UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA ex rel., STEPHEN A. KRAHLING and JOAN A. WLOCHOWSKI, Plaintiffs, v. MERCK & CO., INC., Defendant.	Civil Action No. 10-cv-4374 (CDJ)
IN RE: MERCK MUMPS VACCINE ANTITRUST LITIGATION THIS DOCUMENT RELATES TO ALL ACTIONS	Master File No. 2:12-cv-03555 (CDJ)

EXPERT REPORT

DAVID A. KESSLER, M.D.

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APPENDICES

SCHEDULES[1]

[1] The schedules were prepared by legal staff at my direction and under my review.

I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978. I did my pediatrics training at Johns Hopkins Hospital.

2. I was appointed in 1990 by President George H. W. Bush as Commissioner of the United States Food and Drug Administration ("FDA") and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

3. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal medical and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital.

4. I have held professorships in pediatrics, epidemiology and biostatistics at Yale University, Albert Einstein College of Medicine, and the University of California at San Francisco. I have served as an attending pediatrician on the hospital staffs of these universities. In my role as attending, I have been involved in assessing treatment options in children and the weighing of the risks and benefits of their care.

5. My resume, including a list of my published books and articles, is included in Appendix A. Cases in which I have testified in the last several years are listed in Appendix B.

6. As Commissioner of the FDA, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act (the "FDCA") and the Public Health Service Act (the "PHSA") for vaccines manufactured and sold in the United States. I was responsible for overseeing five Centers within FDA. They included, among others, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, FDA announced a number of new programs, including: the regulation of the marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; measures to strengthen the nation's blood supply; the inter-agency agreement regarding the regulation of biologics as both drugs and biologics; implementation of Compliance Policy Guidance regarding Fraud ("CPG"); creation of an Office of Criminal Investigation within the Agency to investigate suspected criminal violations of the FDCA, FDA regulations and other related laws; and the MEDWATCH program for reporting adverse events and product problems involving both drugs and devices. In addition, I was responsible for overseeing implementation of provisions of the National Childhood Vaccine Injury Act (NCVIA), including the Vaccine Adverse Event Reporting System (VAERS).

7. Vaccines approved by the FDA while I was Commissioner include the following: IPOL[2] (December 21, 1990) (poliomyelitis); Acel-Imune[3] (December 17, 1991) (diphtheria,

[2] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugs areDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf.
[3] http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Disease/ VaccineFinancing/FineBackgroundPaper.pdf; https://www.cdc.gov/mmwr/preview/mmwrhtml/00048610.htm; https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/appdx-full-b.pdf.

tetanus, and pertussis); Tripedia[4] (August 21, 1992) (diphtheria, tetanus, and pertussis); ActHIB[5] (March 30, 1993) (Hib disease, caused by *Haemophilus influenzae* type b); Tetramune[6] (March 30, 1993) (diphtheria, tetanus, pertussis, and Hib disease); Typhim Vi[7] (November 28, 1994) (typhoid fever); HAVRIX[8] (February 22, 1995) (hepatitis A); VARIVAX[9] (March 17, 1995) (varicella); VAQTA[10] (March 29, 1996) (hepatitis A); TriHIBit[11] (September 27, 1996) (diphtheria, tetanus, pertussis, and Hib disease); COMVAX[12] (October 2, 1996) (hepatitis B and Hib disease); and INFANRIX[13] (January 29, 1997) (diphtheria, tetanus, and pertussis).[14]

8. During the 1996-1997 influenza season, while I was Commissioner, all the lots of the Fluogen influenza vaccine manufactured by Parke-Davis, a then-subsidiary of Warner-Lambert Company, were recalled. By FDA requirement, Parke-Davis performed periodic post-release potency testing on its Fluogen influenza vaccine.[15] When it found lots of Fluogen vaccine to have

[4] https://www.cdc.gov/mmwr/preview/mmwrhtml/00048610.htm; https://www.cdc.gov/mmwr/preview/mmwrhtml/00041836.htm; https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/appdx-full-b.pdf.
[5] https://www.cdc.gov/mmwr/preview/mmwrhtml/00020301.htm.
[6] *Ibid.*
[7] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugs areDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf.
[8] http://www.nytimes.com/1995/02/23/us/fda-approves-first-vaccine-to-prevent-hepatitis-a-infection.html; https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4812a1.htm.
[9] http://wayback.archive-it.org/7993/20170723031727/https://www.fda.gov/ BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm142828.htm; http://www.nytimes.com/1995/03/18/us/after-long-debate-vaccine-for-chicken-pox-is-approved.html?pagewanted=all https://www.cdc.gov/mmwr/preview/mmwrhtml/00042990.htm.
[10] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/appdx-full-b.pdf; https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4812a1.htm; https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf.
[11] https://www.cdc.gov/mmwr/preview/mmwrhtml/00044501.htm; https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/appdx-full-b.pdf.
[12] https://www.cdc.gov/mmwr/preview/mmwrhtml/00046158.htm.
[13] https://www.cdc.gov/mmwr/preview/mmwrhtml/00048610.htm.
[14] VARIVAX, VAQTA, and COMVAX were originally and are currently all manufactured by Merck & Co., Inc.
[15] G. A. Poland, *The role of sodium bisulfite in the USA influenza vaccine recall*, 16 VACCINE 1865-1868 (1998) at 1866.

decreased potency over the shelf life after manufacture and release, Parke-David reported the results of the testing to the FDA. *Id*. In November 1996, Parke-Davis voluntarily recalled 11 out of 19 lots of its Fluogen influenza vaccine because of decreased potency. *Id*. This prompted a retrospective study performed by the NYS Department of Health and the CDC. *Id*. On December 16, 1996, the FDA and CDC issued a joint two-page memo that described the issues as they were known at the time, presented a plan for dealing with the issues, and indicated the limitations of the available data.[16] It was recommended that doctors revaccinate those at high risk of flu complications who received the Parke-Davis vaccine, including the elderly and those with chronic heart or lung diseases. *Id*. Approximately 2 million high-risk individuals received the low potency vaccine.[17] On February 14, 1997, Parke-Davis recalled all remaining lots of its Fluogen influenza vaccine. *Id*.

9. I am a senior advisor to TPG Capital, a leading global private equity firm that owns pharmaceutical and biomedical companies. I serve on the boards of Aptalis Pharma and Tokai Pharmaceuticals. In these advising and fiduciary capacities, I have advised companies on the standards and duties of care within the pharmaceutical industry.

10. It is my understanding that *United States ex rel. Krahling and Wlochowski v. Merck & Co.*, Inc., Case No 2:10-cv-4374 (CDJ) (E.D. Pa), was filed in 2010 by Relators Stephen Krahling and Joan Wlochowski against Merck Sharp & Dohme, Corp. f/k/a Merck & Co., Inc. alleging the following claim for relief:

[16] U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services (Director Program Relations, Andy DePirro), *REVACCINATION OF BENEFICIARIES WHO RECEIVED RECALLED INFLUENZA VIRUS VACCINE (FLUOGEN)*, General Medicare Bulletin G-256, January 7, 1997, *available at* https://medicare.fcso.com/Publications_A/1997/137532.pdf.
[17] Gregory A. Poland, *Lessons from the Influenza Vaccine Recall of 1996-1997*, 278 JAMA: THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1022 (1997) at 1022.

- Violation of the False Claims Act (31 U.S.C. § 3729, *et. seq.*)

11. It is my understanding that *Chatom Primary Care, P.C. et al v. Merck & Co., Inc.* (In re: Merck Mumps Vaccine Antitrust Litigation), Master File No. 2:12-cv-03555 (E.D. Pa.), includes the following claims brought by Plaintiffs Chatom Primary Care, P.C., Dr. John Sutter, and Dr. Andrew Klein, on behalf of themselves and a proposed class of all others similarly situated (the "Class") against Merck Sharp & Dohme, Corp. f/k/a Merck & Co., Inc. alleging the following claims for relief:

- Monopolization in Violation of Section 2 of the Sherman Act (15 U.S.C. § 2) (on behalf of Plaintiffs and the Class); and
- Violation of the New York and New Jersey State Consumer Protection Laws (on behalf of Plaintiffs and the State Consumer Protection Subclass).

It is also my understanding that a Motion for Leave to Amend the Complaint is currently pending, and that Plaintiffs seek to add the following claim to the operative complaint:

- Attempted Monopolization in Violation of Section 2 of the Sherman Act (15 U.S.C. §2) (on behalf of Plaintiffs and the Class).

12. The documents provided to me by counsel, or that I accessed independently from various sources including, but not limited to, FDA's website, are listed in Appendix C to this report.[18] At my request, Appendix C was prepared by counsel. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

[18] I understand the two cases have been coordinated for purposes of discovery. Two prefixes to the numbers have been applied to the documents produced by Merck, reflecting their production in each of the respective cases. All future cites using the MRK-KRA designation incorporate by reference the corresponding MRK-CHA prefix.

II. QUESTIONS ADDRESSED IN THIS REPORT

13. It is my understanding that these cases involve allegations relating to Merck's mumps-containing vaccines, and clinical testing of Merck's mumps-containing vaccines to support licensure of vaccines sold to the United States and private purchasers.

14. There are two overarching issues, from my perspective, in these matters. First are potency issues. Specifically, did Merck's mumps vaccine fall below the represented potency for mumps in Merck's label and did Merck have adequate assurance that the mumps vaccine it manufactured would have the required mumps potency for the entire shelf life of the vaccine. Potency of a vaccine is critical to ensuring the efficacy of a vaccine.

15. Second are the efficacy issues. Specifically, did Merck's clinical studies demonstrate that its mumps vaccine "preserv[ed] the excellent … efficacy profile of the vaccine." Efficacy, like potency, is critical to ensuring that the vaccine protects children against disease.

16. One of the specific questions in this matter is whether Merck's mumps vaccine maintained the "not less than 4.3" mumps potency on the MMRII (measles-mumps-rubella) label for the entire shelf life while that specification was represented on Merck's MMRII label. This is a potency issue. It is also an efficacy issue because if the vaccine is insufficiently potent, it will not assure efficacy and protection of children against mumps disease.

17. Merck's efforts to confront issues surrounding its inability to ensure the mumps potency stated on the MMRII label involved a cascade of events that each raise additional issues. These events included the following: (a) Merck proposed doing a clinical trial, Protocol 007, to support lowering the mumps potency claim on the MMRII label; (b) Merck proposed an interim

increase in the amount of mumps virus in each dose of MMRII while it completed Protocol 007; (c) Merck learned that even with the increased amount added to the vaccine, Merck could not assure the required mumps potency for the entire shelf-life; (d) Merck identified 225 lots, representing 23 million doses of MMRII, that Merck could not assure met the 4.3 potency claim on the label for the entire shelf-life, 12 million of which were released to the U.S. market; (e) Merck failed to report 220 of these lots even though Merck identified lower potency doses from these lots as a compliance issue; (f) Merck conducted testing in Protocol 007 using an assay Merck modified by adding anti-IgG[19]; (g) Merck tested Protocol 007 subjects outside the clinical protocol without consent and without informing the FDA; (h) Relators Mr. Krahling and Ms. Wlochowski made accusations of falsification of data in Protocol 007; (i) Merck used the results of the clinical study to represent that children who received MMRII with mumps potency of less than 4.3 would be protected against disease; (j) Merck obtained FDA approval to change the MMRII label to reduce the mumps potency claim using results of Protocol 007; (k) Merck made the interim overfill permanent, even after lowering the mumps potency claim on the MMRII label.

18. These events raise, among others, the central issue of whether Merck had reliable clinical data that demonstrated a lower potency dose of MMRII protects children against disease. To answer this question, there are a series of sub-issues and questions including (a) Did the use of anti IgG in the "anti-IgG enhanced neutralization test" (AIGENT) artificially inflate the seroconversion rate Merck reported using the test; (b) Was Merck correct in representing a correlation between the AIGENT and the Wild Type Enzyme Linked Immunosorbent Assay

[19] *See* Section VII.A.3.4 and VIII.C below describing how Merck modified a standard test with the addition of anti-IgG.

(WT ELISA) in order to use the WT ELISA as a substitute in clinical studies Merck used to support applications relating to its mumps vaccines, MMRII and ProQuad (measles-mumps-rubella-varicella); (c) Was Merck correct, as part of the correlation analysis, that the cutoff used in the WT ELISA was appropriate to use in its clinical studies; (d) Did Merck's clinical studies using either the AIGENT or WT ELISA tests relate to whether a child would be protected against disease after receiving a mumps vaccine; (e) Were Merck's representations to FDA concerning the efficacy of its mumps containing vaccines accurate and supported by reliable clinical study data; (f) Did Merck inform the FDA that it did not know the clinically protective level measured in either the AIGENT or the WT ELISA; (g) Did Merck's representations on its labels impact the ability of competitors to license other mumps vaccines in the United States.

19. With regard to FDA compliance issues, these overarching issues and events raise the following questions: (a) Did Merck's release of product for which it could not assure the mumps potency specification for the shelf life of the vaccine render the product adulterated under the Federal Food Drug and Cosmetic Act? (b) If Merck did not have reliable clinical data related to protection against disease as a result of vaccination with MMRII or ProQuad, as represented on the labels for MMRII and ProQuad, were these products misbranded under the Federal Food Drug and Cosmetic Act?

20. Based on my review of the documents and testimony in these cases and my training and experience, I have a number of opinions regarding these issues, events and questions as discussed in the sections below. My conclusions are discussed in Section XII.

III. BACKGROUND ON MUMPS VACCINES AND MUMPS TESTING

A. The Mumps-Containing Vaccines at Issue In These Cases

21. Merck's mumps-containing vaccines date back to the 1960's.[20] Dr. Maurice Hilleman developed a "monovalent"[21] mumps vaccine and Merck conducted studies to support the efficacy of the vaccine.[22] On December 28, 1967, Merck obtained a license to sell Mumpsvax, the vaccine Dr. Hilleman developed and tested.[23]

22. On April 22, 1971, Merck obtained a license to sell MMR.[24] MMR combined the "monovalent," vaccines for measles, mumps, and rubella into a "trivalent" vaccine.[25]

23. On September 15, 1978, FDA approved a license for Merck to sell a new MMR vaccine, "MMRII"[26] with a different rubella component. The measles and mumps components remained the same as MMR.[27]

24. On September 6, 2005, FDA approved a license for Merck to sell a "quadrivalent" vaccine, ProQuad, combining its measles, mumps, rubella and varicella vaccines into a single dose.[28] Merck had obtained a license for a monovalent varicella vaccine in 1995.[29]

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[20] *See* Schedules 11, 12, 13 (The Product and its Regulatory History).
[21] A monovalent is a vaccine that vaccinates against a single disease. Vaccines to prevent different diseases can also be combined into a single dose, as described below.
[22] *See* Schedule 13 (Regulatory Approval History of Mumpsvax).
[23] http://www.immunize.org/timeline/; *see also, e.g.*, MRK-KRA01962790. *See* Schedule 13 (Regulatory Approval History of Mumpsvax).
[24] http://www.immunize.org/timeline/ (BLA 101069); *see also, e.g.*, MRK-KRA00153450; MRK-KRA01538727.
[25] Merck obtained a license for a measles vaccine in 1963 and a license for a rubella vaccine in 1969. *See* https://www.merck.com/docs/VACC-1213236-0000-Merck-Vaccines-Branded-Timeline-FINAL.pdf.
[26] MRK-KRA01619023. *See* Schedule 11 (Regulatory Approval History of MMRII).
[27] Seven clinical studies performed from 1975 to 1978 supported the licensure of M-M-R®II. MRK-KRA00792125 at '34; MRK-KRA00137876; MRK-KRA000137839; MRK-KRA00018768; *see also*, Weibel et al. "Clinical and Laboratory Studies of Combined Live Measles, Mumps, and Rubella using the RA 27/3 Rubella Virus," Proc. Soc. Experimental Biology and Medicine, 1980, 165, 323-326. *See* Schedule 11 (Regulatory Approval History of MMRII).
[28] The regulatory approval of ProQuad is discussed in more detail in Sections IX.A.5-7, B.3, C.2 below; *see also* Schedule 12 (Regulatory Approval History of ProQuad).

25. Two of Merck's vaccines are primarily at issue in these cases: MMRII and ProQuad. Mumpsvax is no longer sold in the United States. There are three Merck Biological-Based Investigational New Drug ("BB-IND")[30] Application Numbers associated with MMRII and ProQuad relevant to these cases:

BB-IND 1016:	Combined Live Measles-Mumps-Rubella (RA27/3) Virus Vaccine
BB-IND 7068:	Measles (chick embryo cells), Mumps (chick embryo cells), Rubella (WI-38 cells) and Varicella (MRC-5 cells) Virus Vaccine Live, Attenuated
BB-IND 10076:	Measles, Mumps and Rubella Virus Vaccine, Live with Recombinant Human Albumin (S. *cerevisiae,* Aventis Behring) Excipient

26. There are two Merck Biologics License Application (BLA) Submission Tracking Numbers (STN) associated with MMRII and ProQuad relevant to these cases:

BLA/STN# 101069:	M-M-R™II (Measles, Mumps, and Rubella Vaccine Live)
BLA/STN# 125108:	ProQuad (Measles, Mumps, Rubella and Varicella [Oka/Merck] Virus Vaccine Live)

B. Live-Attenuated Vaccines

27. A vaccine is a biological product[31] administered for the purpose of preventing an infectious disease.[32] Whereas therapeutic drugs treat a disease or its symptoms, a vaccine is

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[29] https://www.merck.com/docs/VACC-1213236-0000-Merck-Vaccines-Branded-Timeline-FINAL.pdf; MRK-KRA00145486.

[30] A BB-IND is assigned by FDA to every investigational new drug. The BB-IND is permanent and all subsequent correspondence should reference the BB-IND number.

[31] A vaccine is a "biological product" as defined in 42 U.S.C. § 262 (i)(1) of the Public Health Service Act ("PHSA"). Section 262 (i)(1) states: "The term 'biological product' means a … vaccine …. applicable to the prevention, treatment, or cure of a disease or condition of human beings."

[32] There are vaccines against bacterial infection but since mumps is a virus, this description discusses vaccines in terms of viral infection.

prophylactic, meaning it offers protection against the onset and progression of an infectious disease.[33] Vaccines introduce virus in a weakened form to trigger the immune system[34] to make antibodies[35] to that virus. While the vaccine causes an immune response,[36] it does so without giving the person the disease.[37] Thereafter, if the person is exposed to the virus, the immune system, including the antibodies created in response to vaccination, protects the person from getting sick.[38] Moreover, if the immunized person does not get the disease, he or she helps prevent the spread of the virus to others. The immunity[39] afforded by vaccination is intended to be similar to what the vaccine recipient would acquire from natural infection, without the risk of disease.

28. Merck's mumps vaccines are live, attenuated vaccines.[40] They contain a suspension of live mumps virus[41] that is weaker than the mumps virus circulating in the wild.[42]

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[33] *See* MRK-KRA01339555_0020 ("Vaccines offer protection against the onset and progression of specific infectious diseases; other medications treat the disease and/or its symptoms.").

[34] The CDC defines the immune system as the "complex system in the body responsible for fighting disease. Its primary function is to identify foreign substances in the body (… viruses …) and develop a defense against them. This defense is known as the immune response. It involves production of protein molecules called antibodies to eliminate foreign organisms that invade the body." Center for Disease Control and Prevention, Vaccines & Immunizations – Glossary: Immune System, https://www.cdc.gov/vaccines/terms/glossary.html

[35] An antibody is "a protein found in the blood that is produced in response to foreign substances (e.g. bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them." Center for Disease Control and Prevention, Vaccines & Immunizations – Glossary: Antibody, https://www.cdc.gov/vaccines/terms/glossary.html.

[36] *Id*.

[37] *See* MRK-KRA01339555_0020 ("Immunity and immunologic memory similar to natural infectious but without risk of disease...").

[38] *Id*.

[39] The CDC defines immunity as "[p]rotection against a disease. There are two types of immunity, passive and active. Immunity is indicated by the presence of antibodies in the blood and can usually be determined with a laboratory test." Center for Disease Control and Prevention, Vaccines & Immunizations – Glossary: Immunity, https://www.cdc.gov/vaccines/terms/glossary.html.

[40] The CDC describes other kinds of vaccines, including inactivated vaccines (such as the polio vaccine), toxoid vaccines (such as the diphtheria and tetanus vaccines), subunit vaccines (such as the pertussis vaccine) and conjugate vaccines (such as haemophilius influenza type B (Hib) vaccine). https://www.cdc.gov/vaccines/hcp/conversations/downloads/vacsafe-understand-color-office.pdf

[41] Both MMRII and ProQuad are packaged in single-dose vials that are lyophilized (freeze-dried). They are reconstituted at the doctor's office prior to administration according to the use instructions set forth in the label. *See* Schedules 1 and 2 (discussing the MMRII and ProQuad labels).

A wild type mumps virus is a disease-causing strain of the virus as it exists in nature.[43] The process by which the mumps virus is weakened is called attenuation. When a virus is attenuated, it is passaged through chemical or physical processes in order to produce a virus that will elicit an immune response without causing the severe effects of the disease[44] and it becomes weaker with each passage. The live attenuated virus in Merck's mumps vaccine was developed by "passaging isolated virus in embryonated hen's eggs and then in chick embryo cell culture."[45]

29. When a child receives a live-attenuated virus vaccine it is intended to stimulate an immune response to the live attenuated virus in the vaccine. The antibodies generated in the immune response neutralize[46] the virus administered in the vaccine. Having responded to the virus in the vaccine, the immune system then "remembers" the virus if it encounters it again later in the real world. When that happens, the antibodies will neutralize the virus and prevent the virus from infecting the immunized person.

1. The Mumps Component in Merck's Vaccines

30. Merck's Mumpsvax (monovalent mumps vaccine) was developed after Dr. Maurice Hilleman was able to collect a throat culture from his daughter, Jeryl Lynn Hilleman,

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[42] https://www.cdc.gov/vaccines/hcp/conversations/downloads/vacsafe-understand-color-office.pdf.
[43] MRL's Keith Chirgwin testified: *A. The antibody that you measure, you would like to be active against a wild type virus, because that's what's going to cause disease.* Deposition of Keith Chirgwin, January 26, 2017, 132:4-7.
[44] *See* Centers for Disease Control and Prevention Vaccines & Immunizations Glossary ("Attenuated Vaccine: A vaccine in which live virus is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines currently licensed in the United States include measles, mumps, rubella, polio, yellow fever and varicella. Also known as a live vaccine.") Center for Disease Control and Prevention, Vaccines & Immunizations – Attentuated Vaccine, Glossary:https://www.cdc.gov/vaccines/terms/glossary.html.
[45] MRK-KRA00014028 at '33-34.
[46] When antibody neutralizes a virus, it binds to the virus and destroys it. *See* Centers for Disease Control and Prevention Vaccines & Immunizations Glossary ("Antibody: A protein found in the blood that is produced in response to foreign substances (e.g. bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them") https://www.cdc.gov/vaccines/terms/glossary.html.

when she was infected with mumps in 1963. He named the mumps virus strain he later isolated in the laboratory after Jeryl Lynn.[47] Dr. Hilleman then attenuated the Jeryl Lynn strain of the mumps virus he isolated to use in a vaccine. As discussed above, in order to use the virus in a vaccine it needed to be attenuated, or passaged, enough times that someone getting the vaccine would not get mumps, but not passaged too far as to become so weak that it would not trigger an immune reaction.

31. With respect to the strain of the mumps virus obtained from Jeryl Lynn Hilleman in 1963, this report uses the following terms:

- Wild-Type Jeryl Lynn: The virus as it was collected from Jeryl Lynn Hilleman in 1963 is referred to as the "Wild-Type Jeryl Lynn" strain of the mumps virus.
- JerylLynn™: The virus that is in the MMRII and ProQuad vaccines is referred to as the "JerylLynn™" strain. The JerylLynn™ strain is an attenuated form of the virus and has been passaged 17 times.[48] It is also referred to as the "JL" strain, or the "vaccine strain."
- JL-2 and JL-5: MMRII containing the JerylLynn™ mumps strain is a "mixture of two subpopulations" referred to as "JL-2" and "JL-5."[49] Priorix, a measles, mumps, rubella vaccine manufactured by GlaxoSmithKline ("GSK") and not sold in the United States, "contains only JL-5, isolated by limiting dilution and serial passage."[50]

[47] MRK-KRA00014028 at '33-34 ("In 1963, Dr. Hilleman's daughter, Jeryl Lynn, became ill with mumps. Dr. Hilleman obtained a throat culture from her that would lead to the isolation of the Jeryl Lynn mumps strain, from which he developed the mumps vaccine. The MMRII vaccine contains this mumps strain. … A live attenuated mumps virus vaccine, Jeryl Lynn™ (B level) strain, was developed by passaging isolated virus in embryonated hen's eggs and then in chick embryo cell culture. The mumps virus used in MMRII is the Jeryl Lynn ™ (B level) strain.").
[48] MRK-KRA00511018 at p.26 (power point slide diagramming "Passage History of Mumps Stock Seeds & Vaccines").
[49] MRK-KRA01452741.
[50] *Id.*

- JL-135: The strain that was used as an indicator virus in Merck's AIGENT and WT ELISA assays[51] is referred to as "JL-135." It was neither the Wild Type Jeryl Lynn nor the Jeryl Lynn.™ It was a "low passage" strain (passage 8) "derived from the original wild type Jeryl Lynn isolate in 1963."[52]

32. With respect to strains of the mumps virus that are not derived from the isolate collected from Jeryl Lynn Hilleman, **"**wild type**"** refers to disease-causing viruses that occur naturally in the population, such as the London1, Rubini, Swiss, Tennessee, Iowa, and Barnes strains of mumps that were isolated from different individuals infected with mumps.[53]

2. Vaccine Potency

33. Potency is defined as the "ability of the product ... to effect a given result."[54] The potency of a vaccine is connected to how well the vaccine works.[55] If a vaccine does not have sufficient potency, it may not provide protection from disease.

[51] *See* Sections VII.A and M below discussing these two assays, or tests.
[52] MRK-KRA00018822 at '48. *See also* MRK-KRA01927351 at '53 ("CBER agree[d] that … using JL passage 7-12 would be acceptable."); *See also* MRK-KRA00140056 at '3016-3017 ("... an early passage of the Jeryl Lynn™ mumps virus (<12 passages) which is less attenuated than the Jeryl Lynn™ mumps virus used in the Merck mumps virus-containing vaccines, and is considered to be a wild-type (WT)-like strain...").
[53] The term "wild type" with regard to virus strains typically refers to either a strain of virus that circulates in a population and causes disease or a strain of virus that was isolated from an individual infected with a disease-causing virus. In Merck documents, the term "wild type" can also refer to a low-passage attenuated strain of the virus. Merck refers to the JL-135 strain as a "wild type" strain, and refers to the ELISA assay with a JL-135 indicator virus as the "Wild Type ELISA" (WT ELISA); See also MRK-KRA00198876 at '877 ("...predicting the current protective efficacy of the MMRII vaccine against present wild type strains."). See MRK-KRA00015686 at '86 ("2 independent assays have confirmed that the seroprotection rates against wild type isolates are not ~95%..."); See MRK-KRA01927351 at '53)"...the virus used in the assay must be wild type (early passage) virus, not attenuated virus vaccine"). See also MRK-KRA00140056 at '3016-3017 ("The assay uses an early passage of the Jeryl Lynn™ mumps virus (<12 passages) which is less attenuated than the Jeryl Lynn™ mumps virus used in the Merck mumps virus-containing vaccines, and is considered to be a wild-type (WT)-like strain..."); *See also* Schedule 20 (describing mumps virus strains).
[54] 21 CFR 600.3 § (s).
[55] Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products," (May 1998) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf ("Biological products are approved under authority of section 351 of the Public Health Service Act. Under Section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. Potency has long been interpreted to included effectiveness.") (internal citations omitted).

34. In a live attenuated viral vaccine like MMRII or ProQuad, potency refers to the concentration of live virus in the dose. The potency of a vaccine is expressed as a Tissue Culture Infectious Dose (TCID).[56] When a vaccine such as MMRII or ProQuad has multiple component viruses, the potency specifications may be different for each component. In this report, "mumps potency" refers to the potency of the mumps component of either MMRII or ProQuad.

a. Potency Specifications

35. As described in Section VII below, the potency claim on the label is an end-expiry potency specification. It is the potency the vaccine must have at the end of its dating period, or shelf-life.[57] The current end expiry potency specification for the mumps component of MMRII states that each dose of the vaccine contains "not less than" 12,500 $TCID_{50}$ of mumps virus.[58] Potency can also be expressed on a logarithmic scale. For example, "4.1 $\log_{10}$ $TCID_{50}$" is the same potency as "12,500 $TCID_{50}$." (4.1 $\log_{10}$ = 12,500). Also relevant in this report, "4.3 $\log_{10}$ $TCID_{50}$" is the same potency as "20,000 $TCID_{50}$." (4.3 $\log_{10}$ = 20,000).[59]

[56] MRK-KRA00019685 at '99 ("The components of M-M-R™II are live attenuated viruses. Determination of the potency or infectivity of a live vaccine requires the use of a cell-based assay that can determine how many infectious particles are present and capable of infecting the target cells. In [the $TCID_{50}$ assay], a series of known dilutions of virus are placed in cell culture plates along with cells that will become infected in the virus... After a set incubation period, the assay is read. ...In the $TCID_{50}$ assay, which is used for measuring the potency of M-M-R™II, infectivity is determined by observing which dilution leads to evidence of the cytopathic effect in 50% of the wells. The $TCID_{50}$ potency is typically recorded in the $\log_{10}$ scale.").

[57] MRK-KRA00666494 at '25-26 (internal Merck document stated: "FDA requires that the label specify the minimum claimed potency throughout shelf-life.").

[58] As discussed below, in order to change the mumps end expiry potency specification for MMRII from not less than 4.3 to 4.1, FDA required Merck to provide clinical data to demonstrate the vaccine would remain effective at the lower dose. This was the objective of the Protocol 007 clinical trial discussed in this report.

[59] *See* Schedule 19 (converting log scale measurements).

36. There is also a release potency specification, the minimum potency at which the vaccine is released to the market.[60] A manufacturer sets the release potency by determining the minimum potency a vaccine component must be at release in order to ensure the vaccine will not fall below the end-expiry potency specification before the end of the shelf life.[61] An "overfill" is an increase in the amount of the release potency specification.[62] As discussed below, the release potency specification is informed, in part, by the stability data of how much potency is lost over time. In addition to ensuring that the release potency supports the end-expiry specification, a vaccine manufacturer must also have safety data to ensure that the vaccine is safe at the release potency.

b. Vaccine Stability

37. Live attenuated vaccines lose potency over time.[63] Stability is a measure of how much and how quickly potency is lost under set conditions.[64] Manufacturers reserve batches of product stored under the conditions described in the packing and test the potency of the vaccine

[60] MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows: *Q… how would you define the release potency? A. It's the minimum number value at which the product is released onto the market.* Deposition of Barbara Kuter, December 14, 2016, 133:17-23 190:16-19.

[61] MRK-KRA00141789 at '65. ("Minimum potencies at release were determined using a statistical stability loss model that ensures, with 95% confidence, that the potencies of the measles, mumps, and rubella components do not fall below their end-expiry titer.").

[62] *See* Deposition of Joye L. Bramble, January 6, 2017, 52:12-16 (Overfill is when "*you put more vaccine into each vial to make sure you can maintain the end expiry of 4.3 [for mumps]*.") and Deposition of Emilio Emini, June 6, 2017, 95:2-7 (*"[A] standard terminology within the industry. So, what overfill means is to add more into the unit, whether it be a vial or syringe, whatever the case may be, tied more into the unit than what would normally be required*.").

[63] *See* MRK-KRA00019685 at '99 ("M-M-R™II is manufactured as a lyophilized ('freeze-fried') product. Like other live attenuated viral vaccines, the potency of M-M-R™II is affected by temperature and moisture. While the product is table for years at -70ºC or -20ºC, the potency is gradually reduced when it is stored at refrigerator temperature (2 to 8ºC); a more rapid decline occurs at room temperature (20 to 25ºC) or at 37ºC. Potency is lost quickly once the product is reconstituted with diluent, which is why the vaccine must be given within 8 hours of reconstitution. The three components are not identical with respect to their temperature sensitivity; while measles and mumps are temperature sensitive, rubella is considered more stable even at 37ºC.")

[64] *See*, *e.g.*, MRK-KRA00031864 at '66 (describing the "Stability Window" and the use of a "comprehensive statistical release model" that looks at the characteristics of the product's stability losses from manufacture to delivery to doctor's offices to the administration to patients, calculating the potency loss and variability of the assay at each step to ensure the product meets its end expiry label claim.).

at different points in time as part of a monitoring program.[65] Merck placed one batch each year as representative of product manufactured in that year in its stability monitoring program.[66] From the data collected, a manufacturer can calculate how much potency is lost over time, thereby assessing the stability of the vaccine. This data (stability data) is used in a stability model to estimate how much potency a vaccine is expected to lose over time and how much virus needs to be added to the vaccine to ensure that it will have the requisite potency at the end of the dating period.[67]

c. The Dating Period

38. Each vaccine product has an expiration date printed on its packaging.[68] The expiration date on the product's package marks the end of the dating period, the time period between when the product is released to the market and the expiration date. The end of the dating period is referred to as "expiry" or "end expiry."

39. The dating period is also referred to as the shelf-life of the product. According to a Merck submission to the FDA: "Shelf-life is based on several factors: (1) the stability of the vaccine or virus potency decay over time, (2) knowledge about the minimum vaccine potency required to ensure successful protection, and (3) the release potency at the time the vaccine is manufactured and its correlate, the targeted or 'fill potency.'"[69]

[65] Merck uses an ELISA assay to test the potency of the vaccine. The tests used to measure the potency of the vaccine are different than the testing of the children's responses to the vaccine described in this report.
[66] MRK-KRA00214038 ("One batch of each different presentation was placed on stability-monitoring program every year. This stability batch is a sample, which represents the many batches that are manufactured during the year.").
[67] MRK-KRA00031864 at '66.
[68] "Each biological product shall be plainly marked with … the expiration date of the biological product." 42 USC § 262 (a)(1)(B)(iii).
[69] MRK-KRA00135759 at '86.

40. The dating period shall be determined by appropriate stability testing to ensure the product meets the standards for potency.[70] If stability testing shows that the product cannot meet the standards for potency for the entire dating period set forth in the label, the manufacturer must take corrective action to ensure the applicable standards can be met. One corrective action available to the manufacturer is to shorten the dating period. This is often referred to as short-dating.[71]

41. The dating period for MMRII is 24 months when stored at 2-8°C.[72] The dating period for ProQuad is 18 months.[73]

3. How to Assess Vaccine-Induced Immune Responses

42. There are several types of studies used to assess vaccine-induced immune responses. Clinical efficacy studies are with disease endpoints that assess how well the vaccine protects against disease by comparing the incidence of disease between vaccinated and unvaccinated clinical subjects (participants in the study). Clinical immunogenicity studies use tests a laboratory test endpoint to assess a subject's immune response to the vaccine. Some

[70] "(a)To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in § 211.166; (b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in § 211.166; (c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products." 21 C.F.R. § 211.137.
[71] *See* Deposition of Keith Chirgwin, January 26, 2017, 170:18-171:1 (*So, the term 'short dating' would be before the vial leaves the factory, each vial of vaccine has a date, sort of the -- like on your milk carton, do not use beyond a certain date. You would pull that date back so that the vaccine -- the label, the packaging on the vial would say don't use beyond a date*.); Deposition of Philip Bennett, May 24, 2017, 178:7-10 ("*[Short dating is] lowering the 24-month shelf life of MMRII to some shorter period*."); s*ee also*, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), "Guidance For Industry: Expiration Dating And Stability Testing Of Solid Oral Dosage Form Drugs Containing Iron" (1997) at 2 ("If any of the testing, examinations, or investigations performed by the firm reveal that a product may not meet appropriate specifications prior to the expiration date assigned to the product, the firm will reevaluate the expiration dating period for the product. If, based on the reevaluation, the firm determines that a shortened expiration dating period is appropriate, it will use the shortened period for subsequent marketed lots of the same product.").
[72] MRK-KRA00587151.
[73] *See* Schedule 2 (describing ProQuad labels).

laboratory assays used in immunogenicity testing are considered a surrogate of efficacy,[74] and results of these assays can be used to assess protection from disease because the assay has shown to be connected to protection. If a clinical immunogenicity study uses an assay that has been shown to be a surrogate of efficacy, the results of that study may be used as a substitute for an efficacy trial only if that endpoint has been validated to show that the outcome of the laboratory test (classification as positive or negative for antibodies) predicts a clinical outcome (whether the subject is protected from disease). If a clinical immunogenicity assay has not been validated to be a reliable surrogate of efficacy, the results of the study cannot provide reliable information about protection from disease. Clinical efficacy studies and clinical immunogenicity studies may also assess the safety, tolerability, or reactogenicity[75] of the vaccine.

a. Efficacy Testing

43. In a vaccine clinical efficacy study, a group of subjects is vaccinated and compared to subjects who are not vaccinated. The groups are observed and efficacy is assessed based on the number of subjects in each group that become infected with the disease. The results of the clinical efficacy study are reported as an efficacy rate.[76]

44. For Merck's mumps vaccine, Dr. Hilleman and Merck conducted efficacy studies and clinical immunogenicity studies in the 1960's when children were not regularly vaccinated for mumps. These studies supported the licensure of Merck's Mumpsvax, the monovalent

[74] In this report, I use the term "surrogate of efficacy" to refer to an immune marker that can substitute for a clinical endpoint and, thus, can be used to reliably predict vaccine efficacy.
[75] For example, in the Usonis article discussed below, reactogenicity was defined as "local and general solicited symptoms and all unsolicited symptoms…pain on and within 30 min after vaccination.") GSK-MMR-0029832 at '32-33; *see also* Section III.B.
[76] The CDC defines the "efficacy rate" as "a measure used to describe how good a vaccine is at preventing disease." https://www.cdc.gov/vaccines/terms/glossary.html.

mumps vaccine.[77] Following the licensure of Mumpsvax, Merck licensed its other mumps-containing vaccines. MMR, Merck's first trivalent measles, mumps, rubella vaccine was licensed in 1971; MMRII, which used a different strain of the rubella virus than MMR, was licensed in 1978; and ProQuad, the quadrivalent measles, mumps, rubella, and varicella vaccine, was licensed in 2005. The labels for these vaccines referenced the efficacy studies Dr. Hilleman conducted using Mumpsvax. For example, the Clinical Pharmacology section of the MMRII label states: "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 afforded by the individual vaccine components."[78]

45. Efficacy studies cannot always be performed to assess the protection afforded by a vaccine. Once children began receiving mumps vaccine in this country, it became unethical to withhold the vaccine in order to study how well it works.

46. The clinical studies supporting the regulatory submissions discussed in this report were, therefore, not efficacy studies.[79] Merck instead evaluated subjects' response to mumps-containing vaccines by conducting clinical trials to measure immunogenicity.[80]

[77] *See also* MRK-KRA01955502 at '719 ("The Jeryl Lynn type B strain was chosen for the monovalent anti-mumps vaccine MUMPSVAX®, which was approved in the United States on December 28, 1967. This strain constitutes the mumps component of ... the Merck & Co. trivalent vaccines MMR® and MMR®II.") .
[78] *See* Schedule 1 (describing MMRII labels); *see also* Schedule 2 (describing ProQuad labels citing the same studies).
[79] *See e.g.* MRK-KRA00158320 at '38. ("No formal evaluation of the efficacy of ProQuad™ was conducted. A trial to evaluate the efficacy of ProQuad™ would no longer be considered ethical in view of the availability of effective vaccines to prevent measles, mumps, rubella, and varicella.").
[80] MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows: *Q. What's the definition of "immunogenicity"? A. It's the ability of an individual to mount an immune response. That amount -- that immune response could be cellular, it could be humoral. It has -- it's usually measured through typical assays.* Deposition of Barbara Kuter, December 14, 2016, 133:17-23.

b. Immunogenicity Testing

47. Immunogenicity is the ability of an individual to mount an immune response and is measured using tests performed in a laboratory.[81] A vaccine is considered immunogenic if it elicits an immune response. "Mumps immunogenicity" refers to the ability of an individual to mount an immune response to the mumps virus. In the clinical immunogenicity trials discussed in this report, subjects' serum (blood) was drawn and tested using serologic immunogenicity assays. Since the mumps vaccine is intended to stimulate the production of antibodies, the assays used to test mumps immunogenicity were used to detect the presence of antibodies in the blood.

48. When an efficacy study cannot be performed, immunogenicity testing may sometimes be performed as a substitute. A clinical immunogenicity study based on a laboratory test that is a reliable surrogate of efficacy can be performed to assess protection afforded by the vaccine. In order for a clinical immunogenicity study to use a laboratory test to assess vaccine efficacy, the assay used in the study must demonstrate a reliable connection to protection from disease.

(1) Assays Used in Immunogenicity Testing

49. There are different types of assays used to test immunogenicity; each measures the immune response in a different way. This report discusses two types of assays used to measure immunogenicity, plaque-reduction neutralization assays ("PRN") and enzyme-linked immunosorbent assays ("ELISA").

[81] Deposition of Barbara Kuter, December 14, 2016, 133:17-23; *see* footnote 59.

(a) Serostatus Cutoff

50. Each immunogenicity assay has a serostatus cutoff, a numerical value by which one determines how a sample is classified as negative (the absence of antibodies) or positive (the presence of antibodies).[82] The serostatus cutoff, or cutoff, is defined for each assay.[83]

(b) Seroconversion

51. Seroconversion is a measure of a subject's immune response before and after vaccination.[84] A seroconversion rate ("SCR") is a calculation of how many subjects developed detectable antibodies after vaccination.[85]

52. An assumption of immunogenicity testing is that the pre-vaccination serum samples of most subjects will be negative because they have not yet received the vaccine or been exposed to the virus. In some instances, a pre-vaccination sample may nonetheless test positive. The presence of detectable antibodies in a pre-vaccination sample is sometimes accurate[86] but in other instances it is a misclassification, a false-positive result in the testing.[87]

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[82] MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows: *Q. Okay. Do you know what a serostatus cutoff is? A. Yes. Q. What is it? A. It's a numerical value by which you determine whether someone is seropositive or seronegative.* Deposition of Barbara Kuter, December 14, 2016, 154:17 -154:23.

[83] For example, as discussed below, Merck assigned serostatus cutoffs for both the AIGENT assay and WT ELISA assay it used in its mumps immunogenicity testing.

[84] MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows*: Q. Is there a difference between seroconversion and seroconversion rates? A. Oftentimes they're used in the same fashion. Q. Do you have -- do you see a difference between the two? A. <u>You seroconvert, meaning that you have detectable antibody</u>.* Deposition of Barbara Kuter, December 14, 2016, 140:7-14 (emphasis added). *See also* https://www.cdc.gov/vaccines/terms/glossary.html (Seroconversion is defined as "[d]evelopment of antibodies in the blood of an individual who previously did not have detectable antibodies.").

[85] MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows*: Q. Is there a difference between seroconversion and seroconversion rates? ... A. Seroconversion rate is simply a calculation.* Deposition of Barbara Kuter, December 14, 2016, 140:7-17.

[86] Infants may have maternal antibodies (antibodies passed from the mother to the baby during pregnancy), or they may have antibodies to similar viruses to which they themselves may have been exposed.

[87] A pre-vaccination sample that is classified as seropositive is sometimes referred to in Merck's documents as a "pre-positive." A pre-vaccination sample that is classified as seronegative is sometimes referred to in Merck's documents as a "pre-negative."

53. The results of immunogenicity testing in a clinical study can be reported as a seroconversion rate.

(c) Plaque-Reduction Neutralization Assays

54. In the context of mumps immunogenicity testing, a Plaque-Reduction Neutralization Assay (PRN) measures the concentration of antibodies that are able to neutralize a virus[88] and prevent the virus from replicating. The PRN assay measures antibody activity (neutralization) and does not just measure the presence of antibodies, and is therefore considered a functional assay.[89]

55. Generally,[90] in a mumps plaque-reduction neutralization assay, cells are prepared in a laboratory and placed into a plastic cell plate with multiple wells along with diluted serum. Once the serum and cells are plated, virus is added. This virus is referred to as the "indicator virus."[91] After the plates have been incubated, the layer of cells is inspected for holes, or "plaques," caused by the virus infecting the cells, indicating that antibodies did not neutralize the virus. If antibodies successfully neutralize the virus, the layer of cells is expected to have fewer plaques, hence the name of the assay – plaque reduction neutralization assay.[92]

[88] MRK-KRA00028592 at '93 (Merck Vaccine Clinical Assay Description Approval Form dated Sept. 14, 1999 stated: the Mumps Plaque Reduction Neutralization Assay is a test to "detect neutralization to Mumps virus before and after vaccination with Mumps virus containing vaccine(s).").

[89] MRK-KRA00135723 at '30-31 (Merck submission to FDA stated: "PRN assay … is a functional assay that measures the ability of the vaccine-induced immune response to inhibit viral replication in vitro.").

[90] MRK-KRA00064832 (Standard Operating Procedure number 874.3422 (rev. 00) for a "straight-forward" plaque reduction neutralization assay Merck used setting out these steps). *See also* MRK-KRA00051640 (email from Dr. Krah describing the assay as "straight-forward").

[91] Different strains of virus can be used as an indicator virus in a PRN. A PRN may use a wild-type isolate that has not been attenuated, or it may use an attenuated vaccine strain. A wild-type virus strain may be used to measure the production of antibodies capable of neutralizing a virus that is naturally occurring in the world, and has not been weakened by attenuation. *See* Section III.B.1 above, discussing the indicator virus used in the mumps immunogenicity testing discussed in this report. *See also* Section VII.A.4 below discussing CBER requirements for the indicator virus used in Protocol 007 clinical testing.

[92] Like any assay, a plaque-reduction neutralization assay is run according to a Standard Operating Procedure. Changes to an SOP, including the preparation of the materials used to run an assay, may impact the seroconversion

56. The serostatus cutoff of a plaque reduction neutralization assay is defined in the standard operating procedure.[93] As discussed above, the seroconversion rate reported by the plaque reduction neutralization assay is a calculation of how many subjects seroconverted.

(d) ELISA Assays

57. An enzyme-linked immunosorbent assay, or ELISA, is commonly used to test immunogenicity.[94] ELISA assays are not considered functional assays because they measure the concentration of antibodies that bind to the indicator virus and not what the antibody does (i.e. neutralization).[95] In this report, "ELISA" or "ELISA assay" refers to enzyme-linked immunosorbent assays in general.

58. "WT ELISA" or "Wild-Type ELISA" refers to the ELISA assay that Merck used to test mumps immunogenicity in Protocol 007 and other clinical studies discussed in this

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rate that is reported. Such changes may include the type of cells used, the indicator virus, the addition of complement, the incubation time, and any additional steps taken in preparing plates. *See* Section VII.A.3-5 below discussing changes to the "straight-forward" plaque reduction neutralization assay for the AIGENT assay used in Protocol 007, including the use of vero cells, JL-135 (the low passage Jeryl Lynn virus) as the indicator virus, and the addition of anti-human IgG.

[93] In the plaque reduction neutralization assay used in the Protocol 007 study, the AIGENT assay, the serostatus cutoff was 1:32. A sample with a titer greater than 32 would be classified as positive. A sample with a titer of 32 or less (a sample that did not demonstrate a 50% reduction in plaques at any dilution) would be classified as negative. The samples were assigned a titer based on the highest dilution (ranging from 1:32 – 1:4096) in which a 50% reduction in plaques was observed compared to the control that was run in the assay. For example, a sample would be assigned a titer of 64 if the highest dilution at which a 50% reduction was observed was1:64. Moreover, since 64 is greater than 32, this sample would be classified as positive. Seroconversion was defined as a change from seronegative to seropositive with a four-fold rise in titers following vaccination. To qualify to be counted as part of the seroconversion rate, the pre-vaccination sample for a subject needed to be ≤ 32 (negative). A titer of > 32 in a pre-vaccination sample was a pre-positive. Moreover, to qualify as a seroconversion there needed to be a (1) a pre-vaccination titer of < 32 and (2) a four-fold (four times) increase in the post-vaccination titer. For example, a subject whose titers went from < 32 to > 128 would be reported as a seroconversion. *See* MRK-KRA00002189 (SOP 874.3489 Rev. 00), MRK-KRA01889950 (SOP 874.3489 Rev 02); *see also* MRK-KRA00135759 at '829, '838 (Protocol 007 Clinical Study Report).

[94] MRK-KRA00135759 at '5813 ("Typically, the mumps ELISA is used to detect immunoglobulin gamma antibody (IgG) to mumps virus before and after vaccination.").

[95] MRK-KRA00781533 ("ELISA is not a functional assay but an antibody assay.").

report.[96] Seroconversion in the WT ELISA was defined as a change from seronegative to seropositive following vaccination, and the serostatus cutoff was 10 Ab units (a serum sample with a titer <10 was seronegative, and a sample with a titer of >10 was seropositive).[97]

c. Immunogenicity and Protection from Disease

59. As stated above, immunogenicity testing can be used to assess protection from disease only if the assay is a reliable surrogate of efficacy. The assay must be validated as a measure of an immune response shown to have a connection to protection. When an immunogenicity assay is developed, it is validated and assessed to determine whether it will yield accurate and consistent results.[98] If an assay is to be used to demonstrate that a subject is protected from disease, the assay must also be shown to be a reliable surrogate of efficacy and

[96] Merck's WT ELISA is an ELISA assay. Merck added the "WT" designation to distinguish this assay, using attenuated (<12 passage) JL-135 virus as the indicator virus, from a prior ELISA, using the attenuated JerylLynn™ vaccine strain (17 passage) as the indicator virus. That assay is sometimes referred to as the "legacy" ELISA. An ELISA assay is used to measure antibodies that bind to a virus. The virus used in the assay is called the "indicator virus," and the ELISA assay is used to determine the presence antibodies that bind to that virus. See also MRK-KRA00140056 at '3016-3017 ("...an early passage of the Jeryl Lynn™ mumps virus (<12 passages) which is less attenuated than the Jeryl Lynn™ mumps virus used in the Merck mumps virus-containing vaccines, and is considered to be a wild-type (WT)-like strain..."); *See also* MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows: *Q. So both PRN and the ELISA measure concentrations of antibodies? A. Yes.* Deposition of Barbara Kuter, December 14, 2016, 189:9-11.

[97] *See* Section IX.A.6 below discussing the clinical study reports for the studies using the WT ELISA with the 10 Ab cutoff.

[98] The validation of an immunogenicity assay may include an assessment of characteristics such as sensitivity and specificity. *See* MRK-KRA00017036 at '38, '43 (AIGENT validation submitted with Serial 63). *See also* Deposition of Manal A. Morsy, August 5, 2016, 204:12-17 (*Q. When you say, "sensitivity and specificity" what's the difference? A. Specificity means that it's specific to whatever it is that you're measuring, and it is not picking a lot of garbage and background.*) (emphasis added); *Id.* at 206:1-6 (Q. So is it if a -- when you're looking at specificity, specific means that it actually will identify what you're -- that the test is looking to identify. Correct? A. Yes.) (emphasis added); *Id.* at 203:15 -20:4 (*Q. What is assay sensitivity? A. ... an assay would have specificity and sensitivity. Sensitivity means that it can – it's sensitive to whatever measurement that you're measuring, and you always have a control to see whether you have a real sensitivity or not. So some assays are worth nothing because they're not sensitive enough and that doesn't mean your product is not good. It just means that the assay is worthless...*).

validated to demonstrate that the immune response measured by the assay is connected to protection.[99]

60. While conducting the clinical efficacy studies used to support the licensure of Mumpsvax, Dr. Hilleman also conducted clinical immunogenicity testing using a neutralization assay. Dr. Hilleman reported that the seroconversion rate of subjects who developed mumps neutralizing antibodies (measured by the neutralization assay he used) "correlated" with the results of the efficacy studies.[100] A correlation meant that the children who mounted an immune response measured in the neutralization assay Dr. Hilleman used were also the children who were not infected by the virus, as observed in the clinical efficacy study. The correlation between the clinical efficacy study results and the neutralization assay indicated that the immune response measured by the neutralization assay was connected to protection from disease. Thereafter, Merck asserted[101] that the development of mumps neutralizing antibodies was a correlate of protection from disease,[102] and that seroconversion rate measured using mumps neutralization assay paralleled protection from disease.[103]

[99] MRK-KRA00561452.
[100] *See* Schedule 7 (summarizing early studies) and Schedule 1 (discussing Clinical Pharmacology section of MMRII label stating: "Efficacy of … mumps … vaccine was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components. These studies also established that seroconversion in response to vaccination against … mumps … paralleled protection from these diseases." (internal citations omitted); *see also* MRK-KRA00561452 (internal Merck memo, dated October 19, 2001, discussing criteria for Merck to use ELISA assays, including the requirement that the ELISA measure protection against disease).
[101] *Id*.
[102] "The Food and Drug Administration (FDA) defines a correlate of protection as 'A laboratory parameter that has been shown from adequate and well-controlled studies to be associated with protection from clinical disease.'" MRK-KRA0133955 at slide '61 (powerpoint presentation titled "PRINCIPLES OF VACCINOLOGY" by MMD's Director, Bio/Sterile Validation, Vaccine Technology & Engineering Mike Dekleva, June 2003).
[103] MRK-KRA00561452 (internal citations omitted); *see also* Schedule 7 (summarizing efficacy studies) and Schedule 1 (describing MMRII label, including the Clinical Pharmacology section stating: "Efficacy of … mumps … vaccine was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components. These studies also established that seroconversion in response to vaccination against … mumps … paralleled protection from these diseases.").

