreak in -- Guam is a US territory, isolated area of the world. This case actually came from a nearby island where mumps was circulating and the outbreak went on for about a year

between 2009 and 2010. Total of 505 individual cases out of a population of about 180,000 individuals, and this was in 9 to 14-year-olds.
Q. What was the vaccination status?
A. Two dose recipients, about 60 percent; one dose, 11 percent; and 29 percent were unvaccinated.
Q. Could you describe the 2011 Berkeley outbreak?
A. Yes. So this was in a college campus once again. The index case originated from an individual who had traveled to Western Europe where there's lots of mumps circulating. There's not a lot of mumps vaccines used in Western Europe. This went on between August of 2011 and January of 2012 specifically on the UC Berkeley campus. A very small number of cases, 29 amongst a student population of about 36,000.
Q. What was the vaccination status?
A. Two doses, 76 percent. One

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dose, 7. Zero, 3 percent. Unknown, 7 percent. And three doses, 7 percent.
Q. Would you say that this was a population with high two dose coverage?
A. 76 percent is not nearly as good as it should be, no.
Q. Would you say it's a population with high one dose coverage?
A. Well, by default, if you add the numbers together, if you take the one and two dose, that would still be a 70 -- I'm sorry, an 83 percent, which still isn't good enough.
Q. So if it's 7 plus 76, okay.
A. Yep.
Q. Could you describe the 2013 Virginia University outbreak?
A. I can. It's not nearly as much known about this one. The majority of the information that we found about this basically comes from health department reports. And from the media, frankly. So this is at a couple of different colleges in Virginia between January 2013 and April 2013. Approximate number is about 100

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individuals among college students. And we really have no information about their vaccination status.
Q. Could you describe that 2013 Loyola University outbreak?
A. Sure. Again, this is an outbreak among undergraduates in multiple class years, fairly short period of time, mid-February 2013 to March 2013. At Loyola. 12 cases. We don't know the exact denominator. We don't know much about other vaccination status. And, again, this is really coming out of the news media.
Q. When you say we don't know much about the denominator. What did you mean?
A. In other words, we don't know the total student population on the campus.
Q. Could you describe the 2014 NHL outbreak?
A. Sure. For the hockey lovers in the room, this outbreak occurred among about two dozen players on six different NHL teams. Those players came from the US, Canada, Finland, Germany and Sweden. Some

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of those countries have vaccine policies, many of them do not. For mumps I mean specifically. The time period was from mid-October 2014 to the end of 2014. Again, six teams, approximately 23 players and two officials were involved. These individuals were somewhere between 20 and 34 years of age. Again, we don't have any information about vaccination status.
Q. Of the players from other countries, which of those countries do not have vaccine policies?
A. I would have to double check, but I don't believe that Finland, Germany or Sweden may have a two dose vaccine policy.
Q. They may have a two dose vaccine policy?
A. No, I don't think they do.
Q. Oh, you don't think they do?
A. I don't think they do. I'm not positive. I would have to check that.
These individuals, by the way, are also 20 to 34 years of age. So whether they ever got two doses even if it was recommended is questionable.

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Q. Can you describe the 2016-2017 Arkansas outbreak?
A. Sure. Yes. Again, there's no formal references on this. We got this from the Department of Health and from a presentation from one of the individuals in the community. This was a population in Northeast Arkansas where a Marshallese population exists. Marshallese are -- how should I say it -- they are employed in much of the chicken industry in the area. It also was very much concentrated in the Marshallese but also in some school-age children in various portions of Northwest Arkansas. The Marshallese are a fairly close knit community but they do engage with the rest of the community at times. The time period is from August 2016 to August 2017 and roughly about 2,900 cases including both school-age children and adults. Here, again, the two dose coverage rate was estimated to be about 63 percent, one dose 8 percent and 29 percent with no doses.
Q. And then could you describe

the 2016-2017 Washington outbreak?
A. Yes. This is information that we obtained from the Department of Health. This was outbreaks occurring in about 15 counties in Washington State. The cases occurred between October 2016 and May 2017, approximately 834 cases. And it involved individuals anywhere between, I think it's about four years of age and up to 64 years of age. Again, we don't have information on vaccination status.
Q. Would you consider any of these outbreaks to reflect mumps cases in highly vaccinated populations?
A. Again, what's the definition of highly vaccinated population?
Q. What do you consider a highly vaccinated population?
A. Probably 90 to 95 percent coverage rate for two doses.
Q. So do any of these outbreaks meet that standard?
A. Not really.
Q. I'm going to start with 2006 Midwest outbreak. What does Merck think are

the potential causes of the 2006 outbreak?
A. I think perhaps we should turn to possible causes in outbreaks, Tab Number 5, please. This is extracted from a response from Interrogatory Number 8. And this is based on the information that was discussed first in 2006, really hasn't changed much over the ten years in which some of these outbreaks have occurred, but basically it's accepted in the scientific community that it's a very complex scientific issue, that it's really not clear why the mumps outbreaks have occurred and the cause may be multifactorial. So if you look here, there's actually nine different possible reasons that could explain -- that may be at play, that there's no particular factor that stands out in terms of what's going on.
Q. So all of these nine factors are a possible cause of the 2006 outbreak?
A. Correct.
Q. So just to confirm, "unrecognized importations of mumps" is a possible cause of the 2006 outbreak?

A. It's one of the possible causes.
Q. What does that mean?
A. It means, again, that there could be many factors at play at the same time.
Q. Sorry. Let me rephrase. What does "unrecognized importations of mumps" mean?
A. Sorry. Yeah, unrecognized. You want to turn to page 4, please. So to be honest, there's hasn't been -- there's been very little mumps for many years here and the problem, frankly, is, is that physician don't really see mumps very often, they may not recognize it. It may take them longer to diagnose it. So the point is that the importation of the cases may not be detected initially because they don't -- they're not able to detect the disease. The other possibility is that you could have a milder form of mumps, and so it may go unrecognized until you actually have laboratory studies done. Even with laboratory studies being conducted, you may

not be able to actually determine if it's mumps or not.
Q. Let's take it step by step.
A. Okay. Sure.
Q. Unrecognized means you can't be sure whether or not it's mumps?
A. Unrecognized means that people may not recognize it in the community at first.
Q. I see.
A. Okay.
Q. And then when you say importations, what do you mean?
A. Well, for example, take the very -- let's go back to -- if I can do this, let's go back to our summary of the outbreaks under -- it's right here, isn't it -- under Tab 5. Sorry. Wrong tab. I'll get there.
Q. Tab 4?
A. Yeah. Thanks. Right. Let's go back to there. So, I mean, the first two outbreaks here are classic examples. It may not say it here, but in the 2006 outbreak, this was actually an individual who had been

traveling somewhere else and came back to the US having mumps. It's very clear, for example, in the 2009-2010 outbreak that the index case was an 11-year-old who traveled to the UK where mumps were circulating. So that's usually what I would call an importation.

Q. So just so we're clear, when somebody comes from somewhere else and brings mumps with them?

A. Correct.

Q. It may be unrecognized in the community at first because the doctors aren't expecting to see mumps in the US?

A. Correct. Right.

Q. That's what an unrecognized importation of mumps is?

A. Correct.

Q. The next factor, "delayed recognition of mumps cases," what does that mean?

A. Kind of goes at the same thing I was just saying. That, again, if you want to turn to page 5 in that document. So it means that they may not recognize it right

away. The characteristics of mumps can be also similar to other infectious diseases. It can be adenovirus. It can be the flu. It can be some sort of other rash. It can -- so the point is -- maybe not a rash. I take that back. But it can be another infectious disease. So the point is, is that they may not recognize it right away, may not be able to diagnose them right away.

Q. The next factor is, "differences between the mumps vaccine strain and the circulating mumps wild type strain." Could you just explain that in your own words what that means?

A. Sure. Yeah. So, again, the mumps vaccine as it exists right now, is genotype A. A number of these circulating mumps wild type strains have actually been type G, for example. The question is, is there a mismatch here, will the vaccine work in those situations. I will take you to page 7, if I may. Just so you can see that if you look down, for example, underline 4C says, "Concern was raised that mumps vaccine-immunity may be less effective

against other strains. There is no evidence to date. All sera collected from vaccinated children neutralized diverse mumps virus strains. However, antigenic differences among strains led to lower antibody levels against non-vaccine strains. These differences might become more important with increasing time since vaccination."

But importantly in that sentence is that the difference is regardless of the strain, we were still able to neutralize it with the vaccine.

Q. So strain mismatch is just when the vaccine strain is different from the circulating strain?

A. Yes, correct.

Q. And it's a possible cause of mumps outbreaks?

A. Again, it's one of the possible causes.

Q. One of the possible causes. Has Merck done studies showing neutralization against diverse mumps vaccine strains?

MR. SANGIAMO: Dr. Krah covered this topic about what studies

Merck has done. Dr. Krah described the studies that Merck did in collaboration with the CDC and the FDA. So he is our 30(b)(6) deponent on that topic.

BY MS. MAHENDRANATHAN:

Q. So you don't know, yes or no, you don't have details on that?

MR. SANGIAMO: She is not here to testify about that.

BY MS. MAHENDRANATHAN:

Q. Okay. Just to confirm, does Merck consider strain mismatch as a possible cause of these outbreaks?

A. Based on the information that has been obtained to date, I seriously doubt it.

Q. Why is that?

A. Because of the fact that we were able to neutralize against all the different strains that were tested.

Q. Who is "we"?

A. This is the data that we're referring to, the work that was done by Dr. Rubin and the CDC.

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MR. SANGIAMO: We've been going about an hour.

MS. MAHENDRANATHAN: Do you need a break?

THE WITNESS: It would be a great idea, sure.

MS. MAHENDRANATHAN: Okay.

VIDEOGRAPHER: The time is now 2:33. We're going off the video record.

\- - -

(A recess was taken.)

\- - -

VIDEOGRAPHER: The time is 2:47. This begins media unit number three.

BY MS. MAHENDRANATHAN:

Q. I want to go through the next factor you listed "waning immunity." Does that mean that the protection you get from the vaccine will decrease over time?

A. That's one definition. There's really two. So waning immunity could mean either the decline in your humoral or your cellular immunity over time,

or it could mean basically what you said, which is the protection changes over time.

Q. What does it mean that the change in your humoral or cellular immunity?

A. It means that the antibody levels or whatever you're measuring goes down over time, which is actually a very normal phenomena with most vaccines.

Q. What would the impact of that be?

A. That eventually perhaps you could reach a level where the antibodies are no longer protective.

Q. So under either definition, at some point, it's possible to reach a level where you're no longer protective?

A. Possible.

Q. Does Merck consider waning immunity a possible cause of the outbreaks?

A. So, again, these outbreaks have been investigated by the CDC. These are one of the main reasons that they have identified. Recognize that in some of the studies waning immunity has been listed as a possibility, probably in about six studies

it has and another six it hasn't. So, again, it's a possibility, but it's certainly not the sole factor.

Q. I just want to go back to my question. In Merck's opinion is it a possible cause?

A. Again, we didn't do these outbreak investigations. The experts here at the CDC, we rely on them for their input.

Q. So does Merck have an opinion as to what the possible causes are?

A. No. We support the research that they've done, we think it's very good.

Q. So Merck has no understanding of the possible causes of mumps outbreaks?

MR. SANGIAMO: Object to the form.

THE WITNESS: Again, we're relying on the CDC. They're the experts in this area. We think they've done some very good research. They've looking at the outbreaks for over ten years. They listed nine possible different reasons. It could be any one of these or a multitude of

these.

BY MS. MAHENDRANATHAN:

Q. Does Merck agree that these are possible reasons of the CDC?

A. Certainly these are reasons that they listed. It doesn't mean this is an -- what's the word, exhaustive list. It could be other reasons as well.

Q. But Merck agrees these are possible?

A. According to the CDC, yes.

Q. Does Merck agree with the CDC?

A. This is what they've published. They're the experts.

Q. I asked if Merck agrees with the CDC. Does Merck agree?

A. I understand what you asked. Again, this is research that's done by the CDC. We think they're the experts in the area. We rely on their expertise.

Q. So you can't answer whether Merck agrees with the CDC?

A. I cannot.

Q. Why is that?

A. We don't have a position on

this. We rely on the CDC. They have the expertise in this area.
Q. So Merck takes no position as to whether any of -- anything is a cause of mumps outbreaks?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't answer that. That's speculation.
BY MS. MAHENDRANATHAN:
Q. You can't answer it because Merck does not take a position?
MR. SANGIAMO: Object to the form.
THE WITNESS: I don't think I can answer that.
BY MS. MAHENDRANATHAN:
Q. I asked you --
MS. MAHENDRANATHAN: Could you just read back the question?
- - -
(The court reporter read the pertinent part of the record.)
- - -
BY MS. MAHENDRANATHAN:

Q. Could you answer that question?
MR. SANGIAMO: Object to the form.
THE WITNESS: I can't answer the question. Again, this is the expertise of the CDC. We rely upon them. They have the expertise in this area.
BY MS. MAHENDRANATHAN:
Q. So does Merck know whether the effectiveness of its vaccine is a possible cause of outbreak?
A. One of the issues, if you look at Item Number E here, vaccine effectiveness is one of the possibilities. It's one of them.
Q. But Merck doesn't know whether it's a possible cause?
A. There are multiple causes here. No one cause has been identified for these outbreaks.
Q. I asked, Merck doesn't know whether it's a possible cause. Does Merck know whether it's a possible cause?
A. It's one of the causes that

have been listed by the CDC.
Q. And has Merck investigated whether vaccine effectiveness is a possible cause of mumps outbreak?
A. This is, again, the role of the CDC. Remember when I took you back to the first item here in the booklet, it describes the activities that CDC does. They are the experts in terms of looking at vaccines and outbreaks and getting the associated effectiveness many times from those outbreaks.
Q. I just want to confirm for the record, Merck does not, has not investigated whether vaccine effectiveness is a cause of mumps outbreaks?
MR. SANGIAMO: Object to the form.
THE WITNESS: It's not our role. CDC does that very effectively, much better than we would ever do.
BY MS. MAHENDRANATHAN:
Q. Because it's not your role, Merck has not done it?

A. Correct.
MR. SANGIAMO: Object to the form.
BY MS. MAHENDRANATHAN:
Q. Has Merck done anything to rule out the possibility that vaccine effectiveness has caused mumps outbreaks?
A. No, we have not. Again, there is a bunch of list -- there's a bunch of causes listed here.
Q. And these came from the CDC?
A. Yes, they did.
Q. And Merck has not done anything to rule out the possibility that effectiveness is one of the causes of the outbreaks?
A. No. It could be any one --
MR. SANGIAMO: Object to the form.
THE WITNESS: It could be any one of these nine items.
BY MS. MAHENDRANATHAN:
Q. Merck has not ruled out any of these?
MR. SANGIAMO: Same objection.

THE WITNESS: No, we have not.
BY MS. MAHENDRANATHAN:
Q. So Merck has not ruled out that vaccine effectiveness could be a cause of outbreaks?
MR. SANGIAMO: Object to the form.
THE WITNESS: It's the same answer. One out of nine possibilities here. There could be other reasons as well.
MS. MAHENDRANATHAN: Could you read back my question?
- - -
(The court reporter read the pertinent part of the record.)
- - -
BY MS. MAHENDRANATHAN:
Q. Could you answer that question?
A. It's the same answer I gave. I'm sorry. It could be any one of these reasons.
Q. So what are all of these reasons?
A. Again, these are possible

reasons. It's not clear --
Q. I just want to confirm the universe of the possible reasons.
A. This is the list that we put together in the Interrogatory. This is what we found in the scientific literature. It doesn't mean that these are the only reasons but these are probably the ones that have been identified most often in the publications that have been put out to date.
Q. I see that. I just want you to state on the record what the reasons are so we can see it.
A. You want me to read all nine of these?
Q. Yes, please.
A. Want me to read what's here slowly?
Q. Could you put them in your own words what each of these reasons are?
A. I think they're best stated right here. So the factors that have been considered, but are not necessarily limited to these, are nine different possibilities. One is an "Unrecognized Importation of

Mumps;" two is a "Delayed Recognition of Mumps Cases;" three is "Differences between the Mumps...Strain and the Circulating Wild Type Strain;" four is "Waning Immunity;" five is the "Vaccine Effectiveness;" six is an "Accumulation of Susceptible Individuals;" seven is a "Population Immunity that is Below the Herd Immunity Threshold;" eight is a "Lack of Asymptomatic Natural Boosting due to Substantially Reduced Endemic Disease;" and nine are "Conditions That Foster Frequent, High-Intensity Exposures that Facilitate Transmission."
Q. And these nine factors are what Merck considers the possible causes of outbreaks?
A. These and there could be others.
Q. What are the others?
A. It could be looking at, for example, cellular immunity. It could be looking at --
Q. Let me slow you down. What was what you just said?

A. I said it could be changes in cellular immunity, for example.
Q. Thank you.
A. You're welcome.
Q. You can continue.
A. I mean I think -- I haven't really gone through an exhaustive list of these. These are certainly the largest, these are the top nine if you want to call it that.
Q. Do you think each of these causes is equally likely?
A. I don't know.
Q. Does Merck have an opinion as to whether each of these causes is equally likely?
A. No, we really don't.
Q. You don't know.
What does accumulation of susceptible individuals mean, in your own words?
A. Sure. So think about it this way: As with any vaccine, you don't have either 100 percent protection or 100 percent seroconversion. So let's just take this,

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for example, that we might have a 95 percent seroconversion. Technically that leaves 5 percent of individuals who are not protected, not seroconverted. Over time you build up a cohort of those each year. As you vaccinate, you get another 5 percent and another 5 percent and another 5 percent, and pretty soon you have a large group of individuals who may be susceptible.

Q. So just to make sure I'm understanding, if you have a population of people, some have been vaccinated, some haven't, in each of those populations there could be people that are still susceptible because they weren't vaccinated or they were and for whatever reason they are still susceptible?

A. Right. There's a small percentage of people who, with vaccine, will not have a detectable antibody, and, therefore, we assume that they are not protected.

Q. So -- sorry. Didn't mean to cut you off.

So that population of

Page 159

susceptible people over time could build up to a point where mumps outbreaks are possible?

A. Yes.

Q. The next factor, "Population Immunity that is Below the Herd Immunity Threshold," what does that mean?

A. So herd immunity is the concept that if you get to a particular level, which for mumps could be somewhere around 92 percent, that by vaccinating most people, that you can then protect the unvaccinated. Think about the fact that maybe you have someone who isn't a vaccine candidate, they're immunocompromised, something like that. By having enough people vaccinated, you can, in fact, protect the unvaccinated individuals.

Population immunity is a little bit more of a complex concept here, and that is that population immunity means basically the math behind it is that you take the percentage of people that are vaccinated, let's just say the vaccine coverage rate is -- I'll make these simple

Page 160

numbers, 90 percent. And the effectiveness of the vaccine is also 90 percent. So you multiply .9 times .9 and you get .81. .81 is too low of a population immunity to reach the herd immunity level that's been set of, say, 92 percent.

Q. So there's some percentage of protection you need in the population to prevent outbreaks from happening?

A. Yes, correct.

Q. And this combination of vaccine coverage and vaccine effectiveness is lower. When you, you know, multiply them together --

A. Right.

Q. -- it's lower than what you need to prevent outbreak?

A. That's right.

Q. And then H, could you explain what factor H is?

A. Sure. So "Lack of Asymptomatic Natural Boosting due to Substantially Reduced Endemic Disease." This is actually, if you will, the success of a vaccine which is that with high

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coverage rates and with a good vaccine, you basically have less natural boosting going on because you don't have a wild type disease circulating in the population. So this is actually -- you know, the success of most vaccines which actually reduce that natural boosting.

Q. So it's basically that people aren't exposed to mumps so they're not getting boosted?

A. Correct.

Q. And so --

A. Correct.

Q. -- that could cause outbreaks --

A. Yes.

Q. -- because their protection is lower?

A. Right.

Q. And then the last factor, "Conditions that Foster Frequent, High-Intensity Exposures that Facilitate Transmission," what does that mean?

A. So think about what I told you earlier about the various outbreaks that have occurred to date. Many of those have

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occurred in really very sort of congregate settings, college campuses, religious communities, isolated communities. These are areas in which you have very -- you know, think back to when you were in college. We all had a lot of fun, you eat, drink and sleep together. All right. So in that type of setting, you can really have a very high-intensity exposure going on. So it's that very close living that really allows you to have constant, constant exposure to the virus.

Q. So if somebody has mumps, you can't avoid them because you see them all the time?

A. That's right. In the classroom, in your dormitory, at dinner, everywhere. In the library.

Q. Do you think that this constant -- these high exposure settings, do you think that's more likely to be a possible cause of mumps than the strain mismatch?

A. Again, I don't really think I'm qualified to make that decision. I

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think it's one of the variables at play here.

Q. And Merck doesn't have a position --

A. No.

Q. -- as to whether one is more likely --

A. No.

Q. -- than the other.

Has Merck conducted any test to rule out any of these causes of outbreaks?

A. Well, again, I mean, we participated in the evaluation of the mumps strains, to look at that. Other than that, I don't believe that we have.

Q. So I'm just going to go through them one by one to confirm. So has Merck conducted any test to rule out the possibility that unrecognized importations of mumps have caused outbreaks?

A. Again, we're not in a position to rule out or to evaluate. This is -- for every one of these variables it's the same thing, we don't have access to these

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populations. We don't do these types of studies. The health departments don't invite us in. So we don't really have access to this.

Q. Understood. So Merck isn't studying whether it's these outside importation of mumps that's causing outbreaks?

A. No.

Q. Based on our understanding of some of these studies you've mentioned, the 2009-2010 outbreak where someone traveled to the UK and came back and brought mumps, does Merck have an understanding that that's probably what caused that outbreak?

A. We rely on the CDC to make that assessment. The other ones are in the best position to determine what causes these outbreaks. In the ten years of evaluating this information, to be honest, they have not come to one specific factor. All these nine are still in play.

Q. So for the 2009-2010 Northeast outbreak, does the CDC suggest that the importation of mumps was an actual cause?

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A. It started the outbreak.

Q. Does Merck agree that it started the outbreak?

A. That's what the facts show.

Q. So it caused the outbreak?

A. It didn't cause it. It started it.

Q. What is the distinction there?

A. It's that there was an index case, the first person that comes down with the disease I'm saying that person started the outbreak. It's the first case. Whether that's the only cause of that outbreak, I don't know.

Q. But it's one of the causes?

A. It's one of the causes, yes.

Q. Okay. Could waning immunity be one of the causes?

A. It could be one of the causes. We don't know.

Q. Merck doesn't know?

A. No, we don't know, certainly don't know.

Q. Does the CDC know?

A. Again, no, because they still

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have all these things listed. They haven't changed their opinions on this.
Q. It could be a number of causes?
A. It could be more than one, yes.
Q. They haven't ruled out waning immunity?
A. No, they have not.
Q. And Merck hasn't ruled out waning immunity as a cause?
A. No, again, but we rely on the CDC for their opinion on this.
Q. Merck doesn't evaluate whether waning immunity is a cause of outbreaks?
A. No, not really. I mean, we did -- I don't know if it's time to -- we did talk. We did do some -- you know, we tried to support research in regards to the use of the vaccine. You can take -- perhaps take a look at Tab 17 if you'd like. 16, 17.
Q. Could you describe the research to me? The research referencing.
A. Let's go to 16 and 17 for a

minute, please. Do you remember when I first said that Tab 16 describes our investigator initiated studies program? So if you turn to the second page under that tab, if you want to follow with me, please. So I mean, these on the bottom of the page that says areas of interest for investigator initiated studies. So we're trying to understand more about the vaccine and we support independent investigators to do this type of research.
Q. When you say support, is that funding?
A. It can be funding, it can be vaccine or it could be a combination of those.
Q. So through this program, Merck is encouraging research into vaccine -- into waning immunity?
A. Again, it's persistence of immunity is one of the areas of interest that's listed here, yes.
Q. Has Merck encouraged or funded or any way through this program facilitated research into waning immunity?

A. Yeah. Let's go to that. It's on -- turn to Tab 17 for a minute. Here is -- there's one, two, three, four, five studies that are listed on this page 1 and the next page. So the first two studies we supported were not through this formal MISP program but rather just through provision of vaccine or antigens or infected cells, whatever, to do it. But the first two studies are from Sweden and Finland to actually look at immunogenicity and persistent studies. So that was specific -- both of those are specifically focused on looking at cellular immune responses and persistence of antibody in young adults.
Q. Would you say this reflects, you know, Merck's efforts to evaluate whether waning immunity is a cause of outbreaks?
A. This is one of them, yes.
Q. Has Merck conducted any other efforts to evaluate whether waning immunity is a cause of outbreak?
A. Let's just go through the rest of these, if we could, please. So, again,

on the bottom, the third item that's listed here is a CDC mumps persistent study. We actually tried to join forces, if you will, with the CDC to actually look at the immune responses after -- 15 years after second dose and also to look at what would happen with the third dose. Unfortunately we tried to engage them, but the CDC said it wasn't really appropriate for them to do research with us. As it turns out, the CDC ended up doing the study themselves, which is great. That paper was published by Amy Fiebelkorn in 2014.

Then on the next page are two of the formal studies that we've done to understand more the immunogenicity and persistence. And these were through the Merck Investigator Initiated Studies Program. These are two studies, again, to look at persistence of immune responses, both human and cellular. And the last one specifically says to look at, for example, waning over time. All right. So we have supported both of those studies.
Q. So you had said earlier that

it's not Merck's job to evaluate possible causes of outbreaks and yet Merck is helping assess possible causes of outbreaks here. Right?
A. Where the research can be done yes.
Q. And what other efforts has Merck taken to assess possible causes of outbreaks?
A. This is the extent of it right here.
Q. This is all of it?
A. Yes.
MR. SANGIAMO: Plus what Dr. Krah testified about.
BY MS. MAHENDRANATHAN:
Q. Okay. So -- and this would assess waning immunity as a possible cause?
A. Some of the studies would, yes.
Q. Were there any other possible causes that were assessed?
A. No, just persistence, third dose -- no, I don't think so.
Q. So Merck hasn't evaluated

whether effectiveness is a possible cause?
A. No.
Q. Has taken no efforts to assess whether effectiveness is a possible cause?
A. No. Again, that's really extremely difficult for us to do. We don't have access to those populations. The CDC works with the counties, states, locales that have outbreaks. And that's how would you determine effectiveness.
Q. Has Merck done any test to establish any correlates of effectiveness?
A. No.
Q. Has Merck assessed vaccine protection as a possible cause of outbreaks aside from simply the effectiveness?
MR. SANGIAMO: Object to the form.
THE WITNESS: I'm not sure how you're defining protection here. Again, we have looked at long-term immunogenicity studies, persistence of antibody through these independent grants.
BY MS. MAHENDRANATHAN:

Q. As a -- as part of your investigation into possible causes?
A. Again, to help broaden the scientific knowledge in this area.
Q. What studies are those?
A. The ones I just identified for you.
Q. These were conducted by Merck?
A. No, no, no, no. I'm sorry. No. We supported these studies --
Q. You supported the studies?
A. We did not conduct them. We may have provided reagents. We may have provided vaccine.
Q. But Merck has not conducted its own studies?
A. No, we have not.
Q. As you know in, I think we just went over, in 2016 there were several thousand cases of mumps?
A. Correct.
Q. And in 2017 over 5,000 cases of mumps. Does Merck anticipate that in the coming years there will be as many cases of mumps?

MR. SANGIAMO: I'm going to object. I think that's outside the scope of this notice. Calls for speculation.
BY MS. MAHENDRANATHAN:
Q. You can speculate if you want.
MR. SANGIAMO: No. She has to give truthful testimony. Speculating is not truthful testimony, and it's outside the scope of the notice.
BY MS. MAHENDRANATHAN:
Q. Based on Merck's understanding of the possible causes, which you listed these nine causes, and you said there could be others, does Merck understand that thousands of cases of mumps a year could continue to happen?
MR. SANGIAMO: That's outside the scope of this notice. The notice asks for the understanding of potential and actual causes of mumps outbreaks that have been identified that already occurred. The notice doesn't call upon the witness to try and make predictions for what kind of

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outbreaks may occur in the future.
BY MS. MAHENDRANATHAN:
Q. If waning immunity is a cause of outbreaks, do you have any -- does Merck have any reason to believe that -- strike that.
Merck understands that waning immunity is a possible cause of outbreaks?
A. It is one of the causes identified by CDC.
Q. Is there any reason to believe that the impact of waning immunity will change in the future?
MR. SANGIAMO: Calls for speculation. That's the same question. It's outside the scope of this deposition.
MS. MAHENDRANATHAN: Well, I'm talking about possible causes and I want to learn more about them, their impact now and whether they could change.
MR. SANGIAMO: That's not part of this notice. This notice asks for Merck's understanding of all

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potential and actual causes of the mumps outbreak, and we identified these outbreaks, all of which occurred in the past. It does not call upon Merck giving predictions about what might occur in the future.
MS. MAHENDRANATHAN: I'm asking for her understanding of the potential actual causes, actual causes. This is part of her understanding. Would they change, would they stay the same? That's what I'm asking.
MR. SANGIAMO: Whether they would have changed as to the outbreaks that occurred, is that what you're asking?
MS. MAHENDRANATHAN: I'm asking her understanding of the causes. These causes --
MR. SANGIAMO: She testified to that.
MR. MACORETTA: Is Ms. Keegan going to testify to this, then, under number four, consideration of

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possible solutions? Would you agree that it's a fair question for her then?
MR. SANGIAMO: She'll testify to consideration of possible solutions including changes to the composition, manufacture of mumps vaccine.
MR. MACORETTA: So what do you think is going to happen in the future would go to that, wouldn't you agree?
MR. SANGIAMO: If she wants to ask Dr. Kuter about considerations of possible solutions, she can do that.
MR. MACORETTA: I thought that was Amy Keegan's job? I don't -- I'm just looking at an e-mail from the other day. I thought Amy Keegan was testifying about that.
MR. SANGIAMO: She's going to testify about --
MS. DYKSTRA: Just the manufacturing portion. Just the manufacturing portion.

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MR. MACORETTA: The e-mail says --
MS. DYKSTRA: The manufacturing portion, in the middle of it. So to the extent that you ask about Merck's consideration of possible solutions for or responses to the mumps outbreak, Dr. Kuter can answer that. To the extent you want to talk about changes to the composition or manufacture of the mumps vaccine, Amy Keegan will address that.
MS. MAHENDRANATHAN: Okay.
MR. MACORETTA: Okay. So then why don't we -- what do you think is going to happen in future part of number four then with Dr. Kuter?
MR. SANGIAMO: Hamsa is taking this deposition.
MR. MACORETTA: She's taking this now. I'm taking the Amy Keegan half.
MR. SANGIAMO: I understand. She can ask the question.
MS. MAHENDRANATHAN: Can I see

that?
MR. MACORETTA: Absolutely.
You might wish to visit with the witness about this issue right here. Go ahead, ask the question.
BY MS. MAHENDRANATHAN:
Q. SO going to Topic 4 of the 30(b)(6) notice, in Merck's consideration of possible solutions or responses to the mumps outbreak, what has Merck considered as possible solutions to the mumps outbreak?
A. Again, we're following the lead of the CDC. Right now they're suggesting possibility of a third dose in outbreaks situations.
Q. So Merck is not considering any other possible solution?
A. No.
Q. Is Merck considering a new vaccine as a possible solution?
A. No. You have to realize that would be a huge undertaking. Furthermore, the bar has already been set. The bar has been set in the sense that this vaccine, the Jeryl Lynn vaccine, has a very solid safety

record and a very solid effectiveness record. Recognize the fact that there is no other mumps vaccine in the world that has a safety record that this vaccine has. So when you think about a new vaccine, first and foremost, you not only need to think about the effectiveness of the vaccine but also its safety. Furthermore, think about the fact that this vaccine has been around for 50 years. It's been highly effective. Remember the graph that I showed you earlier with a remarkable reduction in disease, over 98 percent over the 50 years that it's been in use. To show how a new vaccine could compare to that would be a very lengthy trial. You'd have to have a very long discussion with regulatory agencies as to what the appropriate endpoint would be for such a study. But I can assure you that it would not be simply something as simple as showing that the immunogenicity would be better with a new vaccine. So that's a huge, huge undertaking.
Q. So just to go back, Merck is not considering a new vaccine as a response

to outbreaks?
A. No, we are not.
Q. You mentioned that the bar has been set by Merck's vaccine. Does that include the fact that Merck's mumps vaccine induces 96 percent -- induces mumps neutralizing antibodies in 96 percent of people?
A. I think what matters here is not the immunogenicity data but what matters here is the effectiveness data. Any vaccine expert will tell you that what the world relies upon is not immunogenicity data but effectiveness or efficacy data. That's the data that we're talking about that would matter here. That's where the bar has been set.
Q. Is there any other mumps vaccine with comparable effectiveness data?
A. The GSK vaccine has been shown to have similar immunogenicity and similar effectiveness.
Q. Is licensing the GSK vaccine in the US a possible solution to mumps outbreaks?

MR. SANGIAMO: You're asking if Merck has considered licensing of GSK's vaccine as a possible solution, whether Merck has considered that?
BY MS. MAHENDRANATHAN:
Q. Does Merck consider the licensing of GSK's vaccine as a possible solution to mumps outbreaks?
A. No.
Q. Why not?
A. The performance is very much the same.
Q. Does Merck know that the licensing of GSK would not be a possible solution to mumps outbreaks?
MR. SANGIAMO: Object to the form. Objection. You can answer.
THE WITNESS: I'm not sure I understand the question. I'm sorry.
BY MS. MAHENDRANATHAN:
Q. I asked you if Merck has considered it and you said no because the effectiveness is pretty similar?
A. Correct.
Q. Does Merck know that Priorix

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is not a potential solution to mumps outbreaks in the US?

A. Again, based on the information that I just said, which is the immunogenicity and effectiveness of the two vaccines are fairly similar, I could not imagine that it would change the situation.

Q. But do you know it for a fact. Does Merck know it for a fact?

A. Of course I don't know it for a fact, no.

Q. So Merck is not sure?

A. No, that's not what I'm saying. Again, what I'm saying is that based on the scientific information that's out there, you can look in the GSK package circular, for example, it shows similar immunogenicity to Merck's vaccine. I don't think that would be the solution to this issue.

MS. MAHENDRANATHAN: Let's take a short break.

VIDEOGRAPHER: The time is now 3:18. We're going off the video record.

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(A recess was taken.)

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VIDEOGRAPHER: The time is 3:32. We're back on the video record.

MS. MAHENDRANATHAN: I don't have any further questions.

MR. SANGIAMO: We have no questions for Dr. Kuter.

VIDEOGRAPHER: The time is now 3:33. This completes the deposition of Barbara Kuter.

\- - -

(Witness excused.)

\- - -

(Deposition concluded at 3:33 p m.)

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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 February, 2018

Linda Rossi-Rios, RPR, CSR
Notary Public

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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.

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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.

____

BARBARA KUTER

SUBSCRIBED AND SWORN before and to me this ____ day of _________________, 20___.

____

NOTARY PUBLIC

My Commission expires:

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E R R A T A S H E E T

IN RE: USA ex rel vs MERCK

DATE: 2/9/2018

PAGE LINE CORRECTION AND REASON

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(DATE) BARBARA KUTER

10/25/2019
Declaration of G. Reilly
EXHIBIT 147

Case: 23-2553 Document: 45 Page: 498 Date Filed: 11/06/2023

To: Krah, David[david_krah@merck.com]
From: Rubin, Steven
Sent: Wed 8/24/2011 12:51:32 PM
Importance: Normal
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

re word limit, its 1600, not 2500.

From: Rubin, Steven
Sent: Wednesday, August 24, 2011 12:47 PM
To: 'Krah, David'
Cc: Kandil, Amany N
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

Thanks Dave.

Regarding Jan ter Meulen's comment on the need to provide evidence that recent outbreaks have occurred preferentially in older people, this same comment was raised during an internal review. We have addressed this by stating at the end of the second paragraph that although mumps was historically a disease of childhood, nearly all recent outbreaks have occurred in young adults, most of whom had a 2-dose vaccine history. A number of epi studies on these recent outbreaks showing age distribution were reference.

Regarding you comments:

1) consider adding that the vaccinees received Jeryl Lynn-containing vaccine -- done

2) consider adding comment/perspective on the role of SH genotype in cross-neutralization -- done

3) where a subset of 10 of the 96 serum specimens randomly selected, or selected from a targeted titer range? -- the latter. This is now made clear.

4) Regarding the lack of significant effect of anti-F antibody on virus neutralization, would it be possible that anti-F antibody in an overlay might neutralize virus spread/syncytium formation, and provide effective neutralization, versus the standard PRN assay where virus is only pre-incubated with antibody? -- this is a very insightful question and there actually is good evidence for your speculation. Löve at al (J Virol 1986, v58:220-222) demonstrated the ability of F protein specific monoclonal antibodies given subcutaneously to protect hamsters against MuV-induced neuronal necrosis when inoculated with virus intracranially, however, it was determined that protection was via antibody prevention of F protein-mediated cell lysis and hence virus spread, not by direct virus neutralization *in vivo*, additionally supported by the observation that the antibodies were not capable of neutralizing virus *in vitro*. Unfortunately, I have a 2500 word limit and I am already a bit over. I think the statement as written is technically correct. In our study, the F protein did not play a role in virus neutralization.

5) As a general virus question, is the Jeryl Lynn virus used as indicator in neutralization assays the vaccine passage, or is this a low passage of this strain? In this study, we used the JL vaccine virus in the assay because we wanted to look at the effectiveness of the vaccine-induced immune response against the vaccine strain itself. This would not be an acceptable practice for measuring vaccine immunogenicity as a surrogate for efficacy in a clinical trial (given that we are not interested in protection against vaccine virus exposure). Instead, a wild type virus will have to be used. Many years ago Merck argued for use of a low passage version of JL in such an assay, and we accepted (not my decision, I would not have been in favor of stacking the deck). However, from this study, it is obvious that different virus strains used in the

PRN will yield grossly different seroconversion rates. This poses a big problem and one that we are discussing now. I think the way out is to use any wild type virus, but instead of assessing seroconversion rates, one would look at reverse cumulative distribution curves generated from the approved product and from the investigational material and demonstrate non-inferiority by some measure.

Steven

From: Krah, David [mailto:david_krah@merck.com]
Sent: Friday, August 19, 2011 11:48 AM
To: Rubin, Steven
Cc: Kandil, Amany N
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

Hi Steven,
The manuscript that you forwarded as part of lkr46098 has been released through our internal review process (released 18-Aug-2011). There were two sets of discretionary comments (that is questions and comments that you can consider at your discretion) which I attach with this message for your review.

Thanks for providing this for review, and please let me know if you have any questions or feedback to the discretionary comments.

Best regards,
Dave

From: Krah, David
Sent: Thursday, July 28, 2011 1:11 PM
To: 'Rubin, Steven'
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

Hi Stephen,
I will see if I can accelerate the review. At the least I can follow-up with the reviewers to make sure they provide timely feedback.

Best regards,
Dave

From: Rubin, Steven [mailto:Steven.Rubin@fda.hhs.gov]
Sent: Thursday, July 28, 2011 1:07 PM

To: Krah, David
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

Hi Dave,

I was hoping not to have to wait 30 days, but I am in no position to complain about long intervals of wait time post submission! Looks like sometimes the table do indeed turn.

From: Krah, David [mailto:david_krah@merck.com]
Sent: Thursday, July 28, 2011 10:58 AM
To: Kandil, Amany N; Rubin, Steven
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

Hi Steven,

I will submit the manuscript for review through our internal review process as referenced in the MTA. I likely won't be able to do this until early next week, and the review typically takes 30 days. Please let me know if this timing is acceptable with your publication submission timing plan.

Best regards,
Dave

From: Kandil, Amany N
Sent: Wednesday, July 27, 2011 7:06 PM
To: Rubin, Steven
Cc: Krah, David
Subject: RE: Serum sample request MTA w/ CBER & manuscript /lkr46098

HI Dr. Rubin,

I just returned from 10 days of vac yesterday and just digging out.

Dave Krah, copied herein, will be your point of contact.

With kind regards,

Amany N. Kandil

Research Contracts Manager
External Scientific Affairs
Merck, Sharp & Dohme Corp.
770 Sumneytown Pike
West Point, PA 19486
tel: 215-652-7169

fax: 215-652-3143
mailstop: WP53B-330
g

From: Rubin, Steven [mailto:Steven.Rubin@fda.hhs.gov]
Sent: Monday, July 25, 2011 5:34 PM
To: Kandil, Amany N
Subject: RE: Serum sample request

Hi Amany,

As a follow up to the voicemail message I just left on your phone, attached is the 2007 MTA for serum samples provided by Merck to my lab. Also attached is the paper I would like to submit for publication in the Journal of Virology as a note. The sera provided by Merck were the basis for this study. Would you kindly acknowledge receipt of this email and to please forward the email with these attachments to the responsible party? Please also include me on the cc line so I can follow up.

Thanks very much,

Steven

Steven Rubin
FDA/CBER
Building 29A Room 1A-21
8800 Rockville Pike
Bethesda, MD. 20892
Ph: 301-827-1974
Fax: 301-480-5679

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (One Merck Drive, Whitehouse Station, New Jersey, USA 08889), and/or its affiliates Direct contact information for affiliates is available at http://www.merck.com/contact/contacts.html) that may be confidential,

10/25/2019
Declaration of G. Reilly
EXHIBIT 148

Dyer, Dona L.
UN-214

ATTACHMENTS
11/18/98 CDOC MEETING

Att. 1	CBER Communications on M-M-R®II Expiry Study	Dr. K. Chirgwin
Att. 2	Current Status of Plans to Study M-M-R®II Vaccine at Expiry	Dr. S. Thaler
Att. 3	Interim Analysis from the Zoster Pain Validation Study	Dr. P. Coplan
Att. 4	Results from the Vaccination Report Card Validation Study	Dr. P. Coplan
Att. 5	Review of COMVAX EU Proceedings with the Centralized Procedure	Dr. R. Zeldin
Att. 6	Pediatric Studies Update	Dr. W. Roberts
Att. 7	MAPP 28: Essential Documents for Clinical Trials	Ms. J. Keyser
Att. 8	MAPP 1: Follow-up	Dr. C. Cioffe
Att. 9	Update on Financial Disclosure	Ms. S. Stauffer
Att. 10	MK-0966 Alzheimer's Disease Program REDACTED – OMP	Dr. G. Block
Att. 11	Formulations Update/MK-0826	Dr. H. Teppler
Att. 12	Ivermectin: Results of Initial Pediculosis Study	Mr. R. Tipping
Att. 13	Ivermectin: Dose Ranging/Dose Regimen Study	Dr. S. Mann
Att. 14	L-756,423 Phase II Protocol	Dr. B. Y. Nguyen
Att. 15	Protocol: MK-0869 and Imipramine in Treatment of Depression	Dr. M. Kramer
Att. 16	MK-0869 Depression Outcomes Research Measures	Dr. J. Pearson
Att. 17	Protocols and Adjudication Committees: Lessons Learned from AGGRASTAT®	Dr. G. Williams
Att. 18	AGGRASTAT® - Outcome of Mutual Recognition	Dr. S. Caffe
Att. 19	AGGRASTAT® - LMWH Safety Study Protocol	Dr. R. Sax
Att. 20	Update on Strategy for Monkey Neurovirulence Testing for Rotavirus Vaccine and Varivax	Dr. H. Ukwu
Att. 21	Update on HPV Clinical Program Issues	Dr. J. Boslego
Att. 22	STOCRIN – Status of European Regulatory Assessment of Dossier	Dr. U. Taglieber
Att. 23	MK-0869: Summary of Input from Consultants	Dr. J. Arena
Att. 24	MK-0869: Safety Assessment Update	Dr. VanZwieten

MUMPS EXPIRY- REGULATORY ISSUES
Background (12/97 CBER meeting)

Potency Claim in the Label

- Based on available stability data, Merck proposed these expiry titers: measles [redacted] log $TCID_{50}$, mumps 3.7 log $TCID_{50}$, and rubella [redacted] log $TCID_{50}$
- However, lack of clinical data at the proposed expiry claim for mumps
- Interim agreement with CBER to specify release (not expiry) titer in label
- Temporal trend of decreasing stability with mumps and measles of concern and requires further investigation

Expiry Trial:

- Clinical data with trivalent is necessary
- Ratio of antigen to PFU may be important
- Neutralizing antibody recommended

Attachment 1

MUMPS EXPIRY - REGULATORY ISSUES
Follow-up discussions with CBER in 1998

Expiry Trial Design (CBER letter 9/98; follow-up teleconference)

- CBER agrees with accelerated aging approach (versus dilution)
- Use of stability slope to assign potency to aged vaccine will likely be acceptable
- CBER has requested evaluation of measles immunogenicity
  - Concern about temporal trend of decreasing stability
  - Revised stability data/stability investigation report (with adjusted measles stability data) to address this concern

MUMPS EXPIRY - REGULATORY ISSUES
Follow-up discussions with CBER in 1998

Expiry Trial Design (CBER letter 9/98; follow-up teleconference)

- Sample size estimate as a function of seroconversion rate
  - Proposed sample size assumes SCR of 96% (from label)
  - If observed SCR is lower, then sample size re-estimate required
- Statistical criteria
  - Merck proposed 10% equivalence margin
  - CBER recommends 5% equivalence margin and lower limit for SCR at 90%
  - Rationale not clarified by CBER but may be negotiable (depending on assay performance)

MUMPS EXPIRY - REGULATORY ISSUES
Follow-up discussions with CBER in 1998

Potency Claim in the Label

- Revised label approval delayed until resolution of potency claim (9/98)
- CBER proposes reduced shelf-life (based on previously submitted data) (11/98)
- Stability investigation report to address CBER's concerns (target 12/98)
  - temporal trend of decreased stability is no longer apparent with use of consistent methods/timepoints for stability assessment
  - revised statistical model* supports 4.3 log $TCID_{50}$ (95% LB) for expiry
- Need to support 3.7 log $TCID_{50}$ for EP end-expiry

Chen JJ, Hwang JS, Tsong-Y. Estimation of the shelf-life of drugs with mixed effects models. J-Biopharm-Stat. 1995; 5(1): 131-40

MUMPS EXPIRY - REGULATORY ISSUES
Follow-up discussions with CBER in 1998

Serologic assays

- CBER has requested detailed assay methods
- Neutralization assay necessary due to inability to re-establish clinical correlation
- Wild-type antigen in this assay is important (i.e. interested in protection against wild-type, not vaccine strains)
- May be possible to use alternate assay if correlation is established
- Surrogate assay must be highly specific (100%) for WT neutralizing response

MUMPS EXPIRY - REGULATORY ISSUES
Follow-up discussions with CBER in 1998

Conclusions

- Resolving questions about stability is critical
- Increased scrutiny of label and surrogate marker may be related to concurrent review of competitor's PLA?
- CBER considers WT neutralizing antibody assay to be "gold standard"
  - SCR for this assay will determine sample size/equivalence margins
- Stringent success criteria necessitate very sensitive assay

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Stability Investigation Report
Adjustment of measles stability data

REDACTED – OMP

[redacted]

Rationale for the M-M-R®II End Expiry Clinical Studies

- End expiry potencies for the *product* must be on the label.
- CBER believes that additional clinical data are needed to support expiry potencies for mumps.

Attachment 2

M-M-R®II End Expiry Potencies Suggested for the Label

Component	Potency/Dose (log_{10} $TCID_{50}$)
Measles	[redacted]
Mumps	3.7
Rubella	[redacted]

Production of M-M-R®II at Expiry

- Natural Aging (2-8°C)
- Accelerated Aging at Room Temperature (20-25°C)
- Dilution of Components

Activities of the M-M-R®II Team

- A preliminary aging experiment was initiated with Vaccine Biometrics Research in June 1998.
- A background document was sent to CBER June 24, 1998:
  - Reviewed methods of obtaining expiry material.
  - Proposed an initial study of room temperature aged vaccine.
  - Proposed a follow up study of naturally aged vaccine.
  - Suggested a dilution study only if RT aging failed.
  - Described plans for a neut assay using Jeryl Lynn™ as the target virus.

Statistical Considerations in the Initial Study Design

- Sample size was based on the seroconversion rate (96%) by neutralization cited in the package circular.
- A delta of 0.10 was selected based on recent concomitant studies involving M-M-R®II.
- A one sided equivalence test was to be performed at an $\alpha = 0.025$.

Issues To Discuss

- Review the findings and outstanding issues regarding the room temperature aging experiment.
- Review how CBER's response affects our plans:
  - Statistical Considerations
  - Neutralization Assay Considerations
  - Overall Plan To Age the Vaccine

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The Preliminary Aging Experiment

- **Goal:**
  - Reduce potency while minimizing the margin of error
  - Actual potency will be no greater than target.
- **Methods:**
  - Incubate 3 potential clinical lots at room temperature
  - Use a 1x6 potency testing scheme
  - Test weekly for ~27 weeks
  - Generate best fit curves using all available data
  - Begin aging clinical material at week 8

The Preliminary Aging Expe

- **Observations:**
  - REDACTED – OMP [redacted]
  - [redacted]
  - No similar pattern was seen for mumps.
  - REDACTED – OMP [redacted]

Measles House Standard Lot 10

REDACTED – OMP

[redacted]

- CBER May Not Accept the Resu Mumps Expiry Trial If Insufficie is Present.

Interim Plan

REDACTED – OMP

- Data from the preliminary experiment continue to be collected for all 3 lots.

REDACTED – OMP

Measles Assay

REDACTED – OMP

REDACTED – OMP

Summary of Linear Fit I

REDACTED – OMP

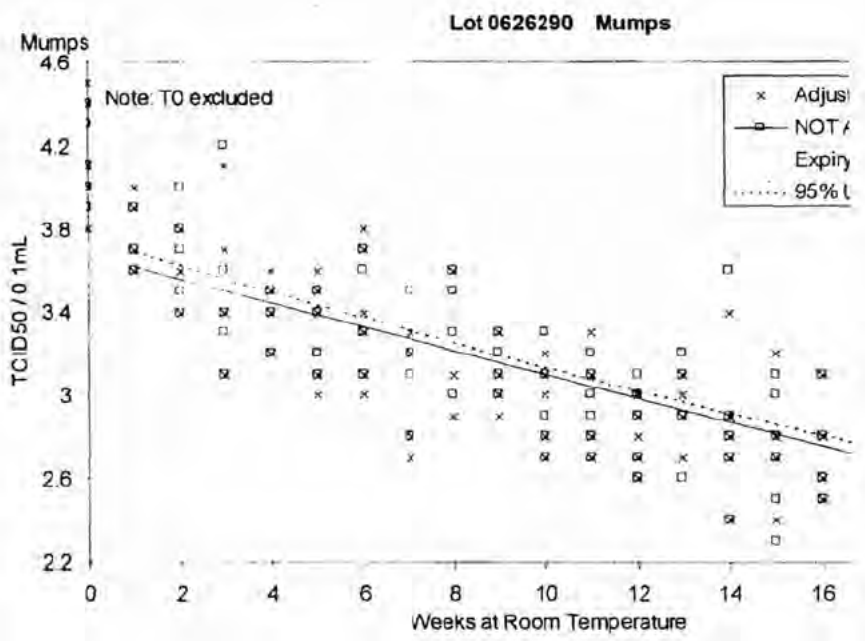
[redacted]

- Minimal effect is seen on mumps potency w adjustment for these lots.
- The optimized GOS lot is more stable at RT with the GOS lots.
- GOS lot #0627847 is the least stable of the 3

Stability Data for Lot 0626290 Showing Effect c
on Potency Estimates for Measles and M

REDACTED – OMP

[redacted]


Lot 0626290 Mumps
Mumps
Note: T0 excluded
Adjus
NOT A
Expiry
95% L
TCID50 / 0.1mL
4.6
4.2
3.8
3.4
3
2.6
2.2
0
2
4
6
8
10
12
14
16
Weeks at Room Temperature

Path Forward

- Optimized GOS clinical material bega September 25, 1998.
  - An initial target of ~4.0 $\log_{10}$ $TCID_{50}$ per reached and material has been removed.
  - Material targeted for ~3.7 $\log_{10}$ $TCID_{50}$ p removed on ~December 18, 1998.
- A data package for HS adjustment wil preliminarily available in January 199
- CBER responded to our June proposa

CBER Response to Merck I Expiry Proposal

- Accelerated aging is acceptable.

REDACTED – OMP

[redacted]

- The mumps neut assay is not validated (corr claim of equivalence will be affected by the response rate in this new assay in the control
- **Virus antigens in serologic assays should r efficacy against natural infection; therefo <u>antigens are appropriate for serologic ass</u>**
- Follow up should be extended to one year to duration of protection.