61. Mumps immunogenicity, measured by a neutralization assay, was used to support the licensure of Merck's other mumps-containing vaccines, including MMRII.[104] The Clinical Pharmacology section of the MMRII label states that "clinical studies demonstrated that MMRII is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced ... mumps neutralizing antibodies in 96%... of susceptible persons."[105]

62. As discussed below, Merck sought FDA approval to lower the mumps end-expiry specification on the MMRII label in 1998, and proposed to support this change with data from clinical studies using lower potency monovalent mumps vaccine.[106] FDA rejected Merck's argument that these studies were sufficient to support the label change, due to the small number of clinical subjects.[107] FDA required Merck to conduct a new clinical immunogenicity trial to demonstrate children would still be protected against disease if they received a lower potency mumps dose.[108] At the time Merck conducted the mumps immunogenicity testing described in this report, plaque-reduction neutralization assays were considered the best means of assessing protection against mumps. This is because a PRN was considered a functional assay, and functional assays had been "judged to be a good surrogate marker of protection."[109] Since the

[104] *Id*.
[105] *See* Schedule 1 (describing MMRII label, including the Clinical Pharmacology section).
[106] *See* Section VI.B below.
[107] MRK-KRA00198876 at '77 ("the Neut[ralization] assay data generated to support protective efficacy … were questioned as to weather [sic] they are still valid in predicting the current protective efficacy of the MMRII vaccine against present wild type strains.")
[108] MRK-KRA01715116 at '28 ("CBER is requesting that a clinical protocol be submitted to them by the end of January which will address expiry efficacy."); *see also* MRK-KRA00615152 at '56 (internal Merck document summarizing negotiation with FDA regarding the mumps immunogenicity testing to support lowering the mumps potency claim).
[109] *See also* MRK-KRA00017826 (email from MRL Principal Investigator, Dr. David Krah, to MRL's Clinical & Regulatory Affairs, Regional Office staff, Gabriele Poerschke, dated November 17, 2000, stated: "By a 'functional assay' we mean an assay that measures a biological activity (such as inactivation of virus infectivity). Immunogenicity can be measured by a variety of means, but typically involves a binding assay (such as an ELISA or hemagglutination inhibition assay) or a biological (infectivity reduction). The immunogenicity assessment is a measure of whether or not the vaccinee responded to the vaccination in some detectable way. This response then

ELISA assay was not a functional assay and "the immunogenicity assessment [wa]s a measure of whether or not the vaccinee responded to the vaccination in some detectable way[,] [t]his [immune] response then need[ed] to be correlated with protection from diseases"[110] in order to use ELISA as a measure of protection.[111] This report discusses the assays Merck used in clinical immunogenicity studies[112] and Merck's assertions with regard to its immunogenicity assays as measures of protection against disease.[113]

IV. BACKGROUND AND CHRONOLOGY OF POTENCY AND EFFICACY ISSUES INVOLVING MERCK'S MUMPS VACCINES

63. Vaccines are vitally important to protect public health. Manufacturers who market these vaccines must insure they are both safe and effective. The Food and Drug Administration ("FDA") also reviews vaccines to make sure they are both safe and effective.[114] The Centers for

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needs to be correlated with protection from diseases. Historically, the functional assays have been judged to be a good surrogate marker of protection.") (emphasis added).

[110] *Id*.

[111] MRK-KRA01927351 at '353 ("...the PRN assay is an immunological endpoint for protection against wild type disease"); MRK-KRA00020425 (A Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin dated September 16, 1999 stated: "A requirement was set forth by CBER to use a functional neutralization assay for the mumps, measles and rubella due to .. [t]he efficacy statement in M-M-R®II label are based on old, limited data and an assay that is no longer used, … [l]ack of data that correlates currently used ELISA assays and efficacy for M-M-R®II [and] .. [e]mergence of out breaks in highly vaccinated populations."); *see also* Section VIII.M below discussing FDA's requirement for a correlation to protection using an ELISA assay.

[112] *See* MRK-KRA00064832 (SOP [Standard Operating Procedure] 874.3422, Merck's "standard" neutralization assay), MRK-KRA00002189 (SOP 874.3489 Rev. 00, Merck's AIGENT assay), MRK-KRA01889965 (SOP 874.3489 Rev. 01, Merck's AIGENT Assay, revised September 7, 2001), MRK-KRA01889950 (SOP 874.3489 Rev. 02, Merck's AIGENT Assay, revised May 3, 2002), MRK-KRA01889623 at '756 (SOP 910.0096 Merck's WT ELISA assay); MRK-KRA00561875 (February 23, 2001 memo with the subject "Bridging Study of the Mumps Legacy ELISA (SOP No. 910.0007) and Mumps 'Wild Type' IgG ELISA (SOP No. 910.0096").

[113] Merck asserted that both neutralization assays and its WT ELISA assay were shown to have a strong correlation with protection from disease. *See also* MRK-KRA00158320 at '65 (The BLA for ProQuad stated: "The presence of detectable antibody by... the neutralization assay of EIA [ELISA] for mumps ... has generally been shown to have a strong correlation with protection from disease.")(emphasis added); *Id*. at '50 ("...Merck & Co., Inc. has assessed the correlation between neutralization antibody (as measured in a plaque reduction neutralization [PRN] assay) and a wild-type enzyme-linked immunosorbent assay (ELISA)... The overall agreement rate was 93.6% (480/513). These data support the use of the results of a wild-type ELISA as a correlate for protection.") (emphasis added).

[114] *See* Section V below discussing FDA's regulation of vaccines.

Disease Control ("CDC") purchases vaccines for the millions of Americans unable to receive vaccination through private insurance.[115] Recommendations about which vaccinations children in the United States should receive are made by the CDC's Advisory Committee on Immunization Practices ("ACIP").[116] There are currently fifteen ACIP-recommended vaccines, including mumps, on the childhood schedule.[117] ACIP recommends that children receive two doses of mumps vaccine, the first at approximately 18 months of age, and a second at 4-5 years.[118] Proof of vaccination is required to attend school in most states.[119]

64. Today, more than fifty years after it obtained a license to sell a monovalent mumps vaccine, Merck remains the only manufacturer licensed to sell a mumps-containing vaccine in the United States.[120]

65. In 1986, Congress passed the National Childhood Vaccine Injury Act ("NCVIA").[121] The NCVIA established a "National Vaccine Injury Compensation Program."[122] The NCVIA also called for a "review of warnings, use instructions, and precautionary information" for vaccines included in the National Vaccine Injury Compensation Program, including MMRII, (the "Section 314 Review").[123] The Section 314 Review was to ensure that vaccines already on the market at the time the NCVIA became law were safe and effective and

[115] *See* Schedule 16 (CDC purchasing described).
[116] *See* Schedule 8 (ACIP recommended vaccines).
[117] *Id.*
[118] *Id.*
[119] *See* Center for Disease Control and Prevention, School Vaccination Requirements, "Vaccination requirements for all grantees, for MMR-Measles, Mumps, Rubella and Kindergarten", https://www2a.cdc.gov/nip/schoolsurv/schImmRqmtReport.asp?s=grantee&d=4&w=WHERE%20a.gradeID=2%20AND%20a.vaccineID=8 (page last updated: July 21,2011) (44 states, including the District of Columbia, Puerto Rico and US Virgin Island, require 2 mumps doses to attend kindergarten).
[120] A timeline of the events spanning the more than half-century described in this report are summarized on a Timeline attached as Appendix D.
[121] 42 USC § 300aa-1. *See also* Schedule 31 (describing Legislative History of the National Childhood Vaccine Injury Compensation Act).
[122] 42 USC § 300aa-10. *See also* Schedule 29 (describing the National Vaccine Injury Compensation Program).
[123] 42 USC § 300aa-1, note.

complied with their label specifications.[124] Label specifications include potency claims and the dating period, sometimes called the "shelf-life."[125]

66. Since Merck's MMRII was on the market at the time the NCVIA was enacted, it was subject to the Section 314 Review.[126] In 1996, FDA identified an issue with the mumps potency claim in Merck's MMRII label[127] as part of the Section 314 Review.[128]

67. The MMRII label in the United States[129] in 1996 stated, in relevant part:

[124] The "National Childhood Vaccine Injury Act of 1986 … contains several other provisions not pertaining to the issue of compensation for vaccine-injured persons, but very much linked to the related questions of vaccine development, safety, and effectiveness." H.R. Rep. No 908, 99th Cong. 2nd Sess. (1986), *reprinted in* 1986 U.S.C.C.A.N. 6344, 1986 WL 31971, *3. *See also* Schedule 31 (Legislative History of the National Childhood Vaccine Injury Compensation Act).

[125] Potency is defined as the "ability of the product ... to effect a given result." 21 CFR§ 600.3(s). The dating period is defined as: "the period beyond which the product cannot be expected beyond a reasonable doubt to yield the specific results." 21 CFR § 600.3 (l). The dating period is sometimes called the shelf-life. According to a Merck submission to the FDA, shelf-life "is based on several factors: (1) the stability of the vaccine or virus potency decay over time, (2) knowledge about the minimum vaccine potency required to ensure successful protection, and (3) the release potency at the time the vaccine is manufactured and its correlate, the targeted or 'fill potency.'" MRK-KRA00001270 at '297 (emphasis added). The end of the dating period is referred to as the expiry, or end-expiry. 42 USC § 262 (a)(1)(B)(iii)) ("Each biological product shall be plainly marked with … the expiration date of the biological product."). The shelf life of MMRII is 24-months. MRK-KRA00587151. The shelf-life of ProQuad is 18 months. *See also* Sections V.B.4 and VI.A and B below and Schedules 1 and 2 (describing the labels of MMRII and ProQuad).

[126] MRK-KRA00095142 (describing a teleconference between Merck and FDA regarding the Section 314 Review).

[127] *Id.*

[128] *Id.*; MRK-KRA01972735 at '37 (describing an additional teleconference between Merck and FDA regarding the Section 314 Review).

[129] MRK-KRA00667054 at '114. I understand that Merck also sells MMRII in other countries. The MMRII label in those countries may not be the same as the label approved in the United States. The opinions in this report are limited to the product released and sold in the United States.

M-M-R®II PACKAGE CIRCULAR

M-M-R® II
(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

DESCRIPTION

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for immunization against measles (rubeola), mumps and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) ATTENUVAX® (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; (2) MUMPSVAX® (Mumps Virus Vaccine Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) MERUVAX® II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture.[1,2] The vaccine viruses are the same as those used in the manufacture of ATTENUVAX (Measles Virus Vaccine Live), MUMPSVAX (Mumps Virus Vaccine Live) and MERUVAX II (Rubella Virus Vaccine Live). The three viruses are mixed before being lyophilized. The product contains no preservative.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 mL and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the U.S. Reference Measles Virus; 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus; and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus. Each dose contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolized gelatin are added as stabilizers.

CLINICAL PHARMACOLOGY

Clinical studies of 279 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95 percent, mumps neutralizing antibodies in 96 percent, and rubella HI antibodies in 99 percent of susceptible persons.

The RA 27/3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine[3-9] and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.[10,11] The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.[11-13] The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,[11,13-15] and provide greater confidence for lasting immunity.

Vaccine induced antibody levels following administration of M-M-R II have been shown to persist up to 11 years without substantial decline.[16,43] Continued surveillance will be necessary to determine further duration of antibody persistence.

68. There were two outcomes from the FDA's Section 314 Review of Merck's MMRII label. First, the claim in the "Description" section that "each dose contains not less than … 20,000 [4.3 log] … of mumps" was found to be an "end expiry" claim.[130] Second, Merck needed to assure that each dose of the vaccine had 20,000 [4.3 log10] TCID50[131] for the entire

[130] MRK-KRA00095142; MRK-KRA01972735; MRK-KRA01972448 at '51; MRK-KRA00756256 at '57; MRK-KRA00666494 at '525-26.
[131] *See* Section III.B.2 above describing a tissue culture infectious dose.

24 month shelf life to comply with the end expiry potency claim set forth in the Description in the MMRII label.[132]

69. In 1998, Merck proposed to lower the mumps end expiry claim on the MMRII label to 5,000 [3.7log10] TCID50[133] to ensure Merck accurately reflected the mumps end expiry potency in MMRII: how potent a dose would be at the end of the shelf life. The shelf-life for MMRII was 24 months. Before Merck could reduce the mumps end expiry claim on the MMRII label, FDA required Merck to submit clinical data demonstrating that reducing the potency of the mumps component in MMRII would not reduce MMRII's clinical effectiveness.[134] The clinical effectiveness of MMRII is described in the "Clinical Pharmacology" section of the MMRII label, as set forth above.

70. Until Merck conducted the clinical trial and had approval to lower the mumps end expiry potency claim on the MMRII label, Merck proposed to increase or "overfill"[135] the amount of mumps virus in each dose of MMRII at the time of manufacture "to provide a high level of assurance that the minimum titers are maintained through expiry."[136] In 1999, with FDA approval, Merck began to overfill[137] the mumps component of MMRII.[138] Merck was permitted

[132] *See* Section VI below describing the Section 314 Review.
[133] MRK-KRA00666494 at '525-26, '557; MRK-KRA00756233 at '35-36; *see also* MRK-KRA00095320.
[134] MRK-KRA00666494 at '57; MRK-KRA00756256 at '57.
[135] MRK-KRA00284623. To support the proposal Merck conducted an analysis of the "stability" of MMRII to determine how much potency MMRII lost over the 24 month shelf life. *See,* MRK-KRA01715116 at '28; MRK-KRA00587151. Stability and potency are inter-connected. The greater the product's stability the less potency loss will occur over time. *See,* 21 CFR § 600.3 (s) (Potency is defined as the "ability of the product ... to effect a given result); MRK-KRA00001270 at '297 ("Shelf-life' is based on several factors: (1) the stability of the vaccine or virus potency decay over time, (2) knowledge about the minimum vaccine potency required to ensure successful protection, and (3) the release potency at the time the vaccine is manufactured and its correlate, the targeted or 'fill potency.").
[136] MRK-KRA00756233 at '35 (emphasis added); *see also*, MRK-KRA00756381 at '85 (minutes of December 1998 Merck/CBER meeting discussing Merck proposal to overfill mumps in MMRII).
[137] The mumps process change increased the target amount of mumps virus added in manufacturing from 80,000 [4.9 log10] TCID50/dose to 160,000 [5.2 log10] TCID50/dose. It set the minimum release specification for mumps

to "formulate all mumps-containing vaccine lots[139] manufactured (filled) on or after September 13, 1999" with the overfilled mumps amount.[140] The first overfilled lots of MMRII were approved for release to the U.S. market on February 11, 2000.[141]

71. As of 1998 two related issues emerged from the FDA's Section 314 Review of Merck's MMRII label. First, Merck needed to assure compliance with the mumps potency claim in the MMRII label "Description" section that "each dose contains not less than … 20,000 [4.3 log] … of mumps"[142] throughout the 24 month shelf life. Second, Merck needed clinical data demonstrating that if a child received a MMRII dose with a potency of less than 20,000/4.3 log, it would still be clinically effective.

72. Merck initiated a clinical trial titled "A Study of An Approved Vaccine at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age"[143] to obtain clinical data to support an application to lower the mumps end expiry potency claim for MMRII. As described in more detail below, Merck enrolled approximately 1800 children to be subjects in the study.[144] The children were divided into three groups, each group receiving a different potency dose.[145] The

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as 100,000 [5.0 log10] TCID50/dose. MRK-KRA01899087 at '212. *See also* MRK-KRA01897091 and MRK-KRA01625225.

[138] MRK-KRA00018614.

[139] Vaccines are manufactured in bulk called lots. A single lot could represent tens of thousands or hundreds of thousands of doses for administration. There is no standard measure of how many doses are contained in a lot.

[140] MRK-KRA00018614.

[141] MRK-KRA01897091.

[142] MRK-KRA00756233 at '35 ("Until this clinical study has been completed, the end-expiry titers for product in the US will be … 4.3 log10 [20,000] TCID50/dose for mumps.").

[143] This Study is also referred to herein as Protocol 007. *See* MRK-KRA01646761 at '93; *see also* https://clinicaltrials.gov/ct2/show/NCT00092391?cond=Mumps&draw=3&rank=11

[144] MRK-KRA01646761 at '93 (Clinical Protocol 007-00); MRK-KRA0136668 at '16 (Clinical Protocol 007-01); '53 (Clinical Protocol 007-02).

[145] *Id.* The three subgroups of approximately 600 children each received a dose of 4.8, 4.0 or 3.7. The 4.8 dose was the marketed product. As described above, since Merck proposed to lower the potency to 3.7 it included two groups that would receive doses with potency of less than the 4.3 claim on the label.

children each had three blood samples taken: (1) prior to vaccination,[146] (2) 46 days post-vaccination,[147] and (3) one year post-vaccination.[148] The children's blood samples[149] were used to conduct immunogenicity testing.[150] As discussed below, FDA required the mumps immunogenicity testing to reflect protection against disease as a result of getting the vaccine.[151] How the study was designed would be relevant to meeting FDA's requirement to conduct immunogenicity testing linked to protection against disease.

73. The "gold standard" for mumps immunogenicity testing is a plaque reduction neutralization assay ("PRN" or neutralization assay).[152] Another test is an enzyme-linked immunosorbent assay ("ELISA").[153] As discussed below, FDA required Merck to use a neutralization assay in Protocol 007 to evaluate the children's immune response 46 days after receiving the vaccine.[154] Moreover, since the "[v]irus antigens used in serological assays enable the assessment of immunogenicity which is reflective of efficacy against natural infection" FDA also required the use of a wild type virus in Merck's immunogenicity testing.[155]

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[146] This is referred to in Merck documents as the pre-vaccination sample.
[147] This is referred to in Merck documents as the post-vaccination sample.
[148] This is referred to in Merck documents as the one-year persistence sample. As described below, because the FDA was concerned about the duration of protection a child received after vaccination, it required Merck to evaluate the "one year persistence" of antibodies after vaccination. *See*, MRK-KRA01646761 at '87.
[149] Testing involving blood samples is also referred to as serologic testing.
[150] *See* Section III.B.3 above discussing mumps immunogenicity testing.
[151] MRK-KRA0001467 at '68; MRK-KRA00198876 at '78-79; MRK-KRA00526241 at '43; MRK-KRA00001255 at '55-56; MRK-KRA01927351 at '52-53; MRK-KRA00561452 at '52-53; MRK-KRA00846451 at '51-52; GSK-MMR-IND-0002235 at 36; GSK-MMR-IND0047687 at '88; GSK-MMR0005742 at '58; Deposition of Keith Chirgwin, January 26, 2017, 78:17 – 79:22.
[152] MRK-KRA01521665 at '67; MRK-KRA01731773 at '79.; MRK-KRA00017826; MRK-KRA00818776 at '78 (Plaque Reduction Neutralization (PRN) assay considered by FDA to be a "biologically relevant reference standard"); MRK-KRA00561452 at '53.
[153] MRK-KRA01646761 at '82 (Merck's description of ELISA assay); *see also*, MRKKRA00135759 at '5820-5821.
[154] MRK-KRA00666494 at '558; *see also* Sections VII.A. and C below describing FDA requirements for the Protocol 007 testing.
[155] MRK-KRA00001467 at '68; *see also* MRK-KRA00666494 at '558. *See also* Section III (describing the differences in mumps viruses and how virus is used in immunogenicity testing).

74. Merck and FDA discussed the use of ELISA assays for testing in Protocol 007 and other clinical trials Merck would be conducting, including to support an application for a license to sell ProQuad[156] and a separate application to support the use of recombinant serum albumin ("rHA") instead of pooled human derived serum albumin ("HSA") as a viral growth media in the bulk manufacturing process and as a component of the bulk diluents in the formation of the final MMRII product.[157]

75. Before it would permit ELISA testing in Merck's mumps immunogenicity testing[158] FDA required (1) Merck's WT ELISA assay ("WT ELISA"[159]) be linked to protection against disease,[160] and (2) the "cutoff" used in Merck's WT ELISA, the definition of whether a sample was negative or positive, be "justified."[161] (the "ELISA issue"). In order to justify the cutoff of the WT ELISA, Merck could compare its proposed WT ELISA assay to a neutralization test,[162] such as the one Merck would use in Protocol 007[163] because FDA considered a neutralization assay a good "correlate for protection" against mumps disease.[164]

[156] BB-IND 7068 related to the ProQuad application.
[157] BB-IND 10076 related to the MMRII change from HSA to rHA. *See* Section IX.A.5, B.2, C.1 below describing the change to rHA.
[158] *See* Section III above discussing relevant terminology.
[159] Merck's WT ELISA is an ELISA assay. Merck added the "WT" designation to distinguish this assay, using JL-135 virus as the indicator virus, from a prior ELISA, using the vaccine strain as the indicator virus. That assay is sometimes referred to as the "legacy" ELISA.
[160] *See* MRK-KRA0001467 at '68-69; MRK-KRA00198876 at '78-79; MRK-KRA00001255 at '55-56; MRK-KRA01927351 at '52-53; MRK-KRA00561452 at '52-53; MRK-KRA00846451 at '51-52. The same requirements were communicated to Merck's competitor, SmithKlineBeecham. *See* GSK-MMR-IND-0002235 at '36 ; GSK-MMR-IND-0047687 at '88; GSK-MMR0005742 at '58; GSK-MMR-IND-0021471; MRK-KRA00885592; Deposition of Keith Chirgwin, January 26, 2017, 78:5-22; *see also* MRK-KRA00088592 at '93.
[161] MRK-KRA00761482 at '83; MRK-KRA00846460; MRK-KRA00155481; MRK-KRA00000315 at '31; Deposition of Keith Chirgwin, January 26, 2017, 78:17-79:22. *See also* Section VIII.M below discussing Merck's analysis to justify the cutoff in its ELISA test.
[162] MRK-KRA0062710; MRK-KRA00561452; MRK-KRA01927351 at '53; Deposition of Keith Chirgwin, January 26, 2017, 316:16-318:10; Deposition of Joseph Antonello, August 3, 2017, 214:3-214:22.
[163] MRK-KRA00761482 at '83; MRK-KRA00846460; MRK-KRA00155481; MRK-KRA00000315 at '31; Deposition of Keith Chirgwin, January 26, 2017, 78:5-22.
[164] MRK-KRA01620035 at '50; MRK-KRA00781533.

76. In comparing the WT ELISA and neutralization tests Merck would need to analyze how each assay "classified" each child's sample to confirm the neutralization assay and the WT ELISA assay reported the child's results in the same way.[165] For example, a negative pre-vaccination sample by neutralization should also be negative by WT ELISA. "Discordance" would occur if the results did not match. For example, if a pre-vaccination sample was positive in one assay and negative in the other, or a post-vaccination sample was positive in one assay and negative in the other. The cutoff is relevant to the analysis of whether the two assays report similar results because the cutoff impacted the discordance between the AIGENT and WT ELISA in addition to the seroconversion rate measured by the WT ELISA.[166] When the WT ELISA cutoff was set higher, Merck found that there was less discordance, or disagreement,[167] but a higher ELISA cutoff would have lowered the seroconversion rate reported by the WT ELISA assay.

77. In 1999, Merck developed what Merck Research Laboratories ("MRL") Principal Investigator, Dr. David Krah called a "straight-forward" neutralization assay that utilized a wild-type indicator virus (the "standard" neutralization assay)[168] to use in a study to compare MMRII to Priorix, the measles, mumps and rubella vaccine manufactured by Merck's competitor, SmithKline Beecham, which is not sold in the United States.[169] Dr. David Krah developed the standard neutralization assay and was also tasked with developing the assay Merck would use in

[165] MRK-KRA00561452 at '53-54; MRK-KRA00024453 at '53-54; MRK-KRA00126468 at '76; MRK-KRA00544296; MRK-KRA00781533.
[166] MRK-KRA00544296; Deposition of Joseph Antonello, August 3, 2017, 201:17-204:9.
[167] Deposition of Joseph Antonello, August 3, 2017, 250:25-252:1; *see also* MRK-KRA00544510 at '11.
[168] MRK-KRA00051640 (email describing the assay design for Protocol 007 compared to the "straight-forward" assay used in the comparison of MMRII and Priorix).
[169] GlaxoSmithKline is the successor entity that currently licenses Priorix. It is not licensed in the United States, as discussed below. *See also* Schedule 15 describing other mumps vaccines.

Protocol 007.[170] An internal Merck document stated that the assay to be used in the mumps end expiry study, Protocol 007, needed to be "highly specific for [a] W[ild]T[ype] neutralizing response."[171] Specificity in mumps testing means measuring mumps-specific neutralizing antibodies.[172] When the results of preliminary experiments with the standard neutralization assay using the wild-type indicator virus showed that Merck would not meet the criteria for success in Protocol 007, Dr. Krah conducted further experiments to develop a neutralization assay that was more "sensitive." As described below, Merck met with FDA and conducted teleconferences to reach an agreement on the neutralization assay to be used in Protocol 007.[173]

78. In early 2000, Merck had not finalized the neutralization assay it would use in Protocol 007. An email from Dr. Krah to MRL's Vice President, Vaccine & Cell Biology, Dr. Emilio Emini, stated that they "plan[ned] to readdress the use of anti-human IgG [rabbit antibodies to human immunoglobulin (IgG)] to enhance N[eu]t[ralization], as a back-up if [Merck] fell short of [its] 90+% target"[174] in Protocol 007. The 90% target represented the percentage that would allow Merck to report the trial successful.[175] Merck documents evidence Dr. Krah's continued work in 2000 on the development of a modified version of the standard

[170] MRK-KRA00051640.
[171] MRK-KRA01731773 at '78.
[172] *See* Section III.B.3 above discussing specificity and sensitivity as it relates to neutralization.
[173] *See* MRK-KRA1927351; MRK-KRA00001262 at '63-64.
[174] MRK-KRA00337397 at '398-399. The neutralization assay using anti-IgG was developed by Dr. Krah and became known as the "Anti-IgG Enhanced Neutralization Test," or "AIGENT." The AIGENT was a modified version of the neutralization test that Merck had used previously, the "Mumps Plaque Reduction Neutralization Assay," SOP 874.3422, which did not include the addition of anti-IgG, and which Dr. Krah referred to as a "straight-forward" neutralization assay. *See also* MRK-KRA00051640; *see also* Section VIII.C below describing Merck's use of the AIGENT assay in Protocol 007.
[175] MRK-KRA00001467 (for the neutralization assay the FDA required a 5% equivalence and an "absolute criterion that the lower limit of [sero] conversion rate is above 90%."). To ensure the 5% equivalence margin is met with a less than 90% seroconversion rate, one would need a 95% seroconversion rate average.

neutralization assay for Protocol 007, including experiments to add the anti-IgG step that Dr. Krah described to Dr. Emini as the "back-up" plan.[176]

79. In August 2000, the potency issue arose again. Merck's Manufacturing Division ("MMD"), agreed to provide additional information about mumps stability[177] to personnel from FDA's Office of Vaccines Research and Review a week before FDA's Office of Compliance was scheduled to conduct its annual inspection of Merck's manufacturing facility.[178]

80. In October 2000, at the conclusion of the Team Biologics inspection, FDA issued a Form 483 citing Merck for, among other things, failing to report thirteen lots of mumps containing vaccine (some were MMRII, some were the monovalent Mumpsvax) manufactured before September 1999 (when the overfill was implemented).[179] The lots were "out of specification" because they fell below the 20,000 [4.3 log10] mumps end-expiry potency before the 24 month expiry.[180] Merck responded to the Form 483 and provided the additional information regarding mumps stability in separate submissions dated October 24, 2000.[181]

81. In response to the Form 483, Merck cited the ongoing negotiation with FDA stemming from the Section 314 Review and the overfill after September 1999.[182] The submission relating to mumps stability analyzed lots manufactured through May 1998.[183] The

[176] MRK-KRA00337397 at '398-399; *see* MRK-KRA00026912; MRK-KRA00001218 at '18-19.
[177] MRK-KRA01522617 at '17, '19 (describing FDA's preliminary comments to materials Merck provided in a July 26, 2000 letter to FDA, and discussing the "mechanism for providing additional information to CBER for them to make an assessment regarding mumps stability.").
[178] *Id.* FDA's Office of Compliance is sometimes referred to as "Team Biologics."
[179] MRK-KRA00071265 at '65-66.
[180] *Id.*
[181] *See* MRK-KRA00784030; MRK-KRA01899087.
[182] MRK-KRA00784030 at '31-33.
[183] MRK-KRA01899087 at '141-44.

average potency loss[184] was higher than the one Merck calculated to determine the amount of the overfill to assure that each lot would meet the 4.3 end expiry specification.[185]

82. After reviewing Merck's submissions, FDA "expressed concern regarding the apparent decline in mumps stability over the shelf life of MMRII."[186] A summary of a meeting of Merck's Clinical Development Oversight Committee, dated November 22, 2000, stated that Merck's "preferred option" to "address the mumps stability issues" was to "lower the end expiry [of MMRII] based upon preliminary subset analysis of data … from the Mumps End Expiry Trial."[187] On November 29, 2000, Merck held a teleconference with FDA to obtain approval for Merck to conduct a preliminary subset analysis[188] of the Protocol 007 study.[189] Merck proposed to use Dr. Krah's AIGENT assay.[190] After obtaining FDA's agreement, Dr. Krah conducted the Protocol 007 preliminary subset analysis in his lab at MRL using the AIGENT from December 2000-January 2001.[191]

83. In February 2001, FDA issued a Warning Letter to Merck related to the same deficiencies in the October 2000 Form 483, including failing to report out of specification mumps containing vaccines.[192] The Warning Letter requested additional information concerning

[184] *Id*.
[185] MRK-KRA00582932 ("Potency losses are 0.1 to 0.2 log higher than previously reported to CBER and are higher than estimates used to determine the minimum fill levels needed to meet the 24 month expiry dating. This may result in product on the market with potency below the label claim. …").
[186] MRK-KRA01727942 at '42-44. A decline in stability would mean an increase in potency loss over the shelf-life.
[187] *Id*.
[188] The preliminary subset analysis was an interim analysis in which approximately 1/3 (approximately 600 total, approximately 200 from each of the 3 treatment groups) of the subjects samples were tested. Merck performed testing for these subjects in December 2000-January 2001. The results of preliminary subset analysis were submitted in March 2001 in Serial 63. *See* MRK-KRA00001218 at '18-19; *see also* MRK-KRA00017036 at '38 (Serial 63). References in this report to the preliminary subset and the preliminary subset analysis are describing this analysis.
[189] MRK-KRA00017036 at '38 (Serial 63).
[190] *Id.* The AIGENT assay was the neutralization assay that included the addition of anti-human IgG, developed by Dr. Krah. *See also* Section VIII.C above.
[191] MRK-KRA00052242 ("The testing of the interim analysis started 06-Dec-2000 … ended 26-Jan-2001").
[192] MRK-KRA00209399.

product manufactured before the overfill that might still be on the market because the expiry period was 2 years.[193] The Warning Letter also requested a "summary of the available data regarding product efficacy at the lower end" of the potency range Merck "would expect the various Mumps Vaccine products to reach at the two-year expiration date."[194] Merck senior management from MMD and MRL prepared Merck's response as part of a "group effort."[195]

84. An email from MRL's Senior Vice President, Dr. Dorothy Margolskee, to MRL's President and Executive Vice President, Science & Technology, and Member of Merck's Board of Directors, Dr. Edward Scolnick, and MRL's Executive Vice President, Clinical Sciences and Product Development, Dr. Douglas Greene, cc'd to MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, and MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MMD's Senior Vice President, Global Quality, Dr. Michael Angelo, and MRL's, Senior Vice President, Science and Technology, Dr. Michael King, with the subject "Mumps end-expiry," dated February 23, 2001[196] summarized MRL's assistance in responding to the Warning Letter.[197] Dr. Margolskee's email[198] can be summarized as follows:

- Merck identified 225 lots still within the 24-month dating period with estimated end expiry potencies below 4.3 $\log_{10}$ [20,000] $TCID_{50}$/dose.[199]

[193] *Id.* at '01.
[194] *Id.* at '01-02.
[195] MRK-KRA00549510.
[196] As described in Section VIII.E.3 below, Dr. Margolskee sent a second email to Drs. Scolnick and Greene on March 5, 2001to update them on the status of the response to the Warning Letter. MRK-KRA00616007 at '08- 09.
[197] MRK-KRA00549510.
[198] *Id.*
[199] Attachment #4 to Dr. Margolskee's email listed 235 lots. It appears that 10 of the lots were not predicted to fall out of specification.

- Merck identified six lots with an estimated end expiry potency of 3.4 to 3.7 $\log_{10}$ [2,500-5,000] $TCID_{50}$/dose.
- Merck identified 100 lots with an estimated an end expiry potency between 3.7 and 3.9 $\log_{10}$ [5,000- 8,000] $TCID_{50}$/dose.
- Merck identified 119 lots with an estimated end expiry potency between 4.0 and 4.2 $\log_{10}$ [10,000 - 16,000] $TCID_{50}$/dose.[200]
- The 106 lots projected to fall below 4.0 $\log_{10}$ [10,000] $TCID_{50}$ at end expiry "will be a compliance issue with the Agency."
- From the results of the AIGENT, Drs. Margolskee and Sadoff felt "3.7 [was] medically ok and may be defensible."
- Lots which would have 24 month end-expiry titers lower than 3.7 would not have data from the study to support shelf-life.
- Complete data from the end expiry trial would not be available for several months.
- Merck documented that lots manufactured "at least since the summer of 1998" were expected to lose a total of ~1.0 $\log_{10}$ $TCID_{50}$ over 24 months, and that lots manufactured starting in September 1999 were projected to have 24 month end expiry titers at or above 4.0$\log_{10}$ $TCID_{50}$, not 4.3 $\log_{10}$ $TCID_{50}$ as stated on the label.
- Attachment #4 identified 12,765,787 total doses released to the United States from low mumps titer lots still within expiry and potentially still on the market.
- The medical assessment of the 101 lots between 3.7 and 4.0 included analysis of the neutralization data in Protocol 007 to support the effectiveness of lower potency product.
- Merck was going to test a set of non-responders (vaccine failures) outside the protocol to evaluate their responses by other assays to get assurance it did not have from the AIGENT testing alone.[201]

[200] *See also* MRK-KRA00086295 (draft response to the Warning Letter identifying 117 lots with end expiry potency between 4.0 and 4.2).
[201] As discussed in Section VIII.E. 2 below, MRL personnel tested Protocol 007 subjects who did not seroconvert in the AIGENT preliminary subset analysis outside the protocol using a neutralization assay without the anti-IgG step.

- Merck proposed a set of surveillance investigations.
- Merck initiated a "Fact Finding" as a prelude to a potential product recall.
- Merck attempted to identify how long a lot may be on the market before it is used.
- Merck proposed to confirm findings from the Worldwide Adverse Events System with a retrospective HMO database study.
- Merck proposed to set up a prospective surveillance study if it could map the lots of interest to an HMO with the appropriate infrastructure.
- The results of testing the nonresponders outside the protocol would be used to evaluate whether Merck needed to have a "high level of concern."
- If nonresponders were truly not responding to the vaccine Merck would need to consider further assessment, including potential revaccination of large infant cohorts.[202]

85. In preparing the response to the 2001 Warning Letter to be supported by the Protocol 007 preliminary subset clinical data using Dr. Krah's AIGENT assay, there was a suggestion to include "A SECTION RE ASSAY DESIGN & PERFORMANCE ISSUES."[203] The response to this suggestion stated: "In talking with Emilio [Emini] the neutralization assay is very artificial because of the IgG added … low-level responders cannot be distinguished from nonresponders."[204]

86. On February 27, 2001, MRL's Statistician, Biostatistics and Research Data Systems, Philip Bennett, sent a memo to MMD's Vice-President, Vaccine & Sterile Quality

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See MRK-KRA00064825 (Workbook pages describing assay 46-01); MRK-KRA00068448 (results of assay 46-01). Merck also compared responses by the AIGENT and the WT ELISA of approximately 10% of the children, broken out by treatment group, to see if the children were "hypo-responders" (i.e. would respond by ELISA even if they were not responding in the AIGENT). *See* MRK-KRA00562247 (tables comparing results broken out by treatment group); *see also* Section VIII.E.2 below (summarizing the results of that comparison).

[202] Cohorts typically refers to children born in the same year.

[203] MRK-KRA00549464 at '71.

[204] *Id.*; *see also* MRK-KRA00562218 (on March 14, 2001, Philip Bennet stated: "Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.").

Operations, Dr. Roberta McKee, the person coordinating Merck's response to the Warning Letter that stated: "Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry,"[205] not the 4.3 mumps end expiry claim on the MMRII label.[206]

87. Thereafter, Merck had a series of regulatory interactions with the FDA summarized as follows:

- On March 5, 2001, Merck submitted a "Biological Product Deviation Report" of a pre-overfilled MMRII lot as out of specification for mumps at end-expiry referencing the overfill as a corrective action taken to assure going forward that product met its end expiry label claim.[207]
- On March 8, 2001, Merck submitted its response to the February 9, 2001 Warning Letter, including its response to Observation #3 regarding mumps stability that stated: "[w]ith regard to expectations for products meeting specifications throughout the labeled expiry period, we agree."[208] The response to the Warning Letter also stated: "As a result of communications with CBER over the last several years, we have implemented changes, including an increase in the mumps content of the product in September 1999 to ensure compliance to the labeled titer through expiry. Today all products have end-expiry specifications consistent with their label."[209]
- On March 12, 2001, Merck submitted the results of the Protocol 007 preliminary subset analysis to support the response to the Warning Letter.[210]
- On April 4, 2001 Merck met with FDA personnel to follow-up the August 2000 discussion regarding mumps stability.[211] FDA's Dr. Carbone "emphasized that

[205] MRK-KRA01896072 at '72-73 (emphasis added).
[206] MRK-KRA00562218.
[207] MRK-KRA00754239; *see* Section VIII.G below discussing this Biological Product Deviation Report.
[208] MRK-KRA0153760; *id.* at '08-10; *see* Sections VIII.E and F below discussing the preparation of and response to the February 2001 Warning Letter.
[209] *Id.* at '08.
[210] MRK-KRA00017036; *see* Section VIII.H below discussing the submission of the Protocol 007 data.

CBER's concern is that vaccines (in this case, mumps-containing vaccines) remain at or above the minimum potency through expiry."[212]

— On April 20, 2001, Merck submitted a second "Biological Product Deviation Report" to report four additional pre-overfill MMRII lots as out of specification for mumps at end expiry referencing the overfill as a corrective action taken and the result of the Protocol 007 preliminary subset analysis to support the effectiveness of any lower potency product potentially administered to children.[213]

88. Merck did not inform the FDA in any of its regulatory discussions the information set forth in Merck's internal documents, summarized in paragraphs 84-86 above, regarding Merck's (1) identification of 225 pre-overfilled lots not meeting the 4.3 end-expiry specification and Merck's assessment of the implications of those lower potency lots, including the potential need to revaccinate large cohorts of children;[214] (2) use of an assay to provide clinical data from Protocol 007 in response to the Warning Letter and the Biological Product Deviation Report that was "very artificial" because of the IgG added … low-level responders cannot be distinguished from nonresponders;"[215] or (3) ongoing internal analysis and discussion that Merck could not ensure compliance with the "not less than 4.3" mumps end expiry claim on the MMRII label, even after the overfill and that MMRII's shelf life needed to be 12 months, not 24.[216]

89. In July 2001, Merck planned a follow up to the April 4, 2001 meeting with FDA regarding mumps stability to occur only after the Protocol 007 data was generated to support lowering the mumps end expiry claim on the MMRII label because "we can't meet 1 of the 2

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[211] MRK-KRA01649955; *see* Section VIII.I below discussing preparation for and meeting on April 4, 2001.
[212] MRK-KRA01977383; MRK-KRA00049238 at '38-40.
[213] MRK-KRA00754233; *see* Section VIII.J below discussing the April 2001 Biological Product Deviation Report.
[214] MRK-KRA00549510 at '14.
[215] MRK-KRA00549464 at '471.
[216] MRK-KRA01896072 at '72-73; MRK-KRA00086318; MRK-KRA00019430 at '30-32; MRK-KRA00562218.

FDA objectives for our annual [stability] program until the expiry spec[ification] is lowered to 4.0."[217] MRL's Director, BARDS, Timothy Schofield stated: "the plan works with 4.0, but not 4.3."[218]

90. In August 2001, before the Protocol 007 AIGENT testing that would support lowering the mumps end expiry claim on the MMRII label was completed, FDA conducted an unannounced inspection in Dr. Krah's lab where that testing was ongoing.[219] The FDA issued a Form 483 with four deficiencies, including that "[r]aw data is being changed with no justification."[220] The FDA inspection was prompted, in part, by a contact made by Steve Krahling,[221] regarding falsification of data in Dr. Krah's lab.[222] Merck prepared and submitted a response to the Form 483 on August 20, 2001.[223]

91. From August 2001 to March 2002, Merck negotiated with FDA to overcome FDA's preliminary position that the deficiencies in the AIGENT testing cited in the Form 483 made the assay results "unacceptable for an end expiry decision."[224] Merck reached an agreement with FDA for use of the AIGENT data in March 2002.[225]

92. During this same time, MRL's Philip Bennett again[226] documented Merck's inability to ensure compliance with the "not less than 4.3" mumps end expiry claim on the

[217] MRK-KRA01977383.
[218] *Id*. at '384.
[219] MRK-KRA02021754. After Dr. Krah conducted the Protocol 007 preliminary subset analysis his lab continued to test the approximately 1200 remaining samples. *See*, MRK-KRA00490592 at '72 (David Krah's Journal, March 13, 2001: "Note: rec[eive]d notification today that the decision has come down from above that we will be doing the balance of the N[eutraliza]t[ion] testing for the pre and 6-week bleeds from Protocol 007").
[220] MRK-KRA01649971.
[221] RELATOR_00001044. Mr. Krahling is one of the two relators in the False Claim Act case.
[222] *See* Section VIII.L below discussing RELATOR_00001044.
[223] MRK-KRA00000481.
[224] MRK-KRA00071082 at '83.
[225] *See* Section VIII.L.3.
[226] *See* MRK-KRA01896072 at '72-73 (February 27, 2001 email: "Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry"); MRK-

MMRII label for 24 months. His prior estimate of less than 12 months' shelf life[227] could be improved "with some creative math."[228]

93. Mr. Bennett further estimated as many as 7% of MMRII lots "were expected to be below 4.3 at end expiry."[229] Merck's Clinical Regulatory Review Committee was kept informed of Mr. Bennett's potency calculations and the inability to assure "not less than 4.3" through end expiry for mumps in MMRII. A power point presentation for the Clinical Regulatory Review Committee, dated January 22, 2002, stated: "Product still not compliant with labeled potency."[230]

94. In an April 10, 2002 email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to Dr. Krah and others, with the subject "Timing for Analysis of mumps neutralization assay data," Dr. Morsy stated: "filing the mumps end expiry and label change is the highest priority from a regulatory and compliance standpoint - every day delay … is a problem for the rest of the team and our ability to resolve this compliance issue which is a concern not only for the US but also for the EU and the rest of the world… [Protocol 007 AIGENT] at this point is the critical path and bottleneck."[231] Merck's documents evidence Merck's continued inability to ensure compliance with the "not less than 4.3" mumps end expiry claim on the MMRII label for 24 months until 2007.[232]

KRA00562218 (March 14, 2001 email: "Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.").

[227] MRK-KRA00562218.

[228] MRK-KRA00024008.

[229] MRK-KRA00561350.

[230] MRK-KRA00019085 at '10.

[231] MRK-KRA00561310.

[232] MRK-KRA00205854 (3/7/2002: "Missbranded – stability continues to be an issue, even with the increase in mumps and reduction of end expiry of 4.0"); MRK-KRA00498914 at '17 (7/16/2002: "Key Issues…current product does not meet expiry specifications"); MRK-KRA01562819 at '20 (9/5/2002: "We have much larger problem than just [Japan] if we can only support 12 month"); MRK-KRA00615152 at '56-57 (10/2/2002: "current expiry dose of 4.3 log … would only support < 12 months expiry using current data in the stability model."); MRK-KRA00040705

95. In January 2002, Merck's ability to use Protocol 007 AIGENT data for an end expiry decision was still uncertain because the resolution of the Form 483 deficiencies in the testing in Dr. Krah's lab was still pending. Merck documented that the WT ELISA issue was "becoming increasingly urgent."[233] MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, contacted FDA's Dr. Carbone to discuss the ELISA cutoff issue.[234] Dr. Chirgwin "reminded her that the mumps ELISA cutoff issue was linked to the mumps PRN assay"[235] because FDA "required [justification] for the new mumps cutoff of 10 ELISA antibody units"[236] and Merck was "in the process of writing study reports for [ProQuad]."[237] According to Dr. Chirgwin's record of the conversation, from Dr. Carbone's perspective, "'there [was] nothing really scientifically wrong' with our mumps P[laque]R[eduction]N[eutralization] assay and she

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at '20, '25 (10/11/2002: "Estimated shelf life with 4.3 log … is ≤12 months, a potentially non-marketable shelf life." "Implementing new stability model, current estimate for shelf-life is < 12 months"); 10/17/2002: "Based on recent stability…model we now believe that we do not have adequate (95%) confidence that the current manufacturing process supports the 4.3 log…. As such, an immediate corrective action must be taken."); MRK-KRA00233586 at '92-93 (10/28/2002: "current end expiry potency claims…will not be met…. By current calculation models, the end-expiry potency claims would justify a shelf life of less than 12 months, a potentially non-marketable product profile."); MRK-KRA00094134 (10/31/2002: "Given that our most recent stability analysis for mumps does not support the current label claim, Merck is required to report this finding to FDA."); MRK-KRA001894982 at '85-86 (7/28/2003: "the current release titers of 5.0 … for mumps ... are also insufficient to meet the current minimum potencies at expiry of 4.3"); MRK-KRA001564065 at '67 (8/20/2004: "The... expiry (dose-claim) window does not support an expiry of 20,000 [4.3 log] after storage for 24 months"); MRK-KRA001574732 at '32-33 (9/18/2004: "Some of those countries have a mumps end expiry of 20,000 in their labels (4.3 log TCID50), which is wrong as we cannot guarantee this potency in our product"). *See* Section VIII.N.9 below.

[233] MRK-KRA00071388.

[234] *Id.*

[235] *Id.* (emphasis added). On October 19, 2001 Merck held a teleconference with FDA staff regarding Merck's WT ELISA assays. During this teleconference "CBER request[ed] additional justification for the cutoff for the mumps ELISA… CBER require[d] a comparison between the PRN and the ELISA cutoff." MRK-KRA00561452 at '53; *see* Section VIII.M.1 below describing FDA's requirements for the mumps ELISA.

[236] MRK-KRA00818776 at '78.

[237] MRK-KRA00071388.

would be willing to use the mumps PRN data as they currently exist as a basis for discussion on the mumps ELISA cutoff."[238]

96. Thereafter, MRL personnel prepared a comparison of the WT ELISA to the AIGENT assay using the clinical data from the Protocol 007 preliminary subset analysis.[239] A WT ELISA cutoff of 10 Ab units was "desirable from Merck['s] perspective."[240] According to an internal Merck "Risk Table," if "CBER d[id] not accept [Merck's] proposed Mumps WT ELISA cutoff" then "Mumps seroconversion rates [would] be lower than what is claimed in the label."[241]

97. In preparing the comparison required by FDA, "things … got[] stuck" with two tables in the draft analysis "showing the breakdown by ELISA strata of the discordant [AIGENT] neg[ative]/ELISA pos[itive] sera."[242] "One concern [wa]s that presenting the data in this fashion may prompt CBER to request that the ELISA cutoff be raised."[243] "It [wa]s also clear that [CBER was] going to look closely at how sera with values around the cutoff are classified in the two assays."[244] "If [Merck was] unable to provide sufficient reassurance about the clinical relevance of the WT ELISA cutoff (which in Kathy [Carbone (FDA)]'s mind means linking this to the PRN) then we may end up with some type of a fold-rise criterion which I

[238] *Id.*
[239] *See* Section VIII.M.3.
[240] MRK-KRA01583397 at '18.
[241] MRK-KRA00544510 (emphasis added).
[242] MRK-KRA00544296.
[243] *Id.*
[244] *Id.* (emphasis added); *see also* MRK-KRA00561452 ("CBER requests that individual titers are identified in the relative range around the cutoff in the PRN and ELISA in order to confirm that these two assays are categorizing sera in a comparable fashion") (emphasis added).

assume we would rather avoid if possible."[245] The two tables were removed from the correlation analysis[246] as "too distracting.[247]

98. In June 2002, Merck submitted BB-IND 1016, Serial 86,[248] including the comparison of the AIGENT and WT ELISA assay concluding "good agreement" between the two assays and requesting FDA concurrence with Merck's recommendation of the 10 Ab cutoff in Merck's WT ELISA assays.[249] The two "distracting" tables from the draft were not included.[250] Moreover, the tables Merck prepared in March 2001 comparing AIGENT and WT ELISA results from the retests of the nonresponders and low level responders tested in the preliminary subset were also not included in the submission.[251] On August 8, 2002, Merck confirmed to FDA that it would use the WT ELISA for measuring persistence of the mumps immune response at the one year time period in Protocol 007.[252]

99. In January, 2004, Merck submitted a Supplemental Biologics License Application[253] to lower the M-M-R®II mumps end expiry specification from "not less than 4.3" to "not less than 4.1" $\log_{10}$ $TCID_{50}$.[254] In June, 2004, Merck submitted a Supplemental Biologics

[245] *See also* MRK-KRA00561418 ("If CBER required a fourfold rise in titer (defined as less than 10 to greater than or equal to 40), the seroconversion rates for these studies would range from 80.9 percent to 85.2 percent.").
[246] MRK-KRA00544514. *See* Section VIII.M.3 discussing the preparation of the submission and the removal of the two tables. Data from one of the tables was submitted and presented in a different table in a different format supporting a different part of the submission.
[247] MRK-KRA00544296.
[248] "Serial" numbers are assigned to regulatory submissions to facilitate later reference. Throughout this report there will be repeated references to Merck's Serial submissions in support of the BB-INDs open with the FDA.
[249] MRK-KRA00126468 at '474.
[250] *Compare* MRK-KRA00544514 (Tables 6c & 6d), with MRK-KRA00126468 (Serial 086).
[251] *Compare* MRK-KRA00562247, with MRK-KRA00126468 (Serial 086). *See* footnote 424 above. The children whose results were summarized in the March 2001 tables were among the children whose results were used for the June 2002 comparison.
[252] MRK-KRA00000561 (BB-IND 1016, Serial 89).
[253] In order to sell a vaccine in the United States, a manufacturer must first obtain a license from the FDA. The application for the license, the BLA, must be supported by substantial evidence of the safety and effectiveness of the product. Substantial evidence is provided in the form of adequate and well-controlled clinical studies. *See* Section V.B.3.
[254] MRK-KRA00135652 (hereinafter referred to as the sBLA for Mumps End Expiry). *See* Section IX.A.5.a below.