Statistical Issues Raised by

- Provide detailed approaches to sample re-estimation if 96% response is incor control group.
- The equivalence margin should be 5%
- An absolute lower limit criterion for seroconversion of >90% should also e
- Address how study site may affect est of equivalence.

Prerequisites to Moving Fo With the Expiry Clinical

- Material must be removed from room incubation at appropriate times (in pro
- In order to assign potencies for all cor *must make a decision on HS adjustme the trial.*
- In order to estimate sample size, we m the assay to be used in the clinical tria understand its performance in the con

Mumps Immunogenicity A

Plaque Reduction Neutralization Assa

- Begins with low titered serum dilution (1:2).
- Validated to assess neutralization of both vaccine and strains.
- Read out requires plaque counting.

Mumps Endpoint Neutralization Assa

- Begins with a 1:10 serum dilution.
- Validated presently only for Jeryl Lynn™
- Read out is via an automated spectrophotometer.
- Without a correlation to a wild type strain, this assay acceptable to CBER.

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Available Sera for Mun
Neutralization Correlation

VARIVAX® Studies:

– PUVV vs 6333 with concomitant M
(N~660, enrollment complete).

– Dose escalation study of PUVV wi
concomitant M-M-R®II (N~1050,
enrolling).

Potential Drawbacks to Correlation Study

- The correlation requires a significant v serum to run all three assays
  - ELISA 100µL
  - MuENA 800µL
  - PRN 400µL
- While CBER will review our plans foı they may or may not accept them. *Sho* *pursue two parallel paths in order to :*

Path Forward

- Continue to remove clinical material on schedule.
- Assign potency with or without adjustment based on preliminary data review January 1999.
- Neutralization Assay Options:
  - Rework MuENA with the LO 1 wild type strain from NIBSC as suggested by CBER.
  - Perform the correlation of the MuENA with the ELISA and with the PRN assay to better understand the expected SCR of the control group and submit data to CBER.
  - Direct resources to V&CB and use the PRN assay for the expiry trial.

Summary

- A plan to develop M-M-R®II at expiry has been successfully executed.
- REDACTED – OMP [redacted]
- A data set to assess the appropriateness of house standard adjustment has been identified.
- Consensus regarding the optimal neutralization assay strategy will be achieved at the clinical assay subteam Thursday November 19, 1998.

10/25/2019
Declaration of G. Reilly
EXHIBIT 149

MERCK
Research Laboratories

M E M O **DATE: February 22, 1999**

TO: **Dr. Henrietta Ukwu** **BLA-34**

FROM: **Dr. Keith Chirgwin** **BLA-34**

SUBJECT: **BB-IND 1016 (M-M-R®II); Summary of CBER teleconference on methods used for the plaque reduction neutralization assay**

CBER participants: Judy Beeler, Kathryn Carbone, Steven Rubin, Luba Vujcic
Merck participants: Keith Chirgwin, David Krah, Bill Long, Alan Shaw, Mary Yagodich

Executive Summary:

1) CBER's plaque reduction neutralization (PRN) assay is similar to that developed in VCB, the chief differences are the number of dilutions and the statistical methods used for the titer calculation.
2) CBER's preference is that dilutions be routinely carried out beyond 1:8 to address the contingency of pre-vaccination sera that are positive at ≥1:4.
3) CBER uses the Karber method to calculate the titer.
4) CBER does not use either complement or IgG to enhance sensitivity and feels that these maneuvers should not be necessary.
5) CBER encourages Merck to evaluate the correlation between the PRN and the ELISA assay; if these assays are correlated then we would be able to revert to the ELISA for future clinical trials.
6) CBER is requesting lot potency information to correlate with the VAERS reports.

Discussion:

A description of the mumps PRN assay developed by VCB was included in the responses to CBER which were submitted on 2/5/99. This teleconference was held at Merck's request to obtain feedback from CBER regarding the methods for Merck's PRN assay and to determine whether our methods were similar to those employed by CBER. Steven Rubin runs the PRN assay at CBER and he highlighted several of aspects of the methods used by CBER in their assay and how these vary from our methods:

1) Serum is heat-inactivated (40 minutes at 56C) then serially diluted 2-fold (1:4-1:128 in 96 well plates)
2) An equivalent volume of virus (titrated to give 12-24 plaques in the control) is added to each well to bring the final dilution range to 1:8 - 1:256
3) Incubate one hour at 37C
4) Overlay with agar
5) After 5-6 days a second layer of agar with neutral red is added to visualize plaques
6) The Karber method is used to calculate the endpoint titer

Endpoint: CBER understands that we will look at seroconversion as the endpoint (and not distribution of GMTs). CBER noted that they were familiar with methods used to enhance sensitivity (e.g. adding complement or immunoglobulin) but they did not feel these were necessary. Concern was expressed with the fact that we will dilute sera only to 1:8. If pre-vaccination sera are positive at ≥1:4 then we will need

dilutions higher than 1:8 to determine seroconversion. In their view it is preferable to carry out these dilutions beyond 1:8 for all sera rather than go back with additional dilutions only for those subjects with pre-vaccination titers ≥1:4. CBER uses the Karber method to calculate the titer (uses plaque counts from all dilutions). This differs from the approach which has been used here (highest dilution which provides 50% neutralization relative to negative control), and may be more statistically robust, although both approaches seem to capture the same information.

Virus strains: CBER concurs with the use of the Tennessee mumps strain in the assay, however they would like sequence information (SH gene) to confirm that this is wild type, as well as information about passage history. They are also interested in obtaining the Tennessee isolate. Alan Shaw will speak with the CDC about sending CBER the isolate (a materials transfer agreement may be needed). Both CBER and Merck have observed that in the ELISA assay JL works well, but that the wild type strains evaluated to date have been less successful. In their measles neutralization assay, CBER uses a low-passage Edmonston strain that is apparently sensitive to neutralization.

Control serum: The appropriate control was discussed. CBER uses serum lot #176, which is the FDA reference serum. The name of the contact at CBER to obtain an aliquot of this reference serum is Chris Anderson (301-827-1899).

Correlation with ELISA: CBER reiterated that if a correlation is demonstrated between the PRN assay and our ELISA assay then we could use the ELISA in the future.

Lot potency data: In the December CBER meeting, Robert Wise had indicated that the VAERS reports oftentimes contain lot identifying information, and that he was interested in looking at AEs in VAERS as a function of lot potency. This statement made was in the context of Merck's proposal to increase the target fill potency in order to be able to meet the expiry claim of 4.3 log for mumps. In follow-up to this, Kathy Carbone mentioned that CBER is interested in receiving additional information on lot potency to correlate with the VAERS reports. It was clarified that limited lot potency information was provided in the January submission from BioLicensing, and that now CBER was interested in obtaining more comprehensive lot potency data. Drs. Carbone and Wise will contact Keith Chirgwin within the next couple of weeks to explain the nature of their request further.

Action Plan/Assignments:

1) Follow-up with CDC with regard to providing CBER with the Tennessee mumps strain **(A. Shaw)**.
2) Obtain FDA's reference serum to use to standardize our own in house standard **(D. Krah)**.
3) When additional data with this assay are available and the range/distribution of titers in the pre-vaccination sera is determined, a decision regarding the appropriate dilutions (i.e. whether there is a need to go above 1:8) can be made. Timing and extent of any such data needed to determine how to run the assay for the expiry trial requires further discussion. **(D. Krah)**
4) As per the agreement in December, CBER will be provided with lot potency information. This discussion will include MMD (BioLicensing) and MRL (WPSE, Regulatory Liaison) **(K. Chirgwin)**.

K.D.C.
Phone: (610) 397-2558
Fax: (610) 397-2962

cc: distribution, RIBL, file, chron

10/25/2019
Declaration of G. Reilly
EXHIBIT 150

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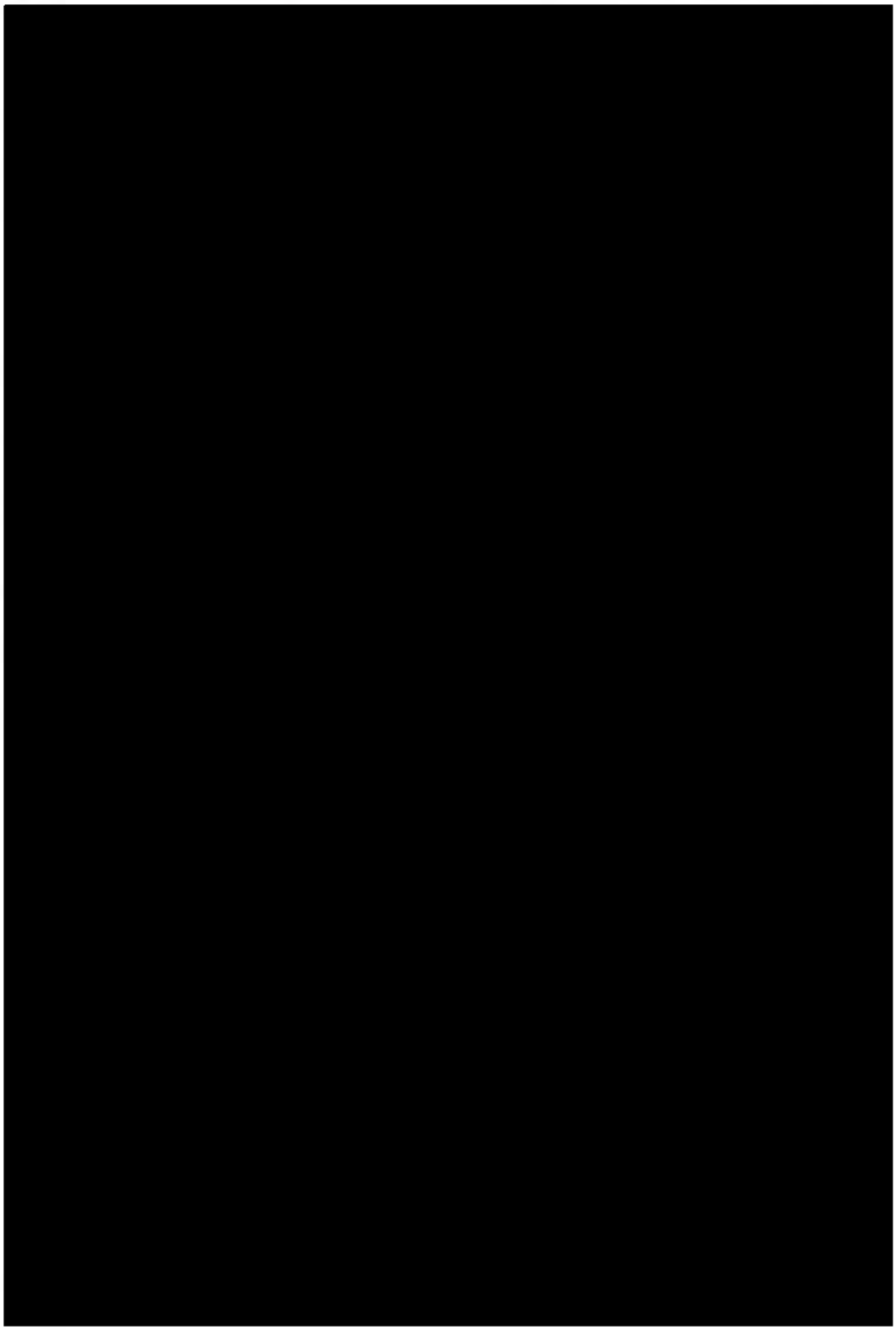
12/08/2011



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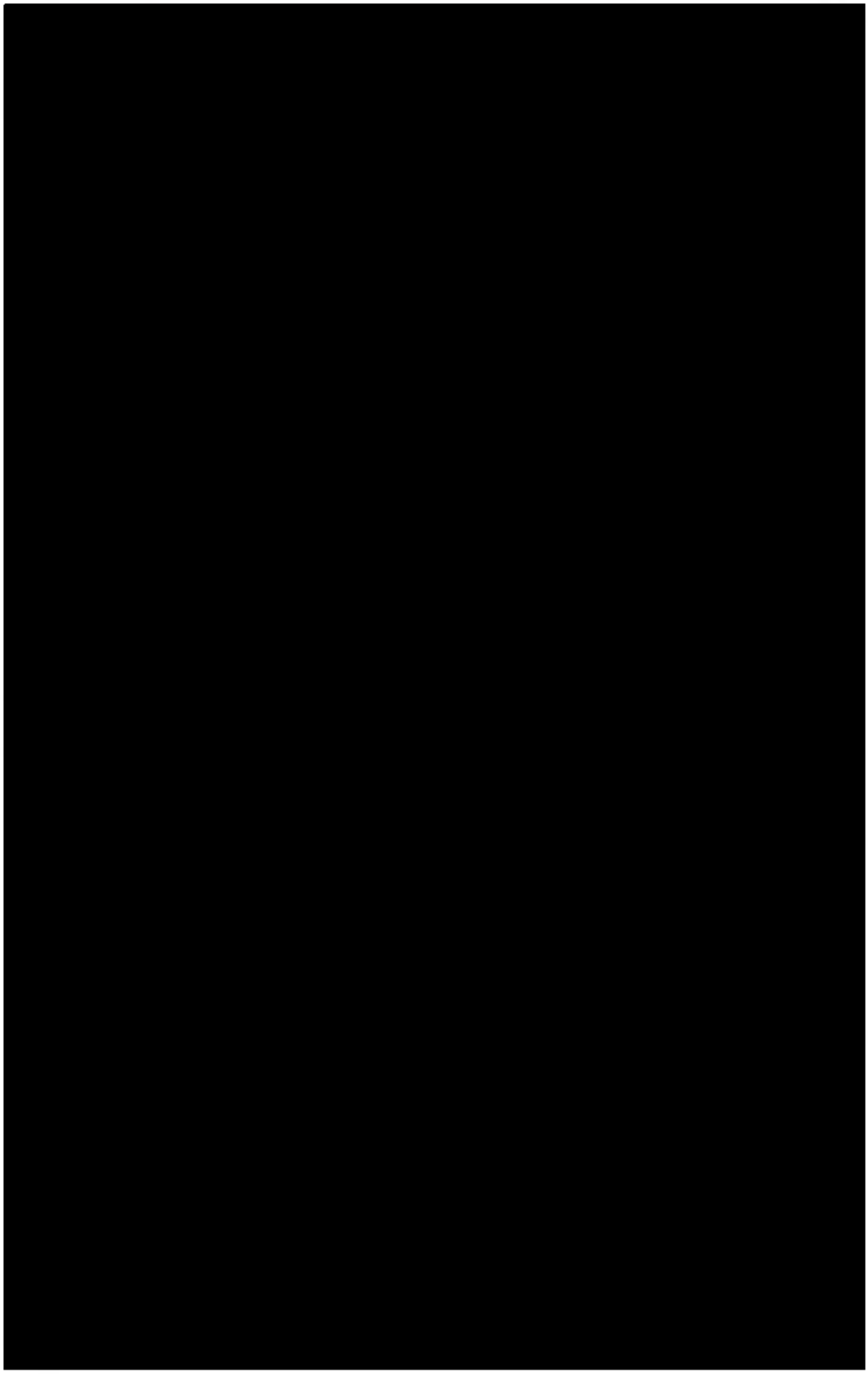

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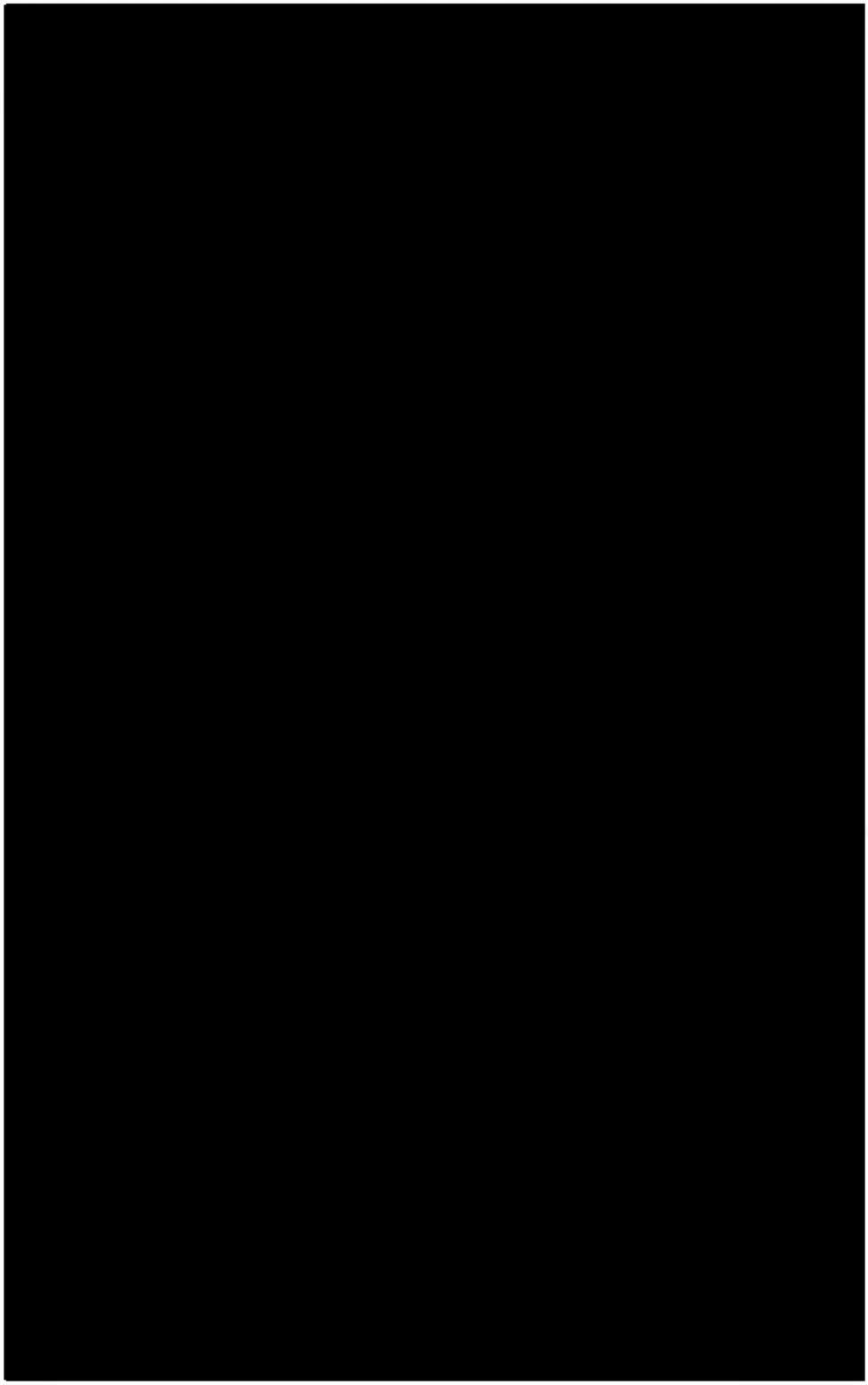

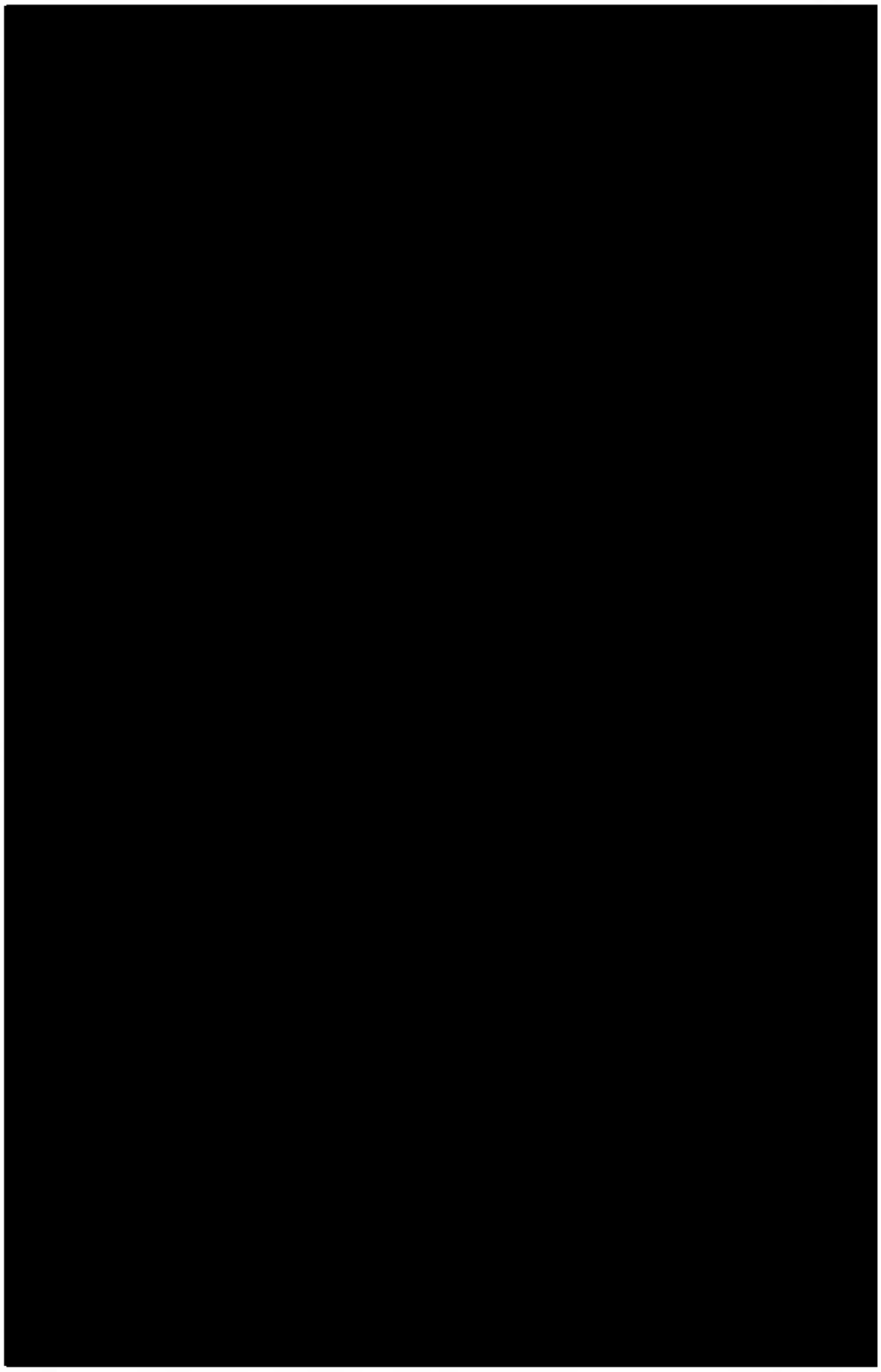

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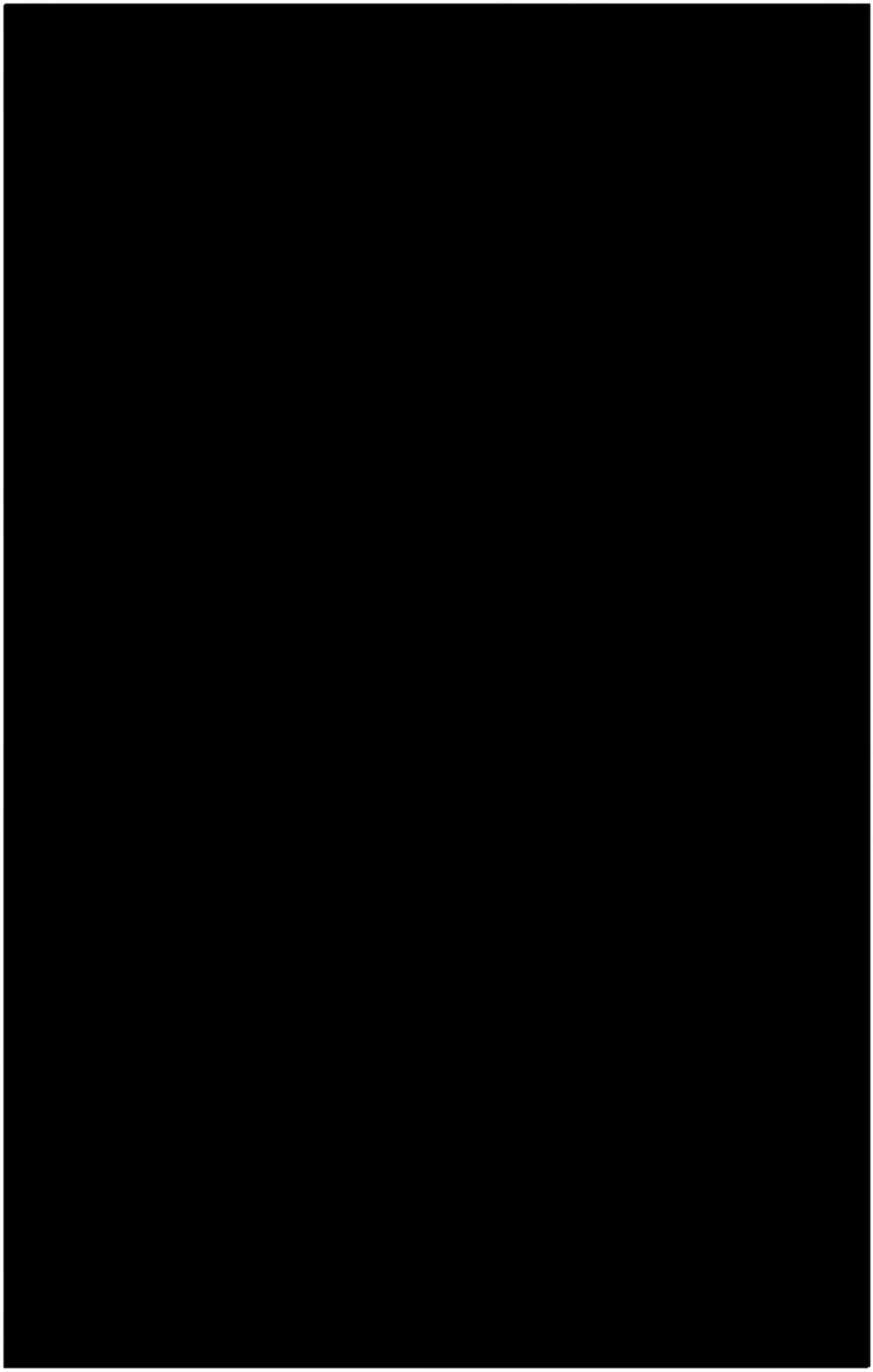

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12/08/2011

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Case: 23-2553 Document: 49-5 Page: 556 Date Filed: 11/21/2023

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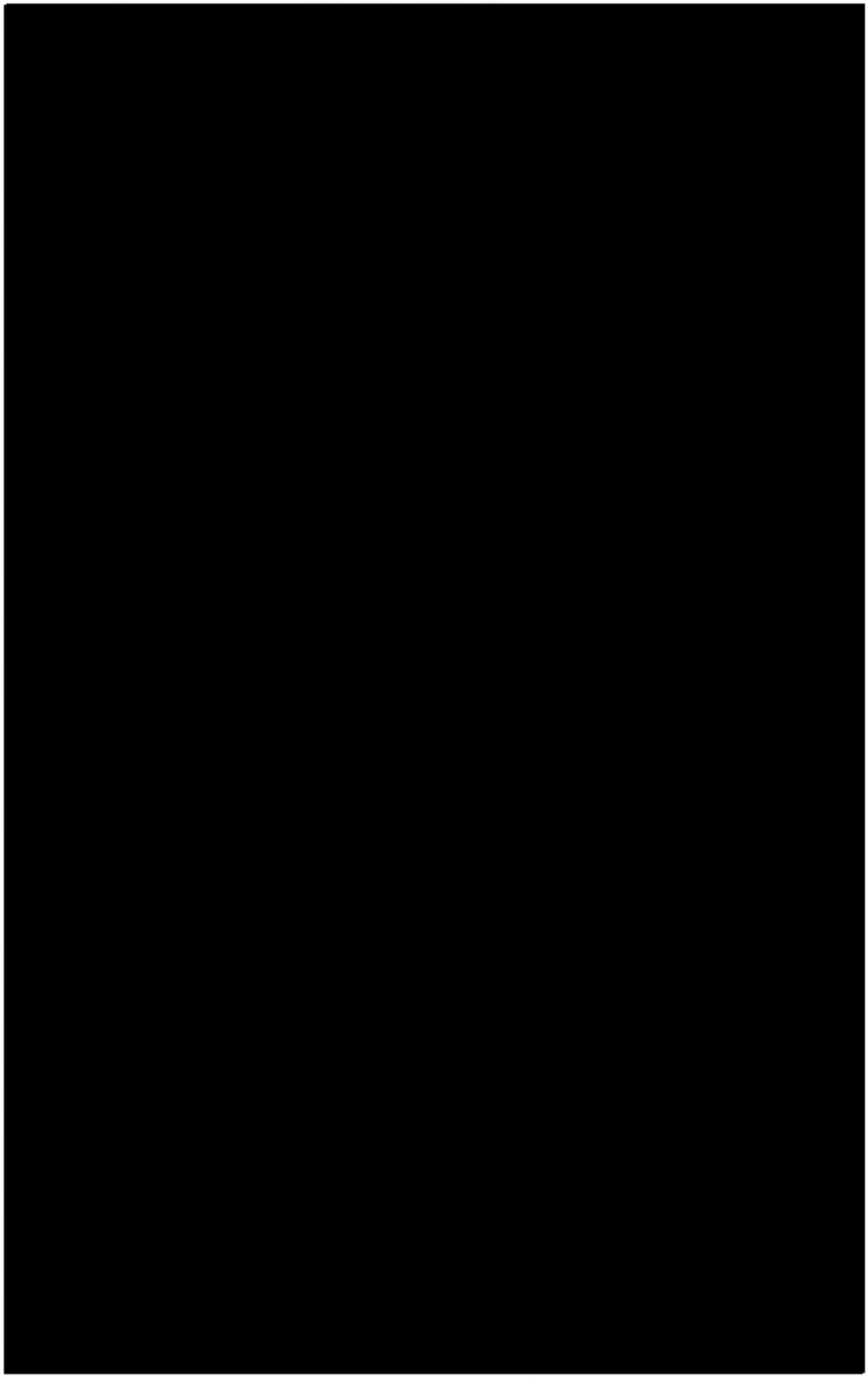

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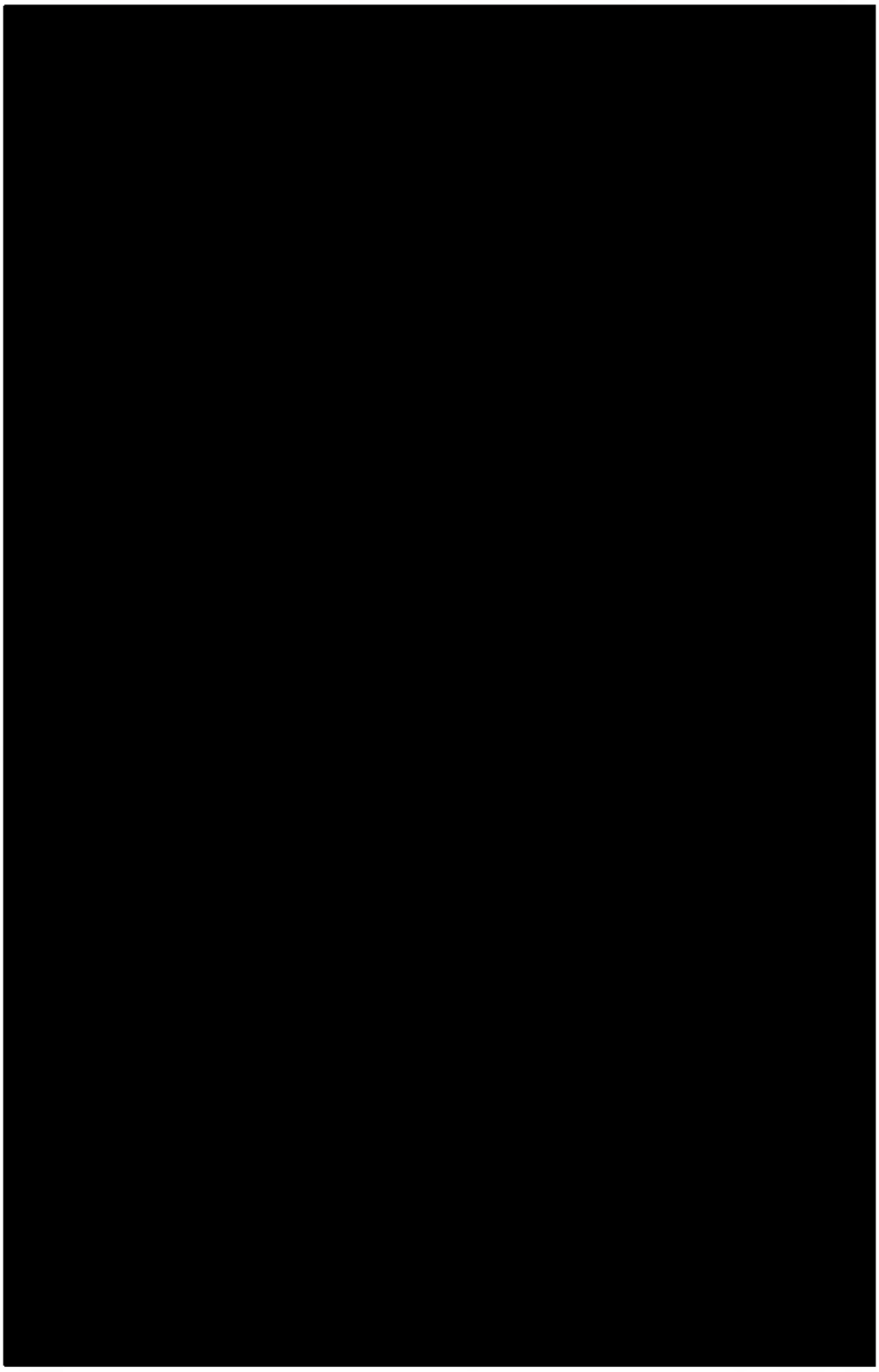

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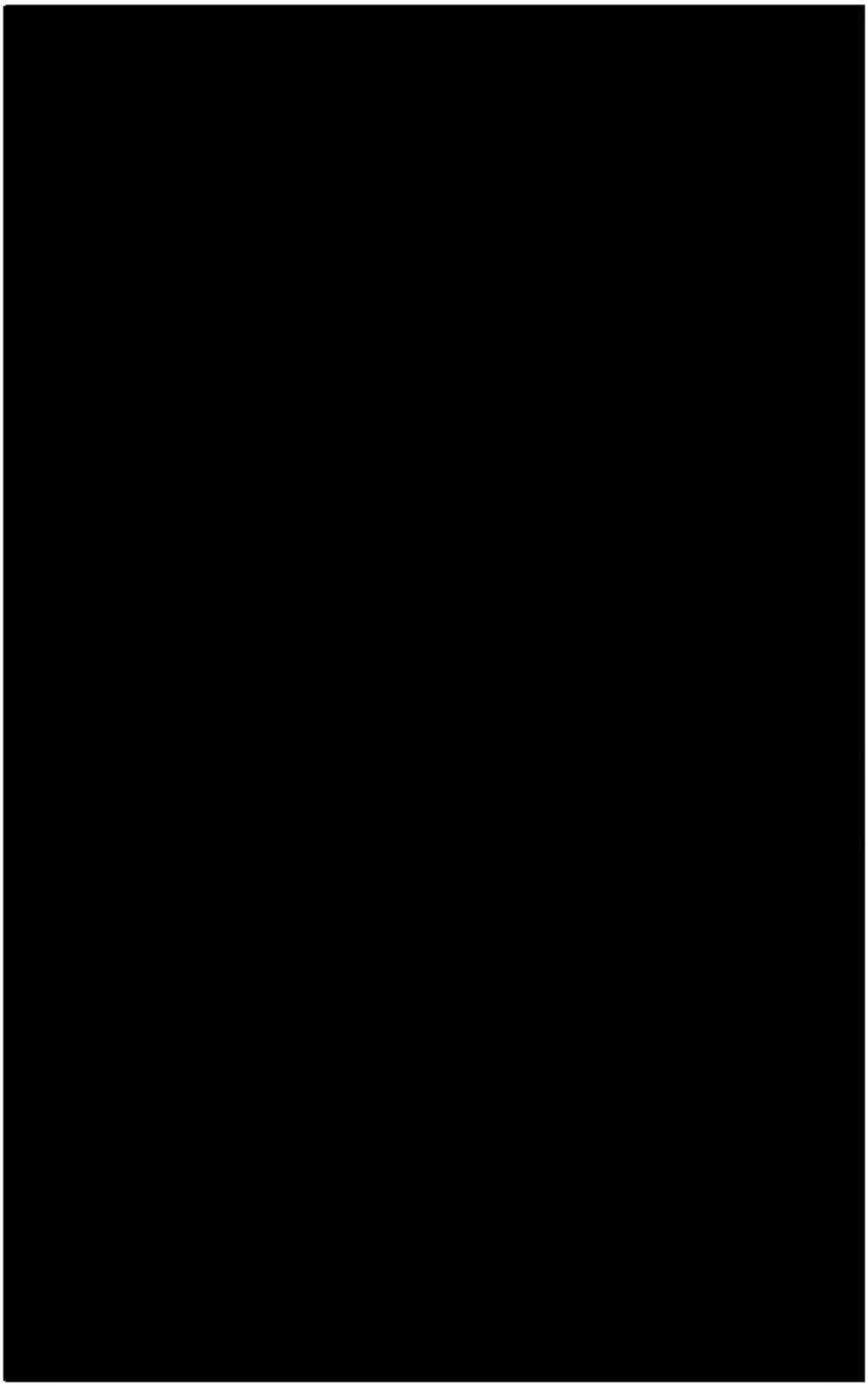

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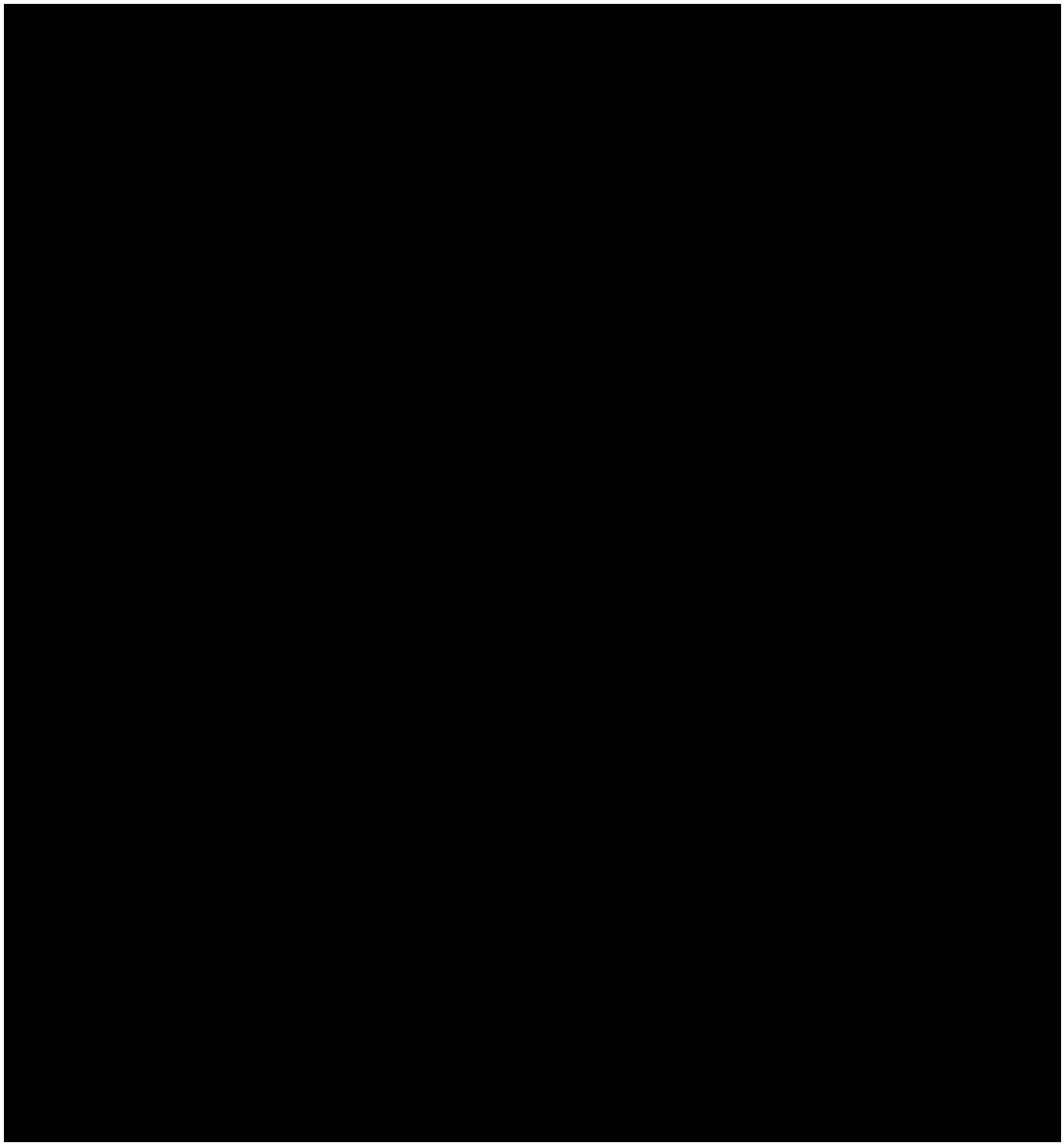
10/25/2019
Declaration of G. Reilly
EXHIBIT 151



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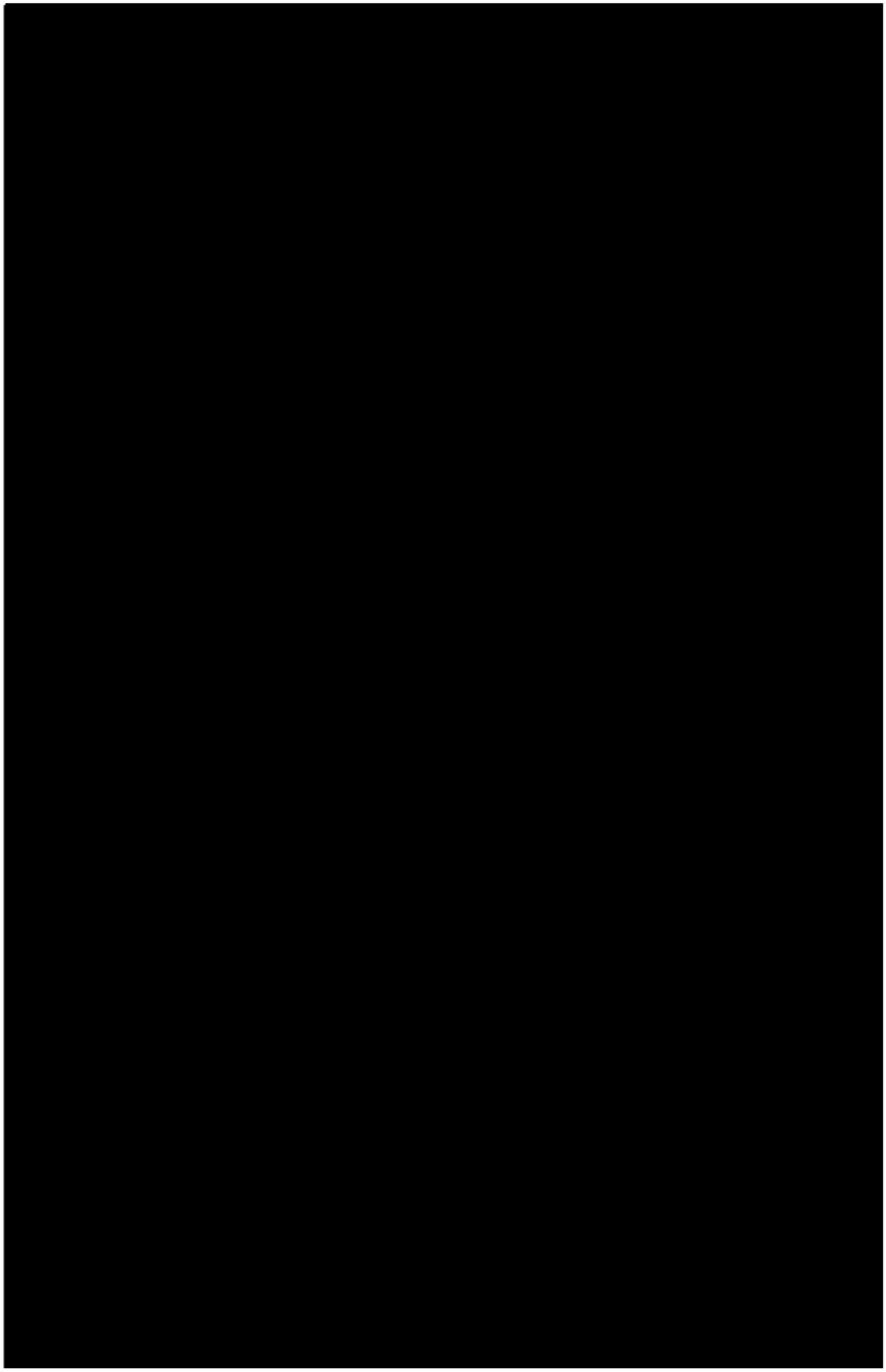

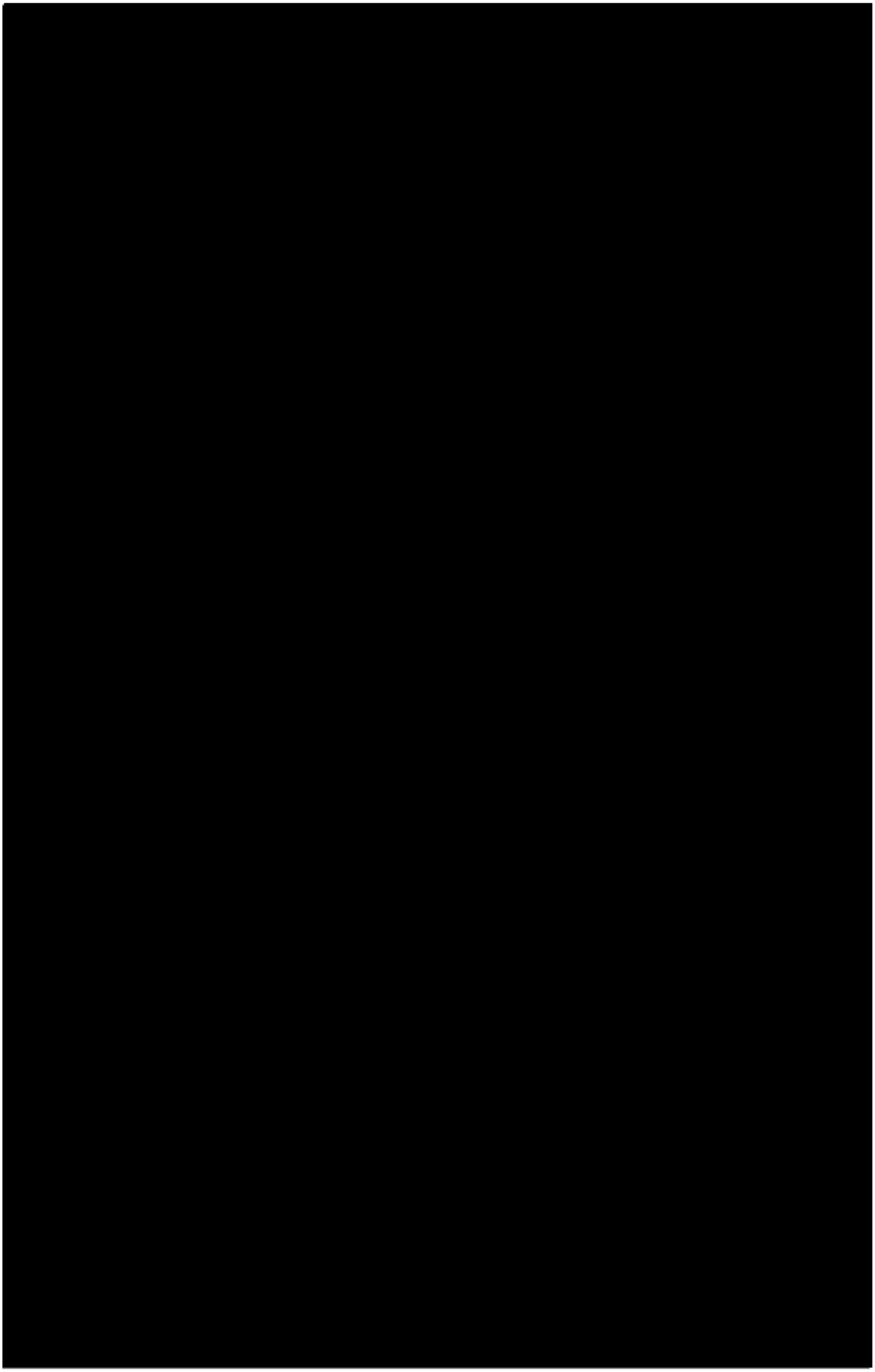

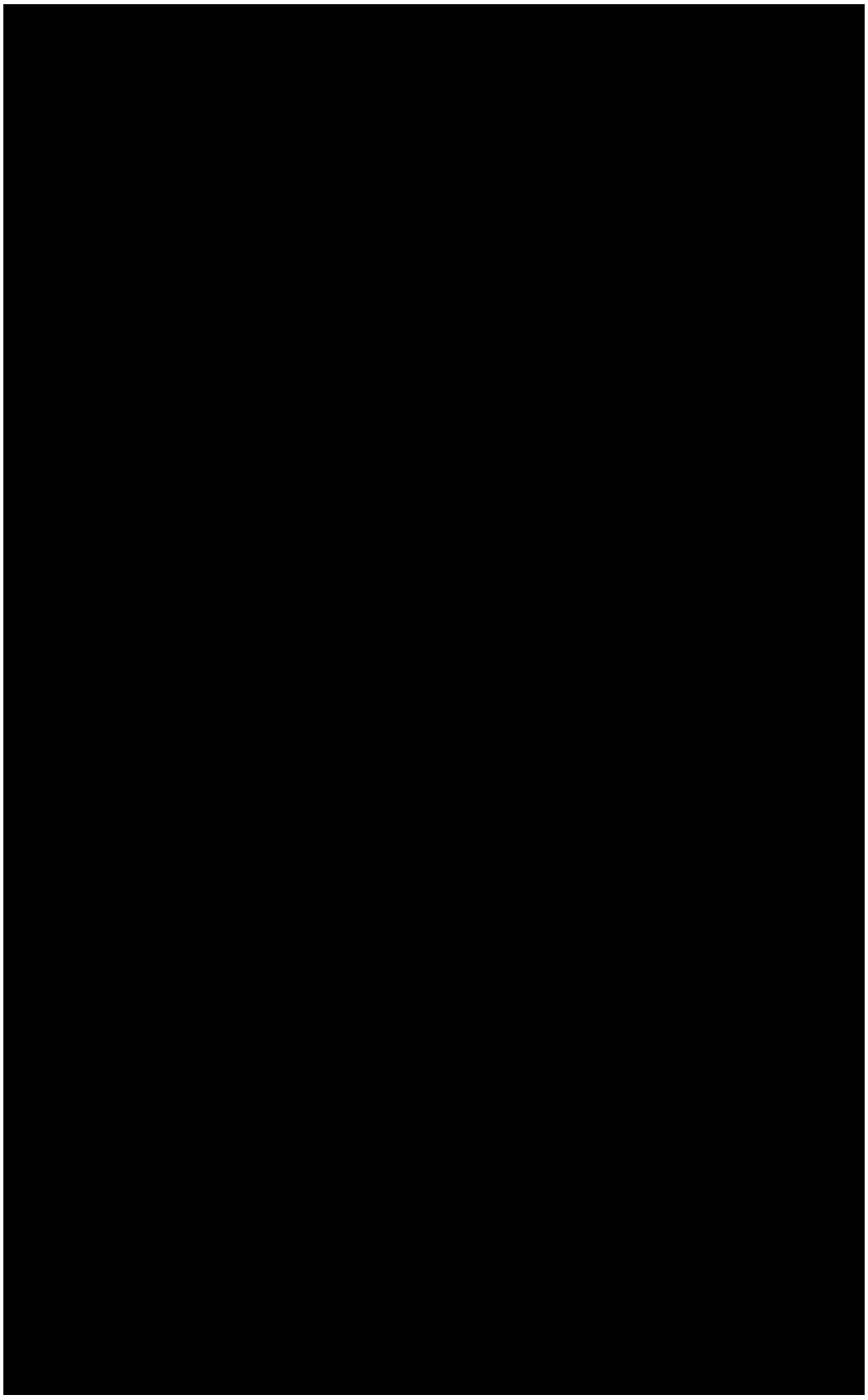

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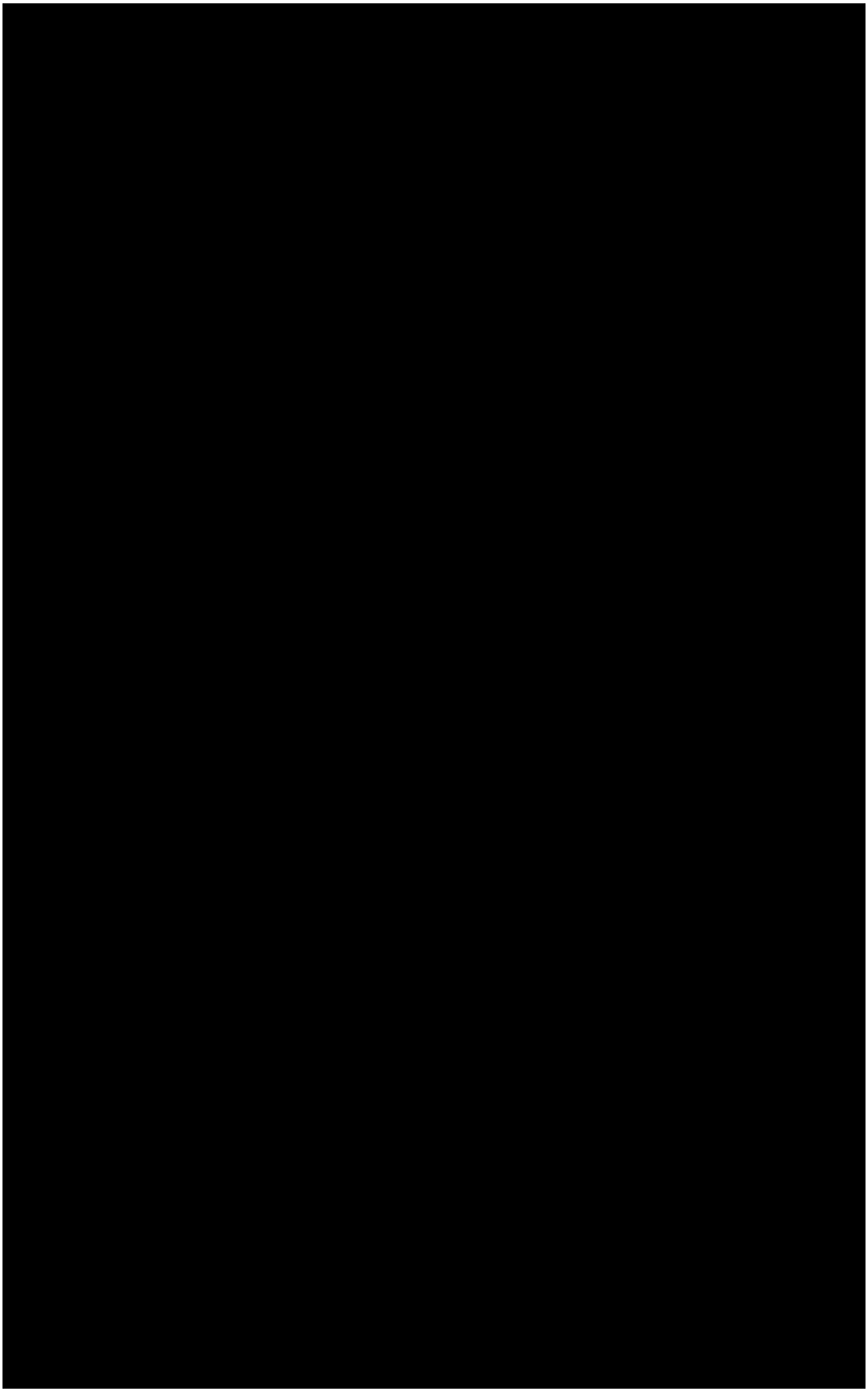