License Application to support the use of recombinant serum albumin ("rHA") instead of pooled human derived serum albumin ("HSA") as a viral growth media in the bulk manufacturing process and as a component of the bulk diluents in the formation of the final product.[255] In August, 2004, Merck submitted a Biologics License Application for approval to sell ProQuad.[256] All three applications included supporting clinical studies using Merck's WT ELISA assay with the 10 Ab cutoff justified by the comparison to the AIGENT in Serial 86.[257]

100. Following the submission of Serial 86 and prior to the approval of the three applications, Merck made additional submissions to the FDA to demonstrate the "biological relevance" of the WT ELISA assay and the appropriateness of the 10 Ab cutoff in response to FDA's requests for additional information.[258] Those submissions can be summarized as follows:

- On June 28, 2004, to respond to FDA's request to provide information in support of the WT ELISA cutoff in the clinical study supporting the sBLA for rHA, Merck referred back to Serial 86.[259]
- On November 12, 2004, to respond to FDA's request for additional information about the WT ELISA cutoff in the clinical studies supporting the BLA for ProQuad, Merck referred back to Serial 86.[260]
- On November 17, 2004, to respond to FDA's request for additional information about the WT ELISA cutoff in the clinical study supporting the sBLA for Mumps End Expiry, Merck referred back to Serial 86.[261]
- On May 4, 2005, to respond to a March 2005 FDA request for clarification of Merck's Serial 221, Merck referred back to Serial 86.[262]

[255] MRK-KRA00137854 (hereinafter referred to as the sBLA for rHA); *see* Section IX.A.5.b below.
[256] MRK-KRA00157572 (hereinafter referred to as the BLA for ProQuad); *see* Section IX.A.5.c below.
[257] *See* Section IX.A.6 below describing Protocol 007, Protocol 009, Protocol 012, Protocol 013 and Protocol 014 and SectionIX.A.7 below describing the results of the clinical studies reported.
[258] *See* Section IX.B below describing FDA's requests and Merck's submissions in response.
[259] MRK-KRA00124554 (BB-IND 10076, Serial 53).
[260] MRK-KRA00155481 (BB-IND 7068, Serial 221).
[261] MRK-KRA00126963 (BB-IND 1016, Serial 102).

101. Following a telephone conversation from FDA's Dr. Steve Rubin to Merck's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, regarding Merck's comparison of the two assays and the clinical relevance of the cutoff,[263] Dr. Chirgwin and other Merck personnel exchanged a series of emails internally at Merck from June 29, 2004 to July 3, 2004, with the subject "Comparing Mumps WT ELISA and AIGENT Assay,"[264] including:

- MRL's Director, Dr. Joseph Antonello, the author of the Comparison of the AIGENT and WT ELISA in Serial 86, agreeing with MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, stated: "We don't really know what a clinically protective level is in either assay."[265]
- MRL's Associate Director, Worldwide Regulatory Affairs Dr. Michael Dekleva stated: "I spoke with Joe Antonell[o] yesterday, and he re-emphasized that the precision with the [AIGENT] assay was very poor, and felt that … it was really hard to say whether the differences in the data sets were significant – influenced to a great extent by the variability in the [AIGENT] data."[266]
- MRL's Executive Director, Vaccine Integration, Dr. Florian Schodel stated: "Agree with Joe [Antonello] – could not overemphasize the weakness of the [AIGENT] (50% specificity!!!!!!)."[267]

102. None of Merck's submissions included discussion of the information regarding the AIGENT and the WT ELISA set forth in Merck's internal documents, including: (1) that the AIGENT was "very artificial because of the IgG added" and "low level responders [could not] be distinguished from non-responders;"[268] (2) "could not overemphasize the weakness of the

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[262] MRK-KRA00846087 (BB-IND 7068 letter).
[263] *See also* Section VII.M below discussing the comparison.
[264] MRK-KRA00791315; *see also* Section IX.B.3 below collecting deposition testimony related to this email.
[265] MRK-KRA00791315 at '319.
[266] *Id.* at '315.
[267] *Id.*
[268] MRK-KRA00549464 at '471.

[AIGENT] (50% specificity!!!!!!)"[269] (3) "precision with [the AIGENT] assay was very poor;"[270] and (4) Merck "[did]n't really know what a clinically protective level [wa]s in either [the AIGENT or WT ELISA] assay."[271]

103. Thereafter, the three applications were approved supported by clinical studies using Merck's WT ELISA with the 10 Ab cutoff. The sBLA for rHA was approved on August 31, 2005.[272] The BLA for ProQuad was approved shortly thereafter, on September 6, 2005.[273] The sBLA to reduce the mumps end expiry claim on the MMRII label to "not less than 4.1" was subsequently approved on December 6, 2007.[274]

104. Starting in 2006 and occurring ever since, there has been a resurgence of Mumps cases and outbreaks in the United States. One of the largest of these outbreaks occurred in 2016-2017, affecting more than 10,000 people in 46 states. The vast majority of these people, along with the vast majority of those affected in the other outbreaks, received the recommended 2-dose regimen of MMRII. Dr. Stanley Plotkin, a noted pediatric infectious disease academician, and the virologist who developed the rubella vaccine in Merck's MMRII, has commented upon the apparent reduced efficacy of the mumps vaccine as evidenced by these recent outbreaks of disease in populations vaccinated according to the recommended schedule.[275] FDA's Dr. Steven Rubin, someone with extensive experience with mumps vaccines and mumps virology, has also

[269] MRK-KRA00079264.
[270] *Id.*
[271] *Id.* at '19.
[272] MRK-KRA00141909; *see* Section IX.C.1 below discussing this approval.
[273] MRK-KRA00761865; *see* Section IX.C.2 below discussing this approval.
[274] MRK-KRA00141976; *see* Section IX.C.3 below discussing this approval.
[275] Plotkin SA., *Commentary: Mumps vaccines: do we need a new one?*, 32 PEDIATRIC INFECTIOUS DISEASE 381-382 (2013). *See also* https://www.bloomberg.com/research/stocks/people/person.asp?personId=20504693&privcapId=1342604

stated that the resurgence of mumps in the United States has made it "quite clear that newer, more immunogenic vaccines are needed."[276]

V. FDA'S REGULATION OF VACCINES

A. FDA Regulates Vaccines as both a Biological Product and a Drug

105. A vaccine is a "biological product" as defined in 42 U.S.C. § 262 (i)(1) of the Public Health Service Act ("PHSA"). Section 262 (i)(1) states: "The term 'biological product' means a … vaccine … applicable to the prevention, treatment, or cure of a disease or condition of human beings."

106. "[B]iological products subject to regulation under section 351 of the Public Health Service Act, are also drugs, within the meaning of Section 201(g)(1) of the Federal Food, Drug and Cosmetic Act, and are therefore also subject to regulation under that Act."[277] Biological Products: Procedures for Review of Safety, Effectiveness and Labeling 38 Fed. Reg. 4319 (February 13, 1973) (to be codified at 21 C.F.R. pt. 273) at 4319.[278]

107. The "Regulation of biological products" is set forth at 42 U.S.C § 262, the Public Health Service Act. The regulation of drugs is set forth at 21 U.S.C. § 355 *et seq*., the Food Drug, and Cosmetic Act.

108. Former FDA Commissioner Charles Edwards stated that a regulatory program was developed under the Public Health Services Act "whereby manufacturers of biological products

[276] NIH000007.
[277] "The regulations in Title 21 of the Code of Federal Regulations (21 CFR) Parts 600-680 pertain to biological products in general." Guidance for Industry "For the Evaluation of Combination Vaccines For Preventable Diseases: Production, Testing and Clinical Studies" at 1 (April 1997). "In addition, certain drug regulations such as 21 CFR 201.56, 201.57, 210, 211, and 312 apply to combination vaccines." *Id*. at 2.
[278] *See also* Intercenter Agreement Between CDER and CBER (effective October 31, 1991). https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm.

are licensed to distribute these products with adequate showing that they are pure, potent, and safe for their intended uses." Proposed Procedures for Review (1972), 37 Fed. Reg. 16679.

109. Commissioner Edwards also stated: "The major objective of the drug provisions of the Federal Food, Drug and Cosmetic Act is to assure that drugs will be safe and effective for use under the conditions of use prescribed, recommended, or suggested in the labeling thereof." Legal Status of Approved Labeling for Prescription Drugs; Prescribing Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16503 (notice of proposed rulemaking August 15, 1972) (to be codified 21 C.F.R. pt. 130).

110. The history of federal regulation of vaccines summarized by the Subcommittee On Health and the Environment of the House Committee On Energy and Commerce in *Childhood Immunizations*, stated:

> Historically, the Federal Government has been involved in licensing and regulating vaccines and vaccine manufacturers since 1902, when Congress passed the Virus Serums and Toxins Act "to regulate the sale of viruses, serums, toxins, and analogous products..." in interstate and foreign commerce. The 1902 Act authorized the Secretary of the Treasury to issue licenses and regulate vaccines in accordance with standards developed by an interagency board. Under the board's direction, the Public Health Service's Hygienic Laboratory was authorized to inspect establishments manufacturing biologics, issue and revoke licenses, and ensure, in whatever ways possible, the safety and efficacy of biologics. In 1948, this responsibility was transferred to the National Microbiological Institute of the National Institutes of Health (NIH). In 1955, the NIH Division of Biologics Standards was established to assume the duties of the biologics control program, and in 1972 these duties and responsibilities were transferred to the newly established FDA Bureau of Biologics.

Staff of the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce, 99th Cong., 2nd Sess., Childhood Immunizations, a Report (Comm. Print 99-LL 1986) (hereinafter "Childhood Immunizations Report") at 44 (emphasis added).

111. Since 1972, "[t]he Food and Drug Administration (FDA), through its Center for Drugs and Biologics (specifically, the Office of Biologics Research and Review), is responsible for setting biological standards for new products, licensing manufacturers to produce the biologics, pre market testing, evaluating, and licensing of the products themselves, inspecting manufacturing facilities, and encouraging continued surveillance of the products once they are approved for use in the general population." *Id.* at 34.

112. In testimony on FDA's Role in the Regulation of Vaccines before the Committee on Homeland Security, Subcommittee on Emerging Threats, Cybersecurity, and Science and Technology, on April 18, 2007, Dr. Jesse Goodman, Director, Center for Biologics, Evaluation and Research, Food and Drug Administration, stated:

> To protect and preserve our scientific independence and judgment, FDA does not involve itself in specific HHS contracting decisions to award or terminate contracts. FDA's longstanding policy is to recuse ourselves from HHS decision making in specific contracting decisions. … At FDA, providing the American public with safe and effective medical products is our core mission." [279]

[279] In general, the federal government procures vaccines under the Vaccine for Children program (VFC) and the 317 program. "The Vaccines for Children (VFC) program is a federally funded entitlement program that provides vaccines at no cost to eligible children. CDC provides the routinely recommended childhood and adolescent vaccines at no charge to participating VFC providers. … Section 317 of the Public Health Service Act authorizes the federal purchase of vaccines to vaccinate children, adolescents, and adults. Over its 50 year history, Section 317-purchased vaccine has been directed towards meeting the needs of priority populations; most recently this has included underinsured children not eligible for VFC, and uninsured adults." Center for Disease Control and Protection, Questions Answered on Vaccines Purchased with 317 Funds - Important Immunization Information for Parents & Healthcare Providers, https://www.cdc.gov/vaccines/imz-managers/guides-pubs/qa-317-funds.html (page last updated: July 19, 2013); s*ee also* Schedule 16 for the process by which the federal government contracts for the purchase of vaccines, including M-M-R II and ProQuad, under both VFC and the 317 program.

Can BioShield Effectively Procure Medical Countermeasures That Safeguard the Nation?: Hearing Before the Subcomm. on Emerging Threats, Cybersecurity and Science and Technology of the Comm. on Homeland Security, 110th Cong. 36-41 (2007) (statement of Jesse Goodman, M.D., MPH, Director, Center for Biologics Evaluation and Research, HHS) at 41. (emphasis added) https://www.gpo.gov/fdsys/pkg/CHRG-110hhrg43559/pdf/CHRG-110hhrg43559.pdf.

B. FDA Regulation of the Vaccine Label

1. Vaccine Labeling, Defined

113. "Labeling" is defined in 21 U.S.C. § 321(m) to mean: "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[280]

114. In proposed rulemaking published on August 15, 1972, FDA stated: "When a new drug is approved for marketing the conditions of use that have been approved are required to be set forth in the official labeling. This labeling must accompany the drug in interstate shipment and must contain adequate information for safe and effective use of the drug … The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information which the supplier of the drug is required to develop from accumulated experience and systemic drug trials of preclinical investigations and adequate, well-controlled clinical investigations that demonstrate the drug's safety and the effectiveness it

[280] Regarding vaccine labeling, FDA has stated: "The term 'labeling,' as defined in 21 U.S.C. § 321(m), means all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article and, therefore, includes any package inserts or information sheets that accompany vaccine products." Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), Guidance for Industry: FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information, 1, ftn 1 (2004) ("FDA Review of Vaccine Labeling (2004)") https://permanent.access.gpo.gov/LPS112955/ucm092196.pdf.

purports or is represented to possess." Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. at 16503 (emphasis added).

2. FDA's Review of Vaccine Labeling in 1972-1973 Upon Acceptance of the Transfer of Responsibility for the Regulation of Biological Products

115. In 1972 FDA published proposed "Procedures for Review of Safety, Effectiveness, and Labeling" for Biological Products that stated:

> The Commissioner of Food and Drugs, in accepting the transfer of responsibilities for the regulation of biological products, concluded that a systematic review of present procedures should be undertaken. This proposal will establish a procedure under which the safety, effectiveness, and labeling of all biological products presently licensed under section 351 of the Public Health Service Act will be reviewed.

Proposed Procedures for Review (1972), 37 Fed. Reg. at 16679.

116. The Proposed Procedures for Review (1972) also stated: "The review procedure proposed in this notice relies for legal authority on both the Federal Food Drug, and Cosmetic Act and Section 351 of the Public Health Service Act." *Id.*

117. The Proposed Procedures for Review (1972) also stated:

> The Commissioner of Food and Drugs is aware of the unique problems involved in applying the requirement of 'substantial evidence of effectiveness' to biological products, under the Federal Food Drug and Cosmetic Act. Where adequate and well-controlled studies are not feasible, and acceptable alternative scientific methods of demonstrating effectiveness are available, the latter will be sufficient." 37 Fed. Reg. at 16679.

118. On February 13, 1973, FDA published "Biological Products: Procedures for Review of Safety, Effectiveness and Labeling" adding 21 C.F.R. § 273.245, "Review Procedures to determine that licensed biological products are safe, effective, and not misbranded under

prescribed, recommended, or suggested conditions of use."[281] 38 Fed. Reg. 4319 (February 13, 1973) at 4321.

119. Section 273.245 (d) *Standards for safety, effectiveness and labeling*, stated "the following standards to determine that a biological product is safe and effective and not misbranded" shall apply:

> (2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 130.12 (a)(5)(ii)[282] of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness."[283]

38 Fed. Reg. 4319 at 4322.

120. In 1982, FDA announced the final regulatory status of the licensed biological products reviewed pursuant to 21 CFR § 601.25.[284] Viral and Rickettsial Vaccines;

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[281]

[282] Section 130.12 (a)(5)(ii) was redesignated to § 314.111(a)(5)(ii) on March 29, 1974. Subchapter D – Drugs for Human Use: Reorganization and Republication, 39 Fed. Reg. 11680 (March 29, 1974); *id*. at 11727.

[283] Section 273.245 was redesignated to 21 CFR § 601.25 on November 20, 1973. Reorganization and Republication, 38 Fed. Reg. 32048. (November 20, 1973); id. at 32053. The reference to § 314.111(a)(5)(ii) in 21 CFR § 601.25 was changed to 21 CFR § 314.126 on April 25, 1986. Biological Products: Corrections and Technical Amendments, 51 Fed. Reg. 15606 (April 25, 1986) at 15607. In 1985, FDA revised its regulations governing the approval for marketing of new drugs and antibiotic drugs for human use and added Section 314.126, "Adequate and well-controlled studies" on February 22, 1985. New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452 (February 22, 1985); id. at 7506-7507. Section 314.126 states, "(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation […] Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs," then delineates the characteristics of an adequate and well-controlled study. *Id*.

[284] Section 601.25 was removed in 2016 as obsolete. . Removal of Review and Reclassification Procedures for Biological Products Licensed Prior to July 1, 1972, 81 Fed. Reg. 7445 (February 12, 2016). The Final Rule cited

Implementation of Efficacy Review, 47 Fed. Reg. 24696 (June 8, 1982). Merck's MMR Virus Vaccine, Live was among the "[b]iological products determined to be safe and effective and not misbranded." *Id*. at 24697.

3. FDA Review of Vaccine Labeling After 1973

121. FDA's "Guidance for Industry: FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information" stated:

> The labeling requirements for biological products are found in several sections of the Federal Food, Drug, and Cosmetic Act (FDCA) and the PHS Act, including: Section 201, 502, and 503 of the FDCA, and Section 351 of the PHS Act. In addition to the statutory provisions, FDA's regulations on labeling requirements, including the content and format requirements for vaccine labeling, are found primarily in 21 CFR Parts 201 and 601.

FDA Review of Vaccine Labeling (2004) at 2.[285]

122. FDA's Review of Vaccine Labeling further stated:

> Under 21 CFR 601.2 (a), manufacturers must submit proposed vaccine labeling to FDA as part of a biological license application (BLA). In addition, changes to existing vaccine labeling requires FDA review pursuant to 21 CFR 601.12(f). Most such changes require a BLA supplement (BLS) and transmittal of Form FDA 2567. In its review, FDA determines whether the information presented in the labeling is scientifically accurate, conforms to regulatory requirements set out in 21 CFR 201.56 and 201.57, and includes requested revisions.

Id.

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newer regulations to assess and ensure the safety and effectiveness of biological products, including the labeling requirements in CFR part 201. *Id*.

[285] FDA Review of Vaccine Labeling (2004). https://permanent.access.gpo.gov/LPS112955/ucm092196.pdf.

123. In 1979, the FDA, as part of a final rule titled "Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs"[286] issued 21 C.F.R. §§ 201.56 and 201.57 which stated in relevant part:

> Section 201.56:
>
> (a) The labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug.
>
> (b) The labeling shall be informative and accurate and neither promotional in tone nor false or misleading in any particular.
>
> (c) The labeling shall be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.
>
> Section 201.57 (c)(2):
>
> All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless the requirement is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

Id. at 37462; 21 CFR §§ 201.56 and 201.57.

124. FDA "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," issued in 1998,[287] stated:

> Substantial evidence was defined in section 505(d) of the [FDC]Act as 'evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be conducted by such experts that the drug will have the effect it purports or is

[286] 44 Fed. Reg. 37434 (June 26, 1979) (to be codified in 21 CFR Parts 201 & 202).
[287] Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," (May 1998). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Id. at 3.

125. The Guidance further stated:

> Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. § 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314. 126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)).

Id. at 4 (emphasis added).

126. In December 2000, the FDA proposed amendments to 21 C.F.R. §§ 201.56 and 201.57; and as background for the amendments, the FDA stated:

> The part of a prescription drug product's approved labeling directed to health care practitioners (also known as its "package insert," "direction circular," or "package circular") is the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals. This part of approved labeling is a compilation of information based on a thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. The regulations governing the format and content of labeling for prescription drugs and biologics appear at §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57). …

> In addition to these regulations, the National Childhood Vaccine Injury Act (Public Law 103-66) requires FDA to monitor the adequacy of labeling for children's vaccines.

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082, 81083 (proposed December 22, 2000) (to be codified at 21 CFR pt 201).

127. In 2006, the FDA adopted a final rule amending 21 C.F.R. §§ 201.56 and 201.57 that stated:

> Section 201.56
>
> (a) *General Requirements.*
>
> (1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.
>
> (2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false or misleading.[288]
>
> (3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in

[288] In finalizing the amended rule, FDA stated: "the agency wishes to make it clear that manufacturers have an ongoing obligation to ensure that claims in labeling have adequate substantiation and are not false or misleading. When new information comes to light that causes information in labeling to become inaccurate, manufacturers must act to change the content of their labeling, in accordance with §§ 314.70 and 601.12 (21 CFR 314.70 and 21 CFR 601.12)." Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 at 62 (January 24, 2006) (to be codified at 21 CFR pt 201) (emphasis added). *See also Wyeth v. Levine*, 555 US 555, 608 (2009), citing 21 U.S.C. § 355(k) (A manufacturer "must periodically submit any new information that may affect the FDA's previous conclusions about the safety, effectiveness, or labeling.").

humans must be identified as such and included with human data in the appropriate section of the labeling

Section 201.57 (c) *Full prescribing information.* (2) *Indications and usage.*

(iv) For drug products other than biological products, all indications listed in this subsection must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined by § 314,126 (b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.[289]

71 Fed. Reg. 3922 at 3986, 3989 (January 24, 2006).

128. None of the changes in the regulation of drugs or biologics changed the responsibility of vaccine manufacturers under the PHSA to establish efficacy by substantial evidence of effectiveness in the form of adequate and well controlled clinical studies.

129. The standards applying to vaccine labeling from the time FDA began regulating vaccines in 1972 to the present can be summarized as follows:

a. "The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug." 21 CFR § 201.56(a)(1).

[289] In the 2000 proposed rulemaking discussing this amendment FDA stated: "FDA believes that it is appropriate to take the characteristics of an adequate and well-controlled investigation, as described in 314.126, into account in evaluating the sufficiency of evidence of effectiveness that sponsors submit in BLA's to satisfy the licensure standards in Section 351 of the PHS Act. (See FDA's Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products," May 1998.)" Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. at 81091.

b. "[T]he labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false or misleading." 21 CFR § 201.56(a)(2)

c. "[A]ll indications … must be supported by substantial evidence of effectiveness." 21 CFR § 201.57 (c)(v).

130. The FDCA deems a drug to be "misbranded" if "its labeling is false or misleading in any particular." 21 USC § 352 (a)(1). "If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account … the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the articles to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual." 21 U.S.C. § 321 (n) (emphasis added).[290] The PHSA states: "No person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package or container of the biological product so as to falsify the label or mark." 42 USC § 262 (b).[291]

[290] *See also* 21 C.F.R § 1.21 ("Failure to reveal material facts. (a) Labeling of a food, drug, device, cosmetic, or tobacco product shall be deemed to be misleading if it fails to reveal facts that are: (1) Material in light of other representations made or suggested by statement, word, design, device or any combination thereof; or (2) Material with respect to consequences which may result from use of the article under: (i) The conditions prescribed in such labeling or (ii) such conditions of use as are customary or usual.").

[291] *See also* Section 300aa-22(b)(2) ("For purposes of [section 300aa-22(b)](1), a vaccine shall be presumed to be accompanied by proper directions and warnings if the vaccine manufacturer shows that it complied in all material respects with all requirements under the Federal Food, Drug, and Cosmetic Act [21 USC §§ 301 et seq.] and the Public Health Service Act [42 USC § 262] (including regulations issued under such provisions) applicable to the vaccine and related to vaccine-related injury or death for which the civil action was brought unless the plaintiff shows …that the manufacturer engaged in the conduct set forth in [300aa-23(d)(2)(A) or (B)]."); Section 300aa-23(d)(2) ("(A) fraud or intentional and wrongful withholding of information … during any phase of a proceeding for approval of the vaccine under [42 USCS § 262], or (B) intentional and wrongful withholding of information relating to the safety or efficacy of the vaccine after its approval.").

131. "[A]ll biological products are subject to the misbranding provisions of both section 502 of the Federal Food, Drug, and Cosmetic Act [21 USC § 352] and section 351(b) [42 USC § 262(b)] of the Public Health Service Act. A biological product whose label purports, represents, or suggests it to be effective and/or safe for certain intended uses and which is not safe and effective for such uses, is misbranded within the meaning of both acts, and therefore should and will not be licensed under Section 351 of the Public Health Service Act. Congress has clearly stated that a misbranded biologic may not be distributed in interstate commerce." Biological Products: Procedures for Review of Safety, Effectiveness, and Labeling, 38 Fed. Reg. at 4319.

4. FDA's Regulation of Vaccines Under the Public Health Service Act, as amended by the National Childhood Vaccine Injury Act

132. In 1986 Congress passed the National Childhood Vaccine Injury Act ("NCVIA") amending the Public Health Service Act. 42 USC § 300aa *et seq*. The origins of the NCVIA are set forth in a court opinion in a personal injury case involving Merck, *Mazur v. Merck,* 767 F. Supp. 697 (E.D. Pa 1991), and the legislative history of the Act.

132.1. [292]The decision in *Mazur v. Merck*, 767 F. Supp. 697 (E.D. Pa 1991) stated:

> [William Freilich, Merck's in-house counsel] saw a way for 'Merck to limit its liability exposure based on the *Reyes* case.' He proposed Merck, other vaccine manufacturers, CDC representatives, the Immunization Practices Advisory Committee ("ACIP"), the Bureau of Biologics, the Food and Drug Administration, the Committee on Infectious Diseases of the American Academy of Pediatrics ("Redbook Committee"), state public health departments, and representatives of parent and consumer groups meet to discuss alternatives programs. At the meeting, three alternatives were suggested.

Id. at 702.

[292] Throughout this report, I have used subparagraphs to collect the evidentiary support for the statements set forth in the corresponding header paragraph. For example, here, the header paragraph is 132. The evidentiary statements supporting it are collected in paragraph 132.1-4.

132.2. The *Mazur* decision also stated:

> The first proposal was to require manufacturers to be responsible for vaccine administration throughout the country…
>
> The second suggestion, one that was adopted by all of the participants at the meeting, was to lobby for the establishment of a no-fault compensation fund for children injured as a result of immunizations. The National Childhood Vaccines Injury Act of 1986, 42 U.S.C. §§ 300aa–33, was the product of this legislative initiative.
>
> The third alternative, one that was adopted by Merck and the CDC, was to require the CDC, as the primary purchaser of Merck's MMRII vaccines, to disseminate warnings to individuals who would receive the vaccine as part of a public health program.

Id. (internal citations omitted) (emphasis added).

132.3. The legislative history of the NCVIA stated:

> The Committee on Energy and Commerce, to whom was referred the bill (H.R. 5546) to amend the Public Health Service Act to establish a National Vaccine Program for the development of new vaccines and the improvement of existing vaccines and a program to compensate the victims of vaccine-related injuries and deaths, and for other purposes, having considered the same, report favorably thereon with amendments and recommend that the bill, as amended, do pass.

House Report No 99-908 at *1.

132.4. House Report No 99-908 also stated:

> H.R. 5546, the 'National Childhood Vaccine Injury Act of 1986,' creates a new system for compensating individuals who have been injured by vaccines routinely administered to children. The system consists of two separate, but related parts and concerns only the actions of those injured by specified childhood vaccines and the manufacturers of such vaccines.

> Part A of the system amends the Public Health Service Act to establish a Federal "no-fault" compensation program[293] under which awards can be made to vaccine-injured persons quickly, easily, and with certainty and generosity. …
>
> Part B of the system deals with the additional remedies that are available to vaccine-injured persons should they elect to reject a judgment and award made under the compensation program and to take action directly against a vaccine manufacturer. …
>
> H.R. 5546 contains several other provisions not pertaining to the issue of compensation for vaccine-injured persons, but very much linked to the related questions of vaccine development, safety, and effectiveness. …

Id. at 1-3.

133. The NCVIA required the Secretary of Health and Human Services to establish a National Vaccine Program and to initiate a review of all vaccines already on the market that would be included as part of the no-fault compensation program. The review of vaccines already on the market was, in turn, delegated to the FDA.

133.1. Section 300aa-1 stated:

> The Secretary shall establish in the Department of Health and Human Services a National Vaccine Program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. The Program shall be administered by a Director selected by the Secretary.

42 U.S.C. § 300aa-1.

133.2. Section 300aa-1, note stated:

> "Review of Warnings, Use Instructions and Precautionary Information.
> Pub.L. 99-660, Title III, § 314, Nov. 14, 1986, 100 Stat. 3782, provided that: Not later than 1 year after the effective date of this title [see other provisions note to this section]

[293] *See* Schedule 29 (summarizing the no-fault compensation program).

> and after consultation with the Advisory Commission on Childhood Vaccines established under section 2119 of the Public Health Service Act [42 USCS § 300aa-19] and with other appropriate entities, the Secretary of Health and Human Services shall review the warnings, use instructions, and precautionary information presently issued by manufacturers of vaccines set forth in the Vaccine Injury Table set out in section 2114 of the Public Health Service Act [42 USCS § 300aa-14] and shall by rule determine whether such warnings, instructions, and information adequately warn health care providers of the nature and extent of dangers posed by such vaccines. If the Secretary determines that any such warning, instruction, or information is inadequate for such purpose in any respect, the Secretary shall at the same time require the manufacturers to revise and reissue such warning, instruction, or information as expeditiously as practical, but not later than 18 months after the effective date of this title.'"

Id. (original bold removed, underline added).

133.3. In 1988 the Secretary of Health and Human Services delegated responsibility for the Section 314 Review to the Assistant Secretary for Health.[294]

133.4. In 1988 the Assistant Secretary of Health and Human Services delegated responsibility for the Section 314 Review to the Commissioner of the FDA.[295]

133.5. In 1993, as FDA Commissioner, I delegated the duty for the Section 314 Review to the FDA's Center for Biologics Evaluation and Research.[296]

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[294] "Notice is hereby given that I have delegated to the Assistant Secretary for Health, with authority to redelegate, all the authorities vested in the Secretary of Health and Human Services under … 314 … of Pub. L 99-660 (42 U.S.C. 300aa-1 note and 300aa-4), as amended hereafter." NCVIA, Delegation of Authority; Assistant Secretary for Health, 53 Fed. Reg. 22054.

[295] "Notice is hereby given that in furtherance of the delegation of authority of June 1, 1988, from the Secretary of Health and Human Services to the Assistant Secretary for Health of all the authorities vested in the Secretary under … Pub. L 99-660 (42 U.S.C. 300aa-1 note) as follows: … To the Commissioner of Food and Drugs: … Section 314 of Pub. L. 99-660 – Review of warnings, use instructions, and precautionary information. NCVIA, Delegation of Authority, 53 Fed. Reg. 36127.

[296] "The Food and Drug Administration (FDA) is amending the regulations for delegations of authority by adding new authorities delegated … to the Commissioner... The new authorities are under certain provisions of the Public Health Service Act and of the National Childhood Vaccine Injury Act of 1986. … under the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs … [t]he Director, Center for Biologics Evaluation and Research (CBER), and the Associate Director for Policy Coordination and Public Affairs, CBER, are

134. The FDA's Section 314 Review applied to vaccines already licensed at the time of passage of the NCVIA, and employed the same regulations used to evaluate approval of a new product. After input from the National Vaccine Advisory Committee the review focused on, among other things: vaccine efficacy, including duration of protection, immunogenicity,[297] vaccine improvements which would improve utilization and administration, and stability of vaccine storage characteristics.

134.1. FDA's 2004 Guidance for Industry: "FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information" stated:

> Section 314 of the NCVIA required FDA to review the warnings, use instructions and precautionary information distributed with each vaccine listed in section 2114 of the Public Health Service Act (PHS Act) at the time of the NCVIA's passage.

FDA Review of Vaccine Labeling (2004) at '2 (footnotes omitted).

https://permanent.access.gpo.gov/LPS112955/ucm092196.pdf.

134.2. The FDA Review of Vaccine Labeling also stated:

> By applying existing drug labeling regulations (e.g., 21 CFR 201.56 and 201.57), current labeling as supplied by the manufacturer, as well as a survey of medical practitioners, FDA created draft Summaries of Important Information (SII) for each applicable vaccine listed in Section 2114's Vaccine Injury Table (VIT) and distributed them to the appropriate manufacturers on March 3, 1992.

Id. at '4.

134.3. The FDA Review of Vaccine Labeling also stated:

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authorized to perform the … Section 314 of the National Childhood Vaccine Injury Act of 1986 – Review of warnings, use instructions, and precautionary information." Delegations of Authority and Organization; National Childhood Vaccine Injury Act of 1986, 58 Fed. Reg. 17105-06 (April 1, 1993).

[297] *See* Section III.B.3 above (discussing immunogenicity).

> Throughout its review process, FDA consulted the Advisory Commission on Childhood Vaccines (ACCV) to assess the warnings, use instructions and precautionary information issued for applicable childhood vaccines. The NCVIA mandated creation of the ACCV to provide expert advice to the Secretary about, among other things, the implementation of the statute.

Id.

134.4. The National Vaccine Advisory Committee, Report of the Subcommittee on Improvement of Existing Vaccines, approved by the full committee, September 13, 1989, stated:

> It is essential to establish a mechanism for systematic review of available vaccines against infectious diseases on a continuing basis. The review should begin with the vaccines covered by the National Vaccine Injury Compensation Program. … Such a review will include the following aspects of current vaccines:
>
> 1. Efficacy, including duration of protection
> 2. Adverse effects/safety
> 3. Immunogenicity
> 4. Vaccine improvements which would improve utilization and administration
> 5. Stability of vaccine storage characteristics
> 6. Public and professional perception of these vaccines.

National Vaccine Advisory Committee, *Report on the Improvement of Existing Vaccines* 1-2 (Wilfert, 1989)[298] (emphasis added).

135. The Section 314 Review initiated following enactment of the NCVIA was to evaluate whether vaccines on the market in 1986 were safe and effective and had accurate, up-to-date labeling. Furthermore, products that were not found to be both safe and effective, or that had inaccurate labeling, would have to have the labeling revised.

[298] available at https://wayback.archiveit.org/3919/20140225190557/http://archive.hhs.gov/nvpo/nvac/Improvement%20of%20Existing%20Vaccines%209-13-89.pdf

136. In my opinion, the Section 314 Review was different than the FDA review conducted in 1973 when responsibility for regulation of vaccines was transferred to the FDA, described above, because the NCVIA's no-fault compensation program for vaccine-related injuries was related to the manufacturers' responsibility to ensure their vaccines are safe and effective and have labeling that is not false or misleading.

137. As a part of the implementation of the no-fault compensation program created by the NCVIA, Congress delegated the duty to warn about potential dangers resulting from the administration of a vaccine manufactured by the manufacturer.[299]

137.1. Section 300aa-22, titled "Standards of Responsibility." Subsection (c) stated:

> Direct warnings. No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after [Oct. 1, 1988] solely due to the manufacturer's failure to provide direct warnings to the injured party (or the injured party's legal representative) of the potential dangers resulting from the administration of the vaccine manufactured by the manufacturer.[300]

42 U.S.C § 300aa-2.

[299] Prior to the NCVIA's enactment, Merck contractually delegated its duty to warn to individuals who received vaccines as part of a public health program to the CDC. *See*, *Mazur v. Merck*, 767 F. Supp. at 702 ("[t]he third alternative, one that was adopted by Merck and the CDC, was to require the CDC, as the primary purchaser of Merck's MMRII vaccines, to disseminate warnings to individuals who would receive the vaccine as part of a public health program."); *see also* Schedule 16 (describing the CDC vaccine purchasing programs).

[300] "Subsection (c) addresses a line of cases in which vaccine manufacturers have been held liable for their failure to provide warnings directly to the injured party. (See, e.g., *Givens v. Lederle*, 556 F.2d 1341 (5th Cir. 1977), *Reyes v. Wyeth Laboratories*, 498 F.2d 1264 (5th Cir. 1974) and *Davis v. Wyeth Laboratories*, 399 F.2d 121 (9th Cir. 1968).) … If the manufacturer provides an adequate warning and adequate directions to an intermediary such as a doctor, nurse, or pharmacist …the manufacturer should not be held liable for any failure to warn or provide directions directly … Thus, once the manufacturer provides adequate warnings and directions to such professionals, the manufacturer meets the requirements of this provision and fulfills its obligations under the law with respect to its duty to warn of potential vaccine risks or hazards." House Report No. 99-908, 1986 U.S.C.C.A.N. 6344, 1986 WL 31971 at *27.

138. To fulfill its obligations under the NCVIA with respect to its duty to warn of potential vaccine risks or hazards, a manufacturer must provide adequate warnings and directions to the intermediary who, in turn, provides the information to the vaccine recipient.

139. In my opinion, this duty is continuous, and the manufacturer must provide updates with any information it later discovers, or in the exercise of reasonable care, should have discovered about its vaccine. The material information that a manufacturer must provide would include any aspects of the vaccine identified as important by the National Vaccine Advisory Committee, such as vaccine efficacy, including duration of protection, immunogenicity, vaccine improvements which would improve utilization and administration, and stability of vaccine storage characteristics.

VI. THE EMERGENCE OF MUMPS POTENCY AND EFFICACY ISSUES IN MERCK'S MUMPS VACCINES

A. FDA's Section 314 Review of Merck's MMRII Label, and Merck's Proposed Response to the FDA's findings

140. Merck's MMRII was one of the vaccines licensed at the time of the NCVIA's passage and subject to the Section 314 Review, discussed above. In 1996, the FDA had not completed its Section 314 review of Merck's MMRII label.

140.1. An email from Merck Manufacturing Division ("MMD"), Biologics Licensing Regulatory Administrator,[301] Katalin Abraham, to MMD's Director, Biologics Licensing, Dr. David Wonnacott, with the subject: "Teleconference, 2/23/96, with B. Yetter" dated February 26, 1996, stated:

[301] Throughout this report, employees are referenced by their title at the time of the document cited, unless otherwise specified.

> On 2/23/96, there was a teleconference with Bob Yetter, CBER[302], regarding the MMRII labeling. In attendance were David Wonnacott, Donna Marron and me.
> The National Childhood Vaccine Injury Act (NCVIA) has mandated CBER review of all vaccine labelling. The first draft of the Federal Register notice must be completed in April. The notice will include copies of all the approved (not necessarily final printing) labelling in the docket. CBER will prepare the first draft of the Federal Register Notice. This will be written under the assumption that the draft of the MMRII revision will be satisfactory.
>
> Donna Marron explained to Bob Yetter that the MMRII label has not completed revision nor internal review due to other priorities and that Merck was not aware of the NCVIA mandate. …
>
> According to Bob [Yetter], Dr. Lundquist, CBER, raised the issue of the mumps labelling. The current label[303] says that 20,000 TCID50 [4.3 log10] are available at reconstitution.[304] According to Bob [Yetter], CBER understands that only 70% of lots will actually contain 20,000 infectious units at expiry. Dave Wonnacott explained that we are currently evaluating this and that historically we have provided the release specification. Bob [Yetter] said that the way it is written it implied that this is met through expiry. He said that for the purposes of the NCVIA, CBER will accept a change in the labelling that is consistent with the data and suggested either "at the time of filling, contains no less than 20,000..." or "at expiry, no less than 5,000 . . ." Bob Yetter reiterated that after this and the 8/11/95 issues are addressed, CBER will turn their review around in short order.

MRK-KRA00095142 (emphasis added).

[302] "CBER" in Merck's documents is a reference to FDA's Center for Biologics Research and Review.
[303] *See* Schedule 1 discussing the MMRII label.
[304] *See* Section III.A above discussing how the freeze dried vaccine is reconstituted at a doctor's office prior to administration.

140.2. An email from MMD's Biologics Licensing Regulatory Administrator, Katalin Abraham, to MMD's Director, Biologics Licensing, Dr. David Wonnacott, with the subject: "Teleconference with Dr. Norman Baylor, CBER," dated October 25, 1996, stated:

> A teleconference was held with Dr. Norman Baylor, CBER, on 10/25/96 by Dave Wonnacott. Also in attendance was Kati Abraham.
>
> The topic of discussion was the apparent discrepancy in claims for human serum albumin[305] among the circulars for the live virus vaccine family of products. Dr. Baylor's concern was that these inconsistencies must be resolved as part of the Section 314 review that is currently in progress. …
>
> The circular revisions have not been finalized due to issues other than the composition of the stabilizers and growth medium. Dave [Wonnacott] told Dr. Baylor that Merck would again review these circulars and correct any inconsistencies in the descriptions of the products.

MRK-KRA01972735 at '737.

141. By the end of 1996, the Section 314 Review identified an issue of the mumps potency claim on the MMRII label that needed to be remedied.

142. By the end of 1997, FDA concluded that the mumps potency claim in the Description section of Merck's MMRII label was an end expiry claim, meaning that each dose of vaccine had to have 20,000 TCID50 [4.3 log10] for the entire 24 month shelf life. Merck planned to submit additional information to address the unresolved mumps potency issues.

142.1. An email from MMD's Biologics Licensing Regulatory Administrator, Katalin Abraham to MMD's Director, Biologics Licensing, Dr. David Wonnacott, with the subject: "Teleconference with Dr. Norman Baylor, CBER," dated January 23, 1997, stated:

[305] *See* Section III above describing BB-IND 10076 explaining the role of human serum albumin in the vaccine.

> The most recent FDA comments regarding the draft measles-, mumps- and rubella containing vaccines included a request to state "the expected minimum potency at the end of the dating period" in the labels for MMRII and for MUMPSVAX. This issue has been raised in an earlier teleconference. The minutes from that teleconference are copied below …
>
> A revision for the domestic circular of MMRII incorporating changes requested by CBER was provided to CBER for review. A number of comments were made by CBER which required further clarification. These points, listed below, were raised in this teleconference:
>
> Description: (release vs. expiry titers): The draft included the release titers for the product as had been discussed in an earlier (2/23/96) teleconference with CBER. The CBER comment required that expiry titers be provided. Dave Wonnacott requested that the circular list the release titers since we do not have strong data for expiry titers due to the variability of the potency assay. Dr. Baylor agreed to leave the release titers in for now, provided we offer some explanation as to how we will obtain better numbers down the road. He further stated that CBER is rethinking how things were done in the past and they are focused on stability.[306] He also commented that the minimum titers available should be known.

MRK-KRA01972735 (emphasis added).

142.2. A letter from MMD's Director, Biologics Licensing, Dr. David Wonnacott, to FDA's Office of Vaccines Research and Review, CBER, Attention Dr. N[orman] Baylor, dated December 5, 1997, stated:

> This letter is a follow-up to a discussion held November 5, 1997 between representatives from CBER … and Merck … regarding the shelf-life titer for mumps. It was apparent from our meeting that there are different interpretations regarding the "release" and "shelf-life" titer for mumps. The license states that "the original strength of the product"

[306] *See* Section III.B.2 above describing vaccine potency and the interconnection between potency and stability.

> is not less than 4.3 log TCID50 (20,000 TCID50 per dose). The current label statement, however, does not indicate that this titer (4.3 log TCID50) is considered the "original" or "release" titer. Therefore, the label statement has been interpreted as the "shelf-life" specification. A meeting will be held with CBER and Merck staff in the near future to provide clarification to these issues.

MRK-KRA01972448 at 451 (emphasis added).

142.3. A letter from FDA's Director, Office of Vaccines Research and Review, CBER, Dr. Carolyn Hardegree, to MMD's Vice President, Vaccine Quality Operations, Dr. Barry Garfinkle, dated December 22, 1997, stated:

> This letter is in regard to your Supplement to your Product License Application dated March 31, 1997,[307] for Measles, Mumps and Rubella Virus Vaccine Live submitted under section 351 of the Public Health Service Act.
>
> The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this Product License Application. We have determined that based on unresolved issues regarding maintenance of mumps potency throughout the current dating period, this Supplement is not approvable at this time.

MRK-KRA01972448 at '450 (emphasis added).

142.4. A letter from MMD's Vice President, Vaccine Quality Operations, Dr. Barry Garfinkle, to FDA's Director, Office of Vaccines Research and Review, CBER, Dr. Carolyn Hardegree, regarding "Measles, Mumps, and Rubella Virus Vaccine Live, Reference Number 97-0431," dated December 31, 1997, stated:

> This letter is in response to your letters to me, dated December 22, 1997. … The purpose of this letter is to inform you that we intend to amend these license supplements, which

[307] *See* MRK-KRA01972719 ("Product License Application Supplement, Alternative to Lot Release for Measles, Mumps and Rubella Virus Vaccine Live" dated March 31, 1997) and Guidance on Alternatives to Lot Release for Licensed Biological Products, 58 Fed. Reg. 38771 (July 20, 1993).

> you determined to be not approvable at this time, by submitting additional information addressing unresolved mumps potency issues.

MRK-KRA01972448 at ‘449 (emphasis added).

143. In my opinion, the Section 314 Review of MMRII was consistent with the goals set forth by Congress to enact the NCVIA, including focus on stability and potency, among other vaccine characteristics.

144. In response to the FDA’s request to define the mumps potency claim on the MMRII label in terms of the minimum titers present at expiry, Merck conducted an analysis to determine if it could meet a 20,000 [4.3 log10] TCID50 mumps end expiry specification. The results of this analysis, reported in January 1998, concluded that for lots manufactured since 1994 the predicted mumps potency at expiry was 8,000 [3.9 log10] TCID50, not the 20,000 [4.3 log10] TCID50 stated on the label. Merck proposed to FDA to lower the mumps end expiry claim on the MMRII label to 5,000 [3.7 log10] TCID50 to ensure its label accurately reflected the mumps potency in the marketed product for the 24 month shelf life. Before Merck could reduce the mumps end expiry claim on the MMRII label, the FDA required Merck to submit clinical data demonstrating that reducing the potency of the mumps component in MMRII would not reduce MMRII’s clinical effectiveness.

144.1. A Merck document titled “CDOC [Clinical Development Oversight Committee][308] Critical Activities” issued January 15, 1998 stated:

> Update Mu[mps] Potency Issue: Germany has short-dated[309] M-M-R II to an 18 mo[nths] expiry and has sent a Dear Colleague[310] letter to CBER recommending the same action.

[308] MRL’s former Vice President, Worldwide Regulatory Affairs, Keith Chirgwin, testified that the Clinical Development Oversight Committee “was a governance committee to provide oversight for the clinical and regulatory activities with MRL, Merck Research Laboratories.” Deposition of Keith Chirgwin, January 26, 2017, 38:17-39:2.

> A meeting with CBER regarding the issue of expiry titers took place on December 16 1997]. [Merck Manufacturing Division] presented the 2-8°C stability data[311] from 1994 to present demonstrating a downward trend in log loss. Based on linear regression modified by a new model, the expiry titers are … 5000 [3.7 log10] …for Mu[mps]... CBER is requesting that a clinical protocol be submitted to them by the end of January which will address expiry efficacy.[312]

MRK-KRA01715116 at '128 (bolded original removed, underline added).

144.2. A Memo from Merck Research Laboratories ("MRL"), Director, Biostatistics and Research Decision Sciences ("BARDS"), Tim Schofield, to MMD's Director, Biologics Licensing, Dr. David Wonnacott, with the subject: "Expiry Potency Calculations for Mumps Containing Live Virus Vaccines," dated January 23, 1998, stated:

> Based on an analysis of the data from the 52-lots of combined products produced between 1987 and 1996, the predicted potency of mumps containing vaccines after 24-months storage at 2-8°C is equal to 4.3 log10 TCID50/dose [20,000 TCID50] (lower 95% confidence bound on the predicted potency. This estimate for the subset of 7 lots produced since 1994 is equal to 3.9 log10 TCID50/dose [8,000 TCID50].

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[309] *See* Section III.B.2.c above describing the vaccine dating period and "short dating."

[310] A "Dear Colleague" or "Dear Doctor" letter is a letter used to notify health care providers about important new or updated information about a drug or vaccine. 21 C.F.R § 200.5; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), "Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information," at 3-5 (2014). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM233769.pdf.

[311] During the 24 month shelf life of mumps, the vaccine is stored at 2-8°C. *See* Section III.B.2 above discussing storage temperature for the 24 month shelf life.

[312] MRL's 30 (b)(6) designee, MRL's Executive Director of Vaccine Affairs, Dr. Barbara Kuter, testified as follows: "*Q. Okay. So tell me, how do you define efficacy? A. Efficacy is determining whether basically a -- I'll use it in the context of vaccines -- whether a vaccine prevents disease. It is one of the critical milestones in licensure of any vaccine, and specifically it is evaluation of the attack rate in vaccinated versus unvaccinated or a placebo group. The classic study is done under very stringent criteria. It's usually done as a double-blind randomized, controlled, placebo-controlled, trial. And the criteria are quite strict, so you may limit the age, you may limit geography, you may limit who's included based on comorbidities, you may limit based on what other vaccines are received. And I think that it's -- it's, again, a key type of study that is done prior to licensure of most vaccines*." Deposition of Barbara Kuter, December 14, 2016, 128:24-129:17 (emphasis added).

> Thus based on the long term stability history of single dose mumps containing vaccines, these products are predicted to maintain 4.3 log10 TCID50/dose [20,000 TCID50] throughout their shelf-life (24 months). The estimate for recent lots of mumps containing vaccines predicts a lower potency at expiry (3.9 log10 [8,000] TCID50/dose). The trend in mumps potency loss in current lots of mumps containing vaccines will be addressed with an active stability monitoring plan, as well as a stability time point retest strategy.

MRK-KRA00587151 (bolded original removed, underline added).

144.3. A letter from MMD's Vice President, Vaccine Quality Operations, Dr. Barry Garfinkle, to FDA's Office of Vaccines Research and Review, CBER, Attention: Dr. Norman Baylor, dated January 28, 1998, stated:

> This letter provides the information addressing unresolved mumps issues. …
>
> During teleconferences in 1996 and in early 1997 as well as in an informal meeting on November 19, 1997, the need to clarify the label claims for potency and to define them in terms of the minimum titers present at expiry became evident. Currently, the minimum release titers of … 20,000 [4.3 log10]… for the mumps … are specified. It was noted that there have been some inconsistencies in the past as to how the current titer claims should be interpreted.
>
> In response to CBER's request to define the potency claims on the label in terms of the minimum titers present at expiry, we have recently performed marketing stability analyses using a mixed effects statistical model to determine these titers. The results of these analyses indicate that, based on our targeted release titers and the observed potency losses over time at the recommended storage temperatures as determined by linear regression, we can define the potency titers present at the end of shelf life for our product. We propose to specify the end of shelf life potenc[y] … to be … 5000 [3.7 log10] TCID50 … for … mumps. …
>
> At the meeting on December 16, CBER requested a draft of the clinical trial protocol designed to support the end of shelf life titer claim for mumps. This protocol is

> undergoing preparation and review. We will set up a preclinical meeting with you to discuss the protocol when it is available.

MRK-KRA00756256 at '257 (emphasis added).

144.4. A Merck document titled: "M-M-R II Competitive Defense Task Force '*Why Take A Chance*' Tactical PAC [Product Approval Committee] Update," dated February 26, 1998, stated:

> End-expiry claim:
> CBER: The FDA requires that the label specify the minimum claimed potency throughout shelf-life. The potencies currently specified in the M-M- R®II label reflect the minimum titers at release, not expiry. CBER has requested that we specify the minimum claimed end-expiry potency for each component (95% lower bound). If the minimum claimed potency is lower than the potency range for which immunogenicity has been demonstrated, then we must provide clinical data supporting this minimum immunizing dose. During discussions with CBER in December 1997, CBER indicated that the shelf-life of the vaccine may need to be reduced pending such data. CBER has expressed an interest in reviewing the study design of the end-expiry trial with Merck prior to its initiation to ensure that regulatory concerns are addressed. Concerns have included 1) the availability of lots with the appropriate expiry titer; 2) methods employed in obtaining the appropriate lots; serologic assays for measuring immunogenicity.

MRK-KRA00666494 at '25-26 (Original bold removed, underline added).[313]

145. In my opinion, by 1998, any assertion by Merck that the 20,000 TCID50 [4.3 log10] mumps potency claim on its MMRII label was anything but an end expiry claim was

[313] In 2002, a section of a MMRII Background package for the Clinical and Regulatory Review Committee, titled "M-M-R®II Label Claims and Interactions with Regulatory Agencies" stated in 2.1.1 Regulatory Interactions with CBER:" "…Arguments for the demonstrated immunogenicity at lower potencies of the monovalents and the apparent effectiveness of Merck's release strategy, due to the virtual eradication of disease in the US and Finland where the product was used exclusively were further rejected, because of the small number of children used in the studies, and the circumstantial nature of the justification. CBER asked Merck to demonstrate that the mumps expiry specification could be met as per their interpretation." MRK-KRA00615152 at '57 (emphasis added); *see also* MRK-KRA00615147 (October 2, 2002 cover email); Schedule 7 (describing the efficacy studies).

rejected by FDA. In response, Merck stated that it could define the potency titers present at the end of shelf life and proposed to reduce the mumps potency claim to 5,000 [3.7 log10] TCID50. Furthermore, to support the change in the labeling to state "at expiry, no less than 5,000 . . ." Merck needed clinical data to demonstrate the clinical effectiveness of MMRII with the proposed lower mumps potency. Merck began preparing and reviewing a clinical protocol to support the proposed mumps end expiry label change.

B. Following the Section 314 Review and While Merck Conducted the Clinical Trial to Meet FDA's Requirement, Merck needed to implement a manufacturing change to ensure MMRII would meet the current end expiry claim of 20,000 [4.3 log10]

146. By early 1998, internal emails between Merck senior management stated that to support a lower mumps end expiry claim on the MMRII label "[w]e all agree that an MMRII end expiry study is needed" and there was "no question that this trial is necessary for regulatory purposes." Merck had only limited clinical data of the effectiveness of MMRII's mumps component at 20,000 [4.3 log10] TCID50 and no data for MMRII below 12,500 [4.1 log10] TCID50.