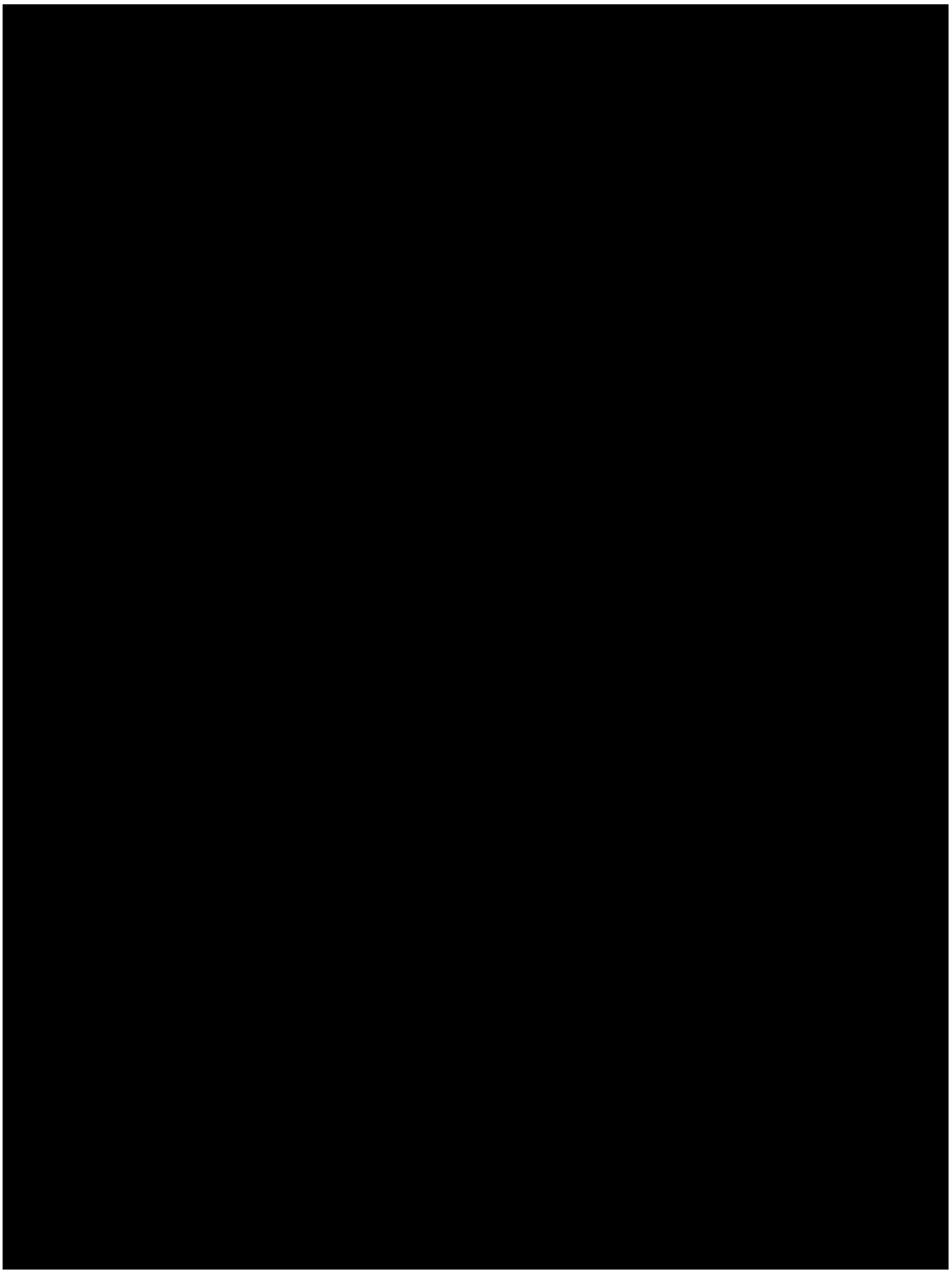

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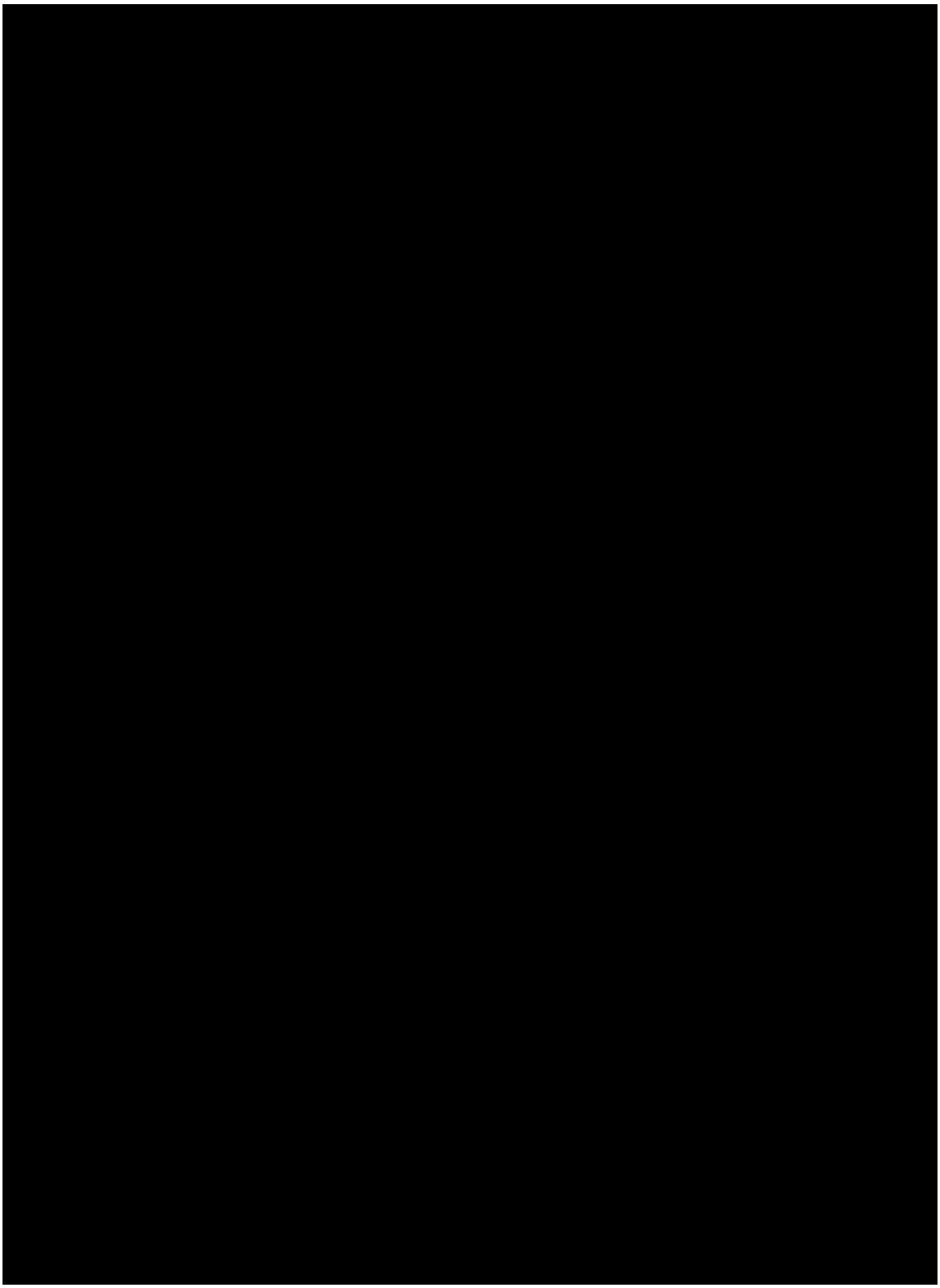

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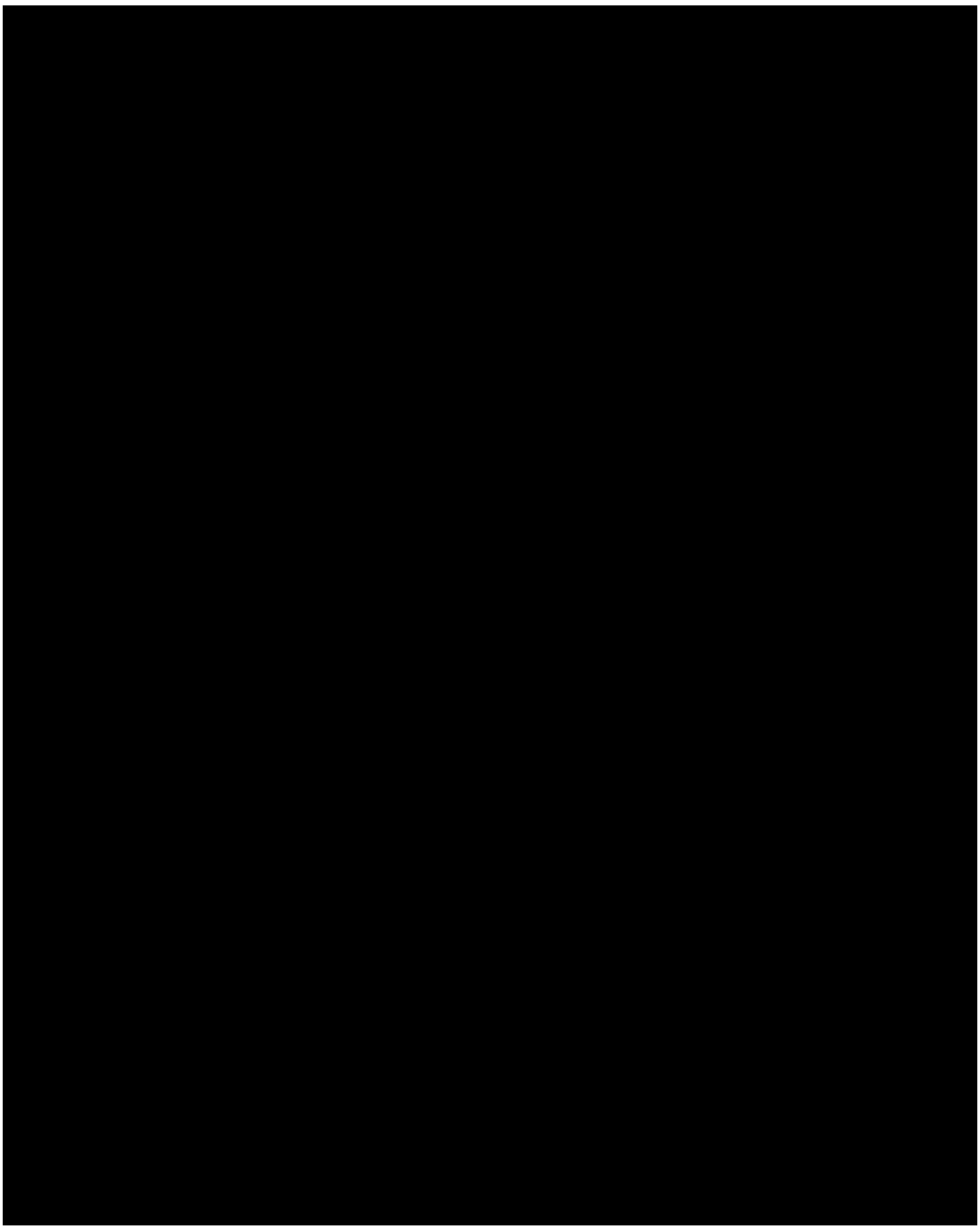

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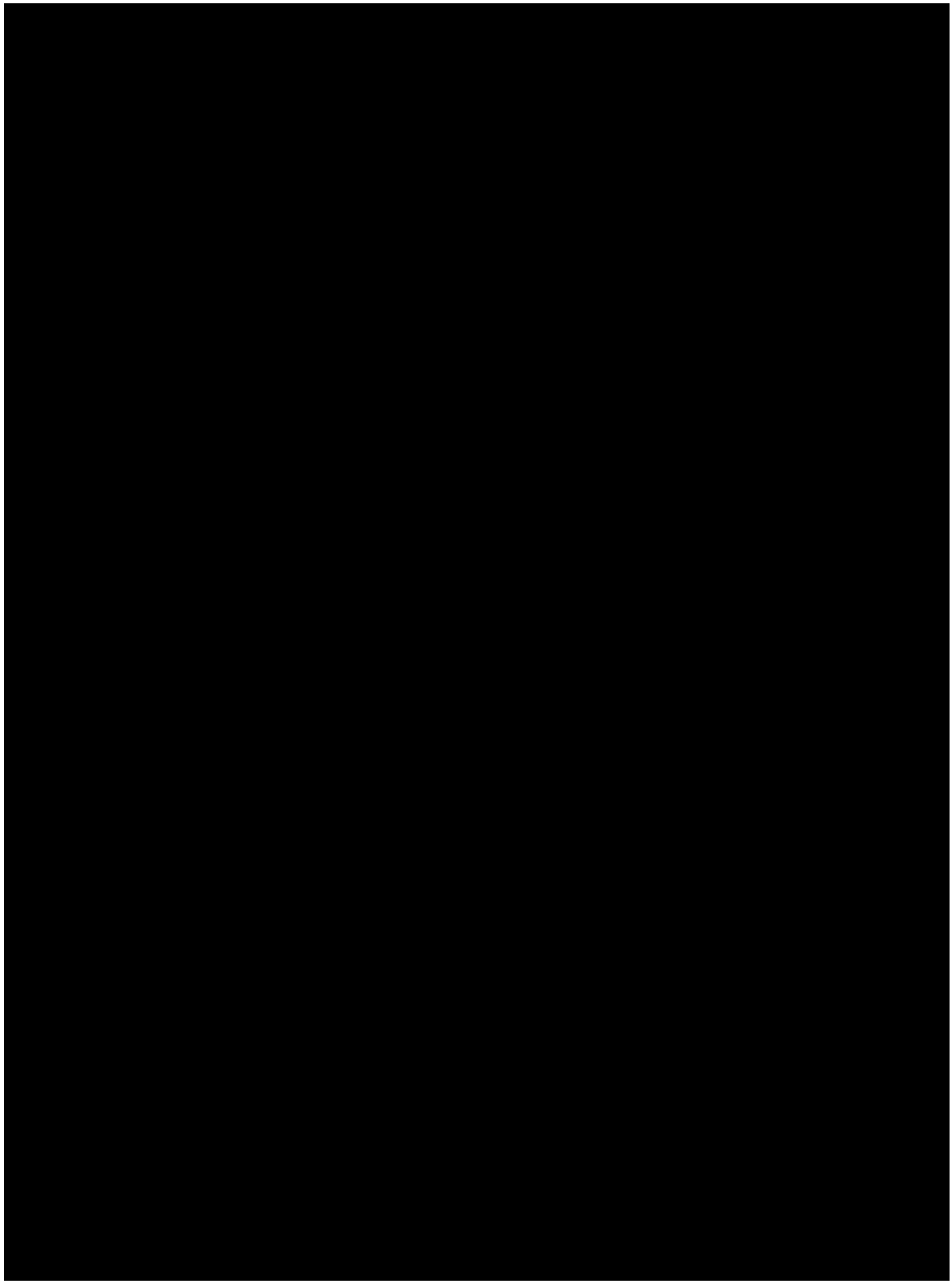

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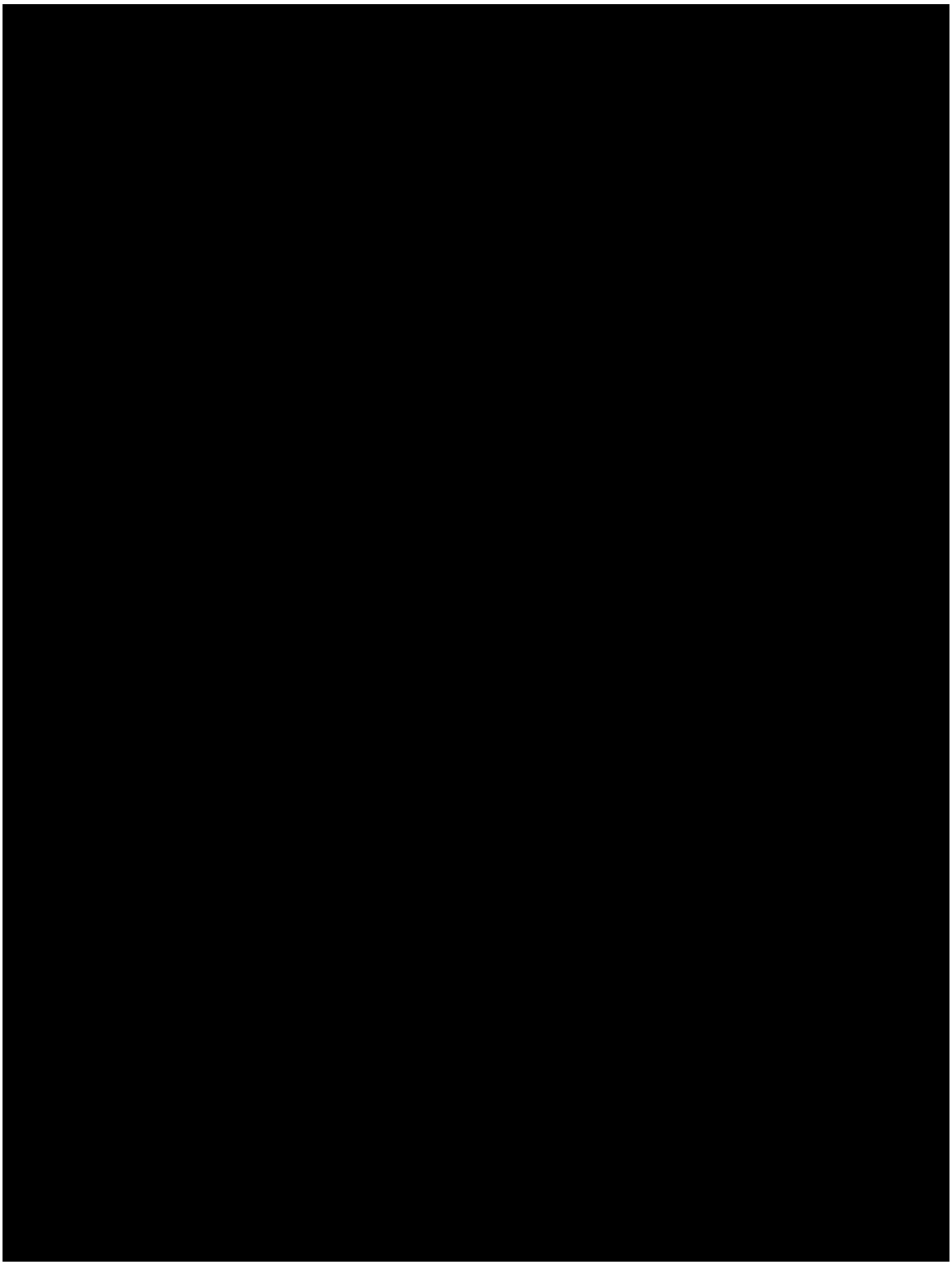

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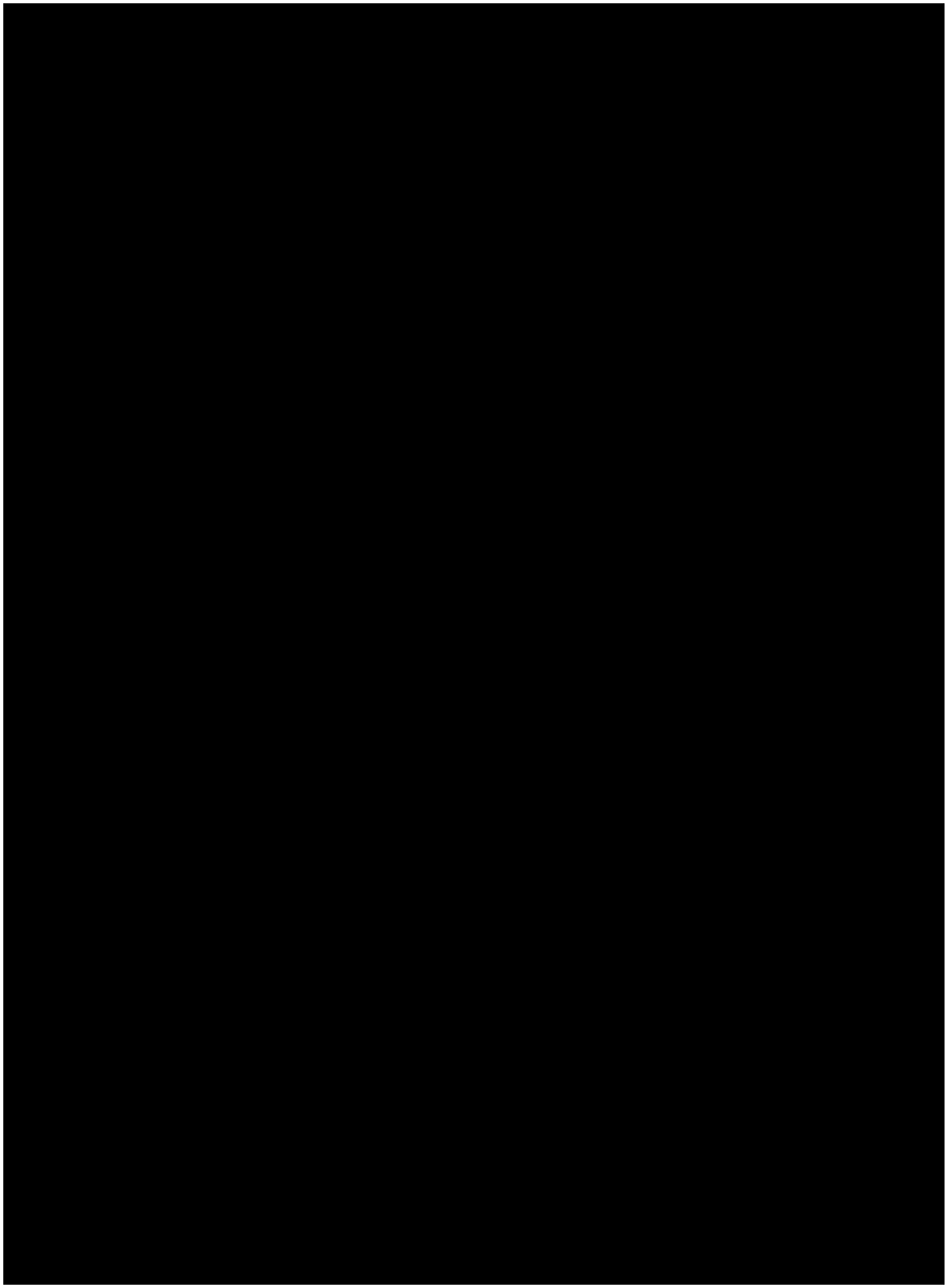