146.1. An email from MRL's Director, Worldwide Regulatory Affairs, Biologics/Vaccines, Dr. Keith Chirgwin, to MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, MRL's Clinical Monitor, Vaccines Infectious Diseases, Dr. Scott Thaler, MMD's Biologics Licensing Regulatory Administrator, Katalin Abraham, MRL's Vice President, Project & Vaccine Integration, Dr. Dorothy Margolskee, MRL's Director, BARDS, Timothy Schofield, cc'd to MRL's Vice President, Worldwide Regulatory Affairs/Vaccine Development, Dr. Henrietta Ukwu, and MMD's Vice President, Vaccine Quality Operations, Dr. Barry Garfinkle, with the subject "Mumps expiry trial," dated March 6, 1998, stated:

> There apparently is an outstanding [Clinical Development Oversight Committee] assignment to review the mumps stability data to determine whether an expiry trial is actually needed, and if so how urgent is that need.
>
> I wanted to re-emphasize that there is no question that this trial is necessary for regulatory purposes. Although there continues to be some ongoing discussion as to the true rate of decay for mumps stability, this debate does not change the requirements for the expiry trial. The current release specification for mumps is 4.3 [20,000 TCID50], i.e. we will release lots with mumps titers as low as 4.3. CBER has been requested to release at 4.3 in the past and this is what prompted this whole discussion in the first place. We have only limited clinical data at this dose and no data at all with the trivalent below 4.1 [12,500 TCID50] Even with the rosiest estimates of mumps stability, we can anticipate potency losses of <0.2 log over 24 months, therefore clinical data at the expiry titer supported by the manufacturing specification is required.
>
> We will be sending CBER a concept sheet for the end-expiry protocol which outlines the approach approved at CDOC last month. This document will propose use of aged (accelerated aging) material for the end-expiry arm and will describe controls, sample size, power and serologic assays to be used. These are the key issues which CBER has indicated it wanted to review prior to initiation of the study. The target date for submission of this document is 3/18. A follow-up teleconference will be scheduled later in the month.

MRK-KRA00095320 at ’20-21 (emphasis added).

146.2. An email from MRL’s Vice President, Project & Vaccine Integration, Dr. Dorothy Margolskee, replying to all the recipients of Dr. Chirgwin’s email, dated March 8, 1998, stated: “We all agree that an MMRII end expiry study is needed.” MRK-KRA00095320 (emphasis added).

147. By late 1998, Merck advised CBER that it had undertaken a clinical study to evaluate the immunogenicity of mumps when administered to children at a targeted expiry titer

of 3.7 log10 [5,000] TCID50/dose. Merck also committed that until the trial was completed the end-expiry titers for product in the United States would be 4.3 log10 [20,000] TCID50/dose for mumps as stated on the MMRII label. To provide a high level of assurance that the minimum titers would be maintained through expiry, Merck proposed to "overfill"[314] the mumps component of MMRII until the study data was available.

147.1. A letter from MMD Executive Director, Dr. Roberta McKee, to FDA's Director, Center for Biologics Evaluation and Research, Office of Vaccine Research & Review, Division of Vaccines and Related Products Applications, Dr. Carolyn Hardegree, dated December 10, 1998, stated:

> Enclosed is a proposal for changes to the release specification for the mumps component and to the procedure for potency assignment for the measles and mumps components of Measles, Mumps, and Rubella Virus Vaccine Live and associated live virus vaccines. The attached document also describes the stability data analysis used to determine the proposed release titer for mumps.

MRK-KRA00756233.

147.2. The document attached to Dr. McKee's December 10, 1998 letter stated:

> I. Introduction
>
> M-M-R®II is currently manufactured at or above the minimum titers of … 20,000 (4.3 log_{10}) … $TCID_{50}$/dose for … mumps ... In 1997 in communications with CBER, the need to clarify the label claims for potency of M-M-R®II and to define them in terms of the minimum titers present at expiry was conveyed to Merck. Merck has undertaken a clinical study to evaluate the immunogenicity of mumps when administered to children at

[314] A vaccine is manufactured to include a certain amount of live virus. Over the course of its shelf-life the live virus degrades or decays. The manufacturer must "fill" the vaccine at the time of manufacture with enough live virus to ensure the product will have the end-expiry potency at the end of its dating period. Merck was proposing to "overfill" the amount of mumps virus (add more at the time of manufacture), to have a high level of assurance that even with degradation the mumps component of MMRII would be at or above 4.3 log10 [20,000] after 24-months, MMR's dating period.

> a targeted expiry titer of 3.7 $\log_{10}$ [5,000] $TCID_{50}$/dose. Vaccine is now available and the clinical study will begin in January. An interim report, based on initial immunogenicity data, will be available 3Q99. The clinical study report will be completed 1Q00. …
>
> Until this clinical study has been completed, the end-expiry titers for product in the US will be … 4.3 $\log_{10}$ [20,000] $TCID_{50}$/dose for mumps … This will be effected by raising the release titer for mumps to accommodate our average projected potency losses over time and by improving the confidence in the release titer assignments. The latter will be accomplished by modifying current testing and release procedures to reduce assay variability. The goal is to provide a high level of assurance that the minimum titers are maintained through expiry.
>
> We are comfortable with this proposal, given the excellent field experience for M-M-R®II under current conditions and given the short interval before formal clinical study data begin to become available. We therefore request CBER's guidance and assistance to develop a mechanism whereby international shipments of M-M-R®II would continue without change in the current release procedures. …
>
> This proposal is an interim plan for product release and expiry dating. When the results of the end- expiry clinical trial are available, the release and dating proposal will be re-evaluated and the appropriate actions taken with CBER concurrence.

MRK-KRA00756233 at '35-36 (bolded original removed, underline added).

147.3. A letter from FDA's Acting Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Dr. William Egan, to MMD's Executive Director, Bio/Sterile Quality Operations, Dr. Roberta McKee, dated August 20, 1999, stated:

> This letter is to confirm the telephone conversations held on August 10, 1999, and August 16, 1999 … regarding increasing the minimum release titer for the mumps component of Merck's mumps containing vaccines to 5.0 $\log_{10}$ [100,000] $TCID_{50}$. It was pointed out that the variability of the mumps potency test at CBER is 0.226 $\log_{10}$ $TCID_{50}$. That the average loss in potency of the mumps component is 0.55 $\log_{10}$ $TCID_{50}$ per two years, and

> that the mumps vaccine must maintain a minimum potency titer of 4.3 $\log_{10}$ [20,000] $TCID_{50}$ throughout the current dating period of two years. Therefore, based on CBER's calculations the average titer of six independent and valid potency assays must be at least 5.0 $\log_{10}$ [100,000] $TCID_{50}$ at the time of release in order to be 95% confident that the lot will maintain potency of at least 4.3 $\log_{10}$ [20,000] $TCID_{50}$ for the two years.
>
> We understand that you will formulate all mumps containing vaccine lots manufactured (filled) on and after September 13, 1999, to contain at least 5.2 $\log_{10}$ [160,000] $TCID_{50}$. These lots will be released by CBER with a dating period of 24 months based upon the CBER potency testing criteria described above. Furthermore, all mumps containing lots submitted for CBER release, regardless of manufacturing date, will be subject to the described CBER release requirements as of November 8, 1999.

MRK-KRA00018614 (emphasis added).[315]

147.4. A Merck memo from MMD's Biologics Licensing Administrator, Katalin Abraham, to FILE, with the Subject "CBER Teleconferences on M-M-R®II: Status of Release with Respect to Potency Testing Format and Mumps Release Potency Changes), dated February 3, 2000, stated:

> According to Dr. McKee, [CBER's] Dr. Baylor … indicated that CBER viewed the higher mumps release titer as an interim measure until the results from the mumps expiry trial became available.

MRK-KRA00095144 at '44-45 (emphasis added).

147.5. A letter from FDA's Director, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Dr. Peter Patriarca, to

[315] In this report, to reflect the change in manufacturing implemented on September 13, 1999, lots manufactured before that date may be referred to as "pre-overfill" lots, and lots manufactured after it may be referred to as "overfilled" lots.

MMD's Executive Director, Bio/Sterile Quality Operations, Dr. Roberta McKee, dated February 11, 2000, stated:

> The Supplements to your License Applications … to include an increase in the minimum release titer for the mumps component to 5.0 log10 [100,000] TCID50 …have been approved.

MRK-KRA01897091.

148. Merck represented the mumps overfill as an interim plan; it was not proposed as a permanent specification change for MMRII. Furthermore, Merck represented it would be a "short interval" before data would be available from the clinical study it agreed to conduct, at which time Merck would re-evaluate the specifications.

VII. MERCK'S CLINICAL TESTING REGARDING THE EFFICACY AND POTENCY OF ITS MUMPS VACCINES

149. Clinical immunogenicity testing regarding the efficacy and potency of Merck's mumps vaccines was being conducted under two Biological-Based Investigational New Drug[316] ("BB-IND") applications for MMRII and one for ProQuad that it sought to license for sale in the U.S. Separate from the pending BB-INDs, Merck initiated a clinical trial comparing MMRII and Priorix as part of a marketing strategy.

A. Merck's Protocol 007: A "Study of An Approved Vaccine at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age"

1. FDA rejected testing by ELISA for Protocol 007

150. Before FDA would allow Merck to change its MMRII label claim from "each dose contains not less 20,000 [4.3 log10] TCID50 of the U.S. Reference Mumps Virus" to some lower number as discussed in Section VI above, Merck needed to provide clinical data of the

[316] *See* Section III.A above describing Merck's open BB-INDs.

immunogenicity of MMRII at expiry potencies. Although Merck used ELISA assays for other testing related to vaccines, FDA stated that a neutralization assay would be necessary in Protocol 007. Internally, Merck documents describe that it could not use ELISA in the mumps end expiry trial because Merck had not demonstrated a correlation between its ELISA and a functional assay.

150.1. A document titled "Phase V Clinical Development Plan MMRII" by MRL's Clinical Monitor for Protocol 007, Dr. Scott Thaler, and others, dated February 3, 1998, stated:

> Phase V Clinical Development Plan (CDP) for M-M-R®II
>
> *I. BACKGROUND AND RATIONALE…*
>
> D. The current assays used to determine seroconversion are ELISAs. Since the ELISA is not a functional assay, many organizations are looking for a neutralization assay as well as ELISA as a measurement of seroconversion.
>
> … For mumps, ELISA appears to be more sensitive than PN [plaque neutralization]. However, sera positive by ELISA may lack antibody to HN [hemagglutination-inhibition] protein, which may be why ELISA is not the preferred assay to assess protection to mumps.

MRK-KRA00667054 at '56 and '61 (original bold removed, underline added).

150.2. The document titled "Phase V Clinical Development Plan MMRII also stated:

> *III. MAJOR DEVELOPMENTAL ISSUES*
>
> A. Marketing Needs
>
> … For mumps virus vaccine strains, studies have shown that seroconversion rates based on ELISA GMTs may not correlate with results from neutralizing antibodies assays, a more sensitive and clinically relevant assay. For this reason, it is important to test mumps virus antibody levels by neutralization assay methods.

Id. at '62-63. (original bold removed, underline added).

150.3. The February 1998 document titled "M-M-R II Competitive Defense Task Force 'Why Take A Chance' Tactical PAC [Product Approval Committee] Update," stated:

> Assay Development Issues
> The assays used to measure immune responses to vaccination have undergone extensive changes in the past several years. For licensure in the United States of M-M-R®II … [f]or mumps, neutralization was utilized. In recent years, improvements in techniques have led to the adoption of ELISA-based (enzyme-linked immunosorbent assay) assays in large protocols because they are highly sensitive and far less labor-intensive compared with neutralization assays. Although ELISA-based assays are used in Merck M-M-R®II protocols presently, we have not yet adequately demonstrated a correlation between the older assays and the ELISA-based assays. In the absence of adequate data to support such a correlation, CBER has stated that for purposes of the expiry protocols, a neutralization assay for mumps will be necessary.

MRK-KRA00666494 at '58 (original bold removed, underline added).

151. According to Merck's documents, a neutralization assay was considered to be a more clinically relevant assay for mumps immunogenicity testing. Furthermore, a neutralization assay in Protocol 007 was necessary in the absence of adequate data to support a correlation between an ELISA and a neutralization assay.

152. In my opinion, in 1998, according to Merck's documents, Merck did not have clinical data to support a correlation between an ELISA and a neutralization assay when it initiated Protocol 007.

2. Merck submitted a proposed Clinical Protocol for FDA's review to "ensure that regulatory concerns,"[317] including the choice of serologic assay, were addressed

153. Merck prepared a "Proposal for Clinical Trials to Support an Expiry Potency for the Mumps Component of MMRII" and submitted it for FDA's review.[318] In response, FDA provided comments and questions regarding the serologic assays. FDA asked Merck to provide clinically valid justification for the serostatus cutoffs to be used in the assays.[319] FDA wanted Merck to demonstrate the cutoffs were linked to protection against the children getting mumps.[320]

153.1. A letter marked "Serial No. 24" from MRL's Director, Worldwide Regulatory Liaison, Biologics/Vaccines, Dr. Keith Chirgwin, to FDA's Center for Biologics Evaluation and Research, Office of Vaccine Research & Review, Division of Vaccines and Related Products Applications, Attention: Ms. Luba Vujcic, regarding "BB-IND 1016: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine)," dated June 23, 1998, stated:

> On December 16, 1997, representatives from Merck and CBER met to discuss the label claims for potency for Measles, Mumps, and Rubella Virus Vaccine Live. …
>
> At this meeting in December, CBER requested a draft of the clinical protocol designed to support the end of shelf life titer claim for mumps (i.e. 5000 TCID50/dose). In response to this request, the attached document entitled "Proposal for Clinical Trials to Support an Expiry Potency for the Mumps Component of M-M-R II" is being submitted to BB-IND 1016. …

MRK-KRA00137711 at '13 (emphasis added).

[317] MRK-KRA00666494 at '525-526.
[318] MRK-KRA00137711.
[319] MRK-KRA01620351.
[320] *Id.*

153.2. The "Proposal for Clinical Trials to Support an Expiry Potency for the Mumps Component of M-M-R-II," stated:

> I. Background and Rationale
>
> A. M-M-R®II Release and Expiry Potencies
>
> … Data on mumps is limited to immunogenicity at a potency of 4.1 - 4.3 log10 [12,500-20,000] TCID50. … However, there are no data for mumps below 4.1 log10TCID50. Therefore, we will demonstrate the immunogenicity of the mumps component of M-M-R®II at the claimed expiry potency of 3.7 $\log_{10}$ [5,000] $TCID_{50}$. …
>
> C. Proposal for Expiry Clinical Trials
>
> … Based on data from the original MMRII submission using an older neutralization assay, the estimated seroconversion rate for mumps is 96%. …

MRK-KRA00137711 at '19 -20 and '22 (original bold removed, underline added).

153.3. The "Proposal for Clinical Trials to Support an Expiry Potency for the Mumps Component of M-M-R-II" also stated:

> D. Assay Development
>
> Although an ELISA-based assay for mumps is used in Merck M-M-R II protocols presently, a correlation between the older (neutralization) assays and the ELISA-based assay has not been demonstrated. In the absence of adequate data to support such a correlation, for the purposes of the expiry protocols, a neutralization assay for mumps has been requested.[321] This assay is presently in the final stages of development and will be validated using serum samples at MRL from children immunized with M-M-R II in the context of several studies, prior to its use in the expiry protocols.

[321] A Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, titled: "Mumps neutralization meeting minutes," dated September 16, 1999 stated: "A requirement was set forth by CBER to use a functional neutralization assay for the mumps, measles and rubella due to: ... [t]he efficacy statement in M-M-R®II label are based on old, limited data and an assay that is no longer used, … [l]ack of data that correlates currently used ELISA assays and efficacy for M-M-R®II [and] .. [e]mergence of out breaks in highly vaccinated populations (Mumps)." MRK-KRA00020425 (emphasis added). *See also*, Schedule 7 (describing studies to support original MMRII submission).

> … For the purposes of the mumps expiry protocols, we assume that the percentage of subjects in the control groups who develop mumps neutralizing antibodies will be 96%, which is the rate in the package circular. If the seroconversion rate in the control group in the new assay differs from 96%, then the sample size may need to be adjusted in order to maintain the power of the study. At the present time, [JerylLynn™] will be the target virus in the neutralization assay. However, discussions are ongoing regarding adding additional strains, wild type strains in particular, to the neutralization assay in order to better assess the ability of the vaccine to neutralize wild type mumps.

MRK-KRA00137711 at '23 (original bold removed, underline added).

153.4. A letter from FDA's Director, Center for Biologics Evaluation and Research, Office of Vaccine Research & Review, Division of Vaccines and Related Products Applications, Dr. Carolyn Hardegree, signed by Dr. Karen Goldenthal, to MRL's Director, Worldwide Regulatory Affairs, Biologics/Vaccines, Dr. Keith Chirgwin, dated September 8, 1998, regarding "BB-IND 1016" stated:

> We have completed our review of the amendment dated June 24, 1998 … and we have the following comments and questions:
>
> 3. With respect to the statistical analysis of the clinical study:
>
> a) The proposed statistical analysis is adequate for the proposed end-expiry trial. Please note, however, that the new assay used to measure neutralizing antibody titers to mumps is not a validated assay and that the final claim of equivalence may be affected if the validated assay results differ from the assumed 96%. Please provide the detailed approaches that may be used to adjust sample size should this be necessary to maintain the power of the study.
>
> b) The equivalence margin should be calculated at a 5 rather than 10 percentage-point drop from an assumed 96% neutralizing antibody response in the control group. In addition, there should be another absolute criterion

that the lower limit of conversion rate is above 90%. We suggest that the sample size be re-estimated and the power adjusted accordingly. …

4. Please provide the Standard Operating Procedures (SOP's) for the validated serological assays to be used for each of the measles, mumps, and rubella components of the vaccine in this clinical study. Please include information on the antigen, the cut-offs for determining seronegativity and seropositivity, and the reference sera. Virus antigens used in serological assays enable the assessment of immunogenicity which is reflective of efficacy against natural infection; thus, wild-type antigens are appropriate for serological assays. Determinations of seropositivity and seronegativity as indicators of protection require clinically valid justification. Please provide additional details regarding the specific serological criteria evaluated in this study (e.g., seroconversion, GMT).

5. There are concerns about long-term protection against mumps … by the vaccine, as opposed to natural infection. As an indicator of duration of protection, the follow-up period should be extended to one year post-vaccination to assure that the vaccine at end-expiry is sufficiently immunogenic. Please comment.

MRK-KRA01620351 at '351-53 (emphasis added).

153.5. MRL's former Vice President, Worldwide Regulatory Affairs, Dr. Keith Chirgwin testified as follows:[322]

Q. So was -- back to what the FDA was requesting in September of 1998. It's your understanding that they were requesting some indicators of protection of kids getting sick, and you testified what they're really asking for is some surrogate of protection, correct?

Defense Counsel: Objection

[322] In this report, deponents are identified by their current title, if still employed with Merck, and their former title if no longer at Merck.

A. Well, the question, I'm reading it.

Q. Yeah.

A. 20 years later is they want clinically valid justification for however we define those cutoffs.

Q. And those cutoffs have to be tied to protection, though, correct, of disease?

A. They need to be justified. Difficult in the absence of a circulating virus to actually make a direct link at this juncture, or in 1998.

Q. But that's what they're asking for, correct?

Defense Counsel: Objection

A. They're asking -- no. I'm reading the letter, and they're asking for a clinically valid justification.

Q. That are indicators of protection?

A. Correct.

Q. And protection, you mean protection could be protection from kids getting disease, correct?

A. Yes.

Deposition of Keith Chirgwin, January 26, 2017, 77:17 – 78:17 (emphasis added).

154. During the development phase of Protocol 007, FDA asked to review the serologic assays Merck would use for mumps immunogenicity testing. Since Merck did not have adequate data to support a correlation between its ELISA assay and the older neutralization assays that supported the efficacy statement in the MMRII label, FDA requested Merck use a neutralization

assay. FDA also required Merck's serologic assays to have clinically valid justification for determining the serostatus of the children in the study. FDA required the assay to be an indicator of protection afforded by mumps vaccination. Moreover, FDA's additional requirement to follow up at one-year would measure duration of that protection.

155. In response to FDA's request to provide clinically valid justification for determining serostatus, Merck concluded that the neutralization assay must be "100% specific" for a wild type[323] neutralization response.[324] Merck documented that FDA was interested in protection against wild type mumps virus. Merck continued to consider the use of ELISA, if it could correlate the assay to a neutralization assay.

155.1. A Merck memo from MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Senior Investigator, Vaccine Basic Research, Dr. David Krah, MRL's Vice President, Project & Vaccine Integration, Dr. Dorothy Margolskee, MRL's Executive Director, Clinical Vaccines, Dr. Jerry Sadoff, MRL's Associate Director, Timothy Schofield, MRL's Executive Director, Virus & Cell Biology, Dr. Alan Shaw, MRL's Clinical Monitor, Vaccines Infectious Diseases, Dr. Scott Thaler, MRL's Senior Director, Worldwide Regulatory Affairs, Biologics and Vaccines, Dr. Henrietta Ukwu, among others, with the subject "Summary of the preparatory meeting (9/30/1998) for the CBER teleconference to discuss evaluation of immunogenicity in the Mumps Expiry Protocol," dated October 2, 1998, stated:

> The following issues were discussed …
>
> 2) Criteria for defining seroconversion:

[323] *See* Section III.B.1 above discussing wild type viruses; *see also* Schedule 20 (discussing various mumps strains, including wild type and vaccine strains).
[324] MRK-KRA01371773 at '78.

> CBER has repeatedly requested that there be some "clinically valid justification" for serologic criteria. Unfortunately there has been no bridge between the different assays used over the years which would permit a correlation between current serologic endpoints and clinical endpoints from an era in which there was a measureable mumps attack rate.

MRK-KRA00086290 at '90-91 (emphasis added).

155.2. A document entitled "Attachments 11/18/98 CDOC [Clinical Development Oversight Committee] Meeting, stamped Donna Dyer," stated:

> Att.1 CBER Communications on MMRII Expiry Study …
>
> Att. 2 Current Status of Plans to Study MMRII Vaccine at Expiry

MRK-KRA01731773.

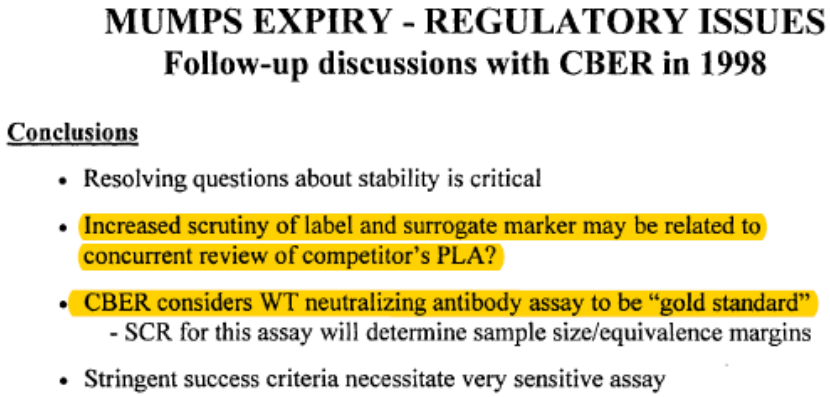
155.3. Attachment 1 stated:

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

Id. at '78 (highlight added).



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

Id. at '79 (highlight added).[325]

155.4. A letter marked "Serial No. 27" from MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to FDA's Director, Center for Biologics Evaluation and Research, Office of Vaccines Research & Review, Dr. Kathryn Zoon, titled "RESPONSE TO REQUEST FOR INFORMATION," dated February 5, 1999, stated:

> With reference to your letter dated September 8, 1998 … we are providing responses to your questions and comments.

MRK-KRA01646761 at '62.

155.5. Attachment 2 to Serial 27 stated:

> Question 4: …
>
> [Merck] Response:
>
> Mumps plaque-reduction neutralization assay...

[325] *See also* Deposition of CDC's Director, Division of Viral Diseases, Dr. Mark Pallansch, October 13, 2018, 127:9-25 (*"Q: And in terms of the interpretation of the results of an ELISA test, what are some of the ways that an interpretation could be misconstrued if a serostatus cutoff is used which wasn't the appropriate one? A: So it can affect both sensitivity and specificity. And that's why usually you will compare an ELISA to some other reference method to try to achieve some correlation – high correlation with what is considered a gold standard. In the specific case of mumps, there isn't really a true gold standard as it relates to the protection. Therefore neutralization has been the de facto gold standard. So you would want to see ELISA results in categorizing response versus response as measured by neutralization. So you would want to see those data side by side."*) (emphasis added).

> Ongoing studies include an evaluation of assay specificity,[326] by determining the mumps neutralization activity of sera pre-incubated with mumps, measles, rubella or uninfected cell extracts …
>
> Studies are … underway to determine the utility of … enhance[ing] assay sensitivity,[327] if required to reliably measure vaccine-induced antibody titers. …

Id. at '79-80 (emphasis added).

155.6. Attachment 2 to Serial 27 also stated:

> Question 5: …
> [Merck] Response:
> The primary immunogenicity endpoint of the clinical trial is the development of mumps neutralizing antibody at ~6 weeks post vaccination. This timepoint will allow us to bridge the responses to other M-M-R®II clinical trials, including those used in the initial approval of M-M-R®II. However, we have incorporated into the protocol a persistence objective to evaluate … mumps … immunogenicity at one year postvaccination.

Id. at '87 (emphasis added).

155.7. A Merck memo from MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Senior Director, Worldwide Regulatory Affairs, Biologics and Vaccines, Dr. Henrietta Ukwu, with the subject: "BB-IND 1016 (M-M-R®II); Summary of CBER teleconference on methods used for the plaque reduction neutralization assay," dated February 22, 1999, stated:

> Executive Summary…
> 4) CBER does not use either complement or IgG to enhance sensitivity and feels that these maneuvers should not be necessary.

[326] *See* Section III.B.3.b above discussing assay specificity.
[327] *See* Section III.B.3.b above discussing assay sensitivity.

> 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….

MRK-KRA00062710 (emphasis added).

155.8. A Merck document titled "M-M-R®II A Model for Live Viral Vaccines," by MRL's Clinical Monitor, Protocol 007, Dr. Scott Thaler, and MRL's Senior Director, Biostatistics and Research Decision Sciences, Joseph Heyse, dated March 7, 1999, stated:

> ELISA antibody may not be a good measure of protection; ELISAs cannot measure function like neutralization.

MRK-KRA00577001 at '32 (emphasis added).

156. According to Merck documents, Merck had several requirements for the serologic assays to be used in Protocol 007: (1) a neutralization assay was necessary; (2) testing against a wild-type virus was important to measure protection; (3) ELISA antibody may not be a good measure of protection; (4) it would be possible to use an assay, such as ELISA, if a correlation to a neutralization assay could be established; and (5) the assays must be highly specific (100%) for wild-type neutralizing response. Furthermore, also according to Merck's documents, FDA considered a wild-type neutralization assay to be the "gold standard" and did not believe modifications to the sensitivity of the neutralization assay were necessary.

157. In my opinion, for Merck to use ELISA for mumps immunogenicity testing in Protocol 007, or future clinical trials, it had to correlate the ELISA to a highly-specific neutralization assay designed as a measure of protection against circulating wild-type mumps infection.

3. After two independent assays confirmed seroconversion rates against wild type mumps were approximately 70%, Merck senior management considered the implications of the results to the MMRII label stating a 96% seroconversion rate

158. By the middle of 1999, Merck had results from two independent assays testing against wild type mumps virus with seroconversion rates of approximately 70% in contrast to the 96% Merck assumed it would measure based on the seroconversion rates from the "original MMRII submission using an older neutralization assay."[328] Merck's Clinical Assay Subcommittee[329] proposed how to present the data to FDA and "defend" the 96% claim on the MMRII label,[330] should FDA "raise the issue of the 96% SCR in the current label."[331] Merck also considered delaying the completion of Protocol 007 until it could develop a more sensitive neutralization assay that would allow Merck to measure a 96% seroconversion rate.

158.1. A Merck memo from MRL's Project Planning and Management Administrator, Vera Byrnes, to the Clinical Assay Subcommittee "CAS distribution" with the subject "Minutes from the CAS meeting: August 16, 1999," dated September 6, 1999, stated:

> DECISIONS
>
> At this point 2 independent assays have confirmed that the seroprotection rates against wild type virus isolates are not ~95%, per CBER's expectations. The team needs to prepare a "white paper" for CBER to summarize the data from both assays and highlighting the impact of the ~70% seroconversion rate on the size of the end expiry study.

MRK-KRA00015686 at '86 (emphasis added).

[328] MRK-KRA00137711 at '22.
[329] The Critical Assay Subcommittee made decisions regarding the development, monitoring, validation, planning, and other criteria of clinical assays. *See* MRK-KRA02142149 and MRK-KRA00027329 at '37.
[330] In the Clinical Pharmacology section of the MMRII label, it stated "Clincal studies … demonstrated that MMRII is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced … mumps neutralizing antibodies in 96% … of susceptible persons." *See* Schedule 1 (describing the MMRII label).
[331] MRK-KRA000273309.

158.2. A Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, and MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, with the subject: "Monthly Highlights for August 1999 (M-M-R II, Varicella-Containing Vaccines)," dated August 30, 1999, stated:

> MMRII …
>
> - Mumps Neutralizing antibody assay: The results of the mumps plaque reduction neutralization (PRN) and cytopathic effect (CPE) assays were reviewed at the CAS [Clinical Assay Subcommittee] on 8/16/99. With JL as the test isolate, the S[ero] C[onversion] R[ate] is ~90%, and with LO[ndon]1 as the test isolate, the PRN SCR is ~70-80%.[332] In the CPE assay the SCR for both JL and LO1 is ~70-80%. … The key elements of the discussion with CBER about the mumps neutralizing antibody assay will include: 1) CBER's feedback regarding further optimization of assay sensitivity; 2) review of the arguments that the current WT neutralization assay may not capture all attributable protective efficacy; … Should CBER raise the issue of the 96% SCR in the current label, the extensive field experience of the vaccine will be emphasized. Should this approach to defending the 96% SCR in the label not be successful, one option may be to propose including the range of observed SCRs in the label.[333]

MRK-KRA00273309 (emphasis added).

158.3. A document titled "Summary: Work-in-Progress as of sept. 19, 1999 Vaccine Programs," with a footer "Manal Morsy Created on 09/01/99," stated:

[332] *See also* MRK-KRA01452741 (ESPID abstract summarizing the results of Protocol 006 reporting similar seroconversion rates for MMRII against the same virus strains, London 1 and JL).

[333] A transcription of a voicemail from Manal Morsy to Henrietta Ukwu dated September 1, 1999 stated: "[T]he implications of label changes reflecting the PRN and CPE assay performances at 70-75% … was addressed by Dorothy [Margolskee] who … pointed out that if [the] data are reflective of the true efficacy in the field then the PRN and CPE may be telling us what the neutralization against wild truly is. … Nick Spring [Marketing] was clear on his position with regards to undesirable label changes at the present time." MRK-KRA00020421-22 (emphasis added).

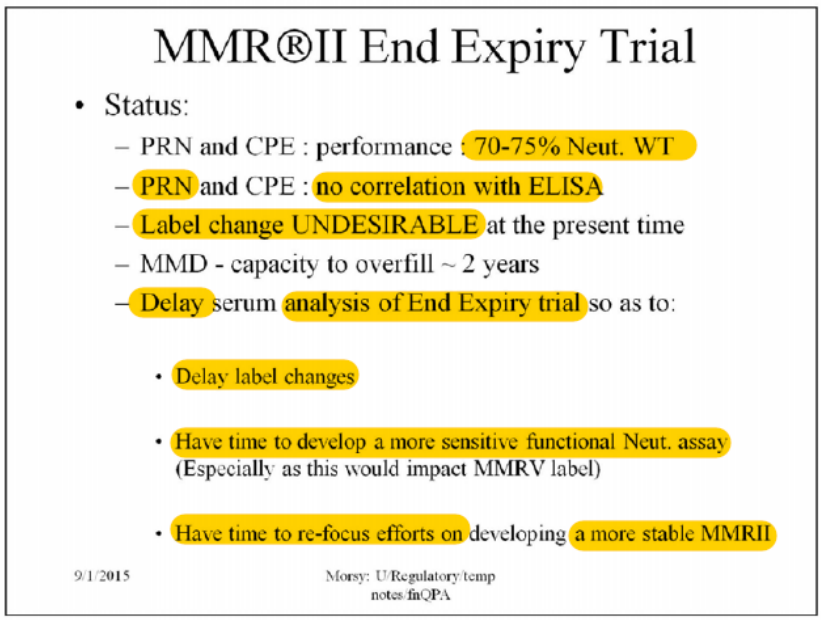
3-Expiry Trial: …

G) My Current Understanding ….

5- CBER requires that SCR reflect protective efficacy

MRK-KRA00198876 at '78.

158.4. A power point presentation titled "MMR®II End Expiry Trial" dated September 27, 1999, stated:



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

9/1/2015 Morsy: U/Regulatory/temp notes/fnQPA

MRK-KRA00020420 (highlights added).

159. According to Merck's documents, when Merck used a neutralization assay and another functional assay, seroconversion rates were 70-75%, not the 96% stated on Merck's label. Furthermore, at the end of September 1999, testing by an ELISA was not an option in the absence of a correlation to a neutralization assay (which was giving seroconversion rates of 70-75%). Delaying Protocol 007 would delay a label change and allow time to develop a more

sensitive assay.[334] FDA still required that seroconversion reflect protection against disease, and did not believe increased sensitivity in the neutralization assay was necessary.

160. In my opinion, as of September 1999: (a) Merck needed to conduct an end expiry study of mumps immunogenicity promptly;[335] (b) FDA required Merck to use a neutralization assay in the end expiry study and did not believe modification to a neutralization assay was necessary; (c) Merck could not use an ELISA test unless it was correlated to a neutralization assay; (d) reporting seroconversion rates of lower than 96% in the end expiry trial could require Merck to change the 96% seroconversion rate in the MMRII label. A reasonable and prudent vaccine manufacturer presented with this information would use a neutralization assay that measures protection against disease, and report the results of that study as promptly as possible.

4. Merck proposed to use JerylLynn™ the vaccine strain of the mumps virus in Protocol 007

161. In December 1999, Merck proposed to use the attenuated JerylLynn™ strain of the mumps virus (referred to as the "vaccine strain" because this attenuated strain of the virus was used in the MMRII vaccine),[336] as the indicator virus in its Protocol 007 neutralization assay. Merck's rationale was that the seroconversion rates in the preliminary experiments using a neutralization assay testing against the vaccine strain were in agreement with the mean seroconversion rate of 96% measured by Dr. Maurice Hilleman in his efficacy studies.[337] Dr.

[334] MRK-KRA00020420.
[335] MRK-KRA00756233 at '36 (Merck's December 1998 proposal to initiate the overfill stated that during the "short interval before formal clinical study data became available," it would be "an interim plan" for product release and expiry dating." "When the results of the end- expiry clinical trial are available, the release and dating proposal will be re-evaluated and the appropriate actions taken with CBER concurrence.").
[336] *See* Section III.A above describing the different JerylLynn related virus strains. The vaccine strain is not a wild type virus.
[337] *See* Sections III.B.1 and 3.a above describing Dr. Hilleman's development of Mumpsvax and the efficacy studies.

Hilleman's "observations" were made in the study demonstrating the clinical efficacy of the mumps vaccine, which is the basis of the MMRII label.[338]

161.1. A letter marked "Serial No 52" letter from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to FDA's Director, CBER, Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications, Dr. Karen Goldenthal, regarding "BB-IND 1016 … RESPONSE TO REQUEST FOR INFORMATION," dated December 30, 1999, stated:

> Reference is made to CBER's comments and questions conveyed in Dr. Karen Goldenthal's August 30, 1999 letter …regarding Protocol 007...

MRK-KRA01619889.

161.2. Serial 52, Attachment 3: "Review of Mumps Neutralization assay performance and impact on MMRII End Expiry Study Hypothesis and Data Analysis," stated:

> Merck designed and initiated [Protocol 007] in response to questions raised by CBER regarding [mumps] immunogenicity … at vaccine expiry …
>
> Over the past year multiple communications occurred between CBER and Merck scientists to several issues concerning …the M-M-R®II End Expiry trial including the specifics of the neutralization assay used to measure antibody response …
>
> The outcome of these multiple communications included the following CBER recommendations:
>
> Wild type antigens should be used in a neutralizing antibody assay, as the ability to neutralize the vaccine strain in such assays may not necessarily predict response to WT strains. …

MRK-KRA01620035 (original bold removed, underline added).

[338] MRK-KRA01620035 at '50-51.

161.3. Serial 52, Attachment 3 also stated:

V. Summary and Implications of These Data

The clinical hypothesis of the MMRII at mumps expiry potency clinical trial was designed on the premise that wild-type neutralization is a correlate of protection from disease. …

Merck's Recommendation:

A. Based upon the above observations and results, we propose to use Jeryl Lynn™ as the target strain in the PRN assay, with seroconversion defined as a ≥4 fold rise in neutralization titer.

Rationale for using Jeryl Lynn™ [vaccine strain] as the target mumps strain in the functional neutralization assay:

1- Results of SCR% using Jeryl Lynn™ as the target strain in preliminary experiments using the PRN functional assay are 91% and 96.2%.

a) These results are consistant [sic] with the current M-M-R®II label claim (a single injection of M-M-R®II vaccine induced mumps neutralizing antibodies in 96% of vaccinees aged 11 month to 7 years).

b) These results are also in agreement with Dr. Hilleman's observations 30 years ago, in which a mean S[ero]C[onversion]R[ate] of 96% was found in children following a single dose of vaccine, using a cutoff of 1:2.[339] In addition, his observations were made in the study demonstrating the clinical efficacy of this mumps vaccine, which is the basis of the M-M-R®II label.

Id. at '50-51 (original bold removed, internal citations omitted, underline added).

[339] *Compare* MRK-KRA00198876 at '77 ("the Neut[ralization] assay data generated to support protective efficacy … were questioned as to weather [sic] they are still valid in predicting the current protective efficacy of the MMRII vaccine against present wild type strains.").

162. According to Merck's documents, in November 1998, using a wild type indicator virus in neutralization testing was the closest virus to what children would be exposed to in the real world. FDA considered a neutralization assay using a wild type indicator virus as a "gold standard."[340] In September 1999, Merck had results of neutralization tests with seroconversion rates lower than the 96% claimed on the MMRII label when it used a wild type indicator virus. In December 1999, Merck proposed to FDA to use the vaccine strain (JerylLynn™) in the Protocol 007 neutralization assay because Merck could measure the same seroconversion rates as Dr. Hilleman[341] if it used the vaccine strain (JerylLynn™) as the indicator virus.

163. In my opinion, the objective of Protocol 007 was to measure MMRII's ability to protect against currently circulating wild-type mumps, especially at a potency lower than the 4.3 log10 [20,000] TCID50 stated on the MMRII label.[342] A reasonable and prudent manufacturer would design a serologic assay that would accomplish the stated goal of the study.

5. Merck and FDA Met in March 2000 to Discuss Proposed Modifications to the Protocol 007 Neutralization Assay

164. On March 13, 2000, Merck and FDA personnel held an in-person meeting to discuss, among other things, Merck's proposed changes to the neutralization assay to be used in Protocol 007. At the meeting's conclusion, Merck and FDA prepared summaries of the discussion.

[340] MRK-KRA01371773 at '78.
[341] *Compare with* MRK-KRA00198876 at '77 (cited above).
[342] *See* MRK-KRA01620035 at '50-51 (Serial 52 stated: "The clinical hypothesis of the MMRII at mumps expiry potency clinical trial was designed on the premise that wild-type neutralization is a correlate of protection from disease."); MRK-KRA00137711 at '720 (Attachment 1 - Proposal for Clinical Trials to Support an Expiry Potency for the Mumps Component of M-M-R-II stated: "we will demonstrate the immunogenicity of the mumps component of M-M-R®II at the claimed expiry potency of 3.7 [5,000] $\log_{10}TCID_{50}$") and; MRK-KRA00001467 at '468 (FDA response stated "Virus antigens used in serological assays enable the assessment of immunogenicity which is reflective of efficacy against natural infection; …") (emphasis added).

164.1. A fax from FDA summarizing a face-to-face meeting between FDA and Merck on March 13, 2000, dated April 11, 2000, stated:

> Discussion Points …
>
> 8. As the PRN assay is an immunological endpoint for protection against wildtype disease, CBER stated that the virus used in the assay must be wild type (early passage) virus, not attenuated virus vaccine. Publications from the 1960s and 1970s with data from the original licensing of J[eryl]L[ynn] vaccine utilized PRN and HI assays with low passage wild type J[eryl]L[ynn] (passage 7). J[eryl]L[ynn] was found to be reactogenic through at least passage 12. CBER agrees that PRN assays using J[eryl]L[ynn] passage 7 to 12 would be acceptable for PRN assay for immunogenicity data.[343] In addition, if Merck can develop an ELISA assay using these low passage JL strains that can be validated against the PRN assay to CBER's satisfaction, the ELISA method would also be acceptable. …

MRK-KRA01927351 at '53 (emphasis added).

164.2. The FDA Minutes also stated:

> 10. Validation and Optimization:
>
> - For PRN assay: Since this assay development is still "in progress", CBER cannot comment on the appropriateness of the Merck assay until the P[laque]R[eduction]N[eutralization] assay S[tandard]Operating]P[rocedure] is finalized and the validation data are provided by Merck.
> - For ELISA: Preliminary concerns were voiced by CBER regarding the statistical analysis provided by Merck. CBER reserves final approval of the ELISA test pending use of wild type mumps virus as antigen, submission of validation data and review by CBER statisticians.
>
> 11. Merck questioned CBER regarding the use of the serological data from the current studies in the label. CBER stated that the label wording depended upon the license

[343] *See* Section III.A above. FDA allowed Merck to use an indicator virus that was not the wild-types it had already evaluated, but also not the vaccine strain (JL™). FDA allowed Merck to use an attenuated mumps strain that had been passaged between 7-12 times, deeming that to be wild-type like. This "low-passage" strain is called JL-135.

> supplement changes. The changes in the label need to reflect the issue for requesting a change in the license, and this change may include discussing the new serologic data in the label….

Id. at '54 (emphasis added).

164.3. The FDA Minutes also stated:

> Action items:
>
> 1. Final S[tandard]Operating]P[rocedure] utilizing wild type mumps virus and validation of the PRN and ELISA will be submitted by Merck to CBER.
>
> 2. The following PRN assay modifications are reasonable to try to enhance the sensitivity of the assay, pending appropriate validation: …
>
> - Additional wild type mumps viruses to consider include the Barnes Isolate.
> - Jeryl Lynn passage 7 to 12.
> - IgG enhancement[344]
> - KARBER method

Id. at '54-55 (emphasis added).

164.4. A Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, with the subject: "BB-IND 1016 (M-M-R®II) and BB-IND 7068 ([ProQuad]); Summary of Face-to face meeting discussion with FDA regarding wild type mumps neutralization and ELISA assays," dated March 13, 2000 stated:

> Discussion: …
>
> Dr. Carbone refused to discuss any clinical implication in this setting when asked how would the data be used in the end expiry trial especially if after assay optimization we are still at the 78% S[ero]C[onversion]R[ate]. … she deferred all discussion related to

[344] Antibodies to human immunoglobulin (IgG) are commercially available and used in laboratory testing. In this context they could modify the assay to make it more sensitive. A more sensitive assay would not necessarily be more specific or more accurate.

> clinical issues until when data are generated. She is optimistic that with further optimization the SCR will be >90%, in which case the issue becomes moot.

MRK-KRA00001262 at '63-64 (emphasis added).

164.5. The March 13, 2000 memo also stated:

> Path forward/assignments: …
>
> 2) Optimization of PRN assay as per CBER's recommendations (David Krah.)
>
> 3) If further attempts at assay optimization are unsuccessful, then a cross-functional consensus on the risks and benefits of proceeding with the expiry trial is required.
>
> 4) Depending on this consensus a follow up discussion with CBER on the path forward will occur in ~ June or July.

Id. at '64-65 (original bold removed, underline added).

165. Following the March 13, 2000 meeting, according to FDA's minutes, (1) the neutralization assay to be used in the end expiry study (Protocol 007) was to measure protection against wild-type disease, (2) the indicator virus used in the assays needed to be wild-type,[345] (3) FDA could not comment on the appropriateness of the neutralization assay Merck was developing until the standard operating procedure was finalized and the validation data provided for FDA's review, and (4) FDA considered it "reasonable to try" to modify the sensitivity of the neutralization assay, pending appropriate validation.

166. MRL's Principal Investigator, Virus and Cell Biology, Principal Investigator, Dr. David Krah, described his objectives in designing the neutralization assay study he developed for Merck to use in Protocol 007.

166.1. An email from MRL's Principal Investigator, Virus and Cell Biology, Dr. David Krah, to MRL's Director, Clinical Research, Leonard Rubinstein, with the subject: Re: Do you need any help?," dated January 17, 2003, stated:

[345] *See* Section III.A above discussing the wild type viruses.

> The M-M-RII [end expiry] study used an anti IgG enhanced neutralization and the low passage Jeryl Lynn indicator virus. We would have used the same assay in 006 for 007 except that we could not achieve the 90% seroconversion sensitivity with any of the wild-type mumps strains without enhancing the sensitivity.[346] We could measure > 90% seroconversion using the vaccine strain as the indicator, but CBER required us to use a "wild-type" indicator virus for 007.

MRK-KRA00051640 (emphasis added).

166.2. MRL's Principal Investigator, Dr. David Krah, testified as follows:

> *Q. So do you recall any communications with the FDA or CBER where they required for Protocol 007 that the assay be linked to protection from disease?*
>
> *Defense Counsel: Object to the Form*
>
> *A. I do not recall any connection to protection.*
>
> *Q. If the assay was required to be linked to protection from disease, would you have developed a different assay?*
>
> *Defense Counsel: Object to the Form*
>
> *A. No.*
>
> *Q. You would have ran the same assay?*
>
> *A. My personal opinion is that the protection from disease and antibody assay are independent events. I would not have automatically or wouldn't automatically consider a different assay as more predictive of protection versus another.*
>
> *Q. So is it your belief that -- I'm trying to understand that answer. You don't believe that any assay that can be developed is any more predictive of protection from disease than any other? Is that your testimony?*
>
> *Defense Counsel: Object to the Form*
>
> *A. My opinion is that the -- my understanding and opinion is that the -- an antibody assay is an imperfect model, imperfect measure of an immune response to a vaccine. It's not a*

[346] *See also* MRK-KRA003337397 at '98-99 (email from MRL's Principal Investigator, Dr. David Krah, to MRL's Vice President, Vaccine & Cell Biology, Dr. Emilio Emini, with the subject: "Update on Mumps N[eutralization] Studies," dated March 30, 2000, stated: "We also plan to readdress the use of anti-human IgG to enhance N[eu]t[ralization], as a back-up if we fall short of our 90+% target.").

given correlate of protection. The assay itself is not -- does not provide an automatic correlate of protection.

Q. Do you understand what a surrogate of protection is?

A. I've heard of correlates of protection. Surrogate I'm not sure about.

Q. You don't know what a surrogate of protection is?

A. I've heard of correlate of protection. Surrogate of protection, it's not a familiar term to me.

Deposition of David L. Krah, July 11, 2017, 94:20 - 96:20 (emphasis added).

166.3. MRL's Principal Investigator, David Krah, further testified as follows:

Q. Do you recall -- you don't – as you sit here today right now, you don't recall ever hearing from CBER that they wanted a plaque reduction neutralization assay that could be clinically linked to protection from disease?

A. I do not recall that – a comment about a link to protection from disease.

Q. Do you believe that an ELISA assay is just as good as a plaque reduction neutralization assay in terms of identifying whether or not a result from those assays is linked to protection from disease, from mumps?

A. I would say -- I'm not familiar with the ELISA results either at Merck or outside of Merck to be able to comment on how well it correlates with protection from disease.

Q. And that's not what you used to develop the assay, is trying to find an assay that would correlate to protection from disease. Correct?

Defense Counsel: Object to the Form

A. For which assay?

Q. The plaque reduction neutralization assay.

A. The objective for the plaque reduction neutralization assay was to provide an assay that was capable of providing 95 percent seroconversion. Whether that - beyond that, I don't have any understanding.

Deposition of David L. Krah, July 11, 2017, 107:2-108:10 (emphasis added).

167. Dr. Krah's emails evidence that he modified the sensitivity of the neutralization assay used in Protocol 007 by adding anti-IgG since he could not measure >90% seroconversion in a neutralization assay without the modification. Dr. Krah testified that his objective in designing the neutralization assay used in Protocol 007 was to develop an assay that was capable of "providing 95 percent seroconversion." He further testified that he had no understanding of the objective of the neutralization assay beyond "providing 95 percent seroconversion," including whether the seroconversion rate reported had any connection to protection against disease.

168. In my opinion, whatever "enhancements," modifications or changes to a serologic assay a manufacturer evaluates in the design of a clinical study, it is ultimately the manufacturer's obligation to design and conduct an adequate and well-controlled study that meets the stated objectives. Furthermore, as stated previously, the objective of Protocol 007 was to measure protection against wild-type mumps disease at a potency less than the 4.3 log 10 [20,000] TCID50 stated on the MMRII label.

B. Merck's Mumps Immunogenicity Testing as part of its effort to license ProQuad in the United States

169. At the same time Merck was conducting Protocol 007 under BB-IND 1016, Merck was pursuing licensure of ProQuad under BB-IND 7068. Merck proposed to use ELISA assays for the mumps immunogenicity testing in the clinical studies to support the ProQuad license application. Before Merck could use ELISA assays in the ProQuad studies, FDA required Merck to demonstrate that the ELISA results would have a link to protection against disease.

169.1. A letter with reference BB-IND 7068 from FDA's Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, CBER, Dr. Karen

Goldenthal, to MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, dated October 26, 1999, stated:

> 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 ELISA needs to be justified. Please comment.

MRK-KRA00761482 at '83 (emphasis added).[347]

170. In my opinion, as FDA has noted, [348] false positive and false negative results are frequently observed when ELISA assays using mumps virus are used to assess antibody response. Furthermore, if an ELISA assay was going to be used instead of a neutralization assay in mumps immunogenicity testing, it would be important to minimize the risk of reporting false positive or false negative results by ELISA. Moreover, one way to minimize this risk, which would have been acceptable to FDA, was to correlate the ELISA to a neutralization assay.

171. In my opinion, the regulatory communications from FDA to Merck from 1998-2000, described above, evidence that mumps immunogenicity testing required the use of a serologic assay that had some connection to protection against disease. Furthermore, the "gold standard" was a neutralization assay using a wild-type indicator virus, but an ELISA assay could be used if it was correlated to a neutralization assay. A correlation to a neutralization assay would minimize the risk of reporting false positive or false negative results by ELISA.

[347] *See also* MRK-KRA00001262 (the March 13, 2000 meeting between Merck and FDA included discussion of the ELISA assays in BB-IND 7068). As discussed below in Section IX.A.5.b, Merck also sought to use ELISA testing for the mumps immunogenicity testing it did to support the rHA change under BB-IND 10076.
[348] MRK-KRA00761482 at '83.

Moreover, FDA's requirements to assess protection afforded by vaccination, and the duration of the protection, in mumps immunogenicity testing was consistent with the National Vaccine Advisory Committee's priorities for evaluating whether a vaccine is safe and effective.[349] These requirements would apply to any mumps immunogenicity testing conducted as part of a clinical study to support an existing license of a mumps vaccine, or an application for the license of a new mumps vaccine.

C. Merck's Protocol 006, a Clinical Trial Comparing Mumps Seroconversion in MMRII and Priorix

172. The licensure of SmithKline Beecham's Priorix in Germany, the United Kingdom and Cyprus in the 1990's was a competitive threat for Merck.[350] As part of its marketing response to Priorix, Merck initiated a clinical trial called Protocol 006, including mumps immunogenicity testing, to compare MMRII and Priorix.[351] In Protocol 006, Merck evaluated which serologic assay to use to measure protection.[352]

172.1. A Merck document titled "Phase V Clinical Development Plan for M-M-R®II" stated:

> Phase V Clinical Studies
> An Exploratory Study to Investigate the Breadth of Mumps Neutralization Induced by M-M-R®II and Priorix™ in Children 12-18 Months of Age. …
> Major Developmental Issues
> Marketing Needs

[349] *See* Section V.B.4 above describing the NVAC's priorities: "efficacy, including duration of protection."
[350] MRK-KRA00626121 at '22 and '27.
[351] MRK-KRA00666494 at '59.
[352] MRK-KRA00526241 at '43.

- Competitive Threat From Recent Licensure of Priorix™ in Germany, the United Kingdom and Cyprus[353]
- Importance of Seroconversion Rates to Physicians

MRK-KRA00626121 at '22 and '27 (original bold removed, underline added).

172.2. A Merck power point presentation titled: "Live Virus Vaccines: Methods of Measuring Protection" by MRL's Virus and Cell Biology, Research Associate, Daniel DiStefano, stated:

> Rationale for the Development of Functional[354] Mumps Assays
>
> - Because functional assays are thought to better estimate protection from disease, such assays are appropriate for comparing vaccine products.

MRK-KRA00526241 at '43 (emphasis in original).

173. A document titled "Summary: Work-in-Progress as of sept. 19, 1999 Vaccine Programs," with a footer "Manal Morsy Created on 09/01/99," stated:

> Protocol #006-00…
>
> Assay to be used for analysis was determined to be PRN …
>
> Also correlation between the Neut[ralization] assay data generated to support protective efficacy in the label were old … and furthermore were questioned as to weather [sic] they are still valid in predicting the current protective efficacy of the MMRII vaccine against present wild type strains.

[353] The February 1998 document titled "M-M-R II Competitive Defense Task Force 'Why Take A Chance' Tactical PAC [Product Approval Committee] Update," stated: "A head to head exploratory study is planned to detect differences between MMRII and Priorix in the breadth of neutralizing antibodies induced against a panel of wild type and vaccine strains by an assay being developed in Basic Research." MRK-KRA00666494 at '496. "In order to maintain the majority market share worldwide, it is necessary to compare Priorix to MMRII…." *Id.* at '59.

[354] *See also* MRK-KRA00017826 (email from MRL Principal Investigator, Dr. David Krah, to MRL's Clinical & Regulatory Affairs, Regional Office staff, Gabriele Poerschke, dated November 17, 2000, stated: "By a 'functional assay' we mean an assay that measures a biological activity (such as inactivation of virus infectivity). Immunogenicity can be measured by a variety of means, but typically involves a binding assay (such as an ELISA or hemagglutination inhibition assay) or a biological (infectivity reduction). The immunogenicity assessment is a measure of whether or not the vaccinee responded to the vaccination in some detectable way. This response then needs to be correlated with protection from diseases. Historically, the functional assays have been judged to be a good surrogate marker of protection.") (emphasis added).

MRK-KRA00198876 at ‘877 (emphasis added).

173.1. An email from MRL’s Principal Investigator, Virus and Cell Biology, Dr. David Krah, to MRL’s Director, Clinical Research, Leonard Rubinstein, with the subject: Re: Do you need any help?,” dated January 17, 2003, stated:

> … The M-M-RII Protocol 006 study used a straightforward non-enhanced neutralization, using several different indicator viruses.

MRK-KRA00051640 (emphasis added).

173.2. MRL’s Virus and Cell Biology, Principal Investigator, Dr. David Krah, testified as follows:

> *Q. Had you ever run clinical samples with human sera in your lab prior to Protocol 007?*
>
> *Defense Counsel: Objection. Form.*
>
> *A. Yes.*
>
> *Q. Were those used for a marketed product?*
>
> *Defense Counsel: Objection to the form.*
>
> *A. Yes.*
>
> *Q. Were those used to – do you recall what that product was?*
>
> *A. It was a comparison between MMR and Priorix.*
>
> *Q. Other than that – that was Protocol 006, do you recall that?*
>
> *A. Yes.*

Deposition of David Krah, July 11, 2017, 119:18-120:14.

173.3. An abstract from the European Society for Paediatric Infectious Diseases (“ESPID”), titled “Evaluation of Mumps Neutralizing Antibody in a Double-Blind Comparative Study of Two Live-Attenuated Measles-Mumps-Rubella Vaccines” by Merck’s Dr. Scott Thaler, Dr. Krah, and Stephanie Olsen, among others, dated 2001, stated:

EVALUATION OF MUMPS NEUTRALIZING ANTIBODY IN A DOUBLE-BLIND COMPARATIVE STUDY OF TWO LIVE-ATTENUATED MEASLES-MUMPS-RUBELLA VACCINES

S. Stojanov, S. Thaler, D. Krah, S. Olsen, E. Harzer, S. Jow, J.G. Liese, B.H. Belohradsky
University Children's Hospital, Munich, Germany; Merck Research Laboratories, USA; Aventis Pasteur, Germany

Background: A more heterogeneous mumps vaccine may induce a broader neutralizing antibody (NA) response which may increase protection from wild-type mumps. M-M-R®II is a measles-mumps-rubella vaccine containing the Jeryl Lynn™ mumps strain which is a stable mixture of two subpopulations (JL-5, JL-2), whereas Priorix® vaccine contains only JL-5, isolated by limiting dilution and serial passage. The primary objective was to examine whether there are large differences between vaccines in mumps NA specificity post-vaccination. Further objectives were a comparison of immunogenicity and clinical safety. **Methods:** 169 children 12-24 months old were randomized in a double-blind multicenter comparative trial to receive M-M-R®II (n=85) or Priorix® (n=84). Mumps-NA against a wild-type (London1), JL-2 and Jeryl Lynn™ strains were measured by a plaque-reduction neutralization assay in pre- and 42 days post-vaccination serum samples. Antibody responses were also measured by ELISA. Local and systemic reactions were recorded in diary cards given to the parents. **Results:** Both vaccines induced NA against all mumps strains. Higher neutralization seroconversion rates (SC) and Geometric Mean Titers (GMT) after vaccination with M-M-R®II were consistently observed, the differences being not statistically significant.

Mumps Strain	London1		JL-2		Jeryl Lynn™	
Mumps Neutralization	SC	GMT	SC	GMT	SC	GMT
M-M-R®II	75.6%	9.6	53.0%	3.4	96.3%	37.7
Priorix®	68.1%	7.9	44.2%	2.5	90.9%	25.3

ELISA SC and GMTs to measles, mumps and rubella were comparable for M-M-R®II and Priorix®. Both vaccines were equally well tolerated. **Conclusion:** Given the statistical power, a significant difference in mumps neutralization titers was not observed. The numerically higher neutralization titers after M-M-R®II could be due to the presence of an additional mumps strain which might increase neutralization activity or due to a subtle increase in attenuation required in the production of Πριορι ξ®.

MRK-KRA01452741 (highlight added).[355]

174. The results of Protocol 006 reported in the ESPID poster can be summarized as follows:

- Both vaccines induced neutralizing antibodies against the three mumps virus strains tested.
- Seroconversion rates for both vaccines were lower in testing against the wild-type (London1) strain than the two vaccine strains (JL-2 and JerylLynn™).

[355] *See* MRK-KRA01452740 (email from MRL's Principal Investigator, Dr. David Krah, to MRL's Clinical Research Physician, Dr. Susan Manoff, with the subject: "2001 ESPID ABSTRACT.doc," dated February 23, 2010, attaching the "abstract for the MMR Protocol 006 summary.").

- The highest seroconversion rates for both vaccines was in testing against the JerylLynn™ strain.

175. In 1999, an article in the Pediatric Infectious Disease Journal titled "Reactogenicity[356] and immunogenicity of a new live attenuated combined measles, mumps and rubella vaccine in healthy children," compared MMRII and Priorix and concluded that Priorix was shown to be superior in terms of local reactogenicity while demonstrating equivalent immunogenicity. Merck responded to the article with a rebuttal letter by two Merck scientists questioning the validity of the testing methods. They asserted that similar immunogenicity as measured by enzyme-linked immunosorbent assays (ELISAs)[357] could not be assumed to mean comparable protection from disease. They also asserted that correlation between ELISA and a functional assay, such as neutralization, had to be established for each vaccine individually to be an indicator of protection against disease.[358] They asserted that this had been accomplished for MMRII but that they were not aware of a similar correlation performed with Priorix.

175.1. An article titled "Reactogenicity and immunogenicity of a new live attenuated combined measles, mumps and rubella vaccine in healthy children," by Vytautas Usonis Vytautas Bakasenas, Achim Kaufhold, Kerim Chitour, and Ralf Clemens in the Pediatric Infectious Disease Journal ,Vol. 18 no. 1, dated January 1999, stated:

> ***Objective.*** **To compare the reactogenicity and immunogenicity of a novel live attenuated measles-mumps-rubella vaccine, SB MMR (Priorix; SmithKline Beecham Biologicals), with a widely used MMR vaccine, Merck MMR (M-M-R II; Merck & Co. Inc).**

GSK-MMR-0029832 (highlight added).

[356] *See* Section III.B.3 above discussing reactogenicity.
[357] *See* Section III.B.3.b.(1)(d) above discussing ELISA assays in immunogenicity testing.
[358] *See* Section A.1 above discussing the role of a correlation between an ELISA and a neutralization assay.

175.1. The article also stated:

Laboratory assays. Separated pre- and postvaccination serum samples were stored at −20°C until antibodies were assayed in a blinded manner at the SmithKline Beecham Biologicals laboratory (Rixensart, Belgium). All antibody titers were measured with commercial enzyme-linked immunosorbent assay (ELISA) kits (kit supplied by Behringwerke AG, Marburg, Germany). The assay cutoffs were 150 mIU/ml for measles, 231 units/ml for mumps and 4 IU/ml for rubella.

Seroconversion was defined as the appearance of detectable level of antibody in the serum of subjects who were seronegative before vaccination. Geometric mean titers (GMTs) for the seroconverters were calculated by taking the antilog of the mean of the log titer transformation.

In five cases samples of saliva were collected in an attempt to identify the mumps virus by cell culture and PCR. The laboratory personnel who tested the serum samples and virus isolates remained blinded to treatment until after the end of the statistical analyses.

Id. at '34 (highlight added).

175.2. The article also stated:

Conclusion. **When administered as primary vaccination in children in the second year of life, the new SB MMR vaccine has been shown to be superior to a comparator vaccine in terms of local reactogenicity, with equivalent immunogenicity.**

Id. at '32 (highlight added).

175.3. A letter in the Pediatric Infectious Disease Journal, Vol. 18, No. 9 (Sept. 1999) 18:42-8, titled "Comparability of M-M-R™II AND PRIORIX," by MRL's Director, Clinical Vaccine Research, Dr. Scott Thaler, and MRL's Senior Director, Clinical Biostatistics, Joseph Heyse, stated:

> Although Usonis et al correctly point out the importance of providing safe and effective measles, mumps and rubella vaccines until these important childhood diseases are eradicated, we would like to raise several concerns regarding their conclusions.

> … we do not agree that similar immunogenicity as measured by enzyme-linked immunosorbent assays (ELISAs) can be assumed to mean comparable protection from disease. In particular, the correlation between ELISAs and functional assays such as neutralization … must be individually demonstrated for each vaccine. This correlation has been accomplished for MMRII. We are not aware of a similar correlation performed with Priorix.
>
> There is precedent to support our concern about relying solely on ELISA values. For instance, in the case of the Swiss Berna vaccine Triviraten, which contains the Rubini mumps strain, excellent ELISA seroconversion rates were achieved. However, the efficacy of the vaccine has been estimated to be as low as 20% against wild type mumps. In one recent publication, when several volunteers were vaccinated with Triviraten, all seroconverted using either ELISA or indirect immunofluorescence, but none developed neutralizing antibody to wild type mumps. Therefore, without demonstrating a correlation between the immunologic response and protection from circulating wild type mumps infection, we question whether an ELISA assay can be assumed to correlate with protection from wild type disease.
>
> In conclusion, we believe that … the reliance on ELISA assays alone is insufficient to support the contention that a vaccine such as Priorix will protect against wild type infection. Therefore we feel that it is inaccurate to assume Priorix and M-M-R™II are "identical" vaccines.

MRK-KRA00088592 (internal citations omitted, emphasis added).[359]

176. In my opinion, to use an ELISA assay as an appropriate measure of protection against circulating wild-type mumps infection, it must be correlated to an assay that measures protection, such as a neutralization assay.

[359] *See also* MRK-KRA00626043 at '44 (high importance internal Merck email regarding Merck's rebuttal); MRK-KRA00429533 at '61-64 (internal Merck document discussing the recent Priorix study); MRK-KRA00285267 (internal Merck email circulating the published Merck rebuttal letter); MRK-KRA00285268 (Appendix 2 – Merck rebuttal letter).

VIII. MERCK DID NOT HAVE ADEQUATE ASSURANCE OF MMRII'S POTENCY

A. Stability of MMRII's Mumps Component Was An Ongoing Regulatory Issue

177. In August 2000, Merck's Manufacturing Division held a teleconference with personnel from FDA's Office of Vaccines Research and Review regarding mumps potency in MMRII.[360] This meeting was part of the ongoing discussion between Merck and FDA regarding mumps potency in MMRII that started with the Section 314 Review in 1996.[361] At the same time, Merck was also preparing for a routine inspection from FDA's Office of Compliance, sometimes referred to as "Team Biologics." According to Merck's record of the teleconference regarding stability, while Merck anticipated citing the ongoing discussion regarding mumps potency in the upcoming inspection, FDA's Dr. Kathryn Carbone made clear that the Team Biologics inspection of Merck's manufacturing facility was a separate issue. Moreover, Dr. Carbone told Dr. McKee that a conclusion had not been drawn and FDA had not made any commitment with regard to the mumps potency issue.

177.1. A Merck memo to File from MMD, Franchise Lead, Global Regulatory Affairs, Bonnie Stankunas, with subject: "8/10/2000 CBER Teleconference Regarding the Mumps Stability Protocol (Reference Letter to McKee and Egan dated 7/26/2000)," dated August 10, 2000, stated:

> On 8/10/00, Dr. Roberta McKee, Dr. Ronald Salerno, Dr. Fang Yin, Mr. Timothy Schofield, Ms. Katalin Abraham and Ms. Bonnie Stankunas spoke with Dr. Kathryn Carbone and Ms. Luba Vujcic … CBER, … regarding the stability study to support an increase in the titer of the mumps component. …

[360] *See* Section III.B.2 above discussing the connection between potency, stability and end expiry potency.
[361] *See* Section VI above discussing the Section 314 Review.

> … CBER requested that Merck submit its retrospective data used to support its ongoing annual stability program along with very detailed statistical analyses and rationale to support the multi-phase kinetics approach to data evaluation proposed by Merck. Merck agreed to re-submit this information, previously submitted, for review by CBER's new statistician. Merck estimated that the data analyses would take approximately two months to prepare. …
>
> Dr. Carbone acknowledged that CBER recognizes that, due to the vagaries of the potency assay, it is expected that a potency value may fall below the expiry titer specification of 4.3 $\log_{10}$TCID$_{50}$/dose for mumps at an individual time point in a stability study.
>
> Dr. McKee made reference to … the upcoming Team Biologics inspection next week. She noted that Merck may reference this teleconference as well as relevant correspondence between Merck and CBER on the topic of mumps stability. Dr. Carbone commented that the inspection by Team Biologics was a separate issue. She highlighted the fact that neither a conclusion has been drawn nor a commitment made on the subject of mumps stability to date.

MRK-KRA01522617 at '17-19 (emphasis added).

177.2. An email from MMD's Director, Biologics Licensing, Dr. David Wonnacott, to MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, among others, cc'd to MRL's Dr. Keith Chirgwin, MMD's Katalin Abraham, and MMD's Dr. Barry Garfinkle, with the subject: "MMRII Stability," dated May 12, 1999, stated:

> I spoke with Dr. Baylor today regarding the compliance status of MMRII relative to the label potency claim. He does not believe the new label has changed substantially from the wording used for potency over the past 20 years. However, CBER also understands that the stated titer does not always meet the shelf life titer of MMRII. Indeed, this was the reason for our January proposal to increase the titer of mumps in MMRII in order to meet a shelf life claim.

> Dr. Baylor indicated that we should go ahead at this time to increase the mumps release titer and submit a supplement to the license. This will give a higher level of assurance of meeting the expiry titer. Lots which are manufactured prior to making this change are still considered acceptable based on historical precedence (grandfathering). If our future clinical data looks OK we can return to the historical potency level.
>
> I reminded Dr. Baylor that we do not consider stability titers below the current MMRII label claim as being "out of specification". We have seen values below the label claim in the past and we will continue to see them until we increase the release titer. We do not plan to report these low values as OOS results. Dr. Baylor agreed with this approach. If our stability data is within our historical experience it need not be reported. He knows that in the past CBER has released lots near or at the minimum shelf life potency (these lots would not meet the label claim through expiry).
>
> Based on the discussion with Dr. Baylor, it is the Biolicensing recommendation that stability data for MMRII should be evaluated in accordance with our historical approach. If the measured titer drops below the label claim (previously considered the release titer) it would not be classified as an out of specification result. The stability data should be reviewed to assure acceptability relative to our historical experience. This recommendation does not apply to the future lots which have new release specifications. However, I assume clinical data will be available before we need to address the stability of lots with new (interim) release specifications.

MRK-KRA00094960 (emphasis added).

177.3. A Merck memo to Distribution List, dated August 14, 2000, with subject "Team Biologics Inspection - Day 1," stated:

> **AGENDA FOR DAY 2 …**
>
> DOCUMENTS PROVIDED …
>
> - Error and Accident Report …
> - Out of Specification Results

MRK-KRA01978905 at '07-09.

178. In my opinion, I have considered the 1999 email documenting a conversation between Merck's Dr. Wonnacott and FDA's Dr. Baylor and Dr. Baylor's purported agreement that Merck did not need to report lots manufactured before September 1999 that had titers below the MMRII label claim before the 24 month expiration as being "out of specification."[362] Merck's summary of the purported agreement is not consistent with FDA's Dr. Carbone's subsequent statement to Dr. McKee documented in the August 2000 memo that "neither a conclusion has been drawn nor a commitment made" regarding mumps potency/stability. Moreover, since the reporting of out of specification product is a compliance issue, I would expect the FDA's position regarding Merck's reporting obligations would be appropriately addressed in the Team Biologics inspection. I note the agenda for Day 2 of the August 2000 Team Biologics inspection included review of Error and Accident Reporting and Out of Specification Results.

179. FDA's regulatory mechanisms, including Form 483s[363] and Warning Letters[364] in which the FDA identifies deficiencies and requests information to ensure compliance, afford a

[362] *See* Section VI.B above. Vaccines manufactured after September 1999 were "overfilled" to provide assurance that MMRII would have "not less than 4.3 log10 [20,000] TCID50 for the full 24-months shelf life.

[363] "Form FDA- 483 is a list of observations noted during an FDA inspection and issued to the firm at the conclusion of the inspection. The firm is expected to respond to the observations and make the necessary corrections." Biological Products: Reporting of Biological Product Deviations in Manufacturing, 65 Fed. Reg. 66621, 66623 (final rule Nov. 7, 2000) (to be codified 21 CFR pts 600 & 606).

[364] The FDA Regulatory Procedures Manual Section 4-1-1 states: "When it is consistent with the public protection responsibilities of the agency and depending on the nature of the violation, it is the Food and Drug Administration's (FDA's) practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning Letters are issued to achieve voluntary compliance and to establish prior notice. (Prior notice is discussed in Chapter 10.) The use of Warning Letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law. ¶ The agency position is that Warning Letters are issued only for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. A Warning Letter is the agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the

manufacturer the opportunity to provide information to clarify any "understandings." In my opinion, it is the vaccine manufacturer who is responsible for assuring that its overall operation and the products it manufactures are in compliance with the law and that the products released to the market are safe and effective. This is not a requirement unique to mumps potency, or even to Merck.

B. FDA Issued a Form 483 for Failing to Report Mumps Potency Failures

180. In October 2000, FDA issued a Form 483 to Merck for, among other things, failing to report mumps potency failures in mumps containing vaccines manufactured before September 1999, the start of the overfill. To address the deficiency in the Form 483 for failing to report out of specification MMRII and Mumpsvax lots with mumps potency failures, Merck prepared a written response to FDA. Merck prepared a separate written response to FDA regarding the mumps potency/stability data discussed on the August 2000 teleconference.[365] Merck submitted both written responses on October 24, 2000. In October 2000, Merck also learned that the estimated potency loss for mumps in MMRII was greater than the loss estimate it used to calculate the amount of the overfill to ensure MMRII would have "not less than 4.3 log 10 [20,000] TCID50" of mumps virus in each dose through the 24-month shelf life.[366] Merck's stability/potency submission analyzed data for product manufactured up to May 1998. Products manufactured after May 1998 were still within the 24 month shelf life in October 2000 and therefore still potentially on the market.

Act)." available at https://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm (emphasis added).

[365] *See* Section VIII.A above discussing the August 2000 teleconference.

[366] MRK-KRA00018614 (August 20, 1999 letter from FDA regarding overfill stated "the average loss in potency of the mumps component is 0.55 $\log_{10}$ $TCID_{50}$ per two years" and "the variability of the mumps potency test at CBER is 0.226 $\log_{10}$ $TCID_{50}$.").

180.1. A Merck memo from MRL's Statistician, BARDS, Philip Bennett, to MRL's Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrissey, cc'd to Kati Abraham, Jim Clair, Joseph Heyse, Timothy Schofield, Bonnie Stankunas, with subject "Stability of Mumps Component in Merck's Live Virus Vaccines," dated October 5, 2000, stated:

> Routine stability study testing has observed an apparent decrease in the stability of the mumps component in Merck's live virus vaccines (LVV's). Statistical analyses have been performed which show a statistically significant increase in the loss (from 0.51 to 0.72 log loss from release through expiry) and the loss rate (from 0.15 to 0.26 log loss per year for the terminal phase slope) for mumps in lots made after April 1994 compared to lots made prior to April 1994.

MRK-KRA00587859 (emphasis added).

180.2. An email from MMD's Regulatory Administrator, Katalin Abraham, to MMD's Franchise Lead, Vaccines & Biologics, Global Regulatory Affairs, Bonita Stankunas, MMD's Director, Biologics Licensing, Dr. Ronald Salerno, and MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy and cc'd to Keith Chirgwin, Joan Staub, Joyce Bramble and Mark Galinski, among others, re "MM Diplovax," dated October 5, 2000, stated:

> In the years since [around 1990]
>
> - we've learned that our titer claims are the ones at the end of the shelf-life (tough lesson) …
> - … but most importantly, we've had a long dialogue with CBER (still continuing) regarding mumps potency. They've made it clear to us that our expiry for mumps is 20,000 and have told us to double our mumps in order to meet it, raising our release spec to 5.0 – this really doesn't leave any room for interpretation. I think the right thing to do is to define the correct specifications and send them out for filing. The question is what the right specifications are. Clearly it's 20,000

> mumps but recent analysis by biometrics seems to indicate that our current manufacturing spec (target 5.2 – 160,000) doesn't support this expiry (I don't have the final report yet.)- but would, with 18 month dating.
>
> We're still talking with CBER and are right now working on a response to CBER regarding mumps stability - it does appear that there was a statistical shift in losses over time for mumps and it occurred around 1994. As I indicated, I'm waiting for the report from stability and biometrics (mumps, it seems, will be shown to be different but we're waiting to hear on measles and rubella, so that we can get the whole picture).

MRK-KRA00284623 (emphasis added).

180.3. A memo from MMD's Christopher Petroski to Distribution with the header "Team Biologics Inspection 8/14/00-10/11/00 Form FDA 483" and subject: "Team Biologics Close Out-Form FDA 483," dated October 11, 2000, stated:

> … The following FDA Form 483 Observations were communicated: …
>
> 3. Error and Accident Reports have not been submitted to CBER for the following product stability failures:
>
> a. MUMPSVAX, finish number 1187E, failed potency at 9 months, 12 months, 18 months, 24 months, and 30 month interval; this lot also failed reconstitute and store potency at the 24 month interval;
>
> b. MUMPSVAX, lot 0616798, failed potency at 12 months, 18 months, 24 months, and 30 months;
>
> c. M-M-R II, lot 0627847[367], failed mumps potency at 6 months, 9 months, 12 months, 18 months, and 24 months; this lot also failed measles potency at 18 months and mumps and measles reconstitute and store potency at 24 months;

[367] Merck first identified "irregularities" with Lot 0627847 in September 1998 as one of the lots Merck considered using to give children in the Protocol 007 study. MRK-KRA00285466. On April 9, 1999, a meeting was held for "Mumps Potency OOS MMR®II Lot 0627847, 6 Months 4°C." MRK-KRA01895942 at '43 ("D. Wonnacott [MMD Director, Biologics Licensing] has been informed about this lot 0627847. He will let the group know what the

d. M-M-R II, lot 0624918, failed measles and mumps potency, and measles and mumps reconstitute and store potency at 24 months;

e. M-M-R II, lot 0628001, failed mumps reconstitute and store potency at 24 months;

f. M-M-R II, finish number 0067H, failed mumps reconstitute and store potency at 24 months;

g. M-M-R II, finish lot 1315B failed mumps potency at 6 months, 12 months, 17 months, 18 months, 24 months and 30 months;

h. M-M-R II, finish lot 1006D, failed mumps potency at 18 months, 24 months, and 30 months

i. M-M-R II, finish lot 13480, failed mumps at 6 months, 12 months, 18 months, 24 months, and 30 months;

j. M-M-R II, finish lot 0624E, failed mumps potency at 24 months;

k. M-M-R II, lot 0621727, failed mumps potency at 24 months and 30 months;

l. M-M-R II, lot 0621999, failed measles and mumps potency at 24 months and 30 months;

m. M-M-Vax, lot 0616340, failed mumps potency at 9 months, 24 months, and 30 months.

MRK-KRA00071265 at '65-66 (emphasis added).

180.4. A Merck memo from MRL's Statistician, BARDS, Philip Bennett, to MRL's Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrissey, with subject

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regulatory strategy would be on this issue. P[hilip] Bennett also update[d] the group that this lot would not be expected to stay within specification limit for the 24-month shelf life, based on our current algorithm of the active stability monitoring, if the [4.3 Log ($TCID_{50}$) per 0.5 mL] is the specification limit. However, this lot would stay in specification for the entire shelf life if the proposed [3.7 Log ($TCID_{50}$) per 0.5 mL] is the specification limit.").

"Stability of Measles, Mumps, and Rubella components in Merck's Live Virus Vaccines," dated October 17, 2000, stated:

> Attached are results of statistical analysis which you requested on the historical live virus vaccine stability database…
>
> Analyses were performed on the two stability metrics (slope and shelf-life loss) to test for a significant trend over time. A statistically significant trend ($p<0.05$) is seen with the mumps shelf-life loss data, with more recent lots having higher loss estimates. No other statistically significant trends were observed. …
>
> CONCLUSIONS
> These stability analyses show a trend to less stabile [sic] product in recent years. This may be a gradual changeor [sic] a shift, and may be due to a combination of interacting factors.

MRK-KRA00562292 at '92-93 (emphasis added).

180.5. A Merck document titled "Response to Form FDA 483 for Merck Biological Manufacturing Facility, West Point,"[368] dated October 24, 2000, stated:

> Merck Response to Observation #3
> We have carefully reviewed this observation and we believe that measles and mumps potency results below release specifications on stability represented a unique situation that did not require filing Error and Accident Reports. Since 1996 we have had an ongoing dialog consisting of teleconferences, written communications and face-to-face meetings with representatives of CBER Office of Vaccine Research and Review concerning the establishment of expiry specifications for the measles, mumps and rubella family of products. It is because of these communications and submission of stability data via direct correspondence that we believed that further notification in the form of Error

[368] *See also* MRK-KRA00784028 at '29 ("attached please find the final responses to the Team Biologics inspection 483 observations. The responses were faxed to CBER on October 24, 2000.").

and Accident Reports was not necessary. Further details regarding the chronology of events are provided below.

Expiry specifications, potency testing, and stability monitoring for measles, mumps, and rubella containing vaccines have been the subject of ongoing communications between Merck and CBER since 1996. In teleconferences with CBER in 1996 and 1997, the need to define the label claims for measles, mumps and rubella potency in terms of the minimum acceptable titers at expiry became evident. Merck considered the specifications described on the package circulars … 20,000 [4.3 log10] TCID50/dose for mumps … as minimum release specifications, and did not consider them expiry specifications. Communications beginning in 1997 focused on defining the expiry specifications for the product. In this context, assay variability was assessed, analyses were performed to determine the product's stability profile, and a clinical trial to evaluate proposed expiry specifications for mumps was initiated. Written direct correspondence contained data and statistical analyses for lots on stability including individual data points below release specifications. The correspondence from Garfinkle to Hardegree, dated January 28, 1998 covered lots on stability 1987-1996, while the correspondence from McKee to Egan, dated January 8, 1999 covered lots on stability 1987-1998. The conclusions from these discussions, including two fact-to-face meetings and numerous written and verbal communications between representatives from Merck and CBER's Office of Vaccine Research and Review, resulted in a prior approval supplement submitted September 15, 1999. This supplement included a change in potency test format to reduce assay variability. It also included a process change to increase the concentration of mumps vaccine in the product formulation by two-fold to support the expiry specification. The supplement was approved on February 11, 2000.

The specific lots noted in this observation were placed on stability studies prior to the implementation of the mumps process change. During finalization of the end-expiry specifications, the Biological Stability Unit conducted Stability Test Investigations on each of these lots for stability interval results which were below … 20,000 [4.3 log10] TCID50/dose for mumps … Statistical analyses of these results showed that although

> individual data points were below these values, the stability profile of each lot investigated was within the expected range based on historical trends. Therefore, there was no further action taken.
>
> End-expiry titers have now been finalized. Additionally, modifications to the release specifications, potency testing format and mumps concentration have been implemented. With these activities completed, we intend to investigate stability interval results for measles, mumps, and rubella potency testing below the end expiry titers and report any future failures in accordance with 21 CFR 600.14 (a) Reporting of Errors for lots made both before and after changes incorporated in the September 15, 1999 prior approval supplement. As described during the inspection, SOP 283-303X, "Error & Accident Reporting," was approved on August 20, 2000 to describe these activities.
>
> With the exception of the unique situation described herein, Merck has in the past and will continue to submit Error and Accident reports for all out of specification stability results across our product line.

MRK-KRA00784030 at '31-33 (original bold and italics removed, underline added).

180.6. A letter from MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, to FDA's Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Dr. Karen Midthun, regarding "Measles Mumps and Rubella Virus Vaccine Live Statistical Analysis of Potency on Stability," dated October 24, 2000, stated:

> A teleconference to discuss stability testing for Measles, Mumps, and Rubella Virus Vaccine Live was held on August 10, 2000. …
>
> During the teleconference, it became evident that although Merck maintains an ongoing stability program supporting Measles, Mumps, and Rubella Virus Vaccine Live, further communications with CBER are necessary in order for CBER to better understand the studies and analyses performed.

> When these analyses requested by CBER were performed, an apparent change in the potency profile for the product was observed. It is unclear whether the difference is due to a shift or to a trend in the data. It is also not known whether these empirical observations are an artifact of the data collection methods. We are further investigating these observations and request an opportunity to discuss our findings with CBER at a face-to-face meeting. We will contact CBER to discuss the timing for this meeting.

MRK-KRA01899087 at '088-89 (emphasis added).

180.7. Attachment 4, Appendix 2 to Dr. McKee's October 24, 2000 letter to FDA's Dr. Midthun titled "Expiry Potency Calculations for Mumps Containing Live Virus Vaccines" stated:

> Summary
>
> The shelf-life of mumps containing vaccines is 24-months at 2-8° C. …
>
> Thus based on the long term stability history of single dose mumps containing vaccines, these products are predicted to maintain 4.3 $\log_{10}$ $TCID_{50}$/dose throughout their shelf-life (24-months). The estimate for recent lots of mumps containing vaccines predicts a lower potency at expiry (3.9 $\log_{10}$ $TCID_{50}$/dose). The trend in mumps potency loss in current lots of mumps containing vaccines will be addressed with an active stability monitoring plan, as well as a stability time point retest strategy.

Id. at '139-140 (emphasis added).

180.8. Attachment 4, Appendix 2 also included the following Table 3 "Maximum Likelihood Estimates and 95% Lower Bound on the Predicted Potency at 24-Months for Mumps Containing Vaccines":

Table 3: Maximum Likelihood Estimates and 95% Lower Bound on the Predicted Potency at 24-Months for Mumps Containing Vaccines

Period of Manufacture	$\hat{\alpha}$	$V(\hat{\alpha})$	$V(\hat{a})$	$Cov(\hat{\alpha},\hat{a})$	$\hat{\beta}$	$V(\hat{\beta})$	$V(\hat{b})$	$Cov(\hat{\beta},\hat{b})$	$Cov(\hat{\alpha},\hat{\beta})$	$Cov(\hat{a},\hat{b})$
1987 to 1996	4.8272	0.0008	0.0042	-0.00046	-0.01467	1.53E-06	1.34E-05	-7E-07	-9.1E-06	-0.00014
1994 to 1996	4.6602	0.0054	0.0058	-0.00345	-0.02322	1.34E-05	1.9E-05	-6.4E-06	-5.3E-05	-0.00011
	$\hat{\chi}$	$V(\hat{\chi})$	$V(\hat{c})$	$Cov(\hat{\chi},\hat{c})$	$Cov(\hat{\alpha},\hat{\chi})$	$Co(\hat{\beta},\hat{\chi})$	$Cov(\hat{a},\hat{c})$	$Cov(\hat{b},\hat{c})$	Lower 1-Sided 95% CB	
1987 to 1996	0.1494	0.0008	0.0010	-2.1E-05	-0.00019	9.13E-06	-0.00014	5.54E-06	4.3	
1994 to 1996	0.2270	0.0054	0.0071	-0.00152	-0.00089	5.29E-05	-0.00105	4.95E-05	3.9	

Note: Variances and covariances associated with the random components of the model are calculated as the weighted average of the estimates associated with the different lots of vaccine.

Id. at '45 (highlight added).[369]

180.9. Attachment 8, to Dr. McKee's October 24, 2000 letter to FDA's Dr. Midthun included the following table:

[369] Table 3 shows that with predicted potency averaged from 1987 to 1996, Merck could ensure "not less than 4.3" for mumps at end expiry as stated on the MMRII label. When predicted potency was averaged using lots from only the more recent years, 1994-1996, there was greater potency loss and 4.3 could not be ensured. Merck conducted separate analyses "based on the observation that potency losses appear elevated since 1994" and the "current trend in potency loss in mumps containing vaccines indicates that there is an enhanced risk that a single stability measurement will fall below the minimum potency requirement (proposed as 3.7 log10 TCID50/dose)." The specification at the time remained 4.3 log 10 TCID50 dose until Merck obtained approval to lower the end expiry claim. *See id.* at '141 and '144.

Table 2.
Stability of Mumps Virus in Merck's Live Virus Vaccines
2-8°C Stability Data Standardized to the Concurrently Tested Control Lot
Fills Made 12/86 to 5/98

Mumps					
Date of Manufacture		Terminal Phase Slope per Year	Forecast of Lots at 24-Month Expiry	Shelf Life Loss	Release
Overall	average	-0.191	4.346	0.588	4.926
	no. of lots	64	64	61	61
	std dev	0.161	0.291	0.255	0.239
12/86 to 8/93	average	-0.162	4.477*	0.506*	4.982*
	no. of lots	36	36	33	33
	std dev	0.186	0.233	0.257	0.238
9/93 to 5/98	average	-0.228	4.176*	0.685*	4.861*
	no. of lots	28	28	28	28
	std dev	0.116	0.271	0.219	0.228
t-test (before vs. after 9/1/93)		0.107	0.000*	0.005*	0.048*
12/86 to 12/94	average	-0.166	4.440*	0.532*	4.968*
	no. of lots	44	44	41	41
	std dev	0.177	0.252	0.253	0.242
1/95 to 5/98	average	-0.247	4.137*	0.703*	4.840*
	no. of lots	20	20	20	20
	std dev	0.103	0.264	0.222	0.214
t-test (before vs. after 1/1/95)		0.063	0.000*	0.013*	0.049*

* Averages marked with an asterisk show a statistically significant difference (P<0.05).

Potency values listed above are $TCID_{50}$ per 0.5 mL dose.

Id. at '04 (highlight added).[370]

181. The "Conclusions and Follow-up Actions" in Attachment 8, to Dr. McKee's October 24, 2000 letter to Dr. Midthun stated:

> The conclusions from the March 1999 manufacturing investigation can be summarized as follows: …
>
> - … The "apparent" stability shift observed beginning 1994-1995 can be attributed to the "bi-phasic" nature of the stability data, the limitations of the linear first-order model, and the large assay variability, especially the systematic error introduced in the potency measurement;[371]

[370] Table 2 shows 0.703 average log loss for lots filled (manufactured) from January 1995 to May 1998. This was a higher estimate of loss than used to calculate the overfill approved by FDA in September 1999. *See* Section VI.B above, discussing MRK-KRA00018614 (FDA's understanding of the calculation used to determine the 5.2 target.) Table 2 did not include information about potency loss for lots manufactured from June 1998-October 2000 which were within the 24-month shelf-life and still potentially on the market.

[371] *Compare* MRK-KRA01727942 at '44, discussed in paragraph 184.1 below ("CDOC supported the proposed approach to address the mumps potency stability issue; however, there is significant risk in proceeding without a thorough understanding of the root cause of the decreasing trend in mumps stability.").

- For … mumps- containing vaccines, the average potency losses and the corresponding lower 95% confidence limits estimated from all the stability data were … ~0.8 Log_{10} $TCID_{50}$ for mumps, after house standard[372] adjustment.
- The current manufacturing process for MMRII products, *after sufficient improvements in the targeted potency of the filling process, the potency assay and the proper establishment in the release specifications,* is likely to be able to meet the proposed expiry specifications of … 3.7 Log_{10} [5,000] $TCID_{50}$/dose for mumps.

Since that report was completed, we have implemented both the mumps process change (increasing the target titer at manufacturing from 4.9 log_{10} [80,000] $TCID_{50}$/dose to 5.2 [160,000] log_{10} $TCID_{50}$/dose) and the change in release specification for mumps (4.3 log_{10} $TCID_{50}$ [20,000]/dose to 5.0 log_{10} [100,000] $TCID_{50}$/dose). Additionally, changes in the potency assay format to reduce variability have been implemented. Decreases in assay variability should improve the precision of values obtained during release and stability testing, and should allow for increased accuracy in analysis of stability slope and overall shelf-life loss. The observation of an increased loss in potency of about … 0.17 log for mumps (table 4) over time periods compared may not be predictive of further stability results on lots tested in an improved potency assay format and manufactured with an increased mumps release titer of 5.0 .

MRK-KRA01899087 at ‘11-12 (emphasis added).

182. FDA’s Form 483 cited Merck as deficient for failing to report low mumps potency as out of specification. Merck responded to the Form 483 by pointing to its ongoing discussion with FDA personnel in the Office of Vaccine Research and Review regarding the mumps potency issue. Merck’s response to the Form 483 set forth the same position that Merck had documented in the record of the August 2000 teleconference with FDA’s Dr. Carbone.[373] Furthermore, in the separate October 24, 2000 submission regarding mumps stability/potency,

[372] *See* Schedule 5 (describing house standard).
[373] MRK-KRA01522617 at ‘19.

Merck's analysis did not include data for lots manufactured after May 1998. Product manufactured after May 1998 was still within the 24 month shelf life in October 2000.

183. In my opinion, Merck's response to FDA's Form 483 and the separate submission of mumps stability data, which did not include analysis of product manufactured after May, 1998, did not provide assurance that mumps containing vaccines manufactured after May 1998 would have "not less than 4.3 log" at end expiry.[374] Furthermore, since product manufactured after May 1998 was within the 24-month shelf life in October 2000, there was risk that some product on the market would not meet the "not less than 4.3 log" end expiry specification. Moreover, because potency is tied to effectiveness,[375] a risk of lower potency vaccine on the market necessarily includes a risk of less effective vaccine on the market.

C. Merck Continued to Address Potency and Efficacy Issues After Responding to the October 2000 Form 483

184. After reviewing Merck's submissions, FDA "expressed concern regarding the apparent decline in mumps stability over the shelf life of MMRII."[376] Merck's Clinical Development Oversight Committee ("CDOC") considered options for addressing FDA's concerns, including lowering the end expiry potency claim on the label, overfilling above the 5.2 log10 [160,000] TCID50 manufacturing target, or shortening the MMRII shelf life.[377] The "preferred option" recommended by the CDOC was to lower the end expiry specification based

[374] *Compare* MRK-KRA01522617 ("CBER requested that Merck submit its retrospective data used to support its ongoing annual stability program along with very detailed statistical analyses and rationale to support the multi-phase kinetics approach to data evaluation proposed by Merck") (emphasis added).
[375] *See* Section III.B.2 above discussing the connection between potency and effectiveness and collecting relevant FDA authority for the connection.
[376] MRK-KRA01727942.
[377] *Id.*; *see also* Section III.B.2 above discussing how overfilling, short-dating and changing the end expiry specification relate to the potency issue.

on a preliminary subset analysis of the data from the Protocol 007 mumps end expiry trial.[378] Dr. David Krah, Merck's principal investigator for Protocol 007, documented Dr. Emilio Emini's characterization of events in this timeframe as the mumps neutralization "emergency." By the end of November 2000, Merck obtained FDA approval to conduct a preliminary subset analysis using an Anti-IgG Enhanced Neutralization Assay ("AIGENT") designed by Dr. Krah in Protocol 007.

184.1. A document produced from Dr. Krah's files stated:

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

MRK-KRA00026912 (highlight added).[379] [380]

[378] *Id.*

[379] MRK-KRA00623926 (Virus & Cell Biology Research Procedure stated "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 incubation of virus and serum."). *See* Section VII.C below discussing the standard neutralization Dr. Krah modified to use in Protocol 007.

[380] A document titled "2000 Schedule," (hereinafter Dr. Krah's 2000 Journal"), dated October 24, 2000 stated "Summarize data leading to a recommendation of 1:6 anti-IgG for use in the anti-IgG [mu]MPS N[eu]T[ralization assay]" and "C[linical]A[ssay]Subcommittee] presentation today: …Provide update on status of [mu]MPS N[eu]T[ralization assay] development Results for pre-positivity Seroconversion rates Training Validation protocol"MRK-KRA00490081 at '470 -71. *See also* Deposition of David Krah, July 11, 2017, 83:22-84:11 (MRL's

184.2. Dr. Krah's document also stated:

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)

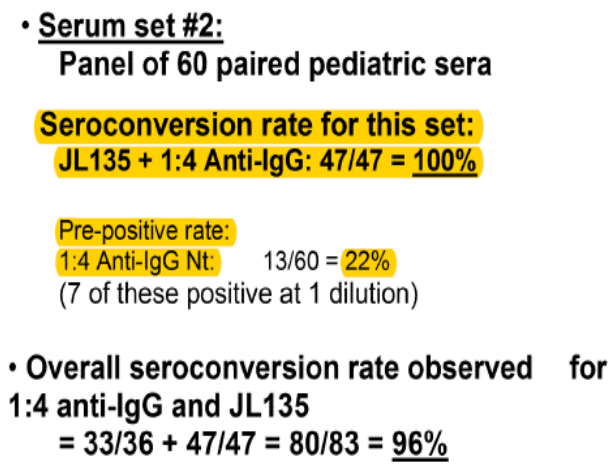
• **Serum set #1**:
Subset of sera from protocol 006
(includes set of 12 sera biased toward non-responders to Jeryl Lynn™ by "standard" Nt)

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:

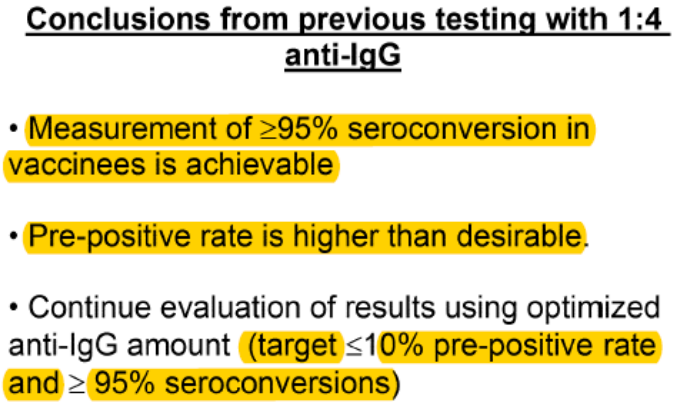
"Standard" Nt:	4/43 = 9%
1:4 Anti-IgG Nt:	2/38 = 5%
1:8 Anti-IgG Nt:	1/35 = 3%

Principal Investigator, David Krah, testified as follows: *Q. Let me show you Exhibits 4 and Exhibit 5 which are the 2000 and 2001 journals. Can you tell me if you recognize those journals as journals that you prepared as part of your duties as you described in your testimony? Defense Counsel: Object to the form. A. The 2001, at least the format looks consistent with the format that I had used previously. There is -- this may have been an error in the date entry. The back end of it, the dates, the year kind of jumps from 2001 back to 2000.*).



MRK-KRA00026912 at '13-14 (highlight added).[381]

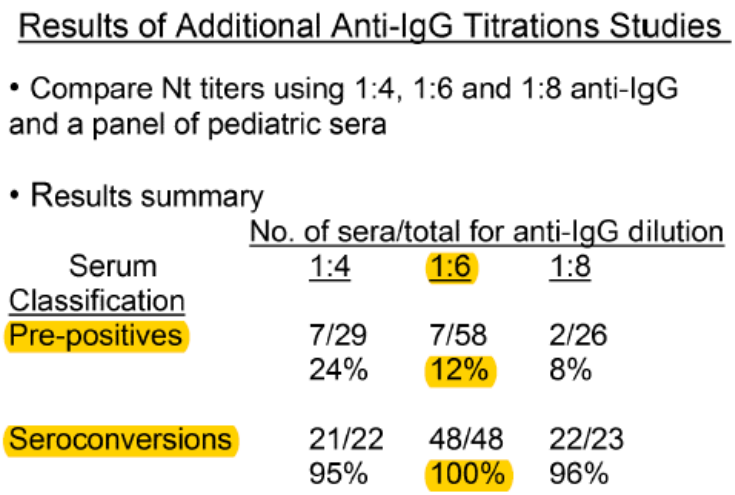
184.3. Dr. Krah's document also stated:



Id. at '15 (highlight added).

184.4. Dr. Krah's document also stated:

[381] *See* Section III.B.3.b.(1)(a) above discussing a "pre-positive" as a sample "pre-vaccination" that tests as a "positive." The pre-positive rate is the calculation of how many children were testing as pre-positive. As discussed above, some children will test positive before vaccination, but Dr. Krah's results suggest his results were higher than he wanted.



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%

Id. at '16 (highlight added).[382]

184.5. Dr. Krah's 2000 Journal also stated:

10/26/00

Note: Emilio suggested that given our [Mu]MPS N[eu]T[realization] "emergency" … Beth won't be released … until the end of the year. … The consensus is that we would be ok staffing-wise w/o her for the upcoming [Mu]MPS N[eu]T[realization] testing.

MRK-KRA00490081 at '472.

184.6. A Merck memo to "Distribution" re: "Summary of the 11/15/00 CDOC [Clinical Development Oversight Committee], dated November 22, 2000, stated:

Attached is the summary of the 11/15/00 CDOC meeting….

Vaccines

MMRII….

[382] Dr. Krah's document stated that he was evaluating the amount of anti-IgG to use in the assay. He conducted testing using different dilutions (concentrations) of anti-IgG. He tested at concentrations of 1:4, 1:6 and 1:8. The seroconversion rate and the pre-positive rate changed depending on the amount of anti-IgG he used. His document stated his conclusion that a "measurement of ≥95% seroconversion … [was] achievable" but the "Pre-positive rate [was] higher than desirable." At the 1:4 dilution, the pre-positive rate was 22%. At the 1:6 dilution, the pre-positive rate was 16%.

> *Mumps Stability Issue/Mumps Expiry Trial:* CBER expressed concern regarding the apparent decline in the mumps stability over the shelf life of MMRII. Potential options under consideration to address the mumps stability issues are as follows: lower the end expiry potency (<4.3 $\log_{10}$ [20,000] $TCID_{50}$/dose), overfill (>5.2 $\log_{10}$ [160,000] $TCID_{50}$/dose), or shorten the MMRII shelf life. Internationally, the latter [sic] option would have a substantial negative commercial impact. The available database of clinical safety experience at >5.2 $\log_{10}$ $TCID_{50}$/dose is being explored to determine if there are data to support the overfill option. Currently, the preferred option is to lower the end expiry based upon preliminary subset analysis of the data (T-15Mar01) from the Mumps End Expiry Trial … Plans are submit a background document to CBER 16Nov00 and hold a teleconference 29Nov00. The objectives of the teleconference are to provide an update on the status of the Neutralization Assay … and to obtain concurrence to use a primary subset analysis of the End Expiry Trial to support the expiry dose for MMRII.
>
> CDOC DECISION: CDOC supported the proposed approach to address the mumps potency stability issue; however, there is significant risk in proceeding without a thorough understanding of the root cause of the decreasing trend in mumps stability. …

MRK-KRA01727942 at '42-44 (original bold removed, underline added).

184.7. A Merck memo from MRL's Director, Biostatistics and Research Data Systems (BARDS), Timothy Schofield to MRL's Senior Vice President, BARDS, Dr. George Williams, cc'd to MRL's Senior Director, Health & Economic Statistics, Dr. Joseph Heyse, MRL's Senior Director, Biostatistics, Dr. Keith Soper, among others, with subject "Vaccine Biometrics Research Highlights 10/16/2000 – 11/17/2000," dated November 19, 2000, stated:

> The stability data from … mumps … vaccines dating from 1987 through 2000 show a decrease in the stability … The trend is statistically significant ($p<0.05$) for mumps… Potency losses are 0.1 to 0.2 log higher than previously reported to CBER and are higher than estimates used to determine the minimum fill levels needed to meet the 24 month expiry dating. This may result in product on the market with potency below the label

claim, requirement for additional overfill, or need to short date and withdraw from some international markets.

MRK-KRA00582932 (emphasis added).

184.8. The November 19, 2000 memo also stated:

Vaccine Biometrics Research and the Vaccine Manufacturing Stability Unit met with Dr. William Fairweather on Friday, November 3, to discuss possible approaches of interpreting stability "out-of-specification" (OOS) results in M-M-R®II stability studies. A high proportion of recent lots (~50%) have been observed by Team Biologics, as having one or more time points below the mumps potency specification (4.3 $\log_{10}$ [20,000] $TCID_{50}$/ml). It was pointed out to Team Biologics that these were lots that were filled prior to a CBER action to require a release potency limit on the product, and were thereby released close to the expiry limit. Lots have since been overfilled with mumps, but may still produce OOS results due to the variability of the mumps potency assay. Dr. Fairweather agreed that the spirit of the FDA Guidelines[383] for the establishment of shelf-life of pharmaceutical and biological products, is directed towards the mean potency of the lot, but recognizes that the Office of Compliance of the FDA is mandated to interpret individual stability time-point results. [Dr. Fairweather] pointed out, however, that the Office of Compliance would not make the final decision on the disposition of a lot with a stability failure, but that this would be made at higher levels in the FDA after careful review of the scientific information, and the implications of a recall. …

… We are continuing to collaborate with Dr. Fairweather, working towards a means of communicating the issues and our solutions to the FDA.

MRK-KRA00582932 at '33 (emphasis added).

[383] The FDA Guidelines were draft guidance issued in 1998. *See* U.S. Department of Health and Human Services, Food and Drug Administration, "Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products, (June 1998), p.41, https://www.fda.gov/ohrms/dockets/98fr/980362gd.pdf When Merck met with Dr. Fairweather again on December 14, 2000, after the FDA issued a Form 483 for out of specification mumps potency at end expiry, Merck's document stated: "there continues to be an unacceptable risk of current product failure. This has serious implications for these vaccines, potentially culminating in a recall or "branding" of the MMR family of vaccines." MRK-KRA00590949.

184.9. A memo from MRL's Associte Director, Worldwide Regulatory Affairs, Dr. Manal Morsy to Kati Abraham, Dr. Joye Bramble, Dr. Joseph Antonello, Dr. Keith Chirgwin, Dr. Jonathan Hartzel, Dr. Joseph Heyse, Dr. David Krah, William Long, Beverly Rich, Holly Matthews, Dr. Jerry Sadoff, Timothy Schofield, Dr. Alan Shaw, Joan Staub, Dr. Scott Thaler, Cathy Wadsworth, Michael Washabaugh, and Mary Yagodich, among others, and cc'd to: David Blois, Dr. Emilio Emini, Dr. Dorothy Margolskee, Dr. Roberta McKee, and Dr. Henrietta Ukwu, among others, with the subject "Mumps End Expiry trial: November 29th, 2000 CBER teleconference," dated November 29, 2000, stated:

> The following is a summary of today's discussion with CBER (11-29-00)
> CBER participants:
> Kathy Carbone, Steve Rubin, Henry Shu, Judy Beeler, Chin Tamani Atreya, and Luba Vujcic
> Merck Participents: [sic]
> Keith Chirgwin, Scott Thaler, Jerry Sadoff, Holly Matthews, John Hartzel, Dave Krah, Manal Morsy, Anal Shaw, Joan Staub, Mary Yagodich, and Joseph Antonello, Tim Schofield
> Executive Summary:
> 1- CBER agreed in general with the parameters and characteristics of the newly developed wild type mumps neutralization assay[384] and congratulated the team that developed it (a few recommendations were made as outlined in the summary).
> 2- CBER agreed with our proposal to conduct a preliminary subset analysis provided that no adjustments or modifications of the assay or study would occur as a result of the analysis.