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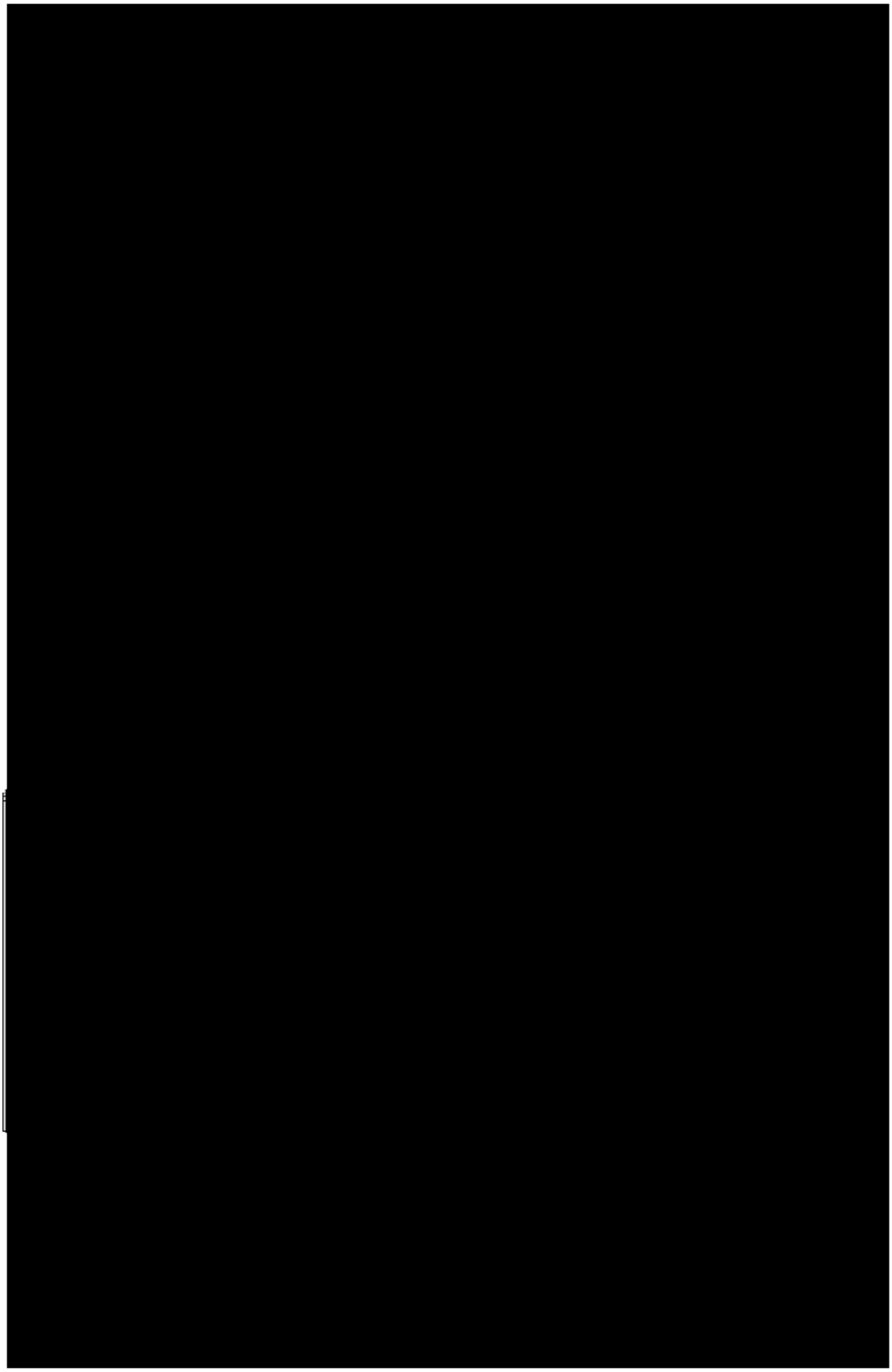

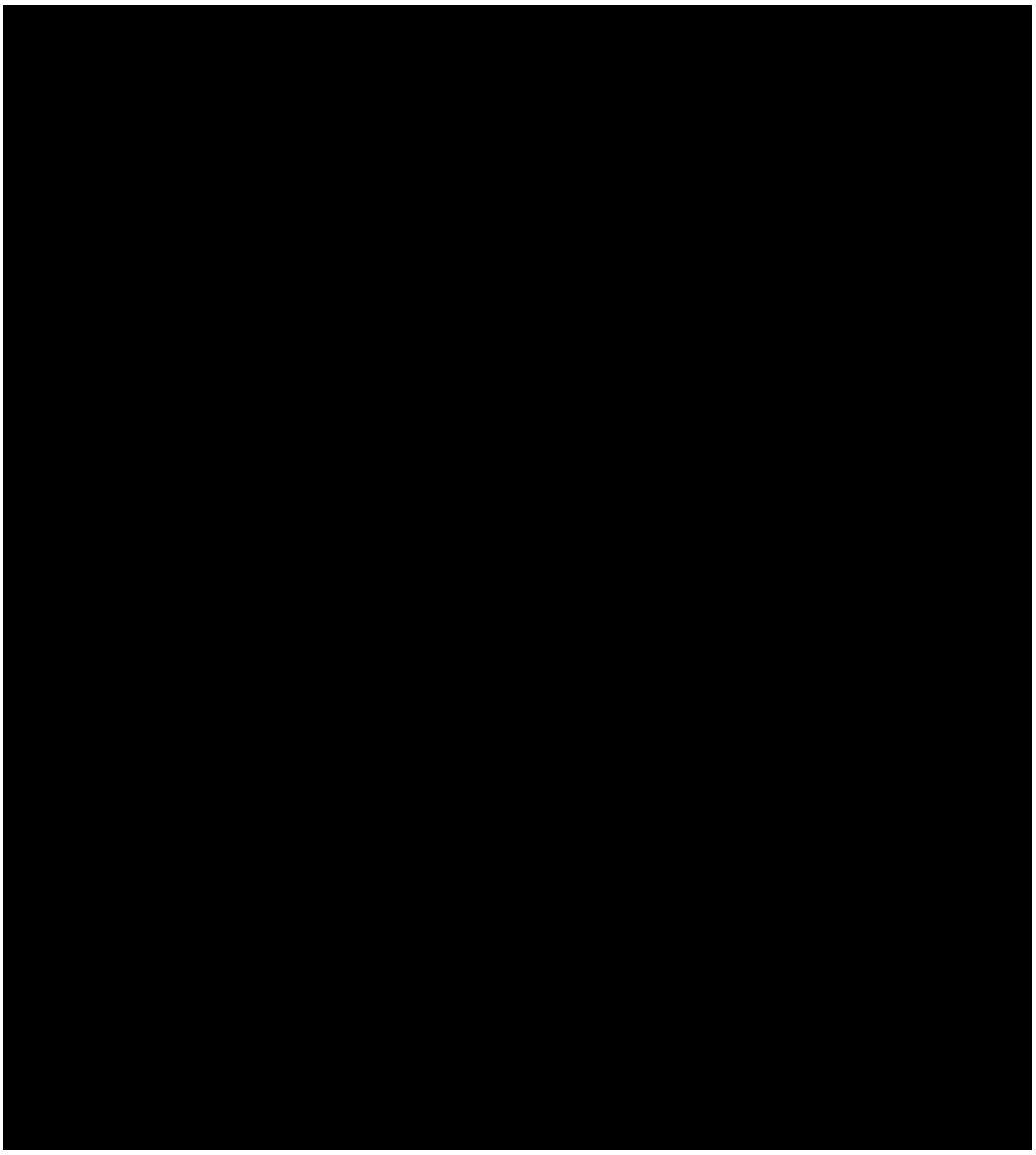

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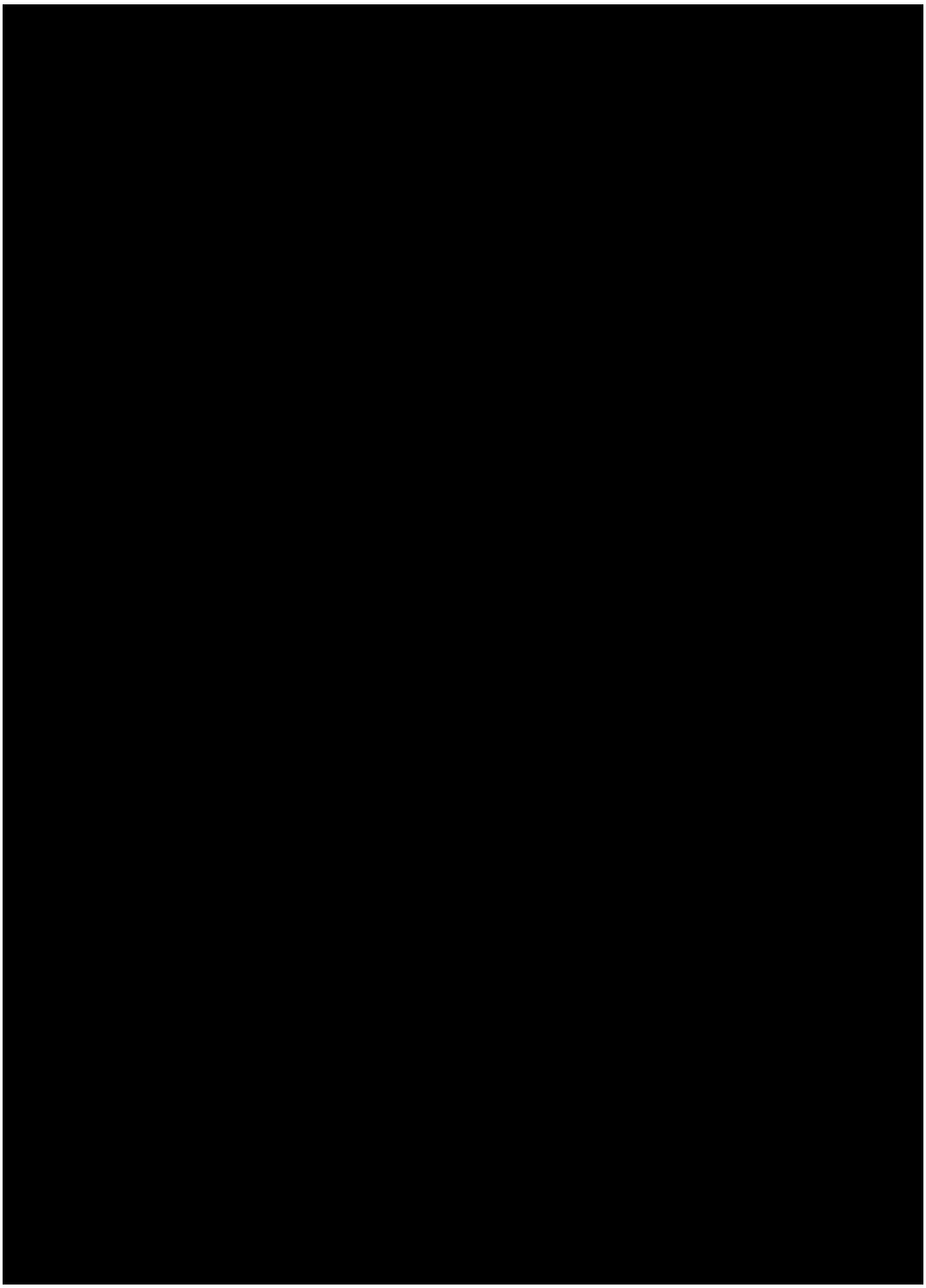

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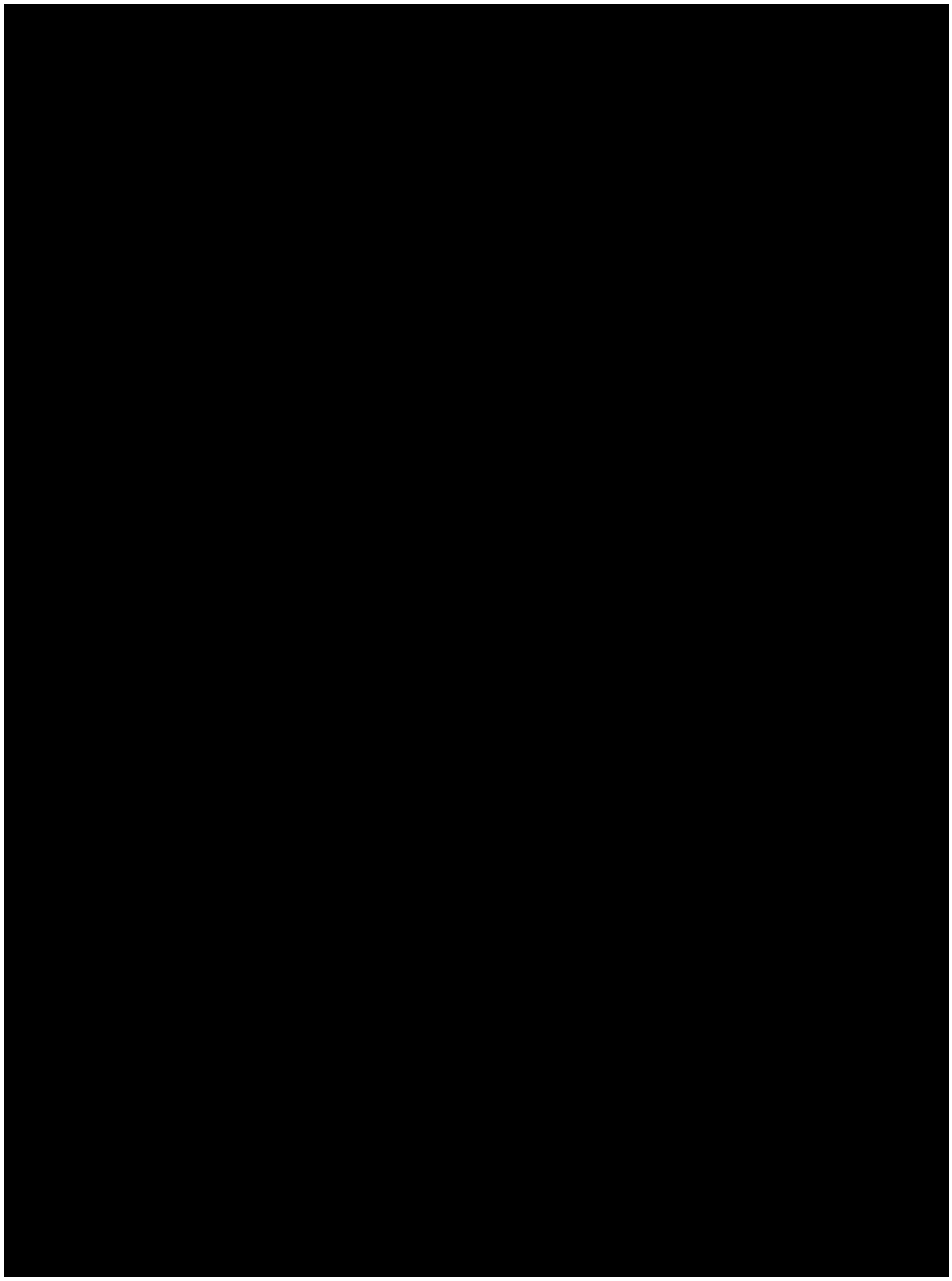

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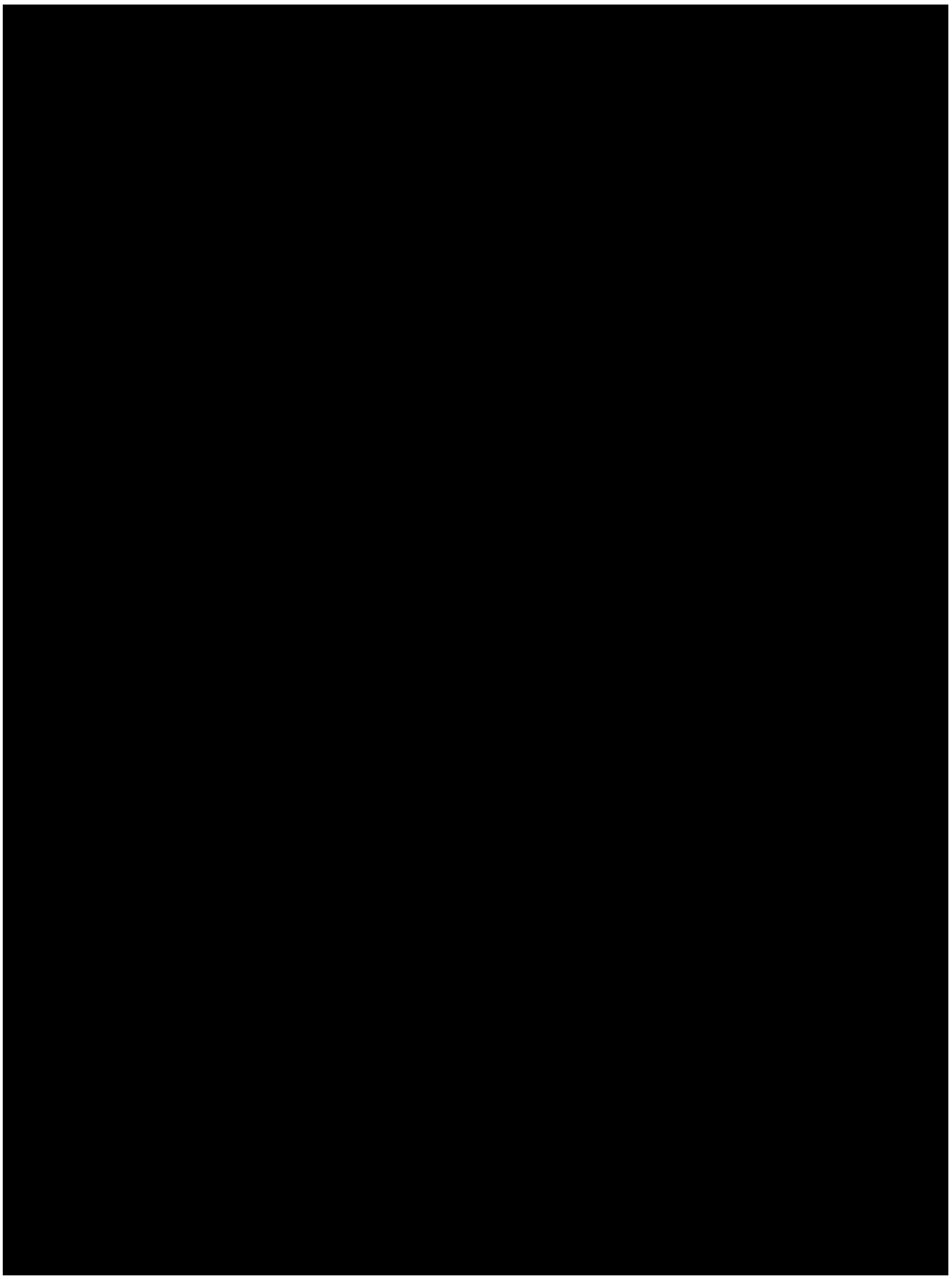

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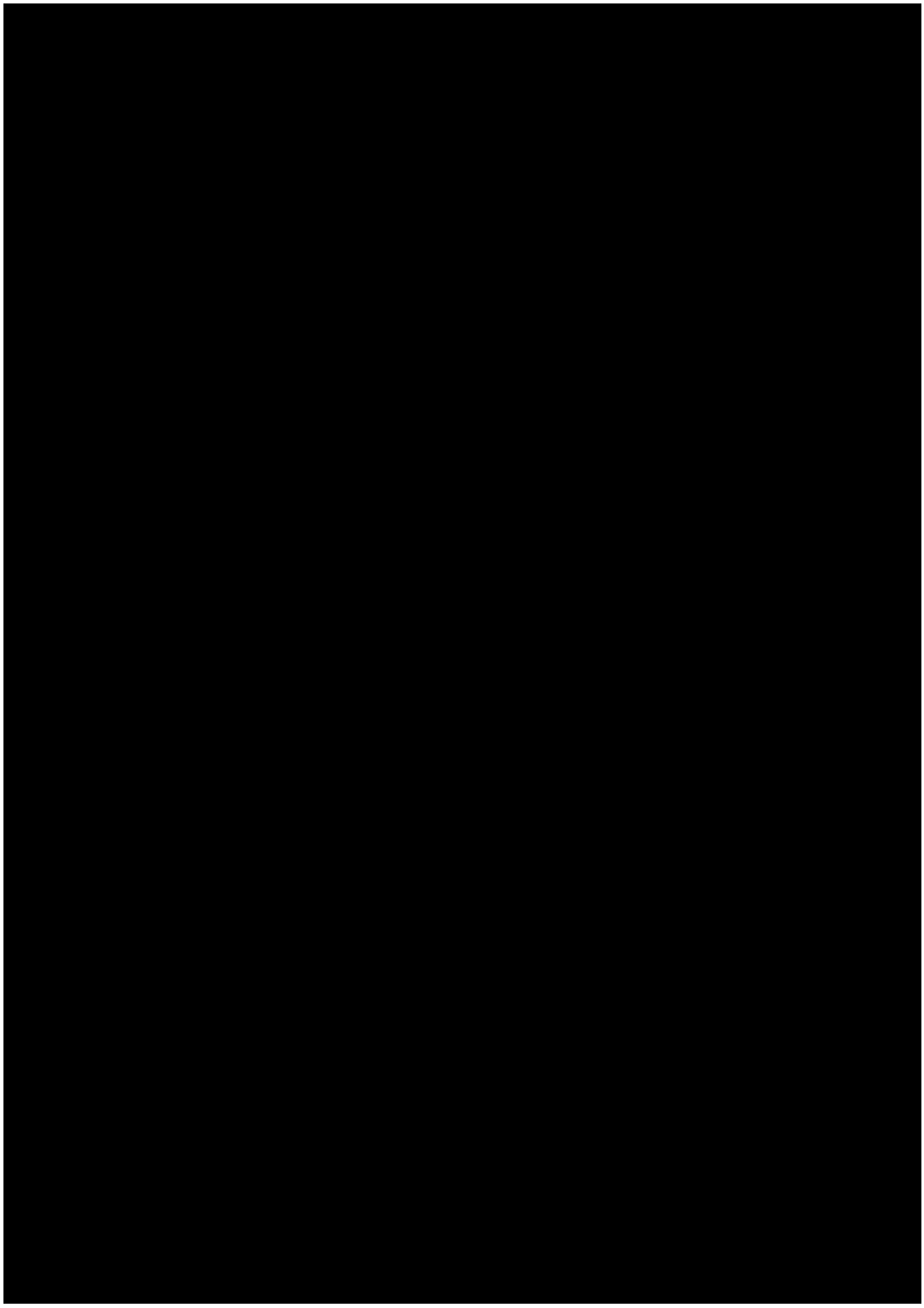

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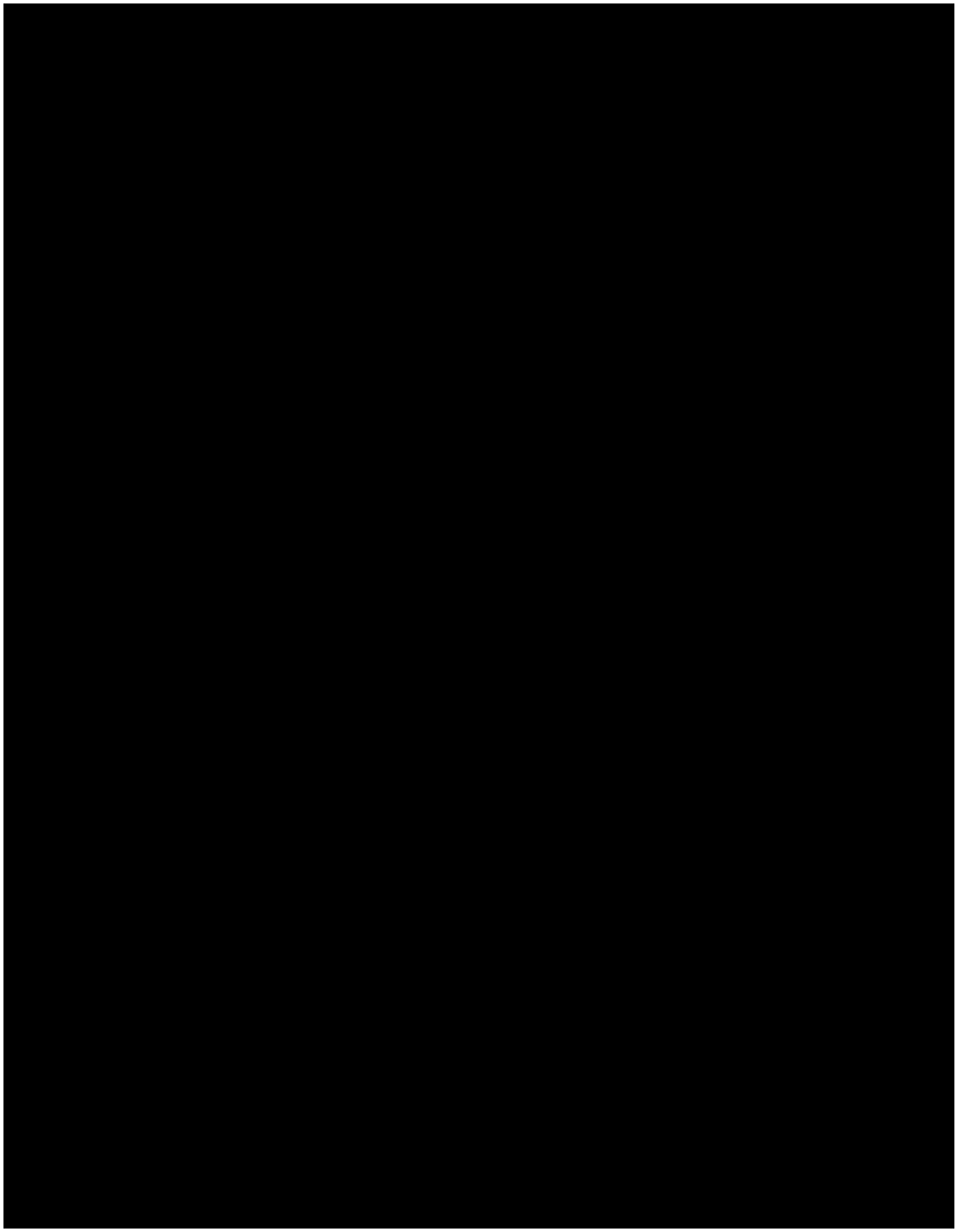