[384] The "newly developed assay wild type mumps neutralization assay" was Dr. Krah's Anti-IgG Enhanced Neutralization Test. *See* MRK-KRA01621897 (background document for the November 29, 2000 teleconference describing the AIGENT); MRK-KRA01621899 (same); MRK-KRA01621900 (same).

3- CBER acknowledged our plans to contact an outside laboratory to run the rest of the sera from the end expiry study provided that appropriate validation and bridging between laboratories will be established.

4- CBER acknowledged that we do not plan to file o[ptimized]G[elatin-Medium]OS[orbitol]

5- CBER suggested (pending internal CBER discussion) that if the data fall within the "ball park" of historical data, bridging between the end expiry data and historical data may be considered.

6- CBER also suggested that bridging – using wild type ELISA – between the end expiry sera and sera from studies using the current product may also be considered (in lieu of CBERs original proposition of a clinical bridging study).

Summary:

Overall the discussion went very well.

MRK-KRA01619298 at '98-99 (emphasis added).

184.10. An email from MRL's Principal Investigator, Dr. David Krah, to MRL's Director, Vaccine Research, Dr. Alan Shaw, with the subject: "Timing for validation experiments for mumps NT assay development, dated December 10, 2001, stated: "The testing of the interim analysis started 06-Dec-2000 and ended 26-Jan-2001." MRK-KRA00052242 (emphasis added).

184.11. A Merck memo from MRL's, Director, BARDS, Timothy Schofield, to "THOSE LISTED" and cc'd to MRL's Senior Director, Health & Economic Statistics, Dr. Joseph Heyse, MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, MMD's Director, Global Regulatory Policy, Dr. Taryn Rogalski-Slater and MRL's Senior Vice President, Biostatistics and Research Data Systems, BARDS, Dr. George Williams, with subject: "Consultation with Dr. William Fairweather on Vaccine Stability," dated December

14, 2000 and identifying Attendees as: Philip Bennett, Jim Clair, Bill Fairweather, Henrietta Grotz, Cindy Morrisey, Tim Schofield and Sally Wong, stated:

> During the Team Biologics inspection it was noted that there has been a high proportion of stability failures for measles and mumps potency in the M-M-R family of products (~50% of stability study lots filled between 19xx and 19xx display stability failures at one or more time points), and that these failures have increased in frequency recently relative to past experience (see figure in Attachment 2). While many of these failures can be accounted for through historically lower mumps fill levels of M-M-R vaccines, there continues to be an unacceptable risk of current product failure. This has serious implications for these vaccines, potentially culminating in a recall or "branding" of the MMR family of vaccines.

MRK-KRA00590949 at '49-50 (emphasis added).

184.12. A power point presentation to the Clinical Development Oversight Committee, dated December 19, 2000,[385] stated:

[385] *See also* MRK-KRA00562322 (December 19, 2000 cover email from MRL's Director, Worldwide Regulatory Affairs, Keith Chirgwin to Alan Shaw, Katalin Abraham, Ronald Salerno, Scott Thaler, Stephanie Olsen, Manal Morsy and Joye Bramble with the subject "CRRC [Clinical and Regulatory Review Committee] mumps expiry update" with attachment "CDOC Mumps expiry_12_20_00.ppt.").

M-M-R®II Mumps Expiry
Mumps Potency Claim in Label

Mumps potency specification

- Lowest mumps dose with clinical data: 4.3 log $TCID_{50}$
- EP mumps potency specification: 3.7 log $TCID_{50}$

Chronology of regulatory discussions about mumps potency

1996 - Clarification with CBER that labeled mumps potency of 4.3 log $TCID_{50}$ considered minimum release specification, not end of shelf-life claim

1999 - CBER required 4.3 log$TCID_{50}$ through end of shelf-life

2000 - Mumps overfill approved by CBER

- minimum release titer raised from 4.3 to 5.0 log$TCID_{50}$

2000 - RIVM (Dutch release laboratory) requests variation for the mumps overfill to be filed throughout EU

M-M-R®II Mumps Expiry
Mumps Stability

Chronology of regulatory discussions about mumps stability

1997-1999 - series of discussions with CBER on mumps stability; concern raised that stability profile changing

2000 - In response to CBER request, retrospective stability analyses submitted (10/24/00)

- apparent change in stability over time
- 24 month shelf-life loss after January 1995 was 0.18 logs higher than before 1995 (current shelf-life loss averages ~0.7 log)
- cause of apparent stability shift is uncertain
- discussions with CBER on stability planned for 2/01

Conclusion: even with new higher mumps target, compliance with labeled mumps potency may not be feasible

M-M-R®II Mumps Expiry Trial

Drivers for Mumps Expiry Trial

- Avoid change to product profile:
  - Increased mumps target above historical experience required to ensure 4.3 through expiry - potential impact on safety profile?
  - WAES reports following the implementation of the increased mumps target do not indicate any change in AE profile
- Compliance:
  - Even with higher mumps target, current stability data suggest 4.3 at expiry cannot be supported
  - Further increases in mumps release titer to support 4.3 at expiry not considered feasible
  - Reduction in the labeled potency for mumps is necessary to ensure compliance with shelf-life claim

M-M-R®II Mumps Expiry Clinical Trial

Mumps Neutralizing Antibody Assay

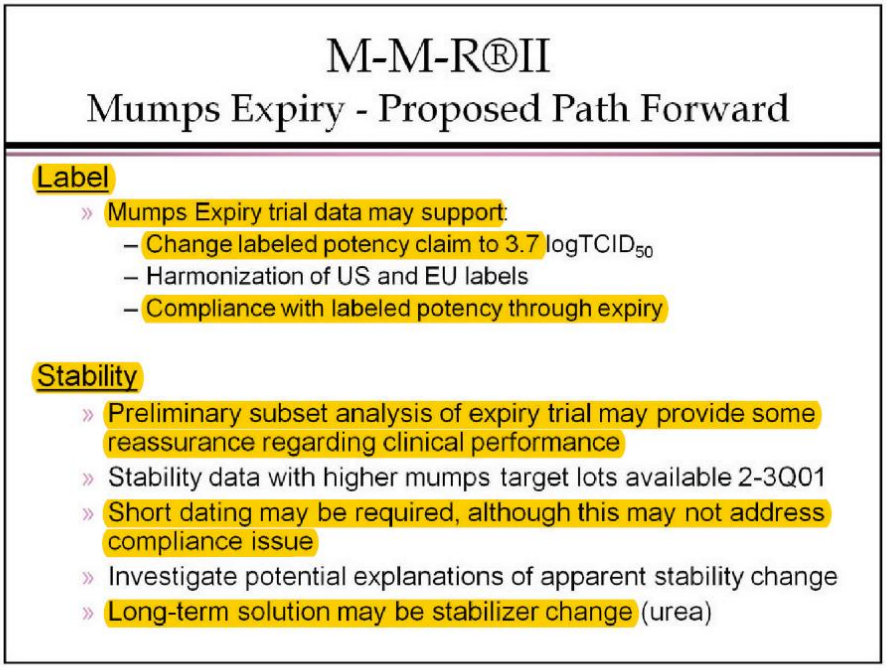
Criteria for success for this trial (90% lower bound for SCR) have required optimization of mumps neut antibody assay

Preliminary data with optimized assay (N=48)

- Seroconversion rate 100%
- Pre-positive rate 12%

CBER concurrence obtained (11/29/00):

- with assay methods
- primary analysis confined to pre-negatives
- not necessary to titer to endpoint
- concurrence expected for bridging plans for OGOS-GOS
- plans for subset analysis (N=600) discussed



Id. at '01, 02, 03, 04 and 06 (highlight added).[386]

184.13. A summary of the December 20, 2000 CRRC [Clinical Regulatory Review Committee] Meeting, dated December 21, 2000, stated:

> MMR®II
>
> *Update on Discussions with CBER Regarding the Mumps Neutralizing Antibody Assay and the Mumps End Expiry Trial*

[386] The CDOC overheads can be summarized as follows: (1) MMRII Mumps Expiry was the topic; (2) the lowest mumps dose for which Merck had clinical data was 4.3 log10 [20,000] TCID50; (3) FDA required 4.3 log10 [20,000] TCID50 through expiration, which was 24-months; (4) Merck identified a shift in the stability of MMRII's mumps component but the cause was uncertain; (5) even with the overfill, Merck's compliance with the labeled mumps potency of 4.3 log10 [20,000] TCID50 cannot be supported; (6) further overfill to ensure 4.3 log10 [20,000] TCID50 had potential impact on the safety of the product; (7) reduction in the label claim of 4.3 log10 [20,000] TCID50 was necessary to ensure compliance (7) for the clinical trial Merck would use to support the label change to be successful, Merck had to "optimize" the assay used (adding anti-IgG); (8) the preliminary results of the optimization experiments showed a seroconversion rate of 100% was possible, but with a pre-positive rate of 12%; (9) the proposed "Path Forward" for the MMRII label was to use the Mumps Expiry trial data to support a label change and compliance with labeled potency through expiry; (10) the proposed "Path Forward" for the stability/potency issue was to use an analysis of a preliminary subset from the expiry trial to provide some reassurance regarding the performance of the vaccine at potencies less than 4.3 log10 [20,000] TCID50. *See also* MRK-KRA01727952 (summarizing the meeting where these overheads were presented).

Dr. K. Chirgwin/Attachment 6

The chronology of CBER discussions regarding Mumps titer at expiry and Mumps stability was presented. Based on efficacy data for the lowest mumps dose established in 1980, CBER has indicated that the potency through expiry must by [sic] 4.3 log $TCID_{50}$ or greater.[387] In order to meet this expiry, CBER agreed to Mumps being overfilled at a higher release titer (5.0) to ensure that the 4.3 log $TCID_{50}$ potency is maintained over the shelf-life. There have been on-going discussions with CBER regarding Mumps Stability due to an apparent (1997-1999) and subsequently confirmed (10/24/00) increased loss rate (0.18 log) during shelf-life. As a result, even the use of a higher release potency overfill may not be sufficient to maintain the CBER requested expiry potency through shelf-life. In order to preserve the current product and AE profile, further increases to the release titer beyond 5.0 will not be pursued. The data from the Mumps End Expiry trial will be used to evaluate the seroconversion rate (SCR) of vaccine at lower end expiry doses (4.0 and 3.7 log $TCID_{50}$). If suitable SCR are achieved with 3.7 log $TCID_{50}$ potency, US and EU labels will be harmonized….

CRRC DECISION: CRRC supported the Team path forward for MMR®II.

MRK-KRA01727952 at '59-60 (emphasis added).

185. By the end of 2000, Merck had confirmed increased potency loss of 0.18 log during shelf life[388] and the cause of the apparent shift was uncertain.[389] The presentation to the Clinical Development Oversight Committee, dated December 19, 2000, concluded: "even with new higher mumps target, compliance with labeled mumps potency may not be feasible."[390] Lowering the end expiry claim on the MMRII label using Protocol 007 was the way Merck

[387] A Merck "Summary of Telephone Discussion," with FDA, dated November 28, 2000, stated: " Dr. Carbone commented that due to assay variability we would need measured mumps potencies at expiry which were greater than 4.3 in order to be able to say with confidence that the true mumps potency was in fact 4.3. MRK-KRA00071398 at '99 (emphasis added).

[388] MRK-KRA01727952 at '59-60. *Compare* MRK-KRA00018614 (1999 letter from FDA stated "average loss in potency of the mumps component is 0.55 log10 TCID50 per two years").

[389] MRK-KRA00562323 at '02.

[390] *Id*.

identified to ensure compliance with the MMRII label potency specification of "not less than 4.3" for mumps.[391]

186. In my opinion, by the end of 2000, Merck could not ensure MMRII lots manufactured after September 1999, after the overfill, met the label potency specification of "not less than 4.3 log" for mumps. Furthermore, Merck could not ensure MMRII lots manufactured before the overfill and still within the 24-month shelf life, met the label potency specification of "not less than 4.3" for mumps. Moreover, in December 2000 Merck did not have clinical data to support lowering the end expiry claim on the MMRII label, or other data to provide reassurance of the efficacy of lower potency product.[392]

D. FDA Issued a Warning Letter in February 2001 Relating to the Ongoing Issue of Mumps Stability in MMRII

187. In February 2001, after reviewing Merck's response to the October 2000 Form 483, FDA issued Merck a Warning Letter.[393] With regard to the mumps potency issue, the Warning Letter stated that "products must meet their specifications, not the historical trend throughout the expiry period."[394] Merck was required to respond within 15 working days.[395]

187.1. A letter from FDA's Director, Office of Regional Operations, Deborah Ralston, to MMD's Vice-President of Vaccine & Sterile Quality Operations, Dr. Roberta McKee, titled WARNING LETTER, dated February 9, 2001 stated:

[391] Merck documents evidence that it considered short-dating the product, implementing additional overfill and developing a new stabilizer for MMRII. MRK-KRA00562323. Merck documents further evidence that the Protocol 007 testing was prioritized in order to address potency related concerns. *See*, MRK-KRA00490081 at '72 (describing the [Mu]MPS N[eu]T[realization] "emergency"); MRK-KRA01727942 at '42-44 (CDOC supported the proposed approach "to lower the end expiry based upon preliminary subset analysis of the [Protocol 007] data" in order "to address the mumps potency stability issue.").
[392] MRK-KRA00562323 ("Lowest mump dose with clinical data: 4.3 log 10 [20,000] TCID50.").
[393] MRK-KRA00209399.
[394] *Id.* at '402.
[395] *Id.*

> The Food and Drug Administration (FDA) conducted an inspection of your facility located at Sumneytown Pike, West Point, Pennsylvania, between August 14 and October 11, 2000. During the inspection, our investigators documented significant deviations from the applicable standards and requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), Parts 211 and 600-680 as follows: …
>
> 3. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet and of its specifications or extend the investigation to other batches that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. …

MRK-KRA00209399 at '399-400 (underline in original).[396]

187.2. The Warning Letter also stated:

> We acknowledge receipt of your responses dated October 24, 2000, and January 15, 2001, to the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letters may be referenced in your response to this letter, as appropriate. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483: …
>
> FDA 483 observation 3
>
> Regarding the Mumps Virus Vaccine Live stability data, your response indicated the stability profile of each lot was within the expected range based on historical trends. Products must meet their specifications, not the historical trend throughout the labeled expiry period.
>
> Our investigators reported that the data in your firm's files showed that a number of Mumps Vaccine stability samples representing lots manufactured before the formulation was changed during February 2000 failed to meet the minimum potency specification.

[396] *See also* https://web.archive.org/web/20100311061607/http://www.fda.gov/downloads/ICECI/EnforcementActions/WarningLetters/2001/UCM078249.pdf.

> Product manufactured before February 2000 may still be on the market because the expiry period is two years. Please submit an analysis of Mumps stability data describing the range of potencies you would expect the various Mumps Vaccine products to reach at the two-year expiration date. For the analysis, assume the initial potency is the minimum release potency specification that was in effect before February 2000. Please summarize the available data regarding product efficacy at the lower end of this potency range.
>
> Regarding your investigation of the Mumps Vaccine stability test failures, it did not include analyses of reserve samples of additional batches. One batch of each different presentation was placed on the stability-monitoring program every year. This stability batch is a sample, which represents the many batches that are manufactured during the year. When the designated stability batch fails to meet its specification, the investigation should include examination of reserve samples of other batches to quickly determine whether the out of specification result represents an anomaly or a serious problem.

Id. at '401-02 (emphasis added).

187.3. The Warning Letter also stated:

> Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.
>
> Please notify this office in writing, within 15 working days of receipt of this letter, of any additional specific steps you have taken to correct the noted deviations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension and/or revocation.

Id. (emphasis added).

187.4. MRL's former Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, testified as follows:

> *Q. So what's a warning letter from CBER?*
> *A. It's exactly what it says. It's a warning letter from CBER in which the agency indicates specific deficiencies that it wishes to see corrected immediately. And it gives the recipient a relatively short period of time to put together a corrective action plan that the agency would then need to certify.*
> *Q. And what could happen if CBER is not satisfied with the correction plan?*
> *A. Again, it depends on what's the nature of the warning letter. If the warning letter reflects a manufacturing facility, they will close down a manufacturing facility. If it refers to a specific product, they can request withdraw of the product. It depends on the details.*

Deposition of Emilio Emini, June 6, 2017, 100:9 - 101:1 (emphasis added).

188. In my opinion, Merck's response to the October 2000 Form 483 did not provide the FDA sufficient assurance that corrective actions had been taken to fix the cited deficiencies, including with regard to mumps potency. The Warning Letter was the next regulatory mechanism after the Form 483 before FDA could initiate an enforcement action to assure Merck's compliance with the law.[397]

E. Merck Prepared Its Response to the February 2001 Warning Letter

189. In February 2001, Merck Manufacturing Division prepared the response to the Warning Letter. MMD's Vice-President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee contacted senior management at Merck Research Laboratory to assist in Merck's response.

[397] *See* FDA Regulatory Procedures Manual Section 4-1-1 available at https://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm.

189.1. An email from MRL's Administrative Assistant, Susan Gallagher, to MRL's Biometrician/Statistician, BARDS, Philip Bennett, with the subject: "URGENT – BPC Emerging Issues – MMR Stability," dated February 14, 2001, stated:

> This is an urgent meeting requested by Dr. McKee to define options regarding the MMR Stability as presented in the Mumps stability submission of October 27 [2000]. (Please refer to Ron Salerno's e-mail of 11/1).

MRK-KRA00684945.

189.2. A high importance e-mail from MMD's Vice-President of Vaccine & Sterile Quality Operations, Dr. Roberta McKee, to MRL's Senior Vice President, Project & Vaccine Integration, Dr. Dorothy Margolskee, MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, and MRL's Director, BARDS, Tim Schofield, with the subject "URGENT - CBER Warning Letter," dated February 14, 2001, stated:

> Today I received from CBER via FAX a Warning Letter in response to the Team Biologics Inspection last year. We are working to develop responses. MRL assistance is required to develop the response to the following:
>
> > "Regarding the Mumps Virus Vaccine Live stability data, your response indicated the stability profile of each lot was within the expected range based on historical trends. Products must meet their specifications, not the historical trend throughout the labeled expiry period.
> >
> > Our investigators reported that the data in your firm's files showed that a number of Mumps Vaccine stability samples representing lots manufactured before the formulation was changed during February 2000 failed to meet the minimum potency specification. Product manufactured before February 2000 may still be on the market because the expiry period is two years. <u>Please submit an analysis of Mumps stability data describing the range of potencies you would expect the various Mumps Vaccine products to reach at the two-year expiration date. For the analysis, assume the initial potency is the minimum release potency specification</u>

> that was in effect before February 2000. Please summarize the available data regarding product efficacy at the lower end of this potency range.
>
> Regarding your investigation of the Mumps Vaccine stability test failures, it did not include analyses of reserve samples of additional batches. One batch of each different presentation was placed on the stability-monitoring program every year. This stability batch is a sample, which represents the many batches that are manufactured during the year. When the designated stability batch fails to meet its specification, the investigation should include examination of reserve samples of other batches to quickly determine whether the out of specification result represents an anomaly or a serious problem."

Please develop the response for the request highlighted above.[398] A draft is required no later than Friday, February 23rd. I'll be contacting you separately to discuss strategy. MRK-KRA01896077 (underline in the original).

189.3. MMD's former Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, testified as follows:

> *Q. Doctor, Exhibit 13 is a document with a Bates No. Public 666 through 670 which is a warning letter from CBER to you, Dr. McKee, dated February 9, 2001, and I will represent to you that Merck had produced a copy of this document, only heavily redacted, bearing Bates stamp numbers 209399 through 403. Can you tell me if you have ever seen this warning letter before?*
>
> *A. Yes.*
>
> *Q. Okay. And what is a warning letter?*
>
> *A. A warning letter is a communication from the agency expressing their concerns outside of the inspection setting with regard to observations at the firm.*

[398] A Merck document titled "CRRC Critical Activities" dated August 15, 2001 stated: "A warning letter was received from the FDA on 14Feb01 following the Team Biologics inspections in 2000. One of the observations in the letter requested that Merck provide an analysis of the projected mumps stability for M-M-R-II lots that are remaining in the market that were produced prior to February 2000 (when our mumps release titer was increased at the request of the FDA) and provide a summary of available efficacy data at the lower end of the potency range for these lots." MRK-KRA01724860 at '67.

Q. Okay. Can you read the first paragraph of the warning letter for the record, please.

A. The Food & Drug Administration (FDA) conducted an inspection of your facility located at Summneytown Pike, West Point, Pennsylvania, between August 14th and October 11th, 2000. During the inspection our investigators documented significant deviations from the applicable standards and requirements of section 502(a)(2)(B) of the Federal Food Drug & Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), parts 211 and 600-680 as follows.

Q. And there is several observations that are made as part of this letter; correct?

A. Correct.

Defense Counsel: Object to form.

Q. And so in your 17 years at Merck, had you seen in your head of quality job duties a warning letter documenting significant deviations?

Defense Counsel. Object to form.

A. In my 17 years at Merck?

Q. Yes.

A. I saw this warning letter.

Q. Any other warning letters?

A. Not to my recollection.

Q. Okay. So this was a -- did you consider this a significant event with respect to your job duties as overseeing the quality of the vaccine products?

MS. HARDWAY: Object to form.

THE WITNESS: This is a significant event.

Deposition of Roberta McKee, March 30, 2017, 151:20-153:15 (emphasis added).

189.4. A document titled "2001 Schedule," (hereinafter Dr. Krah's 2001 Journal"),[399] stated:

> February 15, 2001 …
>
> ✓ Mtg with Emillo @ 1:30 PM to update the [Mu]MPS N[eu]t[ralization] data. Merck has been issued a "warning letter" from the FDA regarding [Mu]MPS

[399] *See* Deposition of David Krah, July 11, 2017, 83:22-84:11 (describing these "schedules" as his journals).

> titers-The data that we have generated will be needed to include in the response (due within 14 days from receipt) to provide a "comfort factor" with the vaccine dose. The full data set from Protocol 007 would be needed to change the label/license.

MRK-KRA00490592 at '640-641 (emphasis added).

190. After receiving the February 2001 Warning Letter, Merck needed to provide FDA two things: (1) information regarding the stability/potency of product that was still on the market; and (2) a summary of available efficacy data at the lower end of the potency range to provide reassurance that, if there was lower potency product on the market, it did not present a risk to the individuals, children mostly, who would receive the vaccine. According to Dr. Krah's journal, the data he generated was going to be the clinical data Merck would use to provide a "comfort factor." Elsewhere, Merck stated that the clinical data was "to justify the efficacy of lower potency product."[400]

191. In my opinion, in responding to the February 2001 Warning Letter, Merck needed to demonstrate appropriate corrective actions to ensure compliance regarding the mumps potency issue identified in Observation #3, or it would face potential regulatory action.

1. Merck Identified 225 Lots of MMRII It Predicted Would Not Meet the Mumps Potency Specification of Not Less Than 4.3 at Expiry

192. On February 23, 2001, the same day MMD's Vice-President of Vaccine & Sterile Quality Operations, Dr. McKee, asked MRL's Senior Vice President, Project & Vaccine Integration, Merck Infectious Diseases, Dr. Dorothy Margolskee, to deliver a draft of Merck

[400] MRK-KRA00207690 at '08.

Research Laboratories' portion of the response to the Warning Letter,[401] Dr. Margolskee sent an email to MRL's President, Dr. Edward Scolnick, updating him on the "group effort."[402]

192.1. The email from MRL's Senior Vice President, Project & Vaccine Integration,[403] Merck Infectious Diseases, Dr. Dorothy Margolskee,[404] to MRL's President and Executive Vice President, Science & Technology, and Member of Merck's Board of Directors, Dr. Edward Scolnick, and MRL's Executive Vice President, Clinical Sciences and Product Development, Dr. Douglas Greene,[405] cc'd to MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, and MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MMD's Senior Vice President, Global Quality, Dr. Michael Angelo, and MRL's, Senior Vice President, Science and Technology, Dr. Michael King, with the subject "Mumps end-expiry," dated February 23, 2001, stated:

[401] *See* paragraph 189.2 describing Dr. McKee's request for assistance.
[402] MRK-KRA00549510.
[403] MRL's former Vice President, Clinical Research, Florian Schodel, testified as follows: *"Q. What is vaccine integration? A. Vaccine integration was a department at the time which was created in anticipation of a number of vaccine filings, quite a few, which made sure that the different departments of Merck collaborated in putting together the right data for the filings.*" Deposition of Florian Schodel, December 22, 2016, 44:7-14.
[404] MRL's former Vice President, Clinical Research, Florian Schodel, testified as follows: "*Q. In the attaching emails from Dorothy Margolskee – who is Dorothy Margolskee during this time frame, what was her position? A. Dorothy was still my boss at the time. She – I can't tell you what her exact title was but she had essentially all of vaccine development on the MRL side under her."* Deposition of Florian Schodel, December 22, 2016, 155:5-13.
[405] MRL's former Vice President, Clinical Research, Florian Schodel, testified as follows: *Q. Also cc'd – do you know who Douglas Greene was? A. Uh-huh. Q. Who is that? A. Doug at the time was the head of clinical. Q. Clinical? A. Yeah. Q. Clinical Research? A. Clinical Research within MRL. So he was reporting to Ed.*" Deposition of Florian Schodel, December 22, 2016, 155:24-156:10.

-----Original Message-----
From: Margolskee, Dorothy
Sent: Friday, February 23, 2001 7:39 PM
To: Scolnick, Edward M.; Greene, Douglas Dr.
Cc: Sadoff, Jerald C.; Ukwu, Henrietta N; Emini, Emilio A; Chirgwin, Keith D.; Angelo, Michael J.; King, Michael L.
Subject: Mumps end-expiry

Ed,

We have been assisting MMD in responding to CBER questions re mumps end-expiry by performing an interim analysis on 600 children participating in the mumps end-expiry study (200 per group, studied at mumps potencies of 4.9, 4.0 and 3.7). On the basis of this analysis and what is currently calculated by MMD as mumps stability in MMR-II (obtained from analyses of recent MMD stability lots since summer 1998), there are MMD "lots in question" that have been released in the past ~ 2 years. These lots may still be in circulation with 24 month end-expiry titers that fall below 3.7 (6 lots) or between 4.0 and 3.7 (100 others). The <3.7 lots are of particular concern; the 3.7-4.0 lots are likely defensible with some additional work. All 106 lots are a compliance issue.

First, the neuts data:

- The clinical study preliminary analysis came out very late Wednesday evening and is in Attachment #1. Recall that we are using a neutralization assay using a low passage (P7) Jeryl Lynn strain as "wild type". The assignment of mumps vaccine potency for the tested material was done by an extended assay method, such that the titers of 4.9, 4.0 & 3.7 are ± about 0.05 (i.e. consider them exact).
- By the neutralization assay, an MMR-II mumps end-expiry of 4.0 meets CBER's demand for a 90% seroconversion rate floor, while the 3.7 log titer misses (88.2% SCR, with 95% CI of 82.3 to 92.6%). (Jerry and I feel 3.7 is medically ok and may be defensible to the Office of Compliance; see below). Lots which would have 24month end-expiry titers lower than 3.7 logs would not have data from this study to support the shelf-life.

- Attachment #2 shows the reverse distribution curves and Attachment #3 displays the individual subject listings.
- These are only partial data - the total study size is ~800 per group. Given the complexity of the assay, it will take several months to finish the neut assays on the remainder.

Attachment #1: Preliminary neutralization data for mumps end-expiry

Attachment #2: Reverse distribution curves

Attachment #3: Individual subject listings

MRK-KRA00549510 at '10-11 (highlight added).

192.2. The February 23, 2001 email to Drs. Scolnick and Greene also stated:

Background/Impact Assessment on Marketed Product:

- When MRL first initiated the mumps neuts study, and using the mumps stability data known at that time, achieving an end-expiry of 4.0 would have covered MMD for all lots released. As we worked through assay conditions in order to make it as sensitive as possible (to deal with CBER's demand for a 90% SCR floor), MMD agreed in September 1999 to increase the mumps release target by 0.2 logs (to 5.2 target, 5.0 release), which gave them additional cushion.

- In the meantime, there have been continuing discussions with CBER re mumps end-expiry titers. In response to the recent CBER inspection from the Office of Compliance to MMD, manufactured mumps stability data were re-examined. In that analysis, it appears that mumps stability has been somewhat less (i.e. ~0.2 logs faster over a 24 month period; a total of ~1.0 log lost over 24 months) for lots manufactured at least since the summer of 1998.

- **Given this new analysis, lots manufactured since September 1999 are still fine with the overfill and 24 month end-expiry titers projected to be at or above 4.0.**

- Unfortunately, with the faster mumps potency loss rates seen since at least summer 1998, there are released lots which, at 24 months, are projected to be below 4.0 (100 lots) or 3.7 (6 lots). This will be a compliance issue with the Agency. [In case you want the details, Attachment #4 is a line listing of the lots - note column 5, which is the release dose per lot and assume ~1.0 log fall over 24 months. (In the table, the reason why the expiry appears to be longer than 24 months from the potency assignment is because it is counted from the time of thawing and packaging, rather than from the release potency assay which is performed just prior to storing frozen in inventory.)]

- Of the 100 lots, 58 lots would be at 3.9; 37 at 3.8; and 5 at 3.7 at end expiry.
- Of the 6 lots, 2 would be at 3.6; 3 at 3.5 and 1 at 3.4 at end expiry.

Attachment #4: Lots released with low mumps potency

Id. at '11-12 (highlight added).

192.3. The February 23, 2001 email to Drs. Scolnick and Greene also stated:

Comments re the 101 lots between 4.0 and 3.7 at 24 month end-expiry.:

- The projected end-expiry titers are the lower 95% C.I. The mean end-expiry would be about 0.1 to 0.2 logs higher. Therefore, in fact all 101 lots between 3.7 and 4.0 are medically fine, given the mean end-expiry at 24 months, the neutralization data at 3.7 in the clinical study, and the likelihood that the vials would have been used well before 24 months.
- **A caveat on the 3.7 data is the set of 20 nonresponders** (see attachment #3). Given our limited experience with the assay, Jerry & I do not know whether these infants are true nonresponders or "hyporesponders" to this WT Jerryl Lynn strain. For this reason, and in discussion with Emilio, the nonresponder sera will be tested by ELISA (our routine assay) and in the neutralization assay using Jerryl Lynn vaccine virus (which appeared to have somewhat higher %SCRs in our hands than did the WT JL strain). Nonresponders from all dose groups will be tested, along with appropriate positive controls. **If these children are in fact "hyporesponders", i.e. respond by ELISA and to JL vaccine strain, we will be reassured.**
- In addition, we are pulling Maurice Hillemann's papers to see if we can further support the validity of a lower % SCR (at first blush, perhaps not, but he used a very different neutralization assay). **Maurice's data did show seroconversion down to a vaccine potency of 2.5 logs.**
- Finally, we propose a set of surveillance investigations as well (especially relevant for next section, so discussed there).

Comments re the 6 lots less than 3.7 at 24 months end-expiry:

- The lowest lot (release of 4.4.) would be at 3.4 at end expiry. Mean end-expiry would be ~3.5 to 3.6, still low. Projecting the "decay" rate over 24 months would suggest that 3.7 would be crossed at ~18 months, so if we can convince CBER that 3.7 is ok, then the window of uncertainty narrows. However, the lowest lot expires in 5/2001, so if it's still out there, it's below the 3.7 cut off.
- MMD & Marketing are tracking down all 106 lots, with a "Fact Finding" ongoing, especially for the 6 lowest lots ("Fact Finding" is a prelude to potential product recall). In addition to distribution data, it would be very good to know what the "burn rate" is (i.e. how long does a lot stay out there before being used up?). We'll have more information on Monday. MMD speaks with CBER on March 1 in person (Mike Angelo, Roberta McKee and perhaps others).

Id. at '12-13 (highlight added).

192.4. The February 23, 2001 email to Drs. Scolnick and Greene also stated:

From a medical perspective concerning potential product recall, I'll focus on the 6 lots & what we will do as a minimum:

- First, Keith Chirgwin and Stan Music have looked at the WAES database; the data are unremarkable at this point. There are 5 cases of mumps since 1998 reported, with only one appearing to be a breakthrough (occurred 6 months post-dose 2, with a lot released in 3/99 with a potency of 4.6, and administered in 8/99 - therefore likely to be host related and not vaccine potency related).
- Depending upon the results of the "Fact Finding" (i.e. where did the lots go?), we first propose to confirm the WAES data with a retrospective HMO database study in an area covered by the low potency lots vs areas covered with routine potency vaccine.
- However, the retrospective data will not be that relevant for infants receiving their first dose at 15 months, since the peak of mumps disease is between 3-5 years old. Therefore, we propose to set up a prospective surveillance study as well, perhaps in a large HMO setting, assuming that we can map the lots of interest to an HMO with the appropriate infrastructure. We are contacting Harry Guess for his advice & help in this.

What will trigger a high level of concern:

- Our level of concern for these 6 lots is dependent upon the further analysis of the ~20 nonresponders at the 3.7 dose in the clinical study. If they respond to JL vaccine strain and/or if their ELISA titers are fine, then we could probably be content with careful post-marketing surveillance of relevant cohorts.
- If the nonresponders are truly not responding to the vaccine, we will need to consider further assessment, including how well we can trace these 6 lots & whether we can sample infants for evidence of seroconversion to field material. Such an assessment would be good to have prior to deciding on further action (including potential revaccination of large infant cohorts!), since the end-expiry study used "aged" material (i.e. artifically aged for several weeks at higher temperature to arrive at the desired potency). An argument could be made that the response may not be reflective of marketed product, gradually expiring in the refrigerator.

That's the status for now. We reconvene on Monday morning as further information comes in. This is a real group effort, with Henrietta, Emilio, Mike Angelo (MMD) & their groups working side by side with me and Jerry. We'll keep you & Doug in the loop.

Id. at '13-14 (highlight added).

192.5. Attachment 4 to Dr. Margolskee's email to Drs. Scolnick and Greene, an excel spreadsheet titled "Total Doses on Low Mumps Titer Lots within Expiry,"[406] contained three worksheets and the "Summary" tab stated:

	A	B	C
1			
2	**Total Doses on Low Mumps Titer Lots within Expiry**		
3			
4	04681-00-00	Total Doses (Distributed 3/99 to 9/00)	56,170
5	04749-00-00	Total Doses (Distributed 4/99 to 12/99)	100,890
6	04011-00-47	Total Doses (Distributed 1/99 to 7/00)	10,868,620
7	04013-00-47	Total Doses (Distributed 9/99)	20,363,210
8			
9	U.S. Doses Distrubuted in 2000		12,765,787
10	JV and ROW Doses Distributed in 2000		10,646,101
11			

MRK-KRA00549518 (highlight added).[407]

193. In my opinion, in response to the pending Warning Letter, I would expect Merck to provide the FDA with similar information to that provided to Drs. Scolnick and Greene, including the following:

- Merck identified 225 lots still within the 24-month dating period with estimated end expiry potencies below 4.3 log 10 [20,000] TCID50/dose.
- Merck identified 213 of those lots to still be within the 24 month dating period on February 23, 2001 when Dr. Margolskee sent her email, and 212 of the lots would

[406] Dr. Margolskee forwarded her email to Dr. Florian Schodel. The four attachments in the email Dr. Margolskee forwarded to Dr. Schodel, "MMR007 Subset Draft Table.doc," "V205-7 A1A-A1B.doc," "serolisting allsubj.doc," and "Low Mumps Target Lots within Expiry.xls" bear the same names as Attachments 1-4 in Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene.

[407] "Attachment #4 Lots released with low mumps potency" identified a total of 235 lots. MRK-KRA00549518. Of the 235 lots identified, 10 lots had a projected end expiry potency of 4.3 log or above. 225 of the 235 lots had projected end expiry potency of less than 4.3 log. As of the date of Dr. Margolskee's February 23, 2001 email, 213 of the 225 lots projected to be below 4.3 log were within the expiration date and could still be on the market. As of the date of Merck's response to the Warning Letter on March 8, 2001 was due, 212 of the 225 lots projected to be below 4.3 log were within the expiration date and could still be on the market. Further, while Dr. Margolskee's email noted 100 lots projected to have an end expiry potency below 4.0 log, but above 3.7 log, Attachment #4 identified 101 lots meeting this criteria. *See also* Schedule 25 (summarizing the lots described in Attachment #4).

still be within the 24 month dating period on March 8, 2001 (when the Warning Letter response was due).

- Merck identified six lots with an estimated end expiry potency of 3.4 [2,500] to 3.7 log10 [5,000] TCID50/dose.
- Merck identified 101 lots with an estimated an end expiry potency between 3.7 [5,000] and 3.9 log10 8,000] TCID50/dose.
- Merck identified 118 lots with an estimated end expiry potency between 4.0 [10,000] and 4.2 log10 [16,000] TCID50/dose.
- The lots projected to fall below 4.0 log 10 [10,000] TCID50 at end expiry "will be a compliance issue with the Agency."[408]
- From the results of the AIGENT Drs. Margolskee and Sadoff felt "3.7 [was] medically ok and may be defensible."
- Lots which would have potency lower than 3.7 at 24 months would not have data from the end expiry trial to support effectiveness.
- Complete data from the end expiry trial will take several more months.
- For lots manufactured at least since the summer of 1998, a total of ~1.0 log is lost over 24 months. Given this new analysis, lots manufactured since September 1999 have 24 month end expiry titers projected to be at or above 4.0 log, <u>not 4.3 log as stated in the label</u>.
- Attachment #4 estimated total doses of low mumps titer lots within expiry released to the United States to be approximately 12 Million doses.[409]
- The medical assessment of the 101 lots between 3.7 and 4.0 depended on the neutralization data in Protocol 007, amongst other things.
- Merck was going to test a set of non-responders from the Protocol 007 preliminary subset analysis outside the protocol to evaluate responses in other assays to get assurance it did not have from the AIGENT testing alone.
- Merck proposed a set of surveillance investigations.

[408] Dr. Margolskee's email stated that it was 106 lots. Attachment #4 identified 107 lots below 4.0 log.
[409] These numbers are only approximate because the totals summarized in the worksheet included all lots in the excel workbook when 10 of the lots were not predicted to be below the end expiry specification.

- Merck initiated a "Fact Finding" as a prelude to a potential product recall.
- Merck attempted to identify how long a lot may be on the market before it is used.
- Merck proposed to confirm findings from the Worldwide Adverse Events System with a retrospective HMO database study.
- Merck proposed to set up a prospective surveillance study if it could map the lots of interest to an HMO with the appropriate infrastructure.
- The results of testing the nonresponders outside the protocol would be used to evaluate whether Merck needed to have a "high level of concern."
- If nonresponders were truly not responding to the vaccine, Merck would need to consider further assessment, including potential revaccination of large infant cohorts.

2. Merck Conducted Assay Testing Outside the Protocol on Protocol 007 Subjects

194. In Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene, she stated:

> Given our limited experience with the assay, Jerry [Sadoff] & I do not know whether these infants are true nonresponders or 'hyporesponders' …. For this reason, and in discussion with Emilio [Emini] non-responder sera will be tested by ELISA (our routine assay) and in the neutralization assay using JerylLynn vaccine virus (which appeared to have somewhat higher % S[ero]C[onversion]R[ate]s in our hands than did the W[ild]T[ype] JL strain. … Non-responders from all dose groups will be tested, along with appropriate controls. If these children are in fact "hypo responders" i.e. respond by ELISA and to JL vaccine strain, we will be reassured."[410]

As part of the "team effort" Dr. Margolskee described to Drs. Scolnick and Greene, MRL personnel tested Protocol 007 subjects who did not seroconvert in the preliminary subset analysis

[410] MRK-KRA00549510 at '12 (emphasis added).

outside the protocol using a neutralization assay without the anti-IgG step.[411] The workbook page for the assay stated: "Data being generated for information only – Not part of formal testing for Protocol 007."[412] These results were never disclosed to the FDA.

194.1. An email from MRL's Senior Vice President, Project & Vaccine Integration, Merck Infectious Diseases, Dr. Dorothy Margolskee, to MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, and MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, with the subject "Information concerning the efficacy of the mumps component of MMRII at potency levels below release," dated February 25, 2001, stated:

> "Jerry et al
> I like the logic- I've edited mostly for clarity. Couple of questions –see within. Emilio, I think we need a section re further analyses of the samples: … what do you think? Will try to reconvene the gang for discussion tomorrow a.m. …

MRK-KRA00549462 at '63 (emphasis added).

194.2. A document titled "Information concerning the efficacy of the mumps component of MMRII at potency levels below release.doc" stated:

> EXECUTIVE SUMMARY:
> Information concerning the efficacy of the mumps component of M-M-R-II at potency levels below the currently accepted end-expiry titer of 4.2 $\log_{10}$ $TCID_{50}$ is discussed.
>
> The information we have is based upon:

[411] *See* MRK-KRA00064825 (Workbook pages describing assay MMRV-46-01); MRK-KRA00068448 (results of assay 46-01).
[412] MRK-KRA00064825.

- Early efficacy and immunogenicity studies performed on monovalent Merck Jeryl Lynn strain vaccine;
- The lack of any demonstrated interference in immunogenicity of Jeryl Lynn in the MMR combination, which permits us to relate the early efficacy findings to M-M-R- II;
- Partial data from a recent end expiry study which utilized M-M-R-II at three mumps potencies: within the release range (4.9 $\log_{10}$ $TCID_{50}$) and at two potential end-expiry titers : ...4.0 $\log_{10}$ $TCID_{50}$ and ...3.7 $\log_{10}$ $TCID_{50}$; and
- Preliminary analysis of epidemiologic adverse experience data from our worldwide adverse experience surveillance (WAES) database, focusing on reports of mumps during a period when marketed material with projected end expiry potencies at or below 4.2 $\log_{10}$ $TCID_{50}$ may have been used.

A review of the literature indicates that mumps vaccine potencies of $\geq$ 3.5 $\log_{10}$ $TCID_{50}$ should provide high levels of clinical protection against mumps. In addition, these studies demonstrate that seroconversion rates as low as ~83%, measured by *in vitro* neutralization assays, are associated with >95% clinical effectiveness. Finally, interim analysis of the mumps end-expiry trial for M-M-R-II (protocol 007) demonstrate that mumps potencies of 3.7 to 4.9 $\log_{10}$ $TCID_{50}$ are associated with seroconversion rates of 88.2- 94.1%, as measured by *in vitro* neutralization of a wild type Jeryl Lynn strain.

Taken together, this review supports the clinical effectiveness of marketed M-M-R-II lots administered during shelf life with potencies at or above 3. 7 $\log_{10}$ $TCID_{50}$.

MRK-KRA00549464 (emphasis added).[413]

194.3. The document also stated:

NEEDS A SECTION RE ASSAY DESIGN & PERFORMANCE ISSUES: EMILIO TO PROVIDE (I'LL CALL HIM)

[413] The document was attached to a later email in the string, including Dr. Margolskee's February 25, 2001 email.

> In talking with Emilio, the neutralization assay is very artificial because of the IgG added; to avoid too many seropositives, very high initial dilutions were required. Thus, low level responders cannot be distinguished from nonresponders. To address this, two approaches will be taken. First, ELISA assays will be performed, along with appropriate controls, which will allow us to benchmark against our usual assay and experience base. In addition, the neutralization assay using JL vaccine strain without the IgG step will be utilized, to detect low level neutralization responses. In this way we will better approach Maurice's initial studies where seroconversion was declared at very low titers.[414]
>
> In order to examine the children in each group that did not respond to the vaccine with 4 fold rises … ELISA assays were run on the sera from these children plus appropriate controls. This was done to determine if these children were low responders beyond the limits of sensitivity of our new neutralization assay or if they were non-responders. There were 10 such children in ~4.9 log10 TCID50/dose group, 12 such children in the ≤4.0 log10 TCID50 / dose group and 20 such children in the ≤3.7 log10 TCID50/dose group…

MRK-KRA00549464 at '471 (original bold removed, underline added).[415]

194.4. An email from MRL's Biometrician, BARDS, Dr. William Wang[416] to MRL's Biometrician, BARDS, Dr. Jonathan Hartzel, with no subject, attached two documents titled "serolisting_allsubj.ZIP" and "AllocNumber_seronegsubj.ZIP," dated February 22, 2001, stated:

> Here is the titer listing for all subjects in the subset.[417]

[414] *Compare with* MRK-KRA01927351 at '353 (In March 2000, FDA rejected Merck's proposal to use the vaccine strain for mumps immunogenicity testing).
[415] Dr. Margolskee testified that she did not recall talking with Dr. Emini, writing this page, or knowing what it meant. Deposition of Dorothy Margolskee, April 21, 2017, 339:22- 342:5. Dr. Chirgwin testified that he did not recall the details and would need to have his recollection refreshed in order to comment. Deposition of Keith Chirgwin, January 26, 2017, 212:12-226:15.
[416] Dr. William Wang was the unblinded statistician for the Protocol 007 interim analysis. *See* MRK-KRA00623716; *see also* MRK-KRA00071102; MRK-KRA00592318.
[417] *See* MRK-KRA00615857 at '66-67 (rows # 349-368); *see also* MRK-KRA00549510 (email from Margolskee to Scolnick and Greene dated February 23, 2001) and MRK-KRA00549519 at '28-29 (attachment #3 with rows # 349-368).

> Here is the allocation number for those initially seronegative subjects with postvaccination titer <=256.[418]

MRK-KRA00615856.

194.5. An email from MRL's Biometrician, BARDS, Dr. Jonathan Hartzel, to MRL's Executive Director, Vaccine Integration, Dr. Florian Schodel and MRL's Director, BARDS, Timothy Schofield, cc'd to MRL's Project Manager, Joan Staub, MRL's Analyst, Capacity Planning and Management, Jeffrey Feldman, MRL's Executive Director, Biologics, Clinical Research, John Boslego, MRL's Executive Director, Clinical Vaccines, Dr. Jerry Sadoff, and MRL's Senior Director, Health & Economic Statistics, Joseph Heyse, replying to Dr. Schodel's February 22, 2001 email, also dated February 22, 2001, stated:

> I have given Emilio ~60 case numbers to re-test (the 42 failures + 17 marginal positives). I believe he will try to re-test them with both ELISA (wild-type mumps) and the wild-type neut.

MRK-KRA00549497 (emphasis added).

194.6. Dr. Krah's 2001 Journal stated:

> February 22, 2001
> Meet with Emilio[419] to review the titration curves for post-negative sera from Protocol 007
> Consider retesting these using J[eryl]L[ynn] vaccine ±anti-IgG or start testing @1:2 dilution to see if positive under some assay condition?
> Picked up exp[erimen]ts from Protocol 007 testing … (to review with Emilio)

MRK-KRA00490592 at '651.

[418] *See* MRK-KRA00615874 (attachment to Dr. Wang's email to Dr. Hartzel titled "MMRII 007 Subset Analysis PRN Assay Listing for Subjects Initially seronegative" with list of 42 failures and 17 marginal positives from the Protocol 007 preliminary subset).

[419] Deposition of Emilio Emini, June 6, 2017, 323:15-24 (*Q. Let me read the first sentence. "In talking with Emilio, the neutralization assay is very artificial because of the IgG added; to avoid too many seropositives, very high initial dilutions were required." Do you think you're the Emilio referred to in this sentence? A. Since I was the only one with that name at the company at the time, I believe so, yes.).*

194.7. Dr. Krah's 2001 Journal also stated:

February 23, 2001
Review tentative testing plan with Emilio?
We will identify the available volumes of sera
Mike Washabaugh and I are to identify the volumes we would need for testing
The [Mu]MPS ELISA will likely be run on these first, and then a decision will be made of the possible benefit of additional N[eu]t[ralization] testing

Id. at '652.

194.8. Dr. Krah's 2001 Journal also stated:

February 23, 2001
Review [Mu]MPS N[eu]t[ralization] data for JL vs JL135[420]
and JL ± anti-IgG?
limited data, suggesting titers to JL?JL135 [sic] by ~2-4 fold (for positive ped[iatric] sera).
For adult lab sera, titers for JL and JL135 comparable
Forwarded the data from these 2 tables (from CAS [Clinical Assay Subcommittee] presentation last year) to Emilio

Id. at '653-654.[421]

194.9. Dr. Krah's 2001 Journal also stated:

February 26, 2001
√· Note: confirmed with Kelly Buckley that they have pulled the sera from Protocol 007 for retesting and they are checking the available volumes. They will get back to me with the info (I left a message re this with Bev Rich as well)
·Check volumes available from sera from Protocol 007
Review volumes available for post-negative pairs?

[420] *See* Section III.A above discussing virus strains. "JL" is the vaccine strain of the virus used in Merck's vaccine. "JL-135" is the "low passage" virus FDA allowed Merck to use in the AIGENT testing
[421] *See also* paragraphs 192-93 discussing MRK-KRA00549510 (Dr. Margolskee's email) and MRK-KRA00549464 (discussing testing plan).

Is this sufficient to run additional assays?

MRK-KRA00490592 at '656.

194.10. Dr. Krah's 2001 Journal also stated:

February 26, 2001

√· Check re status of testing non-responder set from Protocol 007 in w[ild]t[ype] [Mu]MPS ELISA

Also check on sera from case 1581[422]

Bev's group has pulled these and identified volumes available

They will run the ELISA tomorrow and then should be able to transfer the sera to us Wednesday.

MRK-KRA00490592 at '656.

194.11. Dr. Krah's 2001 Journal also stated:

February 26, 2001

Note: Emilio indicates the current [Mu]MPS testing plan = w[ild]t[ype] [Mu]MPS ELISA from the panel of 59 sera identified last week + case 1581

then [Mu]MPS N[eu]T[ralization] using JL vaccine virus

Id.

194.12. Dr. Krah's 2001 Journal also stated:

February 28, 2001

√·Fill in [Mu]MPS N[eu]T[ralization] titers for [Mu]MPS ELISA comparison table and return to Emilio and Alan[423]

Id. at '658.

[422] *See* MRK-KRA00068400 at '03 ("I just received a call from the study coordinator Karen Ross … She received a report today, 2/22/01, that a male subject # 1581 … has been hospitalized with a suspected case of mumps."); *see also* MRK-KRA00068400 at '02 ("I would like to request the sera (pre [vaccinated 7/20/99], 6 week and 1 year persistence [7/10/00] bleeds) from subject # 1581 … Sera from this case will be added to the subset of sera that we discussed on Friday for measurement of titers in the wt Mumps ELISA and in the Mumps neutralization assay.").

[423] MRL's former Vice President, Vaccine & Biologics Research, Dr. Emilio Emini testified as follows: "*Q. The-When it came to staffing did you have any responsibility in staffing decisions in Dr. Krah's laboratory?" … A. That would have been his direct supervisor which would have been Dr. Alan Shaw, who would have worked in collaboration with Dr. Krah at the laboratory.*" Deposition of Emilio Emini, June 6, 2017, 23:25-25:1.

194.13. An email from MRL's Biometrician, BARDS, Dr. Jonathan Hartzel, to MRL's Senior Director, Project Planning and Management/Vaccine Integration Dr. Joye Bramble and MRL's Director, BARDS, Timothy Schofield, with the subject "ELISA Results for 007 Subset Analysis," with attachment "ELISA_NEUT_Analysis.doc," dated March 2, 2001, stated:

> Here are the results of the ELISA testing for the non-converters and low converters from the 007 subset analysis.

MRK-KRA00562246 at '246.

194.14. The document attached to the March 2, 2001 email from Hartzel to Bramble and Schofield titled "ELISA_NEUT_Analysis.doc"[424] stated:

[424] *See* paragraph 192.1 describing "Attachment 1" to Dr. Margolskee's March 5, 2001 email to Drs. Scolnick, Greene, and Kim. *Compare* MRK-KRA00562247, *with* MRK-KRA00616011 duplicate versions of document titled "ELISA_NEUT_Analysis.doc".

M-M-R™ II Protocol 007: Wild-type Mumps ELISA Analysis

6 Week Serostatus for Initially Seronegative Subjects with Titers ≤256

~4.9 $\log_{10}$ $TCID_{50}$ Mumps Potency Group

		ELISA Assay		
	6 Week Serostatus	+	-	Total
Neut Assay	+	6	1	7
	-	7	2	9
	Total	13	3	16

≤4.0 $\log_{10}$ $TCID_{50}$ Mumps Potency

		ELISA Assay		
	6 Week Serostatus	+	-	Total
Neut Assay	+	4	0	4
	-	10	1	11
	Total	14	1	15

≤3.7 $\log_{10}$ $TCID_{50}$ Mumps Potency

		ELISA Assay		
	6 Week Serostatus	+	-	Total
Neut Assay	+	3	2	5
	-	7	13	20
	Total	10	15	25

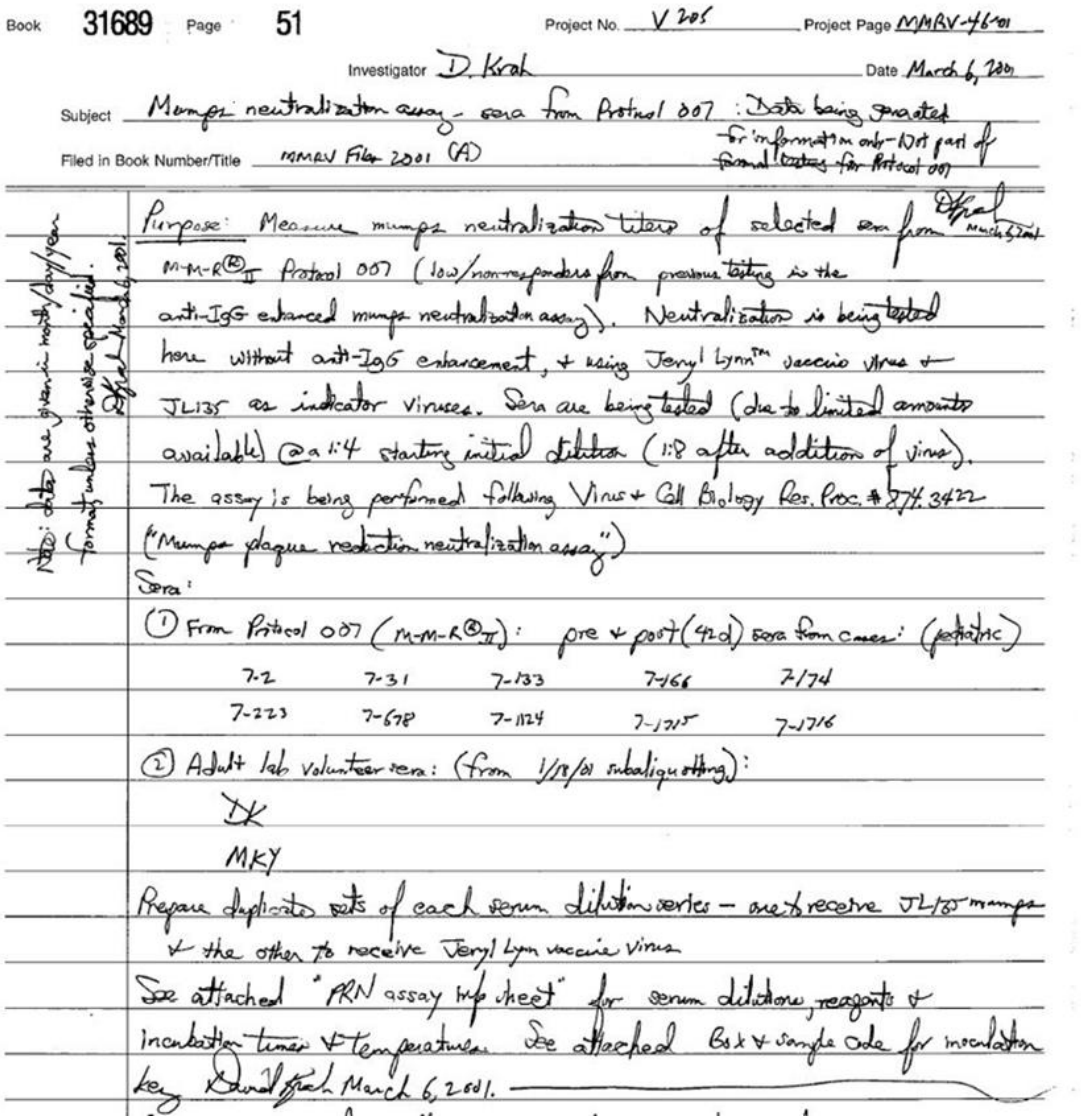
Overall

		ELISA Assay		
	6 Week Serostatus	+	-	Total
Neut Assay	+	13	3	16
	-	24	16	40
	Total	37	19	56

MRK-KRA00562247 (highlight added).[425]

[425] Merck personnel identified approximately 60 children who were "low-responders" or "non-responders" (vaccine failures) in the Protocol 007 AIGENT preliminary analysis for retesting. MRK-KRA00549497. These tables present seroconversion results of 56 of those children by AIGENT and WT ELISA. The first three tables break out results based on which dose of MMRII the child received; the fourth table summarizes the results of all 56 children.
For the children who received the 4.9 dose, the seroconversion rate by WT ELISA was 81% and 43% by AIGENT.
For the children who received the 4.0 dose, the seroconversion rate by WT ELISA was 93% and 26% by AIGENT.
For the children who received the 3.7 dose, the seroconversion rate by WT ELISA was 40% and 20% by AIGENT.
Overall, the seroconversion rates were higher when measured by WT ELISA than AIGENT. For the entire subset of 56 children, the seroconversion rates by WT ELISA were 66% and 29% by AIGENT. About half of the 56 children were classified differently by the two assays, 89% of them were ELISA-positive/AIGENT-negative. In the 4.9 and 4.0 groups, most samples that were classified as seronegative by the AIGENT were classified as seropositive by WT ELISA (7/9 and 10/11, respectively). This was not true for the 3.7 group, in which most children were classified as seronegative by both assays, with only 7 of the 20 subjects seronegative by AIGENT responding by WT ELISA.
Compare MRK-KRA00549510 at '12 (Dr. Margolskee's email to Drs. Scolnick and Greene stated with regard to the

194.15. Laboratory Notebook 31689, Page 51, Project V205, MMRV-46-2001, with the subject: "Mumps neutralization assay – sera from Protocol 007: Data being generated for information only – Not part of formal testing for Protocol 007,"[426] dated March 6, 2001, stated:



Book 31689 Page 51 Project No. V 205 Project Page MMRV-46-01

Investigator D. Krah Date March 6, 2001

Subject Mumps neutralization assay – sera from Protocol 007: Data being generated for information only – Not part of formal testing for Protocol 007

Filed in Book Number/Title MMRV File 2001 (A)

Purpose: Measure mumps neutralization titers of selected sera from Protocol 007 (low/non-responders from previous testing in the anti-IgG enhanced mumps neutralization assay). Neutralization is being tested here without anti-IgG enhancement, + using Jeryl Lynn™ vaccine virus + JL135 as indicator viruses. Sera are being tested (due to limited amounts available) @ a 1:4 starting initial dilution (1:8 after addition of virus). The assay is being performed following Virus + Cell Biology Res. Proc. # 374.3422 ("Mumps plaque reduction neutralization assay")

Sera:

① From Protocol 007 (M-M-R®II): pre + post (42d) sera from cases: (pediatric)

7-2	7-31	7-133	7-166	7-174
7-223	7-678	7-1124	7-1315	7-1716

② Adult lab volunteer sera: (from 1/18/01 subaliquotting):

DK

MKY

Prepare duplicate sets of each serum dilution series – one to receive JL135 mumps + the other to receive Jeryl Lynn vaccine virus

See attached "PRN assay info sheet" for serum dilutions, reagents + incubation times + temperatures. See attached BS x + sample code for inoculation key. David Krah March 6, 2001.

Data are given in mostly day/year format unless otherwise stated. DK March 6, 2001

20 nonresponders who received the 3.7 dose: "If these children are in fact 'hyporesponders', i.e. respond by ELISA and to JL vaccine strain, we will be reassured."). These tables were not provided to the FDA.

[426] *See* Schedule 4 (transcription of the handwritten page in this Merck workbook).

MRK-KRA00064825.[427]

194.16. MRL's Principal Investigator, Dr. David Krah, testified as follows:

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.

Deposition of David L. Krah, July 12, 2017, 702:2-11 (emphasis added).

194.17. MRL's Principal Investigator, David Krah, also testified as follows:

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?

Defense Counsel: Object to the form.

The Witness: That description does not refresh my recollection.

Q. So the date of this is March 6, 2001. Correct?

A. Yes.

[427] The "Purpose" for Assay MMRV-46-2001 stated: "The assay is being performed following Virus & Cell Biology Res. Proc. # 874.3422." MRK-KRA00062845. "Virus & Cell Biology Research Procedure No. 874.3422" was developed by Dr. David Krah and Mary Yagodich in 1999 and did not include an anti-IgG enhancement step. MRK-KRA00064832. *See also* Schedule 4 (transcription of this page).

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 forgot 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, sex, 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?

Defense Counsel: Object to the form.

A. 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 this 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.

Q. What was the higher concentration?

A. The serum concentrations.

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

Defense Counsel: Object to the form.

A. 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.

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 the cutoff was. I don't know if that same cutoff was applied in this assay.

Deposition of David L. Krah, July 12, 2017, 702:23-707:22 (emphasis added).

194.18. A handwritten document titled "x46-01"[428] stated:

[428] Subjects 2, 31, 133, 166, 174, 223, 678, 1124, 1715, and 1716 were among the 600 children that made up the preliminary subset analysis Merck subsequently reported to FDA in Serial 63. *See* Section VIII.H below. These same children were subsequently used for the correlation analysis in Serial 86. *See* Section VIII.M above. The data from eight of the subjects in assay 46-01 was part of the correlation analysis. *See* Section VIII.E.2 (explaining why subjects 223 and 1124 were excluded). The results of assay 46-01 were not included or discussed in Serial 63 or Serial 86.

X 46-01		titer		
Sera		JL vaccine	JL 135	antiIgG + JL135
2	pre	<8	<8	<32
	post	<8 (60%)	<8	<32
31	pre	<8	<8	<32
	post	<8	<8	256
133	pre	<8	<8	<32
	post	<8	<8	<32
166	pre	<8	<8	<32
	post	<8	<8 (68%)	<32
174	pre	<8 (68, 72%)	<8	<32
	post	8 (82, 66%)	<8 (65%)	256
223	pre	<8	<8	<32
	post	<8	<8 (58%)	<32
678	pre	<8	<8	<32
	post	16	8	<32
1124	pre	<8	<8	<32
	post	<8	<8	<32
1715	pre	<8	<8	<32
	post	<8	<8	<32
1716	pre	<8	<8	<32
	post	<8	<8	<32
DK		<8	<8	~512
MKY		8	8	~1024

MRK-KRA00068448 (handwritten original, transcribed).

194.19. MRL's Principal Investigator, Dr. David Krah, testified as follows:

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?

Defense Counsel: Object to the form.

A. I do not recall discussing or disclosing these data with the FDA.

Deposition of David L. Krah, July 12, 2017, 713:7-714:9 (emphasis added)

195. The results of the ten children tested in the preliminary subset analysis, the WT ELISA assay and assay 46-01 can be summarized as follows:

		Serum sample drawn 42 days post vaccination				
		Date of Assay	Dec. 2000 – Jan 2001 (P007 preliminary subset)[429]	March 2001 MMRV-46-2001[430]		March 2001
		Assay	P007 AIGENT Assay[431] (SOP 874.3489 Rev. 00)[432]	"Standard" Neutralization Assay (SOP 874.3422)[433]	"Standard" Neutralization Assay (SOP 874.3422)[434]	WT ELISA[435] (SOP 910.0096)[436]
		Method	Anti-IgG JL-135	No Anti-IgG JL-135	No Anti-IgG JL	No Anti-IgG JL-135
CHILD	**DOSE POTENCY**[437]					
2	**3.7**		N	N	N	N
31	**3.7**		R	N	N	N
133	**3.7**		N	N	N	R
166	**4.9**		N	N	N	R
174	**4.9**		R	N	N	N
223	**4.0**		N	N	N	R
678	**4.9**		N	N	R	R
1124	**4.9**		N	N	N	R
1715	**4.0**		N	N	N	R
1716	**4.9**		N	N	N	R

Key:
N = Subject a "Nonresponder" as measured in the assay, or no detectable antibody.[438]
R = Subject a "Responder" as measured in the assay, or antibody detected.[439]
JL-135 = Low Passage JerylLynn virus considered "wild type" used as indicator virus.
JL = Vaccine strain of JerylLynn virus used in vaccine used as indicator virus.
Shaded data = Information not provided to the FDA.

[429] MRK-KRA00068448 (Handwritten chart comparing the results of x46-01 with the AIGENT results for the same subjects); *see also* MRK-KRA00017036 (Results of preliminary subset testing were submitted in BB-IND 1016 Serial 63); MRK-KRA00759390 (A Merck document with testing results produced as a native Excel spreadsheet).
[430] MRK-KRA00064825 (Laboratory Notebook pages describing MMRV-46-2001, which stated: "Neutralization is being tested here without anti-IgG enhancement, + using Jeryl Lynn TM vaccine virus + JL135 as indicator viruses."); *see also* MRK-KRA00068448.
[431] MRK-KRA00759390 ("Corrected Data Listing" tab).
[432] MRK-KRA00002189.
[433] MRK-KRA00064832.
[434] *Id.*
[435] MRK-KRA00759390 ("Corrected Data Listing" tab); *see also* MRK-KRA00126468 (Serial 86).
[436] MRK-KRA01889623 at '756.
[437] MRK-KRA00135759 at '7080 (Protocol 007 Clinical Study Report Allocation Schedule).
[438] In reference to the results of MMRV-46-2001 "N" or "Nonresponder" indicates that no antibody was detected; In reference to the results of AIGENT or WT ELISA, "N" or "Nonresponder" indicates a seroconversion failure. The "standard" neutralization assay used in MMRV-46-2001 was run using sera concentrations different than those specified in the SOP, and no cutoff for seropositivity had been set for the assay as it was run in MMRV-46-2001. *See also*, Merck witness Dr. David Krah testified that seroconversion was not measured in MMRV-46-2001 *(A.... It's the -- we did not establish a cutoff for sera positivity. ...)*(Deposition of David Krah, July 12, 2017, 71:4-6); (*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.*) (Deposition of David Krah, July 12, 2017, 712:15-25).
[439] *Id.*

196. In my opinion, the results of assay testing outside of protocol should have been disclosed to the FDA. Furthermore, Merck should have disclosed to the FDA that the assay testing outside of protocol, according to Dr. Margolskee, was to provide Merck reassurance of the results it was sending to the FDA as assurance that lower potency MMRII would be effective. Moreover, comparing the results of the ten children who were selected for re-test in assay testing outside of protocol shows the children responding differently depending on which assay was used. Most importantly, children who were non-responders by neutralization were responders in the ELISA, tending to show that the ELISA did not give similar results to a neutralization assay, especially for children with low level responses.[440]

3. Merck's Internal Discussions Concerning MMRII Being Out of Specification Before Merck Responded to the Warning Letter

197. At the end of February, 2001, MRL senior management exchanged drafts of the proposed response to the Warning Letter. These drafts included a table summarizing the 223 lots of low potency vaccine identified in Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene. On February 27, 2001, MRL's Statistician, BARDS, Philip Bennett, sent an email to MMD's Vice-President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, the person coordinating the response to the Warning Letter, that stated: "Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry."[441] On March 5, 2001, Dr. Margolskee sent a second email to Drs. Scolnick and Greene to update them on the status of the response to the Warning Letter. With

[440] *See* Sections VII.A.1 and B above describing false positive results in ELISA assays and the need to correlate an ELISA with a neutralization assay for it to be a reliable substitute for a neutralization assay.
[441] MRK-KRA01896072 at '72-73.

regard to the "implications for children in the field who have received vaccine in recent years," the email stated: "Am optimistic that analysis will support not taking action (i.e. no need for revaccination). Note that tracing lots/assessing time of use would likely be impossible and need for revaccination would probably mean large scale initiative."[442]

197.1. A Merck memo from MRL's Statistician, BARDS, Philip Bennett, to MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, and MMD's Vice-President of Vaccine & Sterile Quality Operations, Dr. Roberta McKee, cc'd to Kati Abraham, Jim Clair, Joseph Heyse, Cynthia Morrisey, Manal Morsy, Mark Rosolowsky and Timothy Schofield with the subject: "Mumps Stability and Potency Estimations," dated February 27, 2001, stated:

> Current Product (For product manufactured on and after 9/13/99, the minimum release specification for mumps is 5.0 $\log_{10}$ $TCID_{50}$ per 0.5 mL dose.) …
> Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry.

MRK-KRA01896072 at '72-'73 (original bold removed, underline added).

197.2. A document titled "Response to FDA 483 Observation 3, Analysis of Mumps Stability Data"[443] stated:

[442] MRK-KRA00616007 at '08- 09.
[443] The date associated with this document in its metadata was February 27, 2001.

Response to FDA 483 Observation 3

Analysis of Mumps Stability Data

The following table gives a summary of the analyses concluding that the estimated minimum 95% lower confidence bound for the distribution of lot potencies is 3.3 $\log_{10}$ $TCID_{50}$/0.5mL dose given that the lots are filled at the previous minimum release specification limit of 4.3 $\log_{10}$ $TCID_{50}$/0.5mL dose.

The average, standard deviation and number of lots is taken from our 10/24/2000 submission to CBER (Table 2 on p. 104 in attachment 8). These are for fills made 1/95 to 5/98 and are the most pessimistic estimate for our product.

The 0.14 assay standard deviation listed is the estimated variability in the 3x1 release potency assay. This variability is included in the calculations of the loss estimates, but is mathematically removed from calculations since our question is to determine the range of expiry potencies for lots with a specified initial potency (of 4.3 $\log_{10}$ $TCID_{50}$).

ave	0.703
sd	0.222
n	20
assay sd	0.14
net sd	0.172
95% LB	1.001

Therefore the worst case estimate for stability losses of mumps from release through the end of a 24 month shelf life during this time period is 1.0 $\log_{10}$ $TCID_{50}$.

Lots with estimated end expiry titers potentially less than 4.3 $\log_{10}$ $TCID_{50}$.

The range of assigned release potencies for lots manufactured before February 2000 which are still on the market is 4.4 - 5.4 $\log_{10}$ $TCID_{50}$/0.5mL dose. Therefore the lowest titer (95% LB of stability losses for the lot with the lowest assigned release potency) through the end of 24 months of shelf life for lots during this period would be 3.4 $\log_{10}$ $TCID_{50}$. There are a total 223 lots with worst case predicted end of shelf life titers less than 4.3 $\log_{10}$ $TCID_{50}$. The distribution of these lots in terms of assigned release potencies and worst case end-of-shelf life potencies (95% LB stability losses) is as follows:

Release Potency	End Expiry Potency	Number of Lots
4.4 – 4.6	3.4 – 3.6	6
4.7 – 4.9	3.7 – 3.9	100
5.0 – 5.2	4.0 – 4.2	117

MRK-KRA00086295 (highlight added).[444]

197.3. A document titled "Response to FDA 483 Observation 3, Analysis of Mumps Stability Data" also stated:

[444] *See* MRK-KRA000549518 (Attachment #4 listing the lots included 225 lots predicted to be below the 4.3 end expiry specification, not the 223 calculated here).

LOTS IN INVENTORY & BURN RATE MARK

- Order freq ; market audits to support burn rate (all sectors); order fulfillment from CDC (public sector)
- ?? specific lots: is possible for 6 lots MARK & KEITH

Clinical data addressing the efficacy of these lots

- RELEASE DOSE/END EXPIRY 3.1: HISTORICAL DATASET
  - Original release dose established by dose ranging of monovalent mumps (see Jerry summary)
  - limited immunogenicity data with neuts
  - vaccine formulated with release criteria established through dose ranging (needs change in TCID50 argument)
  - no interference with Moraten established, same release dose for MMR-II established

FIELD EXPERIENCE KAREN & FLORIAN

- 30 years of effectiveness with monovalent and trivalent vaccines manufactured under such specs
- immunogenicity tested for a decade + with ELISA, MMR-II provides x percent seroconversion rate in ELISA, associated with observed field effectiveness experience
- end-expiry has not been defined over 30 years
- field experience covers release doses of xx

NEUTS STUDY

- Neuts & ELISA support 4.0 end expiry
- Neuts close on 3.7 but we'll stay future state with 4.0
- ELISA is in tomorrow – hopefully will support 3.7 (?) (revaccination needs)

Burn rate + ELISA data suggest no action needed

- stability data suggest that an MMR-II released (modern TCID50) at 4.3 log which is our manufactured experience has an end-expiry of 3.3 to 3.8 logs
- specs adjusted to meet at expiry of 4.3 log based on new interpretation of original potency data, additional stability experience, and most recently end-expiry trial which supports 4.0
- small difference in JL wt neuts sc between 3.7 and 4.0 (88% vs 93%)
- therefore lots of 3.7 no clinical risk

Id. at '96-97 (highlight added).

197.4. A high-importance email from Merck & Co. Associate Director, Scientific Staff, Karen Kaplan, to MRL's Manager, Epidemiology, Dr. Harry Guess, cc'd to MRL's Associate Director, Epidemiology, Dr. Paul Coplan, MRL's Executive Director, Vaccine Integration, Dr.

Florian Schodel, and MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, with the subject: "Mumps expiry-effectiveness data," and sent with attachment "Mumps Surveillance.doc," dated February 28, 2001, stated:

> The original issue is one of compliance with mumps end expiry titer. Apparently 6 lots were released over the past couple of years, in which in a worst case, the end expiry titer would be <3.7 (out of compliance with the label). Nevertheless, MMD has apparently been releasing lots <4.3 for "a long time." Keith noted however, that in the real world, practices run like any small business, keep inventory low and probably don't have vaccine on the shelf for more than a couple of months, not 2 years (and since I work in a practice, I can say that is absolutely the case). Thus the practical consequences of this matter are likely nil
>
> The attached mumps surveillance data are reassuring, in that the public health has not suffered. However in discussions with CBER (expected in the next couple of weeks), the question may come up as to whether, if lots can be traced to (for example a large HMO, like Kaiser), would a post-marketing surveillance efficacy study be feasible. (a lot of "ifs") In essence, such a study (if it were feasible) would be added reassurance that the public health has not suffered.
>
> Keith indicated that the data are fine and I have done what I was asked to do. Surveillance data cannot/do not address the compliance issue.
>
> Keith suggested that on the chance that CBER presses (we would not volunteer) for an epidemiologic study, members of this department may want to discuss the feasibility of such a post-marketing efficacy study. I don't have the tracking of the low-potency lots, but my understanding is that they went to a broad range of customers. Florian has the contacts in MMD and MVD who know where they went. If it comes then to considering an epidemiologic study, I will defer to the real epidemiologists in the department to discuss it.

MRK-KRA00549318 (underline added).

197.5. A high-importance e-mail from MRL's Dr. Dorothy Margolskee, to MRL's Director, BARDS, Timothy Schofield, with the subject: "Fw:[445] burn rate," dated March 2, 2001 stated: "This may also help with the risk analysis…" MRK-KRA01896084 at '91.

197.6. A document attached to Dr. Margolskee's "burn rate" email stated:

> A review of internal Merck Vaccine Division data revealed the following regarding physician order and inventory turnover frequency for M-M-R®II and/or childhood vaccines:
>
> Order Frequency
>
> - Vaccine order frequency for G[eneral]P[ractioners]/F[amily]P[ractioner]… ranged from weekly … to every four to five months … with 42% … ordering monthly.
> - Vaccine order frequency for Pediatricians ranged from weekly … to every four to five months … with 40% … ordering monthly.
> - M-M-R®II order frequency for G[eneral]P[ractioners]/F[amily]P[ractioner]5 ranged from 1-2 times per year … to 25 or more times per year … with 20% … ordering M-M-R®II 7-14 times per year. On average F[amily]P[ractioners]/G[eneral]P[ractioner]s ordered M-M-R®II 7 times per year.
> - M-M-R®II order frequency for Pediatricians ranged from 3-4 times per year … to 25 or more times per year … with 36% … ordering M-M-R®II 7-14 times per year. On average Pediatricians ordered M-M-R®II 15 times per year.
> - Of the physicians offices that … purchase the 10 pack … of M-M-R®II, 96% percent … purchase <20 vials at a time and the average time between orders is 44 days. Of the physicians offices that purchase the single dose … of M-M-R®II, 99% percent of them purchase <20 vials at a time and the average time between

[445] The "original message" preceding Margolskee's "burn rate" email was from a member of Merck's marketing team, Mark Twyman, to MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin and cc'd to Katalin Abraham with the subject: "revised – mmr II" and an attachment titled "mmrlnv.doc." dated February 28, 2001. Dr. Chirgwin forwarded the email to Dr. Margolskee and MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, MRL's Director, Vaccine Research, Dr. Alan Shaw, and MRL's Vice President, Vaccine Research, Dr. Emilio Emini on March 1, 2001. *Id*. *See* Deposition of Barbara Kuter: 291:19-23 (describing Twyman as a member of Merck's marketing team).

orders is 45 days. Ninety-three percent (93%) of all physician offices purchase the 10-pack … of M-M-R®II.

- Of 475 accounts that have ordered any vaccine three or more times … from the Merck … website, the average order frequency over the last 12 months is one order every 1.1 months (34 days).

Inventory Turnover

- Vaccine inventory turnover frequency for G[eneral]P[ractioner]/F[amily]P[ractioner] ranged from less than a month … to greater that six months … with 88% … falling into an inventory turnover frequency range of one month to six months. The average inventory turnover frequency … was approximately three months (2.6)
- Vaccine inventory turnover frequency for Pediatricians ranged from less than a month … to greater than six months … with 80% … falling into an inventory turnover frequency range of one month to six months. The average inventory turnover frequency for all surveyed Pediatricians was three months.
- The average M-M-R®II inventory turnover frequency for physician offices over eight months was 72.3 days. The inventory turnover frequency was calculated using generally accepted accounting principles.

Id. at ‘87 (internal citations omitted) (emphasis added).

197.7. A document titled “Draft Response to FDA 483 Observation 3” [446] stated:

[446] The date associated with this document in its metadata was March 2, 2001.

Range of potencies expected at the two year expiration date

The range of assigned release potencies for lots manufactured before February 2000 ~~which are still on the market~~ which have not yet reached the end of shelf life is 4.4 - 5.4 log_{10} $TCID_{50}$/0.5mL dose. Using the calculation above, t

~~Therefore the lowest titer (~~he lower 95% confidence bound ~~LB of stability losses for the lot with~~ for the end of expiry potency for a lot with the lowest assigned release potency ~~) through the end of 24 months of shelf life for lots~~ during this period would be 3.4 log_{10} $TCID_{50}$. There are a total of 223 lots of M-M-R®II with end of shelf life titers potentially less than 4.3 log_{10} $TCID_{50}$.

The distribution of these lots by assigned release potencies and corresponding lower 95% confidence bound for ~~worst case~~ end-of-shelf life potencies ~~(95% LB stability losses) for lots during this period is as follows~~are presented in Table 1.:

Table 1. Release and end expiry (95% lower bound) potencies of lots released before February 2000 which have not reached the end of shelf life

Release Potency	End Expiry Potency	Number of Lots
4.4 – 4.6	3.4 – 3.6	6
4.7 – 4.9	3.7 – 3.9	100
5.0 – 5.2	4.0 – 4.2	117

Thus 6 lots have an end expiry potency potentially lower than 3.7 log_{10} $TCID_{50}$; 100 lots have an end expiry potency potentially as low as 3.7 – 4.0 log_{10} $TCID_{50}$ and 117 lots have an end-expiry potency potentially as low as 4.0 – 4.2 log_{10} $TCID_{50}$.

[Insert here plans for potency measurement on retention samples from lots]

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MRK-KRA00086298 at '299-300 (highlight added).[447]

197.8. A power point presentation dated March 2, 2001 stated:

[447] This draft shows the breakdown of lots of lower potency MMRII potentially still on the market described in Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene. MRK-KRA00549510. As discussed above, the attachment to Dr. Margolskee's email included 225 lots predicted to be below the end expiry, not the 223 calculated here.

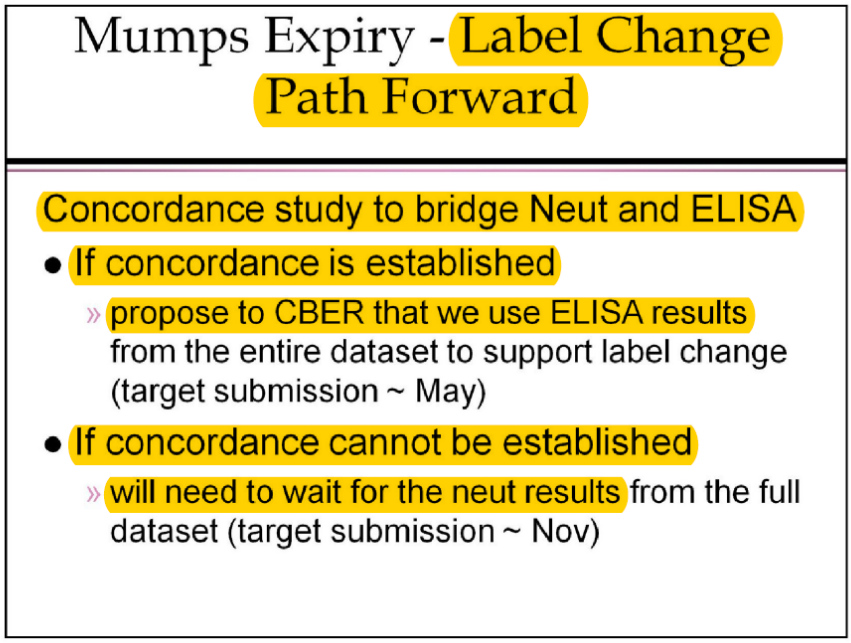
Mumps Expiry- Label Claim

- Stability data do not support current end of shelf life label claim (4.3 $\log_{10}$ $TCID_{50}$)
- Further increase in release potency is not feasible (target 5.2)
- Therefore we must provide clinical data to support a decrease in the labeled potency

Mumps Expiry
Requirements for Label Change

To change the labeled mumps potency claim to 4.0 $\log_{10}$ $TCID_{50}$

- Must satisfy criteria for success for the mumps expiry trial
  - 5% equivalence margins for SCR (release vs expiry)
  - lower bound > 90% SCR
- Insufficient power without full dataset
- Timing is an issue for obtaining full dataset with the neutralizing antibody assay (~Sept)



MRK-KRA00086318 (highlight added).[448]

197.9. An email from MRL's Senior Vice President, Project & Vaccine Integration, Merck Infectious Diseases, Dr. Dorothy Margolskee, to MRL's President and Executive Vice President, Science & Technology, and Member of Merck's Board of Directors, Dr. Edward Scolnick, MRL's Executive Vice President, Research and Development, Dr. Peter Kim,[449] and MRL's Executive Vice President, Clinical Sciences and Product Development, Dr. Douglas Greene, cc'd to MRL'S Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu,

[448] The date associated with this document in its metadata was March 2, 2001. This March 2001 powerpoint can be summarized as follows: Merck's stability data did not support the label claim of 4.3 log, and Merck needed to provide clinical data to support a decrease in the labeled potency. The clinical data would come from the end expiry study in Protocol 007 that would have to be successful for Merck to use it to support the label change. *See also* MRK-KRA01727952 (December 2000 presentation describing the same "Path Forward").

[449] MRL's former Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, testified: "*Peter Kim was obviously there in the company [in 2001] ... So I would have been reporting to Tony Ford-Hutchinson who was, in turn, reporting to Peter Kim. ... And then, in turn, Peter Kim at that point since Ed Scolnick was still there, he had not yet retired, was reporting to Ed Scolnick. ... Who was the president of the research laboratory, and Peter Kim eventually became president of the research laboratory when Ed Scolnick retired*." Deposition of Emilio Emini, June 6, 2017, 205:19-206:14.

MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, MRL's Director, BARDS, Timothy Schofield, MRL's Senior Director, Health & Economic Statistics, Dr. Joseph Heyse, and MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, with the subject "Mumps update," dated March 5, 2001, stated:

-----Original Message-----
From: Margolskee, Dorothy
Sent: Monday, March 05, 2001 8:54 AM
To: Scolnick, Edward M.; Kim, Peter S.; Greene, Douglas Dr.
Cc: Ukwu, Henrietta N; Sadoff, Jerald C.; Schofield, Timothy L.; Heyse, Joseph F.; Emini, Emilio A
Subject: Mumps update

Ed et al

As an update on the mumps end-expiry issues:

- We now have ELISA data on the neutralization nonresponders in the mumps end-expiry study (Protocol 007). Attachment 1 displays the comparison of ELISA vs neutralization results (in addition to the Neut nonresponders, a sampling of low positives were also assayed for comparison). Note that "double" nonresponders (i.e. not seroconverting either by neutralization or ELISA criteria) are more at the 3.7 log titer (n=13) that at 4.0 logs (n=1) or 4.9 logs (n=2).

  Attachment 1.

- Also, we have the reverse cumulative distribution plots for the mumps neuts data....see Attachment 2.

  Attachment 2.

- **Clinical/Stats/Regulatory/V&CB all view the data as supporting 4.0 logs as end expiry & excluding 3.7.**
- **Implications are discussed below.**

MRK-KRA00616007 (highlight added).

197.10. Dr. Margolskee's March 5, 2001 email to Drs. Scolnick and Greene also stated:

- Pending analyses:
  - ELISAs are being performed on the remaining infants from the interim analysis (total n=600). Should be available late next week.
  - (We anticipate that there will be a correlation between neutralization response & ELISA).
  - **ELISAs for the entire study (another 1200 infants) will be run. Availability= ~6-8 wks.**
  - (Mumps neutralization data on remaining 1200 will take several months to complete, given assay complexity).
- Anticipated results:
  - Data will continue to support 4.0 logs as end-expiry potency & will support change of current label to coincide.
  - Data will not support 3.7 logs for this purpose.

Id. at '07-08 (emphasis added).

197.11. Dr. Margolskee's March 5, 2001 email to Drs. Scolnick and Greene also stated:

- Anticipated results:
  - Data will continue to support 4.0 logs as end-expiry potency & will support change of current label to coincide.
  - Data will not support 3.7 logs for this purpose.
- Implications with respect to marketed product:
  - Current material (post 9/99) comply with 4.0 log end-expiry; will need to get label change (using ELISA data from Protocol 007). Urgent need which we plan to support with ELISA data of entire study (and correlation to mumps neuts from 600 subject subset).
  - 107 Lots filled prior to 9/99 are still out there "within stated shelf-life" but with projected potencies lower than 4.0 at 24 months.
    - Retention samples of 6 lowest lots are being assayed; potencies will be back in ~12 days.
    - 101 lots: discussions underway re assaying these as well.
  - **MMD discussions ongoing re disposition of lots (formal process pending).**
    - Note that lots can be traced to distributors and large HMOs, but not consistently to individual doctors offices.

Id. at '08 (emphasis added).

197.12. Dr. Margolskee's March 5, 2001 email to Drs. Scolnick and Greene also stated:

- Implications for children in the field who have received vaccine in recent years:
  - Risk assessment is being done re how to address children in the field who may have received sub-potent vaccine and who are between the ages of 1 and 6 years old (i.e. have not yet received their 2nd dose at school entry).
    - Three components to analysis: probability of child getting dose of <4.0 logs; probability of child being a nonresponder; and probability of child subsequently being exposed to mumps & contracting disease.
    - Probability of low potency dose dependent upon release titer and "burn rate" (i.e. time from release to administration) of lot. Marketing data suggest that only 5-10% of GPs/Pediatricians surveyed have a frequency of inventory turnover of >6 months.
    - Assuming a "burn rate" of 12 months across all physicians and the most recent mumps stability data of 1.0 log loss projected over 24 months, the likelihood of impact on the number of observed clinical mumps cases in the population is exceedingly low.
- **Preliminary analysis is supported by U.S. surveillance data which demonstrate a continuing decrease in U.S. mumps cases over time (data available through yr 2000).**
  - 666 cases in 1998, 391 in 1999 & 330 cases in 2000. Cases generally believed to be either imported or from sectors with low vaccination rates. Rates are highest in 1-4 year olds.
- Am optimistic that analysis will support not taking action (i.e. no need for revaccination). Note that tracing lots/assessing time of use would likely be impossible and need for revaccination would probably mean large scale initiative.

Id. at '08-09 (emphasis added).

197.13. Dr. Margolskee's March 5, 2001 email to Drs. Scolnick and Greene also stated:

- Implications for children in the study:
  - Children who are seronegative by either ELISA or mumps neutralization will be offered revaccination, since we can identify them.

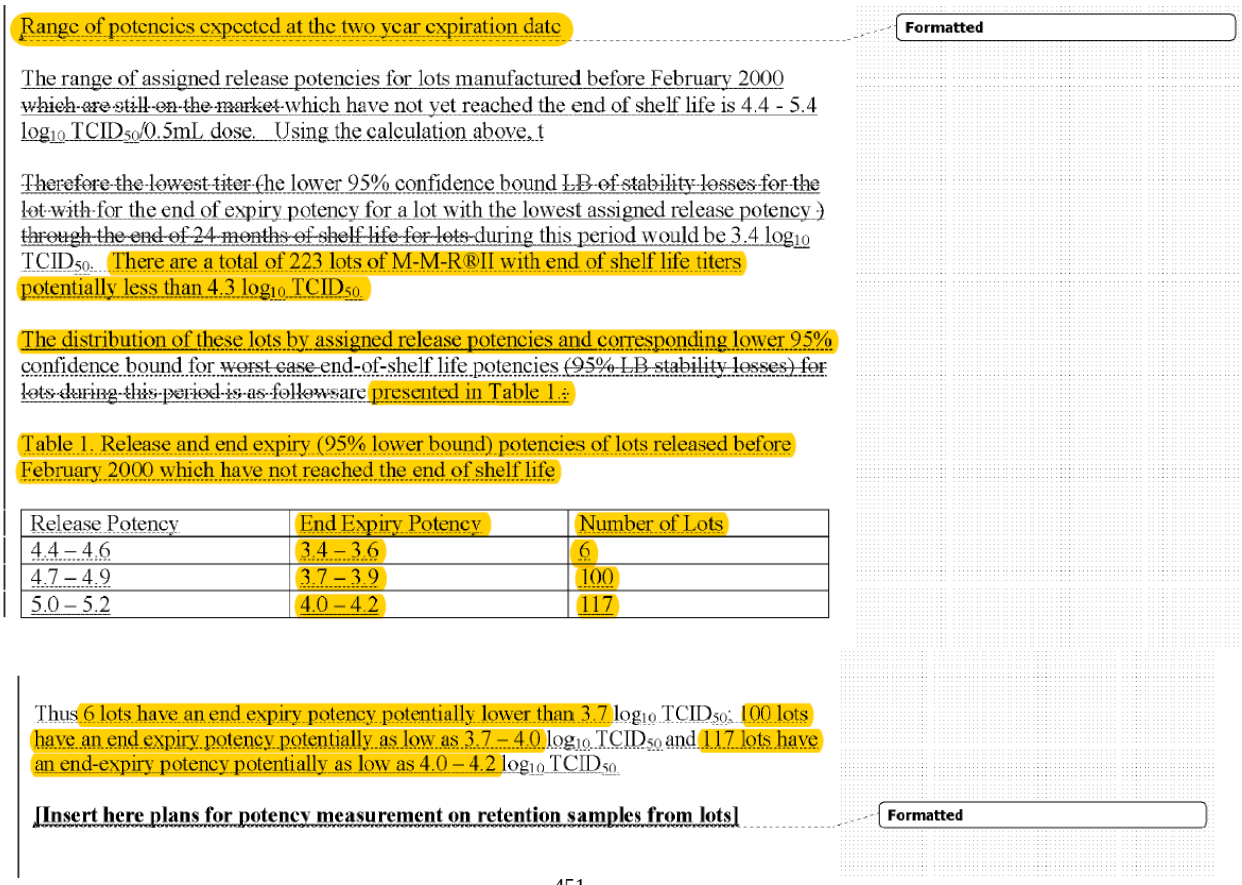
- Next steps/Interactions with CBER:
  - Request for meeting with CBER Product group has been made (K. Carbone has been involved in discussions on Compliance side. We anticipate meeting in mid March). Will discuss end expiry study results and proposed label change to 4.0 logs at that time.
  - MMD (R. McKee & M. Angelo) met with Compliance group on Thursday. Discussions went well (re actions to address warning letter). Agreed that meeting with Product group is needed.
  - Responses to CBER Warning letter due March 8 to Compliance. Will include stability analyses from MMD lots, preliminary analyses from Protocol 007, further steps.

  Plans are to discuss this week.

Id. at '09 (emphasis added).

197.14. A document titled "Mumps expiry response to warning letter.doc" attached to an email from MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to Dr. Jerald Sadoff and Dr. Joye Bramble, dated March 13, 2001,[450] stated:

[450] On March 5, 2001, MMD's Mark Rosolowsky sent an email to Drs. Chirgwin, Sadoff and McKee with changes to the draft response. On March 13, 2001, after the final response was sent to FDA, Dr. Chirgwin forwarded the draft to Drs. Sadoff and Bramble.



Range of potencies expected at the two year expiration date

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The range of assigned release potencies for lots manufactured before February 2000 ~~which are still on the market~~ which have not yet reached the end of shelf life is 4.4 - 5.4 $\log_{10}$ $TCID_{50}$/0.5mL dose. Using the calculation above, t

~~Therefore the lowest titer (he lower 95% confidence bound LB of stability losses for the lot with for the end of expiry potency for a lot with the lowest assigned release potency) through the end of 24 months of shelf life for lots during this period would be 3.4 $\log_{10}$ $TCID_{50}$.~~ There are a total of 223 lots of M-M-R®II with end of shelf life titers potentially less than 4.3 $\log_{10}$ $TCID_{50}$.

The distribution of these lots by assigned release potencies and corresponding lower 95% confidence bound for ~~worst case~~ end-of-shelf life potencies ~~(95% LB stability losses) for lots during this period is as follows~~are presented in Table 1.:

Table 1. Release and end expiry (95% lower bound) potencies of lots released before February 2000 which have not reached the end of shelf life

Release Potency	End Expiry Potency	Number of Lots
4.4 – 4.6	3.4 – 3.6	6
4.7 – 4.9	3.7 – 3.9	100
5.0 – 5.2	4.0 – 4.2	117

Thus 6 lots have an end expiry potency potentially lower than 3.7 $\log_{10}$ $TCID_{50}$; 100 lots have an end expiry potency potentially as low as 3.7 – 4.0 $\log_{10}$ $TCID_{50}$ and 117 lots have an end-expiry potency potentially as low as 4.0 – 4.2 $\log_{10}$ $TCID_{50}$.

[Insert here plans for potency measurement on retention samples from lots]

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MRK-KRA01480844 at '845-46 (highlight added).[451]

198. In my opinion, I would expect Merck to provide the information contained in the draft responses to the Warning Letter in the final response to the FDA, particularly the sections disclosing the 223 lots. Furthermore, I would expect Merck to provide the FDA with the same information Dr. Margolskee provided to Drs. Scolnick, Greene and Kim in her March 5, 2001 email, including the following:

- Comparing the ELISA and AIGENT results for children who were non-responders by the AIGENT, Merck identified that children who received the

[451] This draft of the Response to the Warning Letter, like the prior draft, disclosed the lots described in Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene. MRK-KRA00549510. *See also* MRK-KRA01649600 (March 8, 2001 redline draft "Merck & Co. Inc. Warning Letter Responses"); MRK-KRA00562206 (March 8, 2001 redline unsigned "Merck & Co. Inc. Warning Letter Responses).

lowest potency of 3.7 were not responding by either assay, suggesting children who got doses at that potency were not sufficiently protected.

- Merck's overfilled MMRII lots (manufactured after September 1999) complied with a 4.0 end expiry, not the 4.3 log on the MMRII label.
- Merck identified an "urgent need" to change the label and intended to do that by using ELISA testing, which would be available more quickly than the neutralization data.
- There were 107 lots filled before the overfill potentially still on the market with projected potencies lower than 4.0 at 24 months and the clinical data from the preliminary subset analysis in Protocol 007 did not support the effectiveness of MMRII at a dose below 4.0.
- Merck identified 6 retention samples to test potency at 24 months and was discussing testing the other 101 lots for potency at 24 months.
- Merck was investigating where the lower potency lots were sold. It could trace them to distributors and large HMOs but not individual doctors' offices.
- Merck was conducting a risk assessment for children who had received MMRII in recent years analyzing the probability of a child (1) getting a dose of < 4.0 log, (2) being a nonresponder, and (3) subsequently being exposed to mumps. The assessment depended on how quickly vaccines were used from the time they were sold (the "burn rate") and the risk of mumps exposure.
- Needing to revaccinate children was a potential outcome of the risk assessment and since tracing lots and assessing when the lots were used (i.e. what potency a child received) was likely impossible, the need to revaccinate would "probably mean large scale initiative."
- Children in the Protocol 007 study who were negative by ELISA or neutralization would be offered revaccination.
- The "further steps" Merck would take as a result of its investigation.

199. In my opinion, as of February 27, 2001, the date of Mr. Bennett's email to Dr. Keith Chirgwin and Dr. Roberta McKee[452] that stated: "Current Product … Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry," Merck did not have adequate assurances that MMRII could meet the product specification of not less than 4.3 through going forward, even after the overfill implemented in September 1999.

F. Merck Responded to the Warning Letter Without Reference to the Out of Specification MMRII Lots or Merck's Inability to Assure MMRII Potency in the Future

200. On March 8, 2001, Merck submitted its response to the February 9, 2001 Warning Letter, including its response to Observation #3 regarding mumps stability.[453] The response stated: "With regard to expectations for products meeting specifications throughout the labeled expiry period, we agree."[454] However, the table summarizing the 223 lots with predicted end expiry potencies below 4.3 log [20,000] in the drafts was removed. Further, while internally Merck had stated: "Stability data do not support current end of shelf life claim (4.3 log10 TCID50),"[455] the response to the Warning Letter stated: "As a result of communications with CBER over the last several years, we have implemented changes, including an increase in the mumps content of the product in September 1999 to ensure compliance to the labeled titer through expiry. Today all products have end-expiry specifications consistent with their label."[456]

[452] MRL's Senior Director, Worldwide Regulatory Affairs and MMD's Vice-President of Vaccine & Sterile Quality Operations, respectively.
[453] MRK-KRA01537603.
[454] *Id.*
[455] MRK-KRA01896072 at '72-73.
[456] MRK-KRA01537603.

200.1. A letter from MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, to FDA's Director, Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality, Stephen Masiello, CBER, dated March 8, 2001, stated:

> We acknowledge receipt on February 14, 2001 of the Warning Letter (CBER-01-012) regarding the inspection of our West Point, Pennsylvania facility between August 14 and October 11, 2000. Following receipt of the FDA form 483, at the close of that inspection, we undertook an in-depth critical evaluation of each of the 24 observations and developed a comprehensive remediation plan based on three guiding principles: 1) ascertain the underlying cause of each observation, 2) fix the specific example cited and apply systemic corrections where appropriate, and 3) incorporate additional management oversight to monitor the effectiveness of the corrective actions. Our response, detailing our plan was provided to you on October 24, 2000.
>
> In total, 54 commitments were identified to address the 24 specific observations. To date, 52 of these commitments have been completed and the remaining two, which will be completed by March and December 2001, are in progress and are on track. As we discussed during our meeting on March 1, 2001, we believe that the actions taken to date comprehensively address all concerns raised during the referenced inspection as well as in the subsequent Warning Letter.

MRK-KRA01537603 (emphasis added).

200.2. The March 8, 2001 response to the Warning Letter also stated:

> Merck Response [Observation 3]:
> For clarity, each point will be addressed individually.
> With regard to expectations for products meeting specifications throughout the labeled expiry period, we agree. As stated in our October 24, 2000 communication, we historically considered the M-M-R®II labeled titers to reflect minimum release specifications. As such, measured potency results below label specification observed during stability monitoring of M-M-R®II were not

considered atypical. As a result of communications with CBER over the last several years, we have implemented changes, including an increase in the mumps content of the product in September 1999 to ensure compliance to the labeled titer through expiry. Today all products have end-expiry specifications consistent with their label.

Regarding the request for mumps stability analyses, please refer to an analyses of mumps stability data submitted to CBER on October 24, 2000 in a document entitled "Measles, Mumps, and Rubella Virus Vaccine Live, Statistical Analysis of Potency on Stability" (STN 101069). A retrospective analysis of stability data was performed for lots manufactured from December 1986 through May 1998. Since use of incomplete data sets may influence the conclusions disproportionately due to the bi-phasic kinetics of degradation that was observed, only lots with at least twenty-four months of data were included in the analyses. In order to answer the question regarding the specific time period for which lots were manufactured and may still be within expiry, the stability data from lots manufactured between January 1995 through May 1998 were assessed.

The average estimated loss rate for mumps stored at 2-8° C for 2 years is 0.703 logs as reported in Attachment 8, table 2, page 104 of the October 24, 2000 submission. Thus, if it is assumed that the initial potency is 4.3 log TCID50/dose, the minimum release mumps potency specification in effect prior to February 2000, the expected average potency at expiry is 3.6 log TCID50/dose. In order to estimate the range of potencies around the average loss rate, the standard deviation of the loss rate was calculated and found to be 0.3 logs. Therefore, the 95% upper and lower confidence bounds for mumps potency at the end of a two year expiry is estimated to be 3. 9 and 3.3 log TCID50/dose, respectively.

Regarding available product efficacy data, mumps product efficacy can be expressed by data collected from seroconversion rates and immunogenicity studies and field effectiveness reports. Data from dose ranging and

immunogenicity studies conducted in the mid 1960's demonstrated that all children developed neutralizing antibodies to mumps after administration of doses as low as 3.1 log TCID50 of Jeryl Lynn™ mumps, which is below the lower 95% confidence limit (3.3 log TCID50/dose) predicted for product released at the minimum potency specification in place prior to February, 2000. Preliminary data from end-expiry clinical trials for M-M-R®II utilizing three different mumps potencies (4.9, ≤ 4.0, and ≤ 3.7 log TCID50/dose) have recently become available. These data indicate that mumps neutralizing antibody seroconversion rates at mumps doses of 4.9 and 4.0 log TCID50/dose are comparable at 94.1% and 93.3%, respectively. The seroconversion rate at 3.7 log TCID50/dose was 88.2% with a 95% confidence interval of 82.3 to 92.6%. This seroconversion rate range is consistent with several older field efficacy studies that demonstrated seroconversion rates ranging between 83 and 93 %, which still afforded high levels of protection against mumps infection.

With respect to field effectiveness, it has been reported by the Centers for Disease Control and Prevention that mumps cases are at an all time low. A total of 666 cases were reported in 1998, and declined to 391 and 330 cases in 1999 and 2000, respectively. This is a 99% decrease from the 152, 209 cases reported in 1968. It should be noted that the very high field effectiveness of this product has been maintained over the past 30 years prior to implementing the mumps process change described above. This field experience covers over 330,000,000 doses of M- M-R ®II worldwide and is associated with the sustained control of mumps in several countries, including U.S., Sweden, and Finland, over a period of decades where M-M-R®II family of products have been the only ones available for distribution.

These data taken together provide evidence that M-M-R®II is effective through the predicted range of potencies post-release within a 2-year expiration date. As discussed during our March 1, 2001 meeting, a detailed technical review of the stability and clinical information is being scheduled through the Office of Vaccine

> Research and Review. While the date has not been finalized, we have been informed that the discussion is planned for the mid-March time frame.
>
> With regard to examination of reserve samples as part of a stability failure investigation, we agree that this should be considered as part of any out-of-specification stability investigation. With respect to Merck's investigations of mumps-containing vaccine stability test failures for lots manufactured prior to the September, 1999 process change, a statistical analysis which evaluated the lot against historical mumps-containing lots was performed. In each case to date, this statistical analysis has shown that the stability profiles of lots, which had exhibited out-of-specification stability results, were consistent with historical stability profiles. Since lots with out-of-specification results did not exhibit atypical stability profiles for the manufacturing process in place at the time, testing of reserve samples was deemed not to be required. <u>As noted previously, a process change to increase the mumps content of the product to ensure compliance to the labeled titer through expiry was implemented in September 1999 and approved in February 2000.</u> For all Merck biological products, including mumps-containing vaccine products manufactured after September 1999, examination of reserve samples is considered as part of investigating any out of specification stability results to quickly determine whether the out-of-specification result represents an anomaly or a serious problem.