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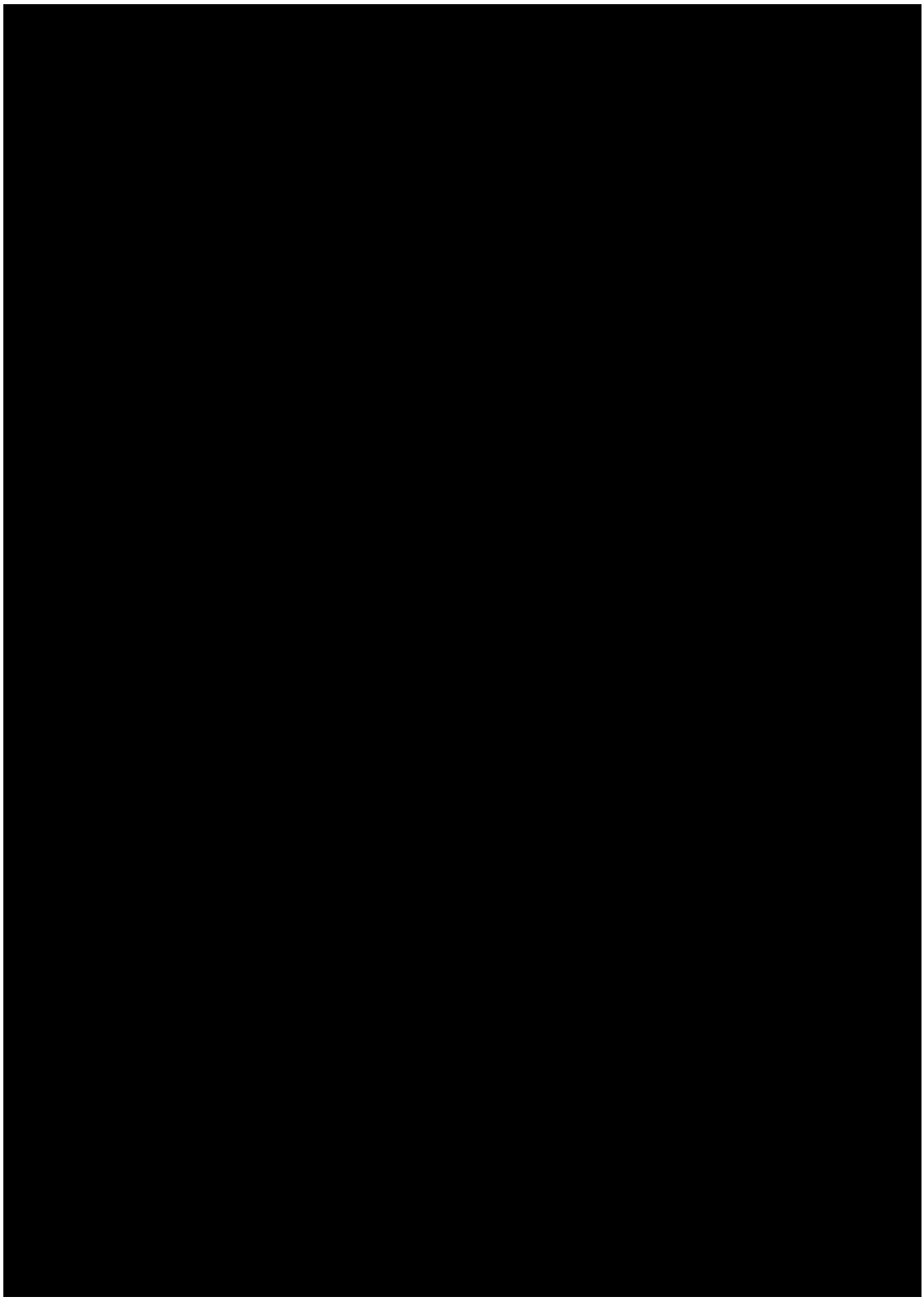

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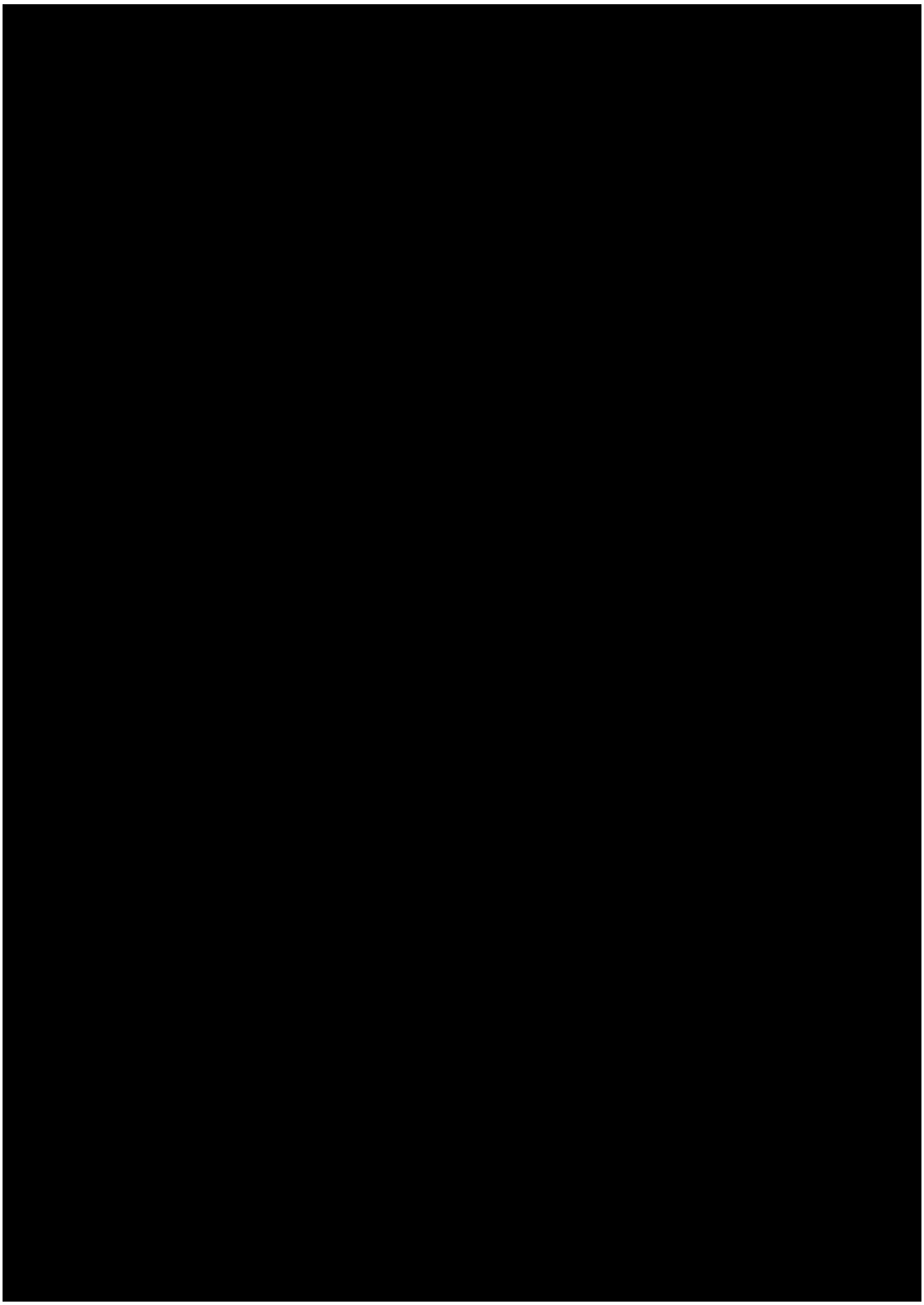

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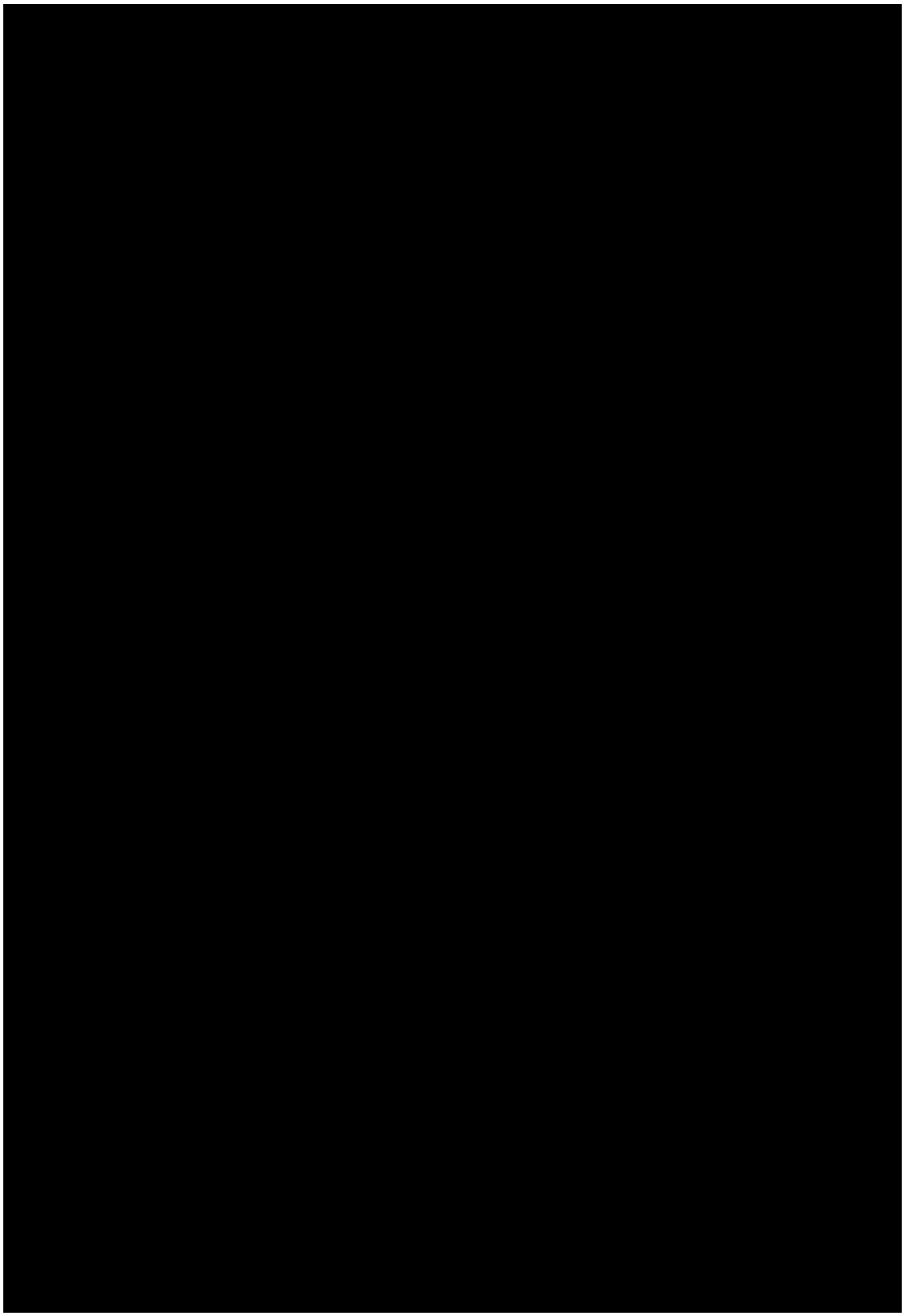

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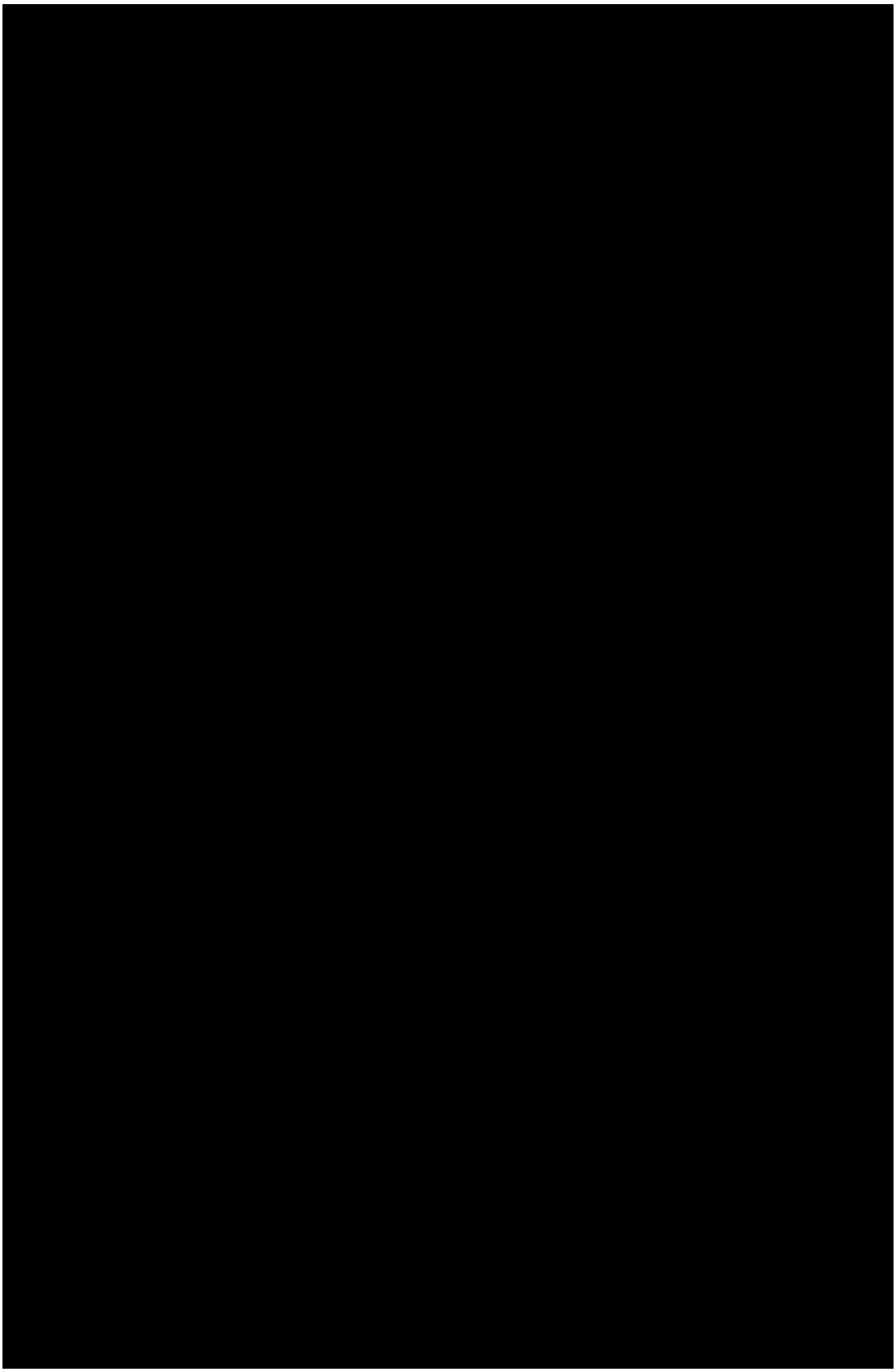

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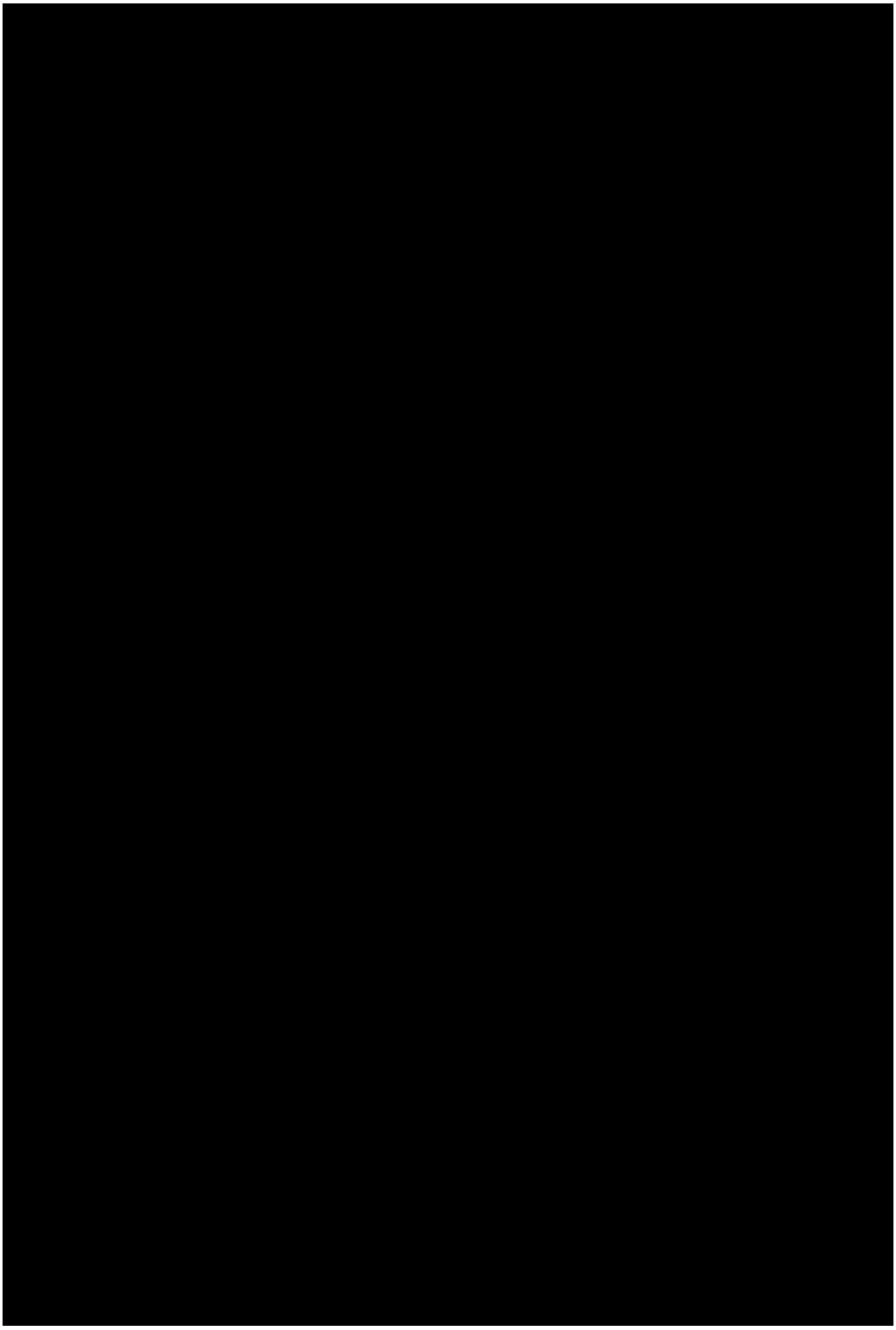

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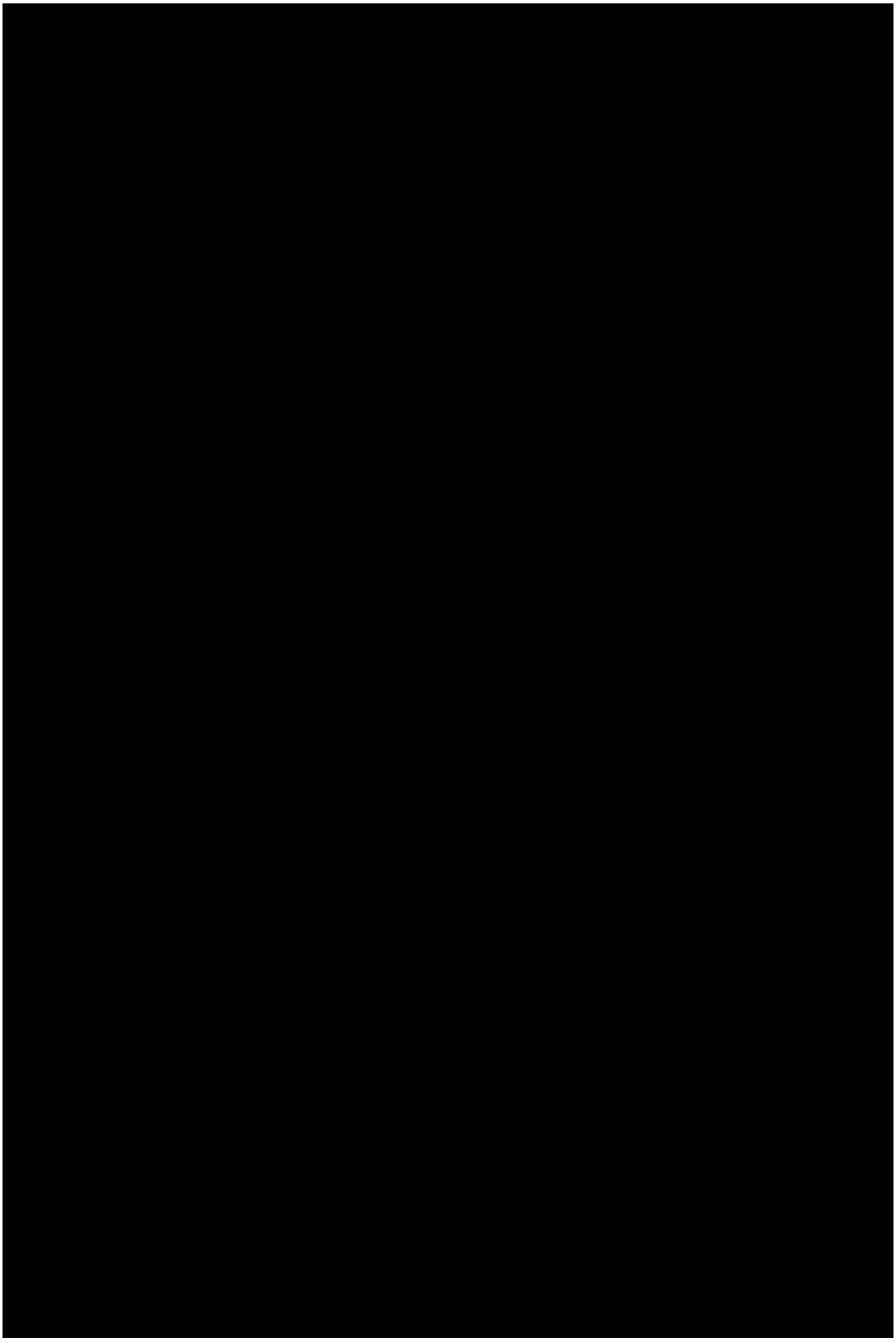

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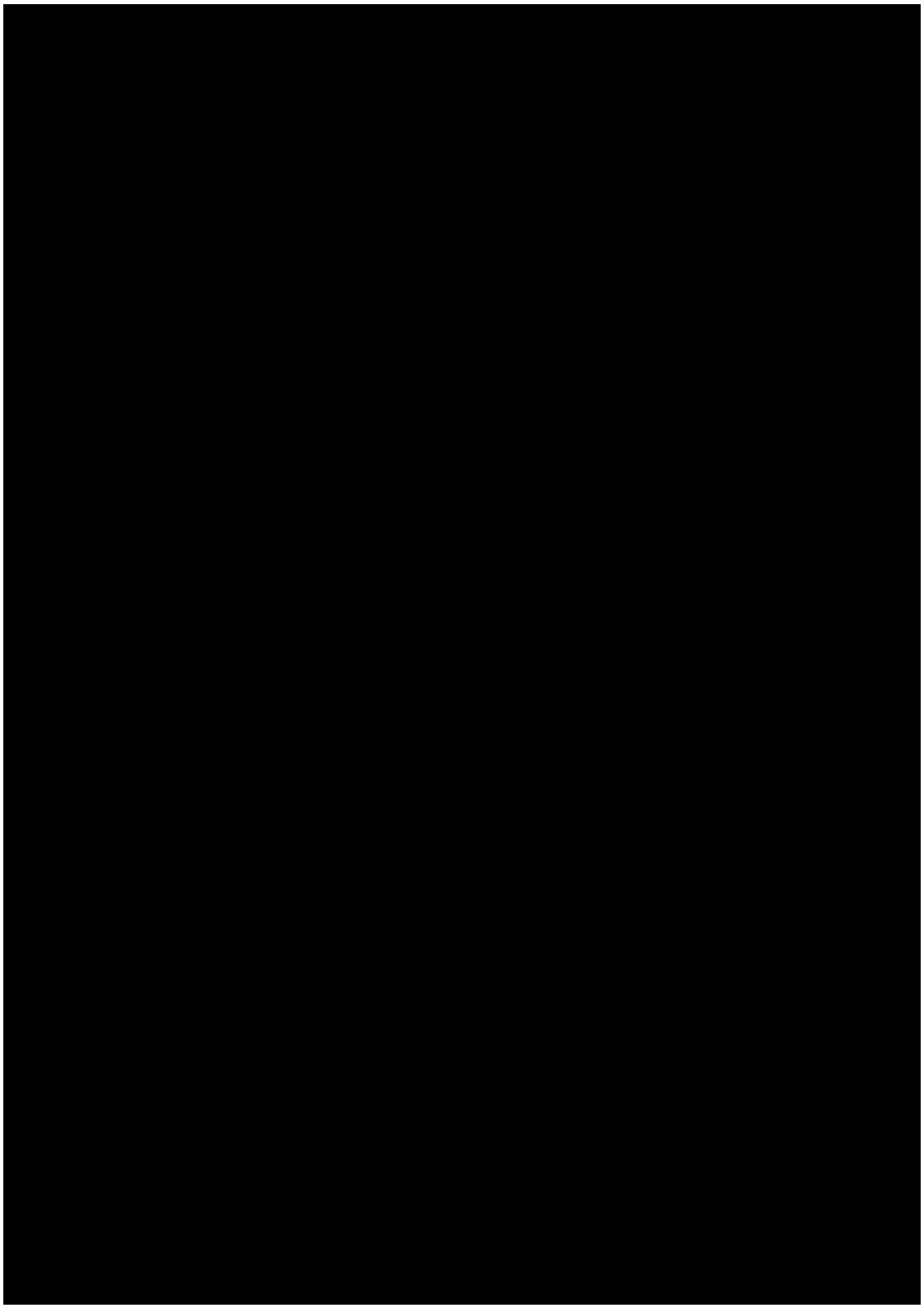

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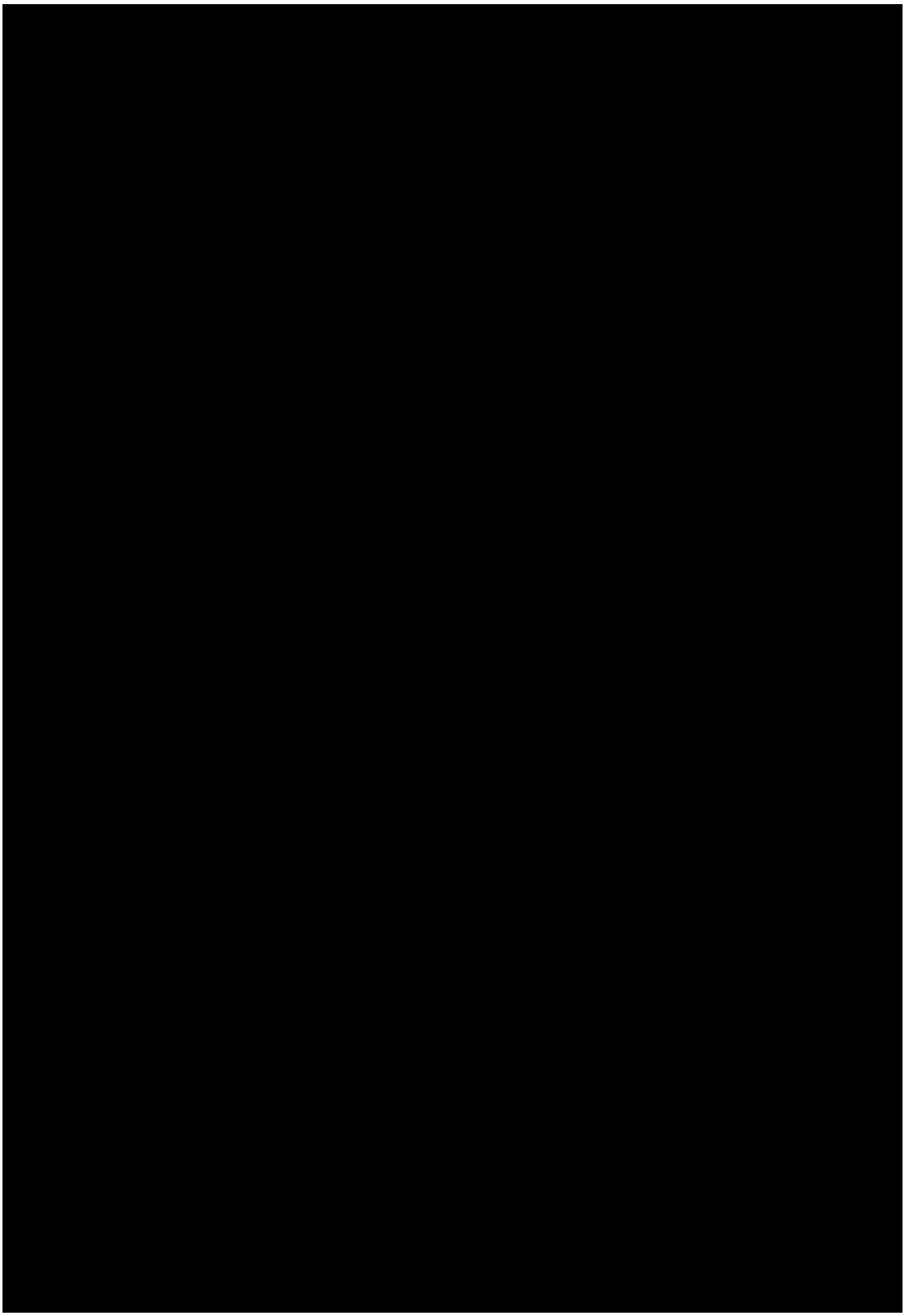

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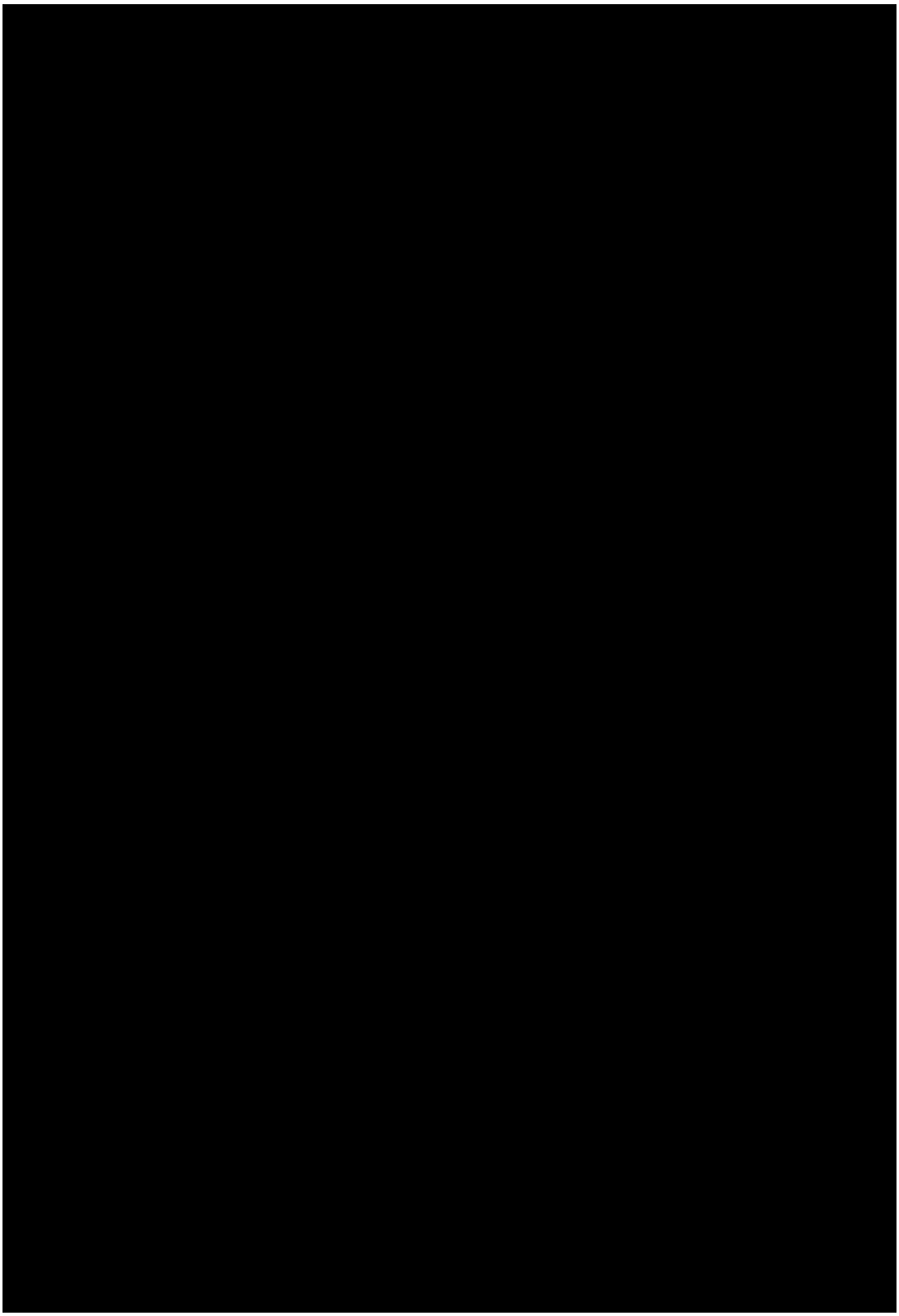

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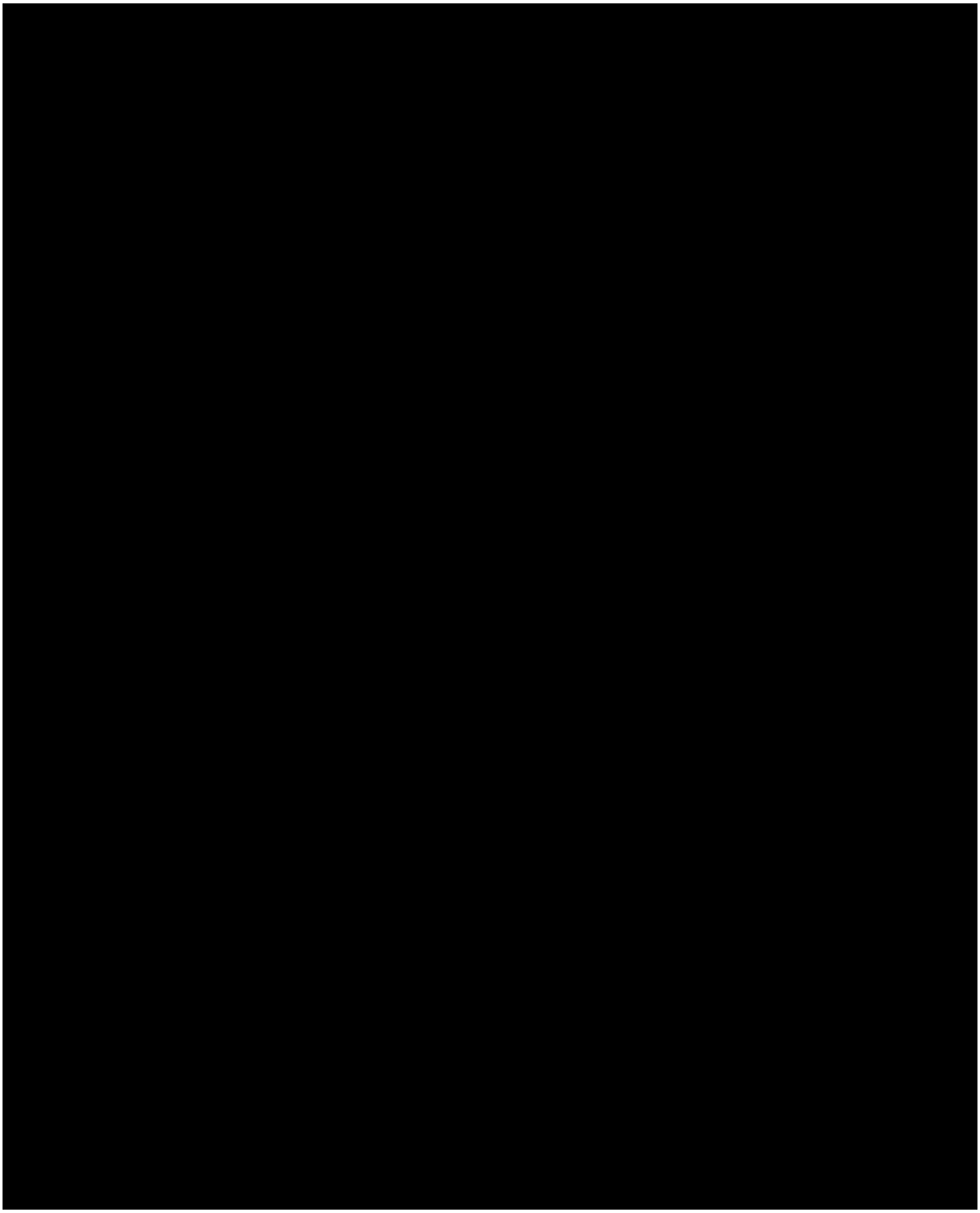

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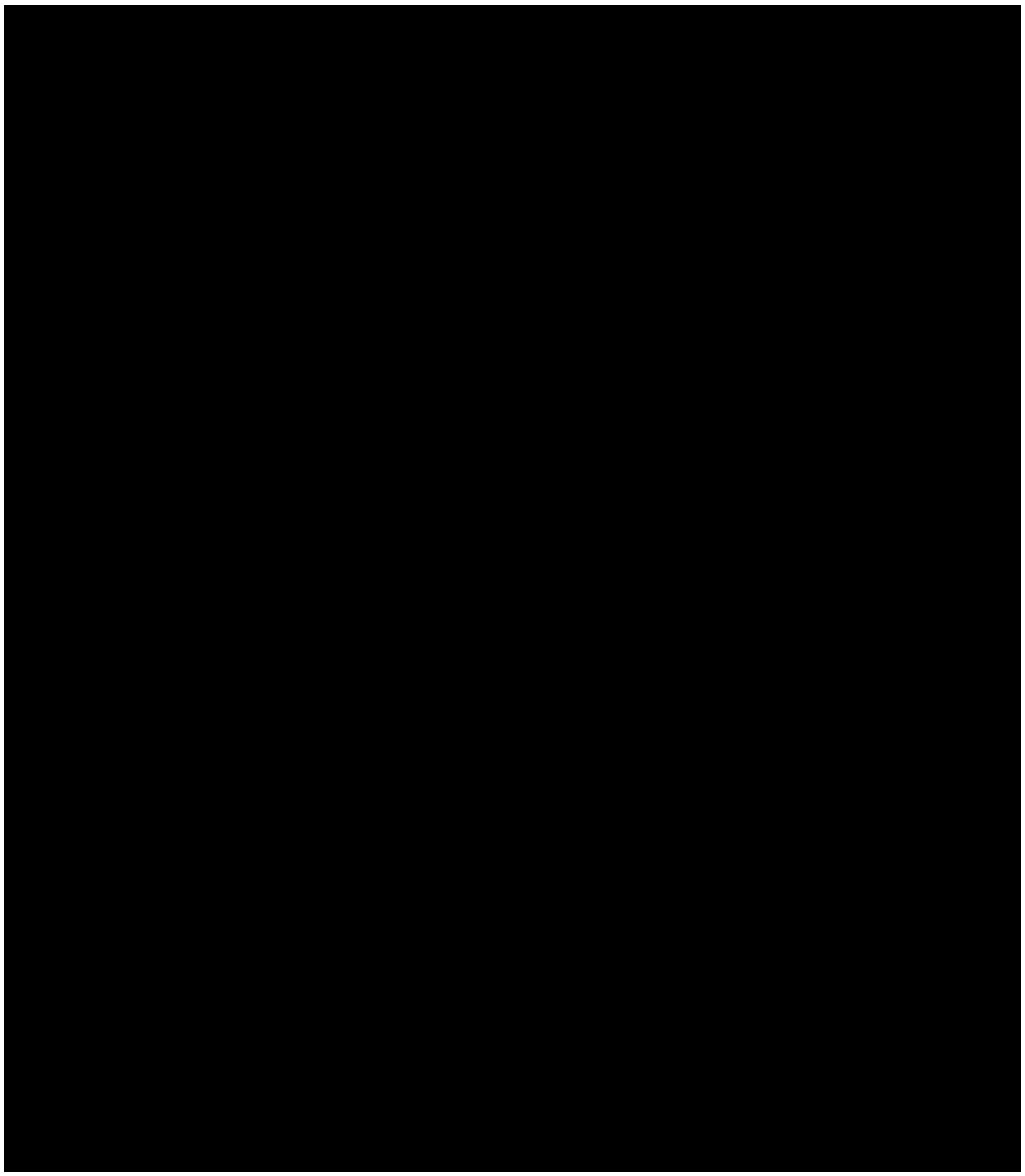

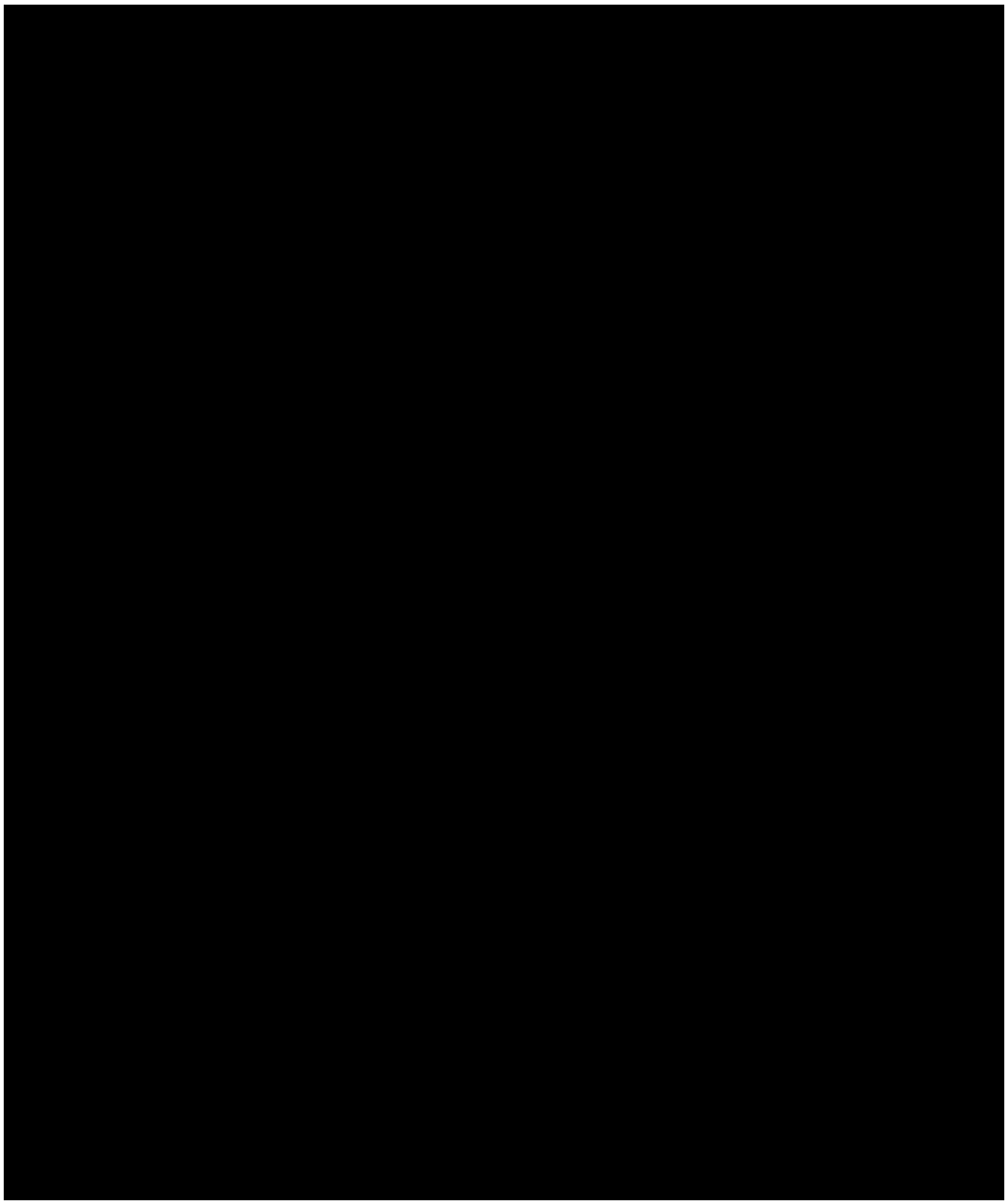

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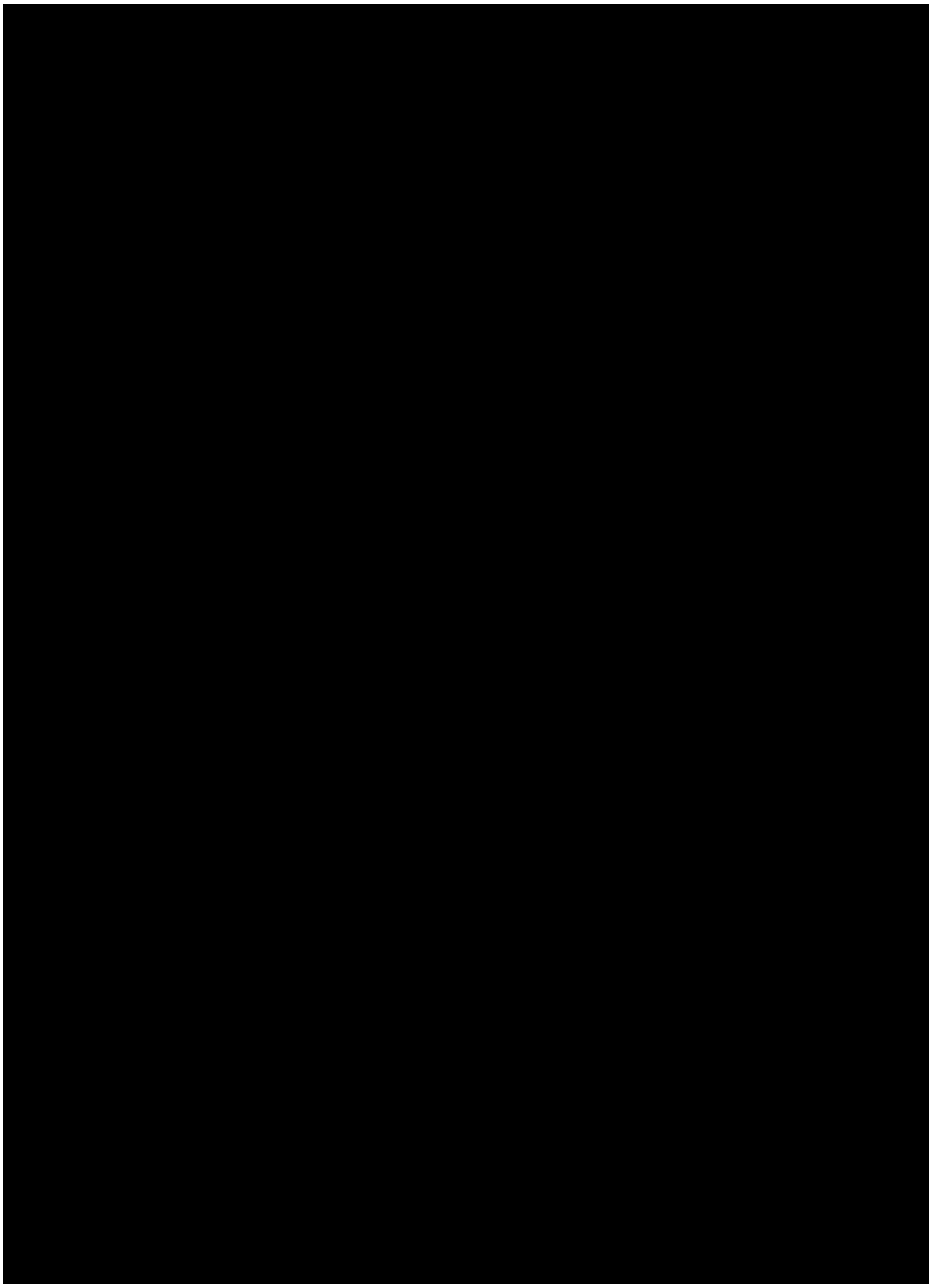

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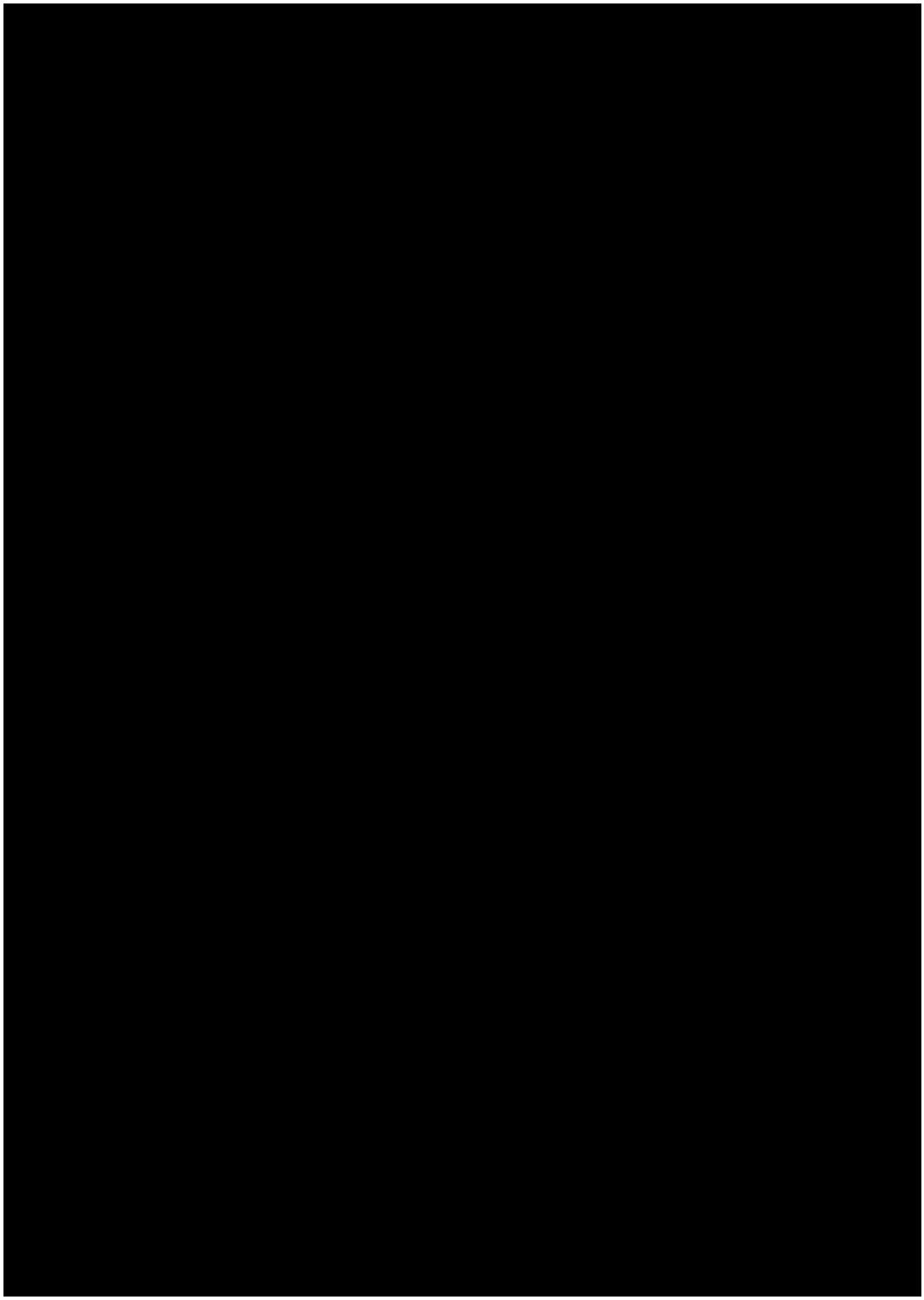

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