MRK-KRA01537603 at '08-10 (original italics removed, underline added).[457]

201. In my opinion, Merck's response to the Warning Letter was inadequate. A reasonable and prudent manufacturer would have included: (1) the identification of the low

[457] A letter from MMD's McKee to FDA's Masiello dated April 6, 2001, reported a minor error in the seroconversion rate percentages reported in the March 8, 2001 response to the Warning Letter and provided corrected percentages. It also stated: "The original conclusions drawn from these data are not impacted by the minor changes. However, we feel it is important that our submission be accurate. This error stemmed from the inadvertent use of an unaudited source data table. Compliance to auditing procedures has been reemphasized among appropriate personnel." MRK-KRA01649598 at '98-99.

potency lots summarized in the draft responses;[458] (2) the medical assessment of children getting MMRII doses with low potency mumps, including the need for potential surveillance studies and revaccination of large groups of children; (3) the assay testing outside of the protocol to provide reassurance of the results of Protocol 007 cited in the Warning Letter to justify the efficacy of lower potency product; and (4) the calculations showing the "process change to increase the mumps content of the product to ensure compliance to the labeled titer" did not assure MMRII could meet the 4.3 mumps end expiry going forward, even after the overfill.

G. Merck Filed a Biological Product Deviation Report for an Out of Specification MMRII Lot Without Referencing Other Out of Specification MMRII Lots or Merck's Inability to Ensure Mumps Potency of Not Less Than 4.3 Through End Expiry

202. On March 5, 2001, Merck filed a "Biological Product Deviation Report" ("BPDR") to report MMRII Lot 0628706 as out of specification for failing to meet the end expiry potency specification for mumps at 24 months.[459] The BPDR stated that clinical studies have shown that the minimum dose required to immunize a seronegative child has been found to be as low as … 3.1 log [1,250] TCID50/dose for mumps.[460] Based on this information, Merck concluded that a lack of immunity would not be expected if a child received a dose at potency lower than the 4.3 on the MMRII label.[461] The BPDR also stated that to "ensure that lots will meet the mumps potency specification of 4.3 TCID50/dose at expiry, the minimum specification

[458] Calculated as 223 lots but 225 lots according to MRK-KRA00549518 (Attachment #4).
[459] MRK-KRA00754239 at '40.
[460] *Id*. at '42.
[461] *Id*.

was revised from 4.3 [20,000] to 5.0log [100,000] TCID50/dose at release."[462] The BPDR concluded that "no further action [was] warranted."[463]

202.1. A Biological Product Deviation Report[464] with Establishment Tracking # BPD 01-003 reported on March 5, 2001 stated:

> An investigation was initiated into a recent out-of-specification result for single-dose vials of M-M-R®II Lot# 0628706[465] at the 24-month stability interval for potency of measles and mumps at the 4-hour and 8-hour reconstitute and store intervals, respectively. The expiry of the product is 24 months. … An average mumps potency value of 4.2 log [16,000] $TCID_{50}$/dose was observed, versus the expiry specification of 4.3 log [20,000] $TCID_{50}$/dose. … M-M-R®II Lot # 0628706 was packaged into Lot # 1540H. This lot has been distributed domestically and expired on 10/03/00.[466]

MRK-KRA00754239 at '40 (emphasis added).

202.2. BPDR 01-003 also stated:

> Description of Contributing Factors or Root Cause
> The manufacturing documentation associated with single-dose vials[467] of M-M-R®II Lot# 0628706 was reviewed. This included a review of the formulation, filling, lyophilization, and inspection process descriptions. There were no atypical events that would result in a lack of potency associated with the manufacture of this lot. The bulk thaw time, time in solution, fill volume, and inspection reject rate were all within

[462] *Id.*
[463] *Id.*
[464] The final rule on "Reporting of Biological Product Deviations in Manufacturing" issued on November 7, 2000 stated: "the final rule more clearly describes the types of events, now termed 'biological product deviations,' that must be reported to FDA. These are events which may affect the safety, purity, or potency of a distributed biological product and which represent either a deviation from CGMP, applicable regulations, applicable standards, or established specifications, or are unforeseen or unexpected." Biological Products: Reporting of Biological Product Deviations in Manufacturing, 65 Fed. Reg. 66622.
[465] Lot 0628706 was manufactured on August 9, 1998. MRK-KRA01898114 ("Titers for released lots filled after May 17, 1995 … to December 31, 1998.").
[466] Because this lot expired on October 3, 2000, it would not be among the list of lots potentially on the market in February 2001 and circulated among Merck's senior management as Attachment #4 to Dr. Margolskee's email to Drs. Scolnick and Greene. *See* MRK-KRA00549510 (Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene); MRK-KRA00549518 (Attachment #4).
[467] Single dose vials are filled for single use. Each child is immunized from a separate vial.

specification. The total time out of refrigeration for inspection and packaging was within allowable limits. … The mumps potency test result at release was 4.9 log [80,000] $TCID_{50}$/dose, which was above the release specification of ≥4.3 log [20,000] $TCID_{50}$/dose. All other release testing for this lot was satisfactory.

The investigation also included a review of the testing documentation associated with the 24-month stability intervals. Reconstitute and store potency testing is performed at the initial and 24-month intervals. Samples are reconstituted with sterile diluent, incubated at 2-8°C for 0, 4, and 8 hours and tested using a 3x1-potency assay format. For Lot# 0628706 samples were stored, based on the protocol, in both an upright and inverted orientation. Samples are required to meet minimum potency specifications … ≥4.3 log[10] [20,000] $TCID_{50}$/dose for mumps). … Three vials of Lot# 0628706 were tested for mumps reconstitute and store potency resulting in a mumps potency value of 4.2 log[10] [16,000] $TCID_{50}$/dose, at the 8-hour interval, upright. Expanded testing was completed on three additional vials resulting in an average mumps potency value of 4.2 log[10] [16,000] $TCID_{50}$/dose for this interval (see table 2). Additionally, 24-month potency results for … mumps obtained when the vaccine was reconstituted and not stored were within specification (… 4.4 log[10] 25,000]$TCID_{50}$/dose for mumps). There were no atypical events associated with these tests. All instruments were within calibration, the ranges among individual potency values for the samples and the positive control House Standards were within established limits, and the House Standard values were within the control limits.

Active Stability Monitoring methods were used to evaluate the data from the 24-month reconstitute and store stability time point against pooled historical data from single and multi-dose images of measles and mumps containing vaccines. It should be noted that Active Stability Monitoring is based on House Standard adjusted values. Adjustment to the daily House Standard has been proposed to compensate for some of the variability associated with the M-M-R®II potency assays. The Active Stability Monitoring evaluation concluded that results for both measles and mumps are consistent with our historical experience and process capability for this product.

Id. at '41 (emphasis added).

202.3. BPDR 01-003 also stated:

> Follow Up
> M-M-R®II Lot# 0628706 was packaged into Lot# 1540H. All vials from Lot# 1540H (115,270 vials total) were distributed domestically and expired on 10/03/00. No product quality complaints have been registered against this lot. Two adverse experience reports were received. Neither report related to a lack of potency or failure to seroconvert. Our medical assessment determined that clinical studies have shown that the minimum dose required to immunize a seronegative child has been found to be as low as … 3.1 $logTCID_{50}$/dose for mumps.
>
> Therefore, for a child who might receive a sub-optimal dose of vaccine in the range of … 4.2 $logTCID_{50}$/dose for mumps, as measured in the stability study, the possibility of not seroconverting, potentially leading to a lack of immunity, would not be expected.
>
> Our investigation concluded that the specific out of specification results for … mumps are within the variability of the potency assay. These results are consistent with potency values at or near the minimum specification. Active Stability Monitoring indicates that the performance of this lot is consistent with the historical performance of previous lots of this product …. To ensure that lots will meet the mumps potency specification of 4.3 $TCID_{50}$/dose at expiry, the minimum specification was revised from 4.3 to 5.0 $logTCID_{50}$/dose at release. On 2/11/00, a Prior Approval Supplement was approved that included these changes.
>
> Based on the fact that potency values in the range of … 4.2 $logTCID_{50}$/dose for mumps would not be expected to lead to a lack of immunity Merck & Co., Inc. believes that no further action is warranted for Lot# 1540H.

Id. at '42 (emphasis added).

203. In my opinion, Merck's BPDR 01-003 was inadequate. In light of the public health significance of the issues involved, a reasonable and prudent manufacturer would have

included investigation of other single-dose vial MMRII lots manufactured in 1998, the same year as M-M-R®II Lot# 0628706.[468] Furthermore, since some of the 225 lower potency lots identified in Attachment #4 were manufactured in 1998,[469] the investigation I would have expected to see in this BPDR would have included those lots.

204. In my opinion, BPDR 01-003 was also inadequate because it stated that "[t]o ensure that [future] lots will meet the mumps potency specification of 4.3 TCID50/dose at expiry, the minimum specification was revised from 4.3 to 5.0 logTCID50/dose at release." A reasonable and prudent manufacturer would have reported that it did not have adequate assurances that future lots would meet the mumps potency specification of 4.3 TCID50/dose at expiry even after the overfill.[470]

H. Merck Submitted the Results of the Protocol 007 Preliminary Subset to Justify the Efficacy of Low Potency MMRII

205. On March 12, 2001, Merck submitted the results of the Protocol 007 preliminary subset analysis to FDA.[471]

205.1. A letter marked "Serial No. 63," from MRL's Associate Director, Worldwide Regulatory Affairs, Vaccines/Biologics, Dr. Manal Morsy, [472] to FDA's Director, Office of

[468] *See* Section VIII.D above (the 2001 Warning Letter stated: "This stability batch is a sample, which represents the many batches that are manufactured during the year. When the designated stability batch fails to meet its specification, the investigation should include examination of reserve samples of other batches to quickly determine whether the out of specification result represents an anomaly or a serious problem.").
[469] MRK-KRA00549510 (Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene); MRK-KRA00549518 (Attachment #4).
[470] MRK-KRA01896072 at '72-73 (emphasis added) (Bennett's February 27, 2001 email stated: "Current Product … Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry."). *See also* MRK-KRA00086318 ("stability data do not support current end of shelf life label claim").
[471] MRK-KRA00017036.
[472] Serial No. 63 was signed by MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy. MRK-KRA00017036 at '39. It included Form FDA 1571 "Investigational New Drug Application" that stated: "(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18 Sec. 1001.)" *Id*. at '41.

Vaccines Research & Review, Division of Vaccines and Related products Application, CBER, Dr. Kathryn Zoon, dated March 12, 2001, stated:

> Reference is made to the teleconference of November 29, 2000 with CBER regarding the Anti-IgG Enhanced Mumps Wild -Type Plaque Reduction Neutralization Assay developed for use in the study … Protocol 007, and the above indicated Investigational New Drug Application.
>
> The following are included in this submission:
> A- Summary of the Validation of the Anti-IgG enhanced mumps wild-type plaque reduction assay (AIGENT) and validation package.
> B- Summary of the Mumps End Expiry preliminary subset analysis (n=600).[473]
> C- Proposal to validate the wild-type mumps ELISA assay to support use of the wild-type mumps ELISA in the Mumps End-Expiry Study.

MRK-KRA00017036 at '38 (emphasis added).

205.2. Serial 63 also stated:

> B- Summary of Mumps End Expiry preliminary subset data analysis (n=600)[474]:
> Preliminary data from the end expiry study which utilized M-M-R®II at three different mumps potencies (4.9, ≤ 4.0, and ≤ 3.7 $\log_{10}$ $TCID_{50}$) have become available. These data indicate that:
>
> - Mumps neutralizing antibody seroconversion rates at mumps vaccine doses of 4.9 and 4.0 $\log_{10}$ $TCID_{50}$ are comparable (94.1% and 93.3% respectively).
> - The seroconversion rate at 3.7 $\log_{10}$ $TCID_{50}$ (88.2%, 95% CI 82.3%- 92.6%), while somewhat lower than the other two doses is also well within the historical

[473] *See also* MRK-KRA00207690 at '08 (a memo from the M-M-R®II P[roduct]D[evelopment]T[eam] to Vaccine T[actical]P[roduct]A[approval]C[ommittee], dated July 26, 2002, stated: "In February 2001, Merck received a Warning Letter reiterating concerns from the Team Biologics inspection. In addition, and more seriously, they challenged the efficacy of marketed product at the lowest predicted potencies (below label claim). With regard to product efficacy, we provided an interim analysis of an ongoing mumps end-expiry trial to justify efficacy of lower potency product. CBER accepted the Merck response.").

[474] *See also* Section VIII.E.2 above. Subjects 2, 31, 133, 166, 174, 223, 678, 1124, 1715, and 1716 were among the 600 whose samples were retested outside the protocol. The results of assay testing outside of protocol were not included in Serial 63 or otherwise disclosed to the FDA.

> seroconversion range for mumps neutralizing antibody responses that have been associated with high field effectiveness in clinical trials (references 1-3).

MRK-KRA0017036 at '45 (emphasis added).

205.3. Serial 63 also stated:

> C. Proposal to validate the wild-type mumps ELISA assay to support use of the ELISA in the Mumps End-Expiry Study.
>
> > As noted previously by CBER, if the results from the Mumps End-Expiry Study support a change in expiry titer, the seroconversion rate observed in this study will be used to modify the label ... It is understood that the preliminary subset data summarized here do not support a label change and that completion of the serologic evaluation for the entire study will be required.
> >
> > In previous communications … CBER has noted, "if Merck can develop an ELISA assay using these low passage JL strains that can be validated against the PRN assay to CBER' s satisfaction, the ELISA method would also be acceptable." …
> >
> > We are seeking CBER's concurrence with this proposal to conduct a bridging study with the ELISA and PRN assays and if the results of this study are supportive, to then use the data generated by the ELISA for the entire study (N = 1770) to support a mumps potency label modification.

MRK-KRA00017036 at '51 (emphasis added).

206. In my opinion, the submission of Serial 63 to the FDA, including the results of the AIGENT testing of the Protocol 007 preliminary subset analysis, were part of the response to the February 2001 Warning Letter. Furthermore, Merck provided that interim analysis "to justify the efficacy of lower potency product."

207. In my opinion, with regard to the proposal to complete the end expiry study using WT ELISA testing, a reasonable and prudent manufacturer would have informed the FDA that it

did not have assurances that it could meet the mumps end expiry specification of 4.3 on the MMRII label,[475] and that the request to bridge to ELISA and complete the end expiry study using ELISA proposed in Serial 63 was to expedite a label change to reduce the end expiry claim.[476]

I. Merck Met With FDA Regarding Mumps Stability Without Referencing Merck's Inability to Ensure MMRII Mumps Potency of Not Less Than 4.3 Through End Expiry

208. On April 4, 2001, Merck personnel met with FDA personnel regarding the mumps stability issues.[477] This was part of the ongoing discussion of mumps stability that included the August 2000 teleconference and Merck's October 24, 2000 mumps stability submission to the FDA.[478] In anticipation of the meeting, Merck's statistician Philip Bennett circulated an email that stated: "Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry."[479] During the April 4, 2001 meeting, the question of expiry dating did not come up.[480] Mr. Bennett's calculations of the required expiry dating were not provided to FDA.

208.1. An e-mail from MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, with subject "Preparations for CBER discussion on mumps stability/expiry," dated March 13, 2001, stated: "Attached please find summary/assignments from today's planning

[475] MRK-KRA01896072 at '72-'73 (Bennett's February 27, 2001 email stated: "Current Product … Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry."). *See also* MRK-KRA00086318 ("stability data do not support current end of shelf life claim").
[476] MRK-KRA00086318 (March 2001 powerpoint describing Path Forward to label change).
[477] MRK-KRA00049238.
[478] MRK-KRA01522617 at '19; MRK-KRA01899087.
[479] MRK-KRA00562218.
[480] MRK-KRA01522617 at '19; MRK-KRA01899087.

meeting for the anticipated CBER discussion on mumps stability/expiry later this month." MRK-KRA00562218.[481]

208.2. A Merck memo from MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to the recipients of his March 13, 2001 email regarding "Planning for CBER discussion on mumps stability," dated March 13, 2001, stated:

> In preparation for the CBER meeting on stability and mumps expiry later this month, several topics require development for inclusion in a background document and/or discussion during the meeting with CBER. …
>
> 1) General stability issues: …
>
> c) Investigation into apparent shift in stability over time …
>
> 2) If CBER proposes short-dating[482] of product in order to address label compliance issue:
>
> a) Statistical assessment to determine what shelf-life is needed to maintain 4.3; issue of biphasic kinetics
>
> b) Assessment of practical and logistical implications of shorter shelf-life
>
> 3) Options with regard to the completion of serologies for the Mumps Expiry Trial:
>
> a**)** Calibrate the ELISA cutoff to the neut[ralization] cutoff (i.e. raise the ELISA cutoff) and use ELISA to complete the study. This will likely be necessary to

[481] Recipients of Dr. Chirgwin's March 13, 2001 email included: MMD's Regulatory Administrator, Katalin Abraham, MMD's Director, Biologics Licensing, Dr. Ronald Salerno, MMD's Senior Director, Regulatory and Analytical Sciences, Dr. Mark Roslowsky, MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, MRL's Director, BARDS, Timothy Schofield, MRL's Biometrician/Statistician, BARDS, Philip Bennett, MRL's Associate Medical Program Clinical Specialist, Dr. Jonathan Hartzel, MRL's Senior Director, Health & Economic Statistics, Dr. Joseph Heyse, MRL's Holly Matthews, MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, MRL's Senior Director, Project Planning and Management/Vaccine Integration, Dr. Joye Bramble, MMD's Director, Vaccine Technology & Engineering, Dr. Mark Galinski, MRL's Manager, Vaccine Regulatory and Analytical Science, Cynthia Morrisey, MRL's Bill Collingwood, MRL's Marketing, Mark Twyman, MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, MRL's Senior Vice President, Project & Vaccine Integration, Dr. Dorothy Margolskee, and MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu.

[482] *See* Section III.B.2.c above discussing the circumstances when short dating may be required.

> make ELISA acceptable as a substitute for the neut[ralization] to address repeatedly stated CBER concern that neut[ralization] nonresponders will be classified as responders in the ELISA
>
> Pros: 1) Timing, 2) ELISA less variable than neut[ralization]
> Cons: 1) This approach (calibration of cutoff to neut[ralization]) may result in a lower SCR potentially impacting ability to meet success criteria for 4.0,
> 2) substituting ELISA for neut[ralization] changes how we will handle the primary endpoint for this study following the interim look (CBER has already voiced concern about this scenario); 3) links the ELISA to neut[ralization] which could have implications for [ProQuad] with lower seroconversion rate for [ProQuad] as well and possible impact on ability to meet criteria for success (90% floor) …
>
> b) Second option is to complete the study with the neut[ralization] assay for the label supplement
> Pros: 1) Adheres to agreement with CBER, 2) may possibly have higher likelihood of success (if ELISA calibration to neut[ralization] results in lower SCR for ELISA)
> Cons: Timing, however this may not be an issue for CBER
>
> i. Need to make decision about whether to do neut[ralization]s in house versus transfer to outside lab …
>
> ii. Confirm timing for data with neut[ralization] for label supplement (CBER's willingness to wait for neut data may be dependent on timing)…

MRK-KRA00024453 at ‘453-54 (original bold removed, underline added).

208.3. An email from MRL’s Statistician, BARDS, Philip Bennett replying to all the recipients of Dr. Chirgwin’s March 13, 2001, dated March 14, 2001, stated:

> Following are the loss and variability estimates for mumps at various timepoints. Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.

MRK-KRA00562218 (emphasis added).[483]

208.4. MRL's former Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, testified as follows:

> *Q. "Our expiry dating needs to be 12 months in order to provide 95 percent confidence that a lot released at 5.0 will be above 4.3 at expiry." Do you see that?*
> *A. Yes.*
> *Q. What does that mean to you?*
> *A. That means by looking at the available stability data that was available to Phil Bennett at the time and then modeling that data on a statistical model, he comes to the conclusion that if we establish 4.3 as an expiry dating and you fill with a potency of 5, that there is – that if you want to be guaranteed with a 95 percent probability, that you will be at the end of shelf life at 4.3 starting at 5, okay, then the length of that shelf life can be no more than 12 months.*

Deposition of Emilio Emini, June 6, 2017, 155:8-25 (emphasis added).

208.5. A Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Vaccines/Biologics, Dr. Manal Morsy, to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu and MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, with the subject: "Preparations for the Mumps Stability – CBER discussion," dated March 19, 2001, stated:

> In preparation for the CBER meeting to discuss Mumps stability and expiry titer … a memo with assignments was distributed by Keith [Chirgwin]. …In a follow-up meeting (March 16, 2001) … it became apparent that the team was finding difficulty in moving forward with putting together a background package without some feedback from CBER. In summary the following was outlined as areas anticipated for discussion in preparation for CBER: …
>
> 2) Short Dating:

[483] *See also* MRK-KRA0562219 (chart of loss and variability estimates for mumps at various timepoints).

> If CBER proposes short-dating of product in order to address label compliance issue:
>
> a) … The assessment of shelf life needed to maintain 4.3 was reported P[hillip] Bennett to be limited 12 month only.

MRK-KRA00019430 at '30-32 (original bold removed, underline added).

208.6. A final set of slides for MRL's section of the Tactical Product Approval Committee presentation on mumps stability, dated March 21, 2001,[484] stated:

> Expiry trial results Implications
>
> - Label Change
>   - Stability data require lowering labeled mumps potency from 4.3 to 4.0 log
>   - Preliminary clinical results support the 4.0 log dose …
>
> Summary
>
> - Collaboration with CBER since 1996
> - Increased titer (5.0 log TCID50 min release) at request of CBER in Sept. 1999 to meet 4.3 log TCID50 at expiry
> - Updated stability analysis shows current log loss of 1.0
> - Current release with 1.0 log stability loss supports 4.0 log TCID50 expiry
> - Interim clinical data supports 4.0 log TCID50 mumps expiry titer

MRK-KRA00616622 at '38 and '40 (emphasis added).

208.7. A document titled: "Background Information for CBER Meeting on April 4, 2001 Mumps Stability,"[485] stated:

> Attachment 2
>
> Nonlinear Kinetics of Live Virus Vaccines …

[484] *See* MRK-KRA00616610 (March 21, 2001 cover email from Dr. Joye Bramble with the Subject "Final-TPAC Presentation-Mumps Stability attaching the final slides).

[485] *See also* MRK-KRA00548598 (high importance email dated March 30, 2001 circulating "Background Information for CBER Meeting on April 4, 2001 Mumps Stability," stated: "A copy of the attached was faxed today to the attention of Luba Vujcic, Norman Baylor, Peter Patriarca and Kathy Carbone at CBER.").

> … The conclusions from [Merck] analyses have been communicated to CBER in recent correspondence related to the inspection by Team Biologics,[486] and are also the basis for the rules utilized in the "Active Stability Monitoring" protocol followed to monitor lots on stability.
>
> The conclusions of those analyses will be discussed in detail during our working group meeting on April 4, 2000 [sic] …

MRK-KRA00548600 at '04-07 (original bold removed, underline added).

208.8. A memo from MMD's Biologics Licensing, Katalin Abraham, to File, with subject "Minutes, Meeting with CBER on 4/4/01 Regarding Mumps Stability," dated April 9, 2001, stated:

> Meeting Summary
>
> The goals and agenda for the meeting were presented by Dr. McKee, followed by an overview of the stability program by Ms. Morrisey … The subsequent presentation by Mr. Schofield on mumps degradation kinetics and house standard adjustment initiated active discussion among attendees on these topics. This discussion consumed the remainder of the time scheduled for the meeting and the rest of the agenda items were not discussed. …
>
> CBER representatives acknowledged at several points during the discussion that they know that M-M-R®II is a "good product that we don't want to have to recall." Dr. Carbone commented that we are now "swimming in new waters," referring to compliance.

[486] The response to the Team Biologics inspection, including the two submissions on October 24, 2000 and the response to the Warning Letter, do not state that Merck could not ensure 4.3 for mumps, even after the overfill, or that the predicted shelf-life for MMRII in order to ensure 4.3 was less than 12 months. *See* MRK-KRA00784030 (October 2000 response to the Form 483); MRK-KRA01899087 (October 24, 2000 stability/potency submission) and MRK-KRA01537603 (response to February 2001 Warning Letter). Moreover, although Dr. McKee reported a "minor error" in the response to the Warning Letter on April 6, 2001 stating: "we feel it is important that our submission be accurate," the update did not include the predicted shelf life of less than 12 months. MRK-KRA01649598 at '98-99.

Merck demonstrated to CBER that their concerns have been taken seriously and that Merck has made appropriate modifications to the stability program. On several occasions, Dr. Carbone stated that she was "glad to see we were doing that," referring to the use of various data analysis methodologies. It was evident that CBER was not familiar with the details provided to them in previous supplements addressing stability monitoring, despite the fact that the backgrounder provided for this meeting summarized and referenced them. They were directed to various sections within the supplements for their post-meeting review.

Outcomes

1. Dr. Carbone emphasized that CBER's concern is that vaccines (in this case, mumps-containing vaccines) remain at or above the minimum potency through expiry. Although they were interested in the Company's efforts to analyze degradation kinetics and assure manufacturing consistency over time, they felt this was more in the manufacturer's area of concern. Dr. Carbone explained that CBER wants, with 95% confidence, that lots be at or above 4.3 log10 TCID50 mumps/dose at expiry. She explained that 4.3 is the lower bound of the expiry potency and that CBER calculations indicated that the expiry titer should be 4.6. Although this point was not discussed further, CBER did indicate that their purpose for annual stability studies is to assure that the minimum potency is met for batches made within the time period covered by the studies. To that end, they felt that one annual lot was insufficient and look to Merck for a proposal that will address their concern. They expect the number of lots on stability to increase and indicated that the number of lots manufactured per year should fit into the equation. They also inquired about how the stability lot was chosen and what assurances were in place to prevent the choice from being biased. Merck's goal for stability studies has been to monitor the process to assure that the release specifications continue to be appropriate. To address CBER's purpose will require a re-evaluation of the program. …

4. Dr. Carbone requested that Merck notify CBER when it appears that a lot on stability may go out of specification, noting that, if additional data proved otherwise, that should also be communicated. She requested that this be worked into the SOPs for stability studies. Dr. Baylor commented that the logistics of implementing this need to be discussed. …

MRK-KRA00049238 at '38-40 (original bold removed, underline added).

208.9. A Merck memo from MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, to MMD's President, Dr. Bernard Kelley, cc'd to MMD's Senior Vice President, Global Quality, Dr. Michael Angelo, and MMD's Vice President, Vaccine Manufacturing, James Laser, with the subject: "Executive Summary – CBER/Merck Meeting April 4, 2001," dated April 8, 2001, stated:

> A team of Merck representatives met with CBER on April 4, 2001 to review and discuss Merck's stability program for biological products.
> OBJECTIVES: …
> 3) Review the interim analysis of the mump end-expiry clinical trial to address any specific concerns CBER may have regarding Merck's response to mumps stability questions raised in the Warning Letter. *Note that at no point in the preparatory discussions or during the face-to-face meeting did CBER raise any concern with regard to the efficacy of the product on the market.…*
>
> COMMENTS:
> Given the active discussion during the course of the meeting, only a subset of the agenda items was covered….
>
> Although the focus of the meeting was spent on the stability program elements, a question was raised during the discussion regarding Merck's procedure for notifying CBER when a lot falls below label claim during a stability study. I described our "Biological Product Deviation Reporting" SOP (formerly known as "Error & Accident"). Dr. Carbone expressed concern regarding the timing for notification (up to 45 days after

> the result is determined to be valid). She went on to request that Merck notify CBER in advance if we predict that based on a slope analysis a lot would not meet potency at expiry (i.e., before any OOS result is obtained). Dr. Baylor intervened indicating that he did not believe CBER should necessarily be notified in such a circumstance. He was aware of the new "Biological Product Deviation Reporting" rule and understood that our actions were in compliance with this. He stated that he would take this issue up with the Office of Compliance and discuss it further with me at a later time.
>
> After the meeting but prior to departure, a few Merck representatives (McKee, Rogalski-Salter, Sadoff) chatted with Dr. Carbone about various stability-related topics. She restated that she knows that M-M-R-II is a "good product" but that CBER has to consider compliance as well. She said that she "probably shouldn't say this" to us but when the Office of Compliance asked her opinion regarding what action CBER should take about the marketed lots within expiry manufactured before the increased mumps process change, she told them "none." She said that all the appropriate actions were taken by the Company and she was not concerned. She did say that the "Office of Compliance makes the final decision".

MRK-KRA01649955 at '55-56 (underline added).

208.10. MMD's former Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, testified as follows:

> *Q. Did you ever get a formal written confirmation of that understanding that you didn't have to file a B[iological]P[roduct]D[eviation]R[eport] if your projections showed a projected – if your models projected that your product could not meet end expiry for a certain percentage of lots released to the public?*
>
> *A. No. I mean – no, we never got – so we generally would have minutes to meetings, but I don't recall specifically the follow-up from Norman [Baylor] on that point.*

Deposition of Roberta McKee, March 30, 2017, 88:6-16.

209. In my opinion, in April 2001, Merck still did not have adequate assurance that MMRII would have "not less than 4.3" mumps potency at the end of the 24 month shelf life. Furthermore, Mr. Bennett's conclusion that "expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry"[487] was relevant to the April 4, 2001 discussion with FDA about the ongoing questions of mumps stability/potency in MMRII that started with the Section 314 Review in 1996. A reasonable and prudent manufacturer would have described the results of Mr. Bennett's analysis to the FDA personnel in attendance. Moreover, a reasonable and prudent manufacturer would have updated its response to the Warning Letter four weeks earlier that had stated: "we believe that the actions taken to date comprehensively address all concerns raised during the referenced inspection as well as in the subsequent Warning Letter."[488]

J. Merck Filed a Biological Product Deviation Report for Four Out of Specification MMRII Lots Without Referencing Other Out of Specification MMRII Lots or Merck's Inability to Ensure Mumps Potency of Not Less Than 4.3 Through End Expiry

210. On April 20, 2001, Merck filed Biological Product Deviation Report ("BPDR") 01-005 to report four MMRII lots as out of specification for failing to meet the end expiry potency specification for mumps at 24 months.[489] Merck's clinical assessment concluded that "there would be no public health risk of an increased incidence of mumps in children vaccinated with mumps vaccine with an end expiry potency value of 3.9 log [8,000] TCID50/dose or

[487] MRK-KRA00562218.
[488] MRK-KRA01537603 ("we have implemented changes, including an increase in the mumps content of the product in September 1999 to ensure compliance to the labeled titer through expiry. Today all products have end-expiry specifications consistent with their label."); *see also* MRK-KRA01649598 at '98-99 (updating an inaccuracy in the response to the Warning Letter).
[489] MRK-KRA00754233.

above."[490] Merck cited to the results of the preliminary subset analysis from Protocol 007 submitted in Serial 63 on March 12, 2001 for support.[491] In the follow up section of BPDR 01-005, Merck stated: "a Prior Approval Supplement was approved that included an increase in the mumps release potency specification from 4.3 [20,000] to 5.0 log [100,000] TCID50/dose. Furthermore, changes were made to the potency test format,[492] which were designed to reduce assay variability by increasing the number of replicates tested. These changes were implemented to ensure that, in the future, potency for lots at expiry would meet the current specification of 4.3 log [20,000] TCID50/dose."[493]

210.1. A BPDR with Establishment Tracking # BPD 01-005 reported on April 20, 2001 stated:

> B5. Description of BPD
>
> An interim analysis from an ongoing clinical trial to evaluate expiry titers for the mumps component of M-M-R®II has recently been performed. In the trial, two end-expiry titers were proposed: 4.0 and 3.7 log $TCID_{50}$/dose. Analysis of sera from approximately one-third of the subjects has been completed. The preliminary results demonstrate that mumps neutralizing antibody seroconversion rates at release (~4.9 log $TCID_{50}$/dose) and the proposed expiry titer of 4.0 log $TCID_{50}$/dose are comparable. The seroconversion rate of the 3.7 log $TCID_{50}$/dose arm is slightly lower, but consistent with several older field effectiveness studies that demonstrated high levels of protection against mumps infection. A summary of this analysis was provided to CBER on March 12, 2001.
>
> As part of this interim analysis, retention samples of specific M-M-R®II lots within expiry were evaluated for mumps potency. Lots were chosen to be tested if, based on recent stability analyses, expiry potencies would be predicted to be below 3.7 log

[490] MRK-KRA00754233 at 236.
[491] *Id.*
[492] *See* Section III.B.2 above discussing potency testing of vaccine as part of monitoring stability.
[493] MRK-KRA00754233 at '36 (emphasis added).

> $TCID_{50}$/dose, the lowest dose evaluated in the clinical trial. For the purposes of this evaluation, the predicted worst-case expiry potencies were calculated based on the measured release potency and applying the lower 95% confidence limit of the loss rate. Based on these criteria, five domestically distributed lots were analyzed.[494] Four of the five lots tested yielded results below the label claim of 4.3 log $TCID_{50}$/dose, but higher than the projected worst-case values of less than 3.7 log$TCID_{50}$/dose; one lot met the current expiry specification. The results are summarized in Table 1.

MRK-KRA00754233 at '34 (original bold removed, underline added).

210.2. BPD 01-005 also stated:

> B6. Description of Contributing Factors or Root Cause
>
> The manufacturing documentation associated with single dose vials of M-M-R®II lots that did not meet the minimum potency requirement (lot #'s 0538J, 0539J, 1070J and 1071J) was reviewed. ... There were no atypical events that would result in lower than expected potencies associated with the manufacture of these lots.
>
> The investigation also included a review of the release testing documentation associated with the four lots. Lots #'s 0538J, 0539J, 1070J and 1071J were release tested on 4/15/98, 4/23/98, 6/4/98, and 6/2/98, respectively. The mumps potency test results at release were 4.5, 4.5, 4.4 and 4.5 log $TCID_{50}$/dose, respectively, which were above the release specification of ≥4.3 log$TCID_{50}$/dose. No deviations from the procedure and no atypical events were observed during testing. All equipment was within calibration. The house standard was within the control limit and the range of individual potency values was within established limits. All other release testing for these lots was satisfactory and typical for product manufactured during this period.

[494] The five lots reported in BPDR-01-005 (0538J, 0539J, 0926J, 1070J and 1071J) are highlighted in the native file version of Dr. Margolskee's Attachment #4 to the February 23, 2001 email to Drs. Scolnick and Greene. MRK-KRA00549510; MRK-KRA00549518. In Dr. Margolskee's February 23, 2001 email, she described six lots for which Merck pulled retention samples to test. As stated in the BPDR, the sixth lot tested was not released in the United States. MRK-KRA00548824 ("we may have a potential compliance issue in some countries where the label currently specifies 4.3 at expiry (Germany?) and the JV regulatory group might need to be in the loop." *See also* Schedule 25 (describing Joint Venture); *see* Section III.B.2 above discussing potency testing of vaccine as part of monitoring stability.

A review of the retention sample testing documentation associated with the four lots was performed. No deviations from the procedure and no atypical events were observed during testing. All equipment was within calibration. The house standard was within the control limit and the range of individual potency values was within established limits. Therefore, the results outlined in Table 1 are considered valid.

The Absolute Potency Method of Active Stability Monitoring was used to compare the retention results of lot #'s 0538J, 0539J, 1070J and 1071J to multiple historical lots at the same time interval. Since the lots were at the 22-month and 24-month time points the stability 24-month time interval was used for comparison. It should be noted that Active Stability Monitoring is based on House Standard adjusted values. Adjustment to the daily House Standard has been proposed to compensate for some of the variability associated with the M-M-R®II potency assays. The Active Stability Monitoring evaluation concluded that these results are typical and consistent with our historical experience and process capability for this product manufactured during this time frame.

Id. at ‘35 (original bold removed, underline added).

210.3. BPD 01-005 also stated:

B7. Follow-up (Continued)

All four M-M-R®II single dose lots were distributed domestically. Lot # 0538J and 0539J expired on 3/26/01. Lot # 1070J expires on 5/15/01 and Lot # 1071J expires on 5/18/01. There have been no product complaints or adverse experience reports for these lots related to a failure to seroconvert.[495]

For the lots included in this evaluation, the lowest potency value obtained during retesting was 3.9 log$TCID_{50}$/dose. Our medical assessment, based on both historical and recent clinical data, indicates that the mumps component of M-M-R®II at a potency of

[495] *Compare with* MRK-KRA00549510 and MRK-KRA00616007 (Dr Margolskee’s emails to Drs. Scolnick and Greene discussing the failure to seroconvert, including that the results of Protocol 007’s preliminary subset analysis could not support effectiveness at potency less than 4.0, and the limits of their investigation regarding product complaints and adverse experience reports).

> 3.9 logTCID$_{50}$/dose is efficacious and the possibility of seroconverting is essentially equivalent to that of a child who receives a dose at 4.9 or 4.0 logTCID$_{50}$/dose. For individuals who fail to seroconvert, the risk of acquiring mumps is extremely low due to the low prevalence of the disease and the herd immunity that exists. Our clinical assessment concludes that there would be no public health risk of an increased incidence of mumps in children vaccinated with mumps vaccine with an end expiry potency value of 3.9 logTCID$_{50}$/dose or above. These points were included in our response to CBER Warning Letter (01-012) on March 8, 2001 in response to specific questions regarding efficacy of the product at potencies below label claim.
>
> Evaluation by Active Stability Monitoring indicates that the performance of these lots is consistent with the historical performance of this product manufactured during this time frame. On 2/11/00, a Prior Approval Supplement was approved that included an increase in the mumps release potency specification from 4.3 to 5.0 logTCID50/dose. Furthermore, changes were made to the potency test format, which were designed to reduce assay variability by increasing the number of replicates tested. These changes were implemented to ensure that, in the future, potency for lots at expiry would meet the current specification of 4. 3 logTCID$_{50}$/dose.
>
> Based on the fact that potency values in the range of 3.9 logTCID$_{50}$/dose or above are not likely to lead to a lack of immunity against mumps, Merck & Co., Inc. believes that no further action is warranted for Lot #'s 0538J, 0539J, 1070J and 1071J.

Id. at ‘36 (original bold removed, underline added).

211. In my opinion, with regard to product manufactured before the overfill (September 1999) Merck’s BPDR 01-005 was inadequate in light of the public health significance of the issues involved. Merck tested lots 0538J, 0539J, 0926J, 1070J and 1071J. The only lot that met the end expiry specification was 0926J. A reasonable and prudent manufacturer would have investigated other single-dose vial MMRII lots manufactured in the same years as lots 0538J,

0539J, 1070J and 1071J.[496] Furthermore, since all five lots were on the list of 225 "Low Mumps Titer Lots Within Expiry" in Attachment #4 to Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene,[497] I would have expected to see an investigation reported in this BPDR to include the lots in that list. While Dr. Margolskee's March 5, 2001 email to Drs. Scolnick and Greene stated that discussions were "underway" to assay 101 lots of the lots identified,[498] none of those lots are reported or discussed in this BPDR or elsewhere. Moreover, the remaining lots on the list of 225, also predicted below the label claim, were also not reported or discussed in the BPDR or elsewhere.

212. In my opinion, with regard to FDA requirements, a vaccine is adulterated if a manufacturer does not have procedures that are designed to assure that the product has the identity, strength, purity or potency it purports or represents it to have. From at least 1998 – September 1999, Merck did not have procedures to assure that MMRII vaccine had "not less than 4.3 log10 [20,000] TCID50" per dose through end expiry. Merck's actions with regard to the identification of product manufactured before the overfill for which it could not assure "not less than 4.3 log10 [20,000]" at end expiry can be summarized as follows:

– Merck identified 225 lots it predicted could not meet the end expiry specification of "not less than 4.3" on the MMRII label	MRK-KRA00549518
– Merck identified six of the lots with predicted lowest potency identified on the list of 225 lots	MRK-KRA00616007 at '08

[496] These five lots were manufactured in 1998 and 1999 before the manufacturing change to begin the overfill. MRK-KRA00549518. *See* MRK-KRA00209399 at 402 (February 2001 Warning Letter stated: "This stability batch is a sample, which represents the many batches that are manufactured during the year. When the designated stability batch fails to meet its specification, the investigation should include examination of reserve samples of other batches to quickly determine whether the out of specification result represents an anomaly or a serious problem."
[497] MRK-KRA00549510 (Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene); MRK-KRA00549518 (Attachment #4).
[498] MRK-KRA00616007 at '08.

– Merck tested five of the six lots, 0538J, 0539J, 0926J, 1070J and 1071J, and reported the results in BPDR 01—005: – Lot 0538J (117,970 doses) was out of specification – Lot 0539J (115,320 doses) was out of specification – Lot 1070J (118,040 doses) was out of specification – Lot 1071J (117,550 doses) was out of specification – Lot 0926J (57,720 doses) was within specification	MRK-KRA00754233; MRK-KRA00549518
– The sixth lot, Lot 0517J (115,400 doses) was not tested or reported to the FDA. Merck documents indicate it was exported outside the United States. [499]	MRK-KRA00548824; MRK-KRA00548114

With regard to the remaining 219 lots (225-6= 219), Merck could not assure those lots met the end expiry claim of 4.3 log10 [20,000] TCID50/dose, and never informed the FDA.[500] Moreover, with regard to children immunized in the United States with vaccines from lots Merck manufactured from May 1998 – September 1999 for which Merck did not have adequate assurance, no one can determine whether these children who are now young adults (approximately 18-23 years old) have been sufficiently immunized because the end expiry potency fell below Merck's specification.[501]

213. In my opinion, Merck used the results of the preliminary subset analysis of Protocol 007's AIGENT testing as part of the medical assessment in BPDR-005 for why no

[499] As a part of this report I have attempted to identify the lots that may have been sold in the United States. Without additional documentation, I cannot say conclusively which of the 225 lots were distributed in the United States. Schedule 26 (summarizing incomplete available information regarding the 225 lots). Tracing where distributed lots went requires a formal process outside the scope of this report. *See* MRK-KRA00616007 (Dr. Margolskee's March 5, 2001 to Drs. Scolnick and Greene discussing need for formal tracing process).

[500] Without being able to trace where all the lots went, it is not possible in the context of this report to identify whether some of these lots went to countries where label specifications were different/lower than the specifications on the U.S. label. However, since the results of the Protocol 007 preliminary subset analysis did not support the effectiveness of product at potency lower than 4.0, and potency and effectiveness are interconnected, all of these lots remain an issue.

[501] *See* Section XI below (discussing the resurgence of mumps cases and outbreaks in the United States among fully vaccinated young adults).

further action was required in response to Merck's reporting of four MMRII lots out of specification for failing to meet the end expiry potency specification for mumps at 24 months. Furthermore, the submission of clinical data from the testing conducted in Dr. Krah's lab was inadequate to support the medical assessment of the risk of receiving lower potency vaccine because raw data was changed without justification during the testing in Dr. Krah's lab.[502]

214. In my opinion, BPDR 01-005 was also inadequate because it stated the September 1999 overfill and other "changes were implemented to ensure that, in the future, potency for lots at expiry would meet the current specification of 4.3 logTCID50/dose"[503] when Merck did not have assurance that the overfill would ensure not less than 4.3 at end expiry. A reasonable and prudent manufacturer would have disclosed that, at the time it was reporting these out of specification lots, it did not have adequate assurances that future lots of product would meet the mumps potency specification of 4.3 TCID50/dose at expiry.[504]

K. Merck Could Not Meet FDA's Objectives for Merck's Mumps Stability Program Because Merck Could Not Ensure Not Less Than 4.3 At Expiry

215. After filing BPDR 01-003 and BPDR 01-005, Merck could not assure with 95% confidence that the overfilled lots would be above 4.3 at expiry, even after the overfill.[505] A label change to lower the mumps end expiry claim on the MMRII label was "the most expeditious and sound alternative. This change in mumps expiry specification [wa]s feasible

[502] *See* Section VIII.L below (discussing a Form 483 citing deficiencies in the testing in Dr. Krah's lab including changes to the raw data without justification.).
[503] MRK-KRA00754233 at '36.
[504] *See* MRK-KRA01896072 at '073 ("Current Product … Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry"); MRK-KRA00086318 ("stability data do not support current end of shelf life label claim") and MRK-KRA00562218 ("expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.") (emphasis added).
[505] MRK-KRA00562218.

only on the basis of clinical efficacy data which [wa]s currently being generated."[506] Merck expected to have Protocol 007 clinical data to support that specification, but the data would not be ready until September 2001 at the earliest. Meanwhile, Merck planned a follow up to the April 4, 2001 meeting with the FDA regarding mumps stability to occur after the Protocol 007 data was generated because "we can't meet 1 of the 2 FDA objectives for our annual [stability] program until the expiry spec is lowered to 4.0."[507] MRL's Director, BARDS, Timothy Schofield stated: "the plan works with 4.0, but not 4.3."[508]

215.1. A Merck memo from MRL's Statistician, BARDS, Philip Bennett, to MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, cc'd to Jim Clair, Joseph Heyse, Timothy Schofield and Bonnie Stankunas with the subject, "Minimum Expiry Specification Limit for Mumps Potency in M-M-R®II," dated July 5, 2001, stated:

> An apparent decrease in the stability of the mumps component in Merck's live virus vaccines has been observed in routine stability study testing. An analysis has been performed which shows a statistically significant increase of 0.19 log in the average shelf-life loss for mumps for lots made after April 1994 compared to lots made from January 1990 to March 1994. Although the reason for this change in stability is as yet unknown, investigations and special stability testing are ongoing. In the interim, until these investigations are concluded, it is prudent to pursue changes which will allow Merck to continue to provide a high degree of assurance that M-M-R®II will meet its mumps labeling and regulatory requirements through its shelf life.
>
> This goal may be met by various methods, including new stabilizer formulations, higher initial mumps potency, and the proposed change in the label claim (minimum allowable expiry titer). Given the time and efforts required for new formulations, and the supply

[506] MRK-KRA01896349.
[507] MRK-KRA01977383 (emphasis added).
[508] *Id*. at '84 (emphasis added).

> and safety concerns associated with higher initial potency, the label change is the most expeditious and sound alternative. This change in mumps expiry specification is feasible only on the basis of clinical efficacy data which is currently being generated.

MRK-KRA01896349 (emphasis added).

215.2. An email from MRL's Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrisey, to MRL's Statistician, BARDS, Philip Bennett, MRL's Director, BARDS, Timothy Schofield, Robin Wolchko, and Roseanne Przanyski, cc'd to Christopher Petroski and Mark Rosolowsky, with the subject: "Enhancements to Annual Stability," dated July 18, 2001, stated:

> Roberta [McKee] would like for us to send a letter to CBER by the end of this month indicating that we are ready for our meeting with them to communicate our proposal for an enhanced annual stability program.

MRK-KRA01977383 at '84.

215.3. An email from MRL's Director, BARDS, Timothy Schofield replying to Cynthia Morrisey, Philip Bennett, Robin Wolchko, and Roseanne Przasnyski, cc'd to Christopher Petroski and Mark Rosolowsky, dated July 19, 2001, stated:

> We're working towards putting the finishing touches on this, and documenting our recommendations. Will you check with clinical whether they're ready to support an expiry potency of 4.0? Should this be coordinated with that activity? As we've discussed, the plan works with 4.0 but not 4.3.

Id. (emphasis added).

215.4. An email from MRL's Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrisey, to MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, and MRL's Executive Director, Clinical Vaccines, Dr. Jerald Sadoff, with the subject: "FW: Enhancements to Annual Stability," dated July 20, 2001, stated:

> Manal and Jerry- see below. Do you know when we are expecting the clinical data analysis to be completed to lower mumps expiry spec. from 4.3 to 4.0? Roberta [McKee] is hoping for us to schedule our follow up meeting with CBER soon. Thanks!!

Id. at '83-84 (emphasis added).

215.5. An email from Dr. Manal Morsy replying to Cynthia Morrisey and Dr. Jerald Sadoff, cc'd to Dr. Alan Shaw, Holly Matthews, Dr. Jonathan Hartzel, and Dr. Keith Chirgwin, dated July 21, 2001, stated:

> My understanding is that the data would be available by September – I have copied Alan [Shaw][509] and Jon [Hartzel] since the data would be coming out of [Alan's] shop and analyzed by Jon.

Id. at '83 (emphasis added).

215.6. An email from Alan Shaw replying to Dr. Morsy, Cynthia Morrisey and Dr. Jerald Sadoff, cc'd to Holly Matthews, Dr. Jonathan Hartzel, and Dr. Keith Chirgwin, dated July 22, 2001, stated:

> This is still the plan. Dave [Krah]'s crew has run all of the sera through once and have now, I think, finished the re-tests where the primary runs failed for one technicality or another. They have been checking and sending the data to Q[uality]A[ssurance] on an "as available" basis so as not to swamp them with a bazillion datasets at once. September still looks good.

Id. (emphasis added).

215.7. An email from Cynthia Morrisey replying to Dr. Alan Shaw, Dr. Jerry Sadoff, Dr. Manal Morsy, Chris Petroski, Timothy Schofield and cc'd to Holly Matthews, Dr. Jonathan Hartzel and Dr. Keith Chirgwin, dated July 23, 2001, stated:

> Mark and Chris – can we try to schedule the next meeting in the Sept[ember] timeframe? This would be strongly preferred, since we can't meet 1 of the 2 FDA objectives for our

[509] Dr. Alan Shaw was Dr. Krah's immediate supervisor. Dr. Shaw reported to Dr. Emini.

> annual program until the expiry spec[ification] is lowered to 4.0, as per Tim's email below.

Id.

215.8. A Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, and cc'd to Katalin Abraham, Deitra Arena, Robert Barber, David Blois, Gary Bolino, John Boslego, Joye Bramble, Keith Chirgwin, Guy Demol, Jonathan Hartzel, Luc Kuykens, Dorothy Margolskee, Donna Marron, Holly Matthews, Charles Osborne, Michael Severino, Florian Schodel, Barbara Thompson, Michael Washabaugh and Helen Winterbottom with the Subject "M-M-R®II: Mumps End Expiry label change – filing strategy," dated August 2, 2001, stated:

> Preliminary data indicate that the 4.0 Log_{10} [10,000] $TCID_{50}$/dose provides comparable immunogenicity to the release dose (4.9 Log_{10} [80,000] $TCID_{50}$/dose). Therefore, the change in claimed potency from 4.3 log_{10} [20,000] $TCID_{50}$/dose to 4.0 log_{10} [10,000] $TCID_{50}$/dose is required as current stability data do not support an end-expiry mumps potency claim of greater than 4.0 log_{10} [10,000] $TCID_{50}$/dose.

MRK-KRA00247149 (emphasis added).

216. In my opinion, in August 2001, Merck could not assure the end expiry potency of the mumps component of MMRII [4.3 log10/20,000 TCID50], even after the overfill initiated in September 1999, because Merck's stability data only supported an end expiry potency of 4.0. With an end-expiry potency of 4.3, Mr. Bennett calculated that MMRII's shelf life was less than 12 months, not the 24 months in MMRII's labeling.[510] A reasonable and prudent manufacturer

[510] MRK-KRA00247149 ("current stability data do not support an end-expiry mumps potency claim of greater than 4.0") and MRK-KRA00562218 ("expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.").

would have described this issue to the FDA, and not waited for "the clinical efficacy data that was being generated."[511]

L. FDA Issued a Form 483 for Deficiencies in the AIGENT Testing in Dr. Krah's Lab After Accusations of Falsification of Data in the Testing

217. In August 2001, FDA issued a Form 483 to Merck related to deficiencies in "the clinical efficacy data that was being generated"[512] in Dr. Krah's lab. As a result of the Form 483, all testing in Dr. Krah's lab stopped, and Merck's ability to complete Protocol 007 and use it for an end expiry change came into question.[513]

1. FDA Made an Unannounced Inspection to Dr. Krah's Lab Resulting in a Form 483 citing four deficiencies

218. In August 2001, FDA conducted an unannounced inspection in Dr. Krah's lab where the Protocol 007 testing was ongoing. The FDA issued a Form 483 with four deficiencies, including that "[r]aw data is being changed with no justification."[514] The FDA inspection was prompted, in part, by a contact made by Steve Krahling, regarding falsification of data in Dr. Krah's lab.[515] Merck prepared and submitted a response to the Form 483 in September 2001.

218.1. A FDA Form 483 signed by Debra J. Bennett and Dr. Kathryn Carbone, dated August 6, 2001, stated:

> IND 1016:
>
> 1) Raw data is being changed with no justification, for example; NB 31689 pg 343, NB 31688 pg 13; 31688 pg 15; 31688 pg. 17.

[511] MRK-KRA01896349.
[512] *Id*.
[513] Merck had already relied on the Protocol 007 AIGENT data in response to the Warning Letter and BPDRs relating to MMRII potency issues in March and April 2001. *See* Sections VIII.F, G and J above discussing Merck's use of the results of the Protocol 007 preliminary subset analysis in response to the Warning Letter and in two Biological Product Deviation Reports.
[514] MRK-KRA01649971.
[515] RELATOR_00001044 (Relator Krahling's handwritten statements in Merck's workbook).

2) There is no procedure in place to determine when a Research Lab is assessed to assure suitability for clinical testing prior to start up. For example: Bldg 16 Rooms 203 and 213 has not been evaluated for testing IND 1016 samples.
3) Spreadsheets used to determine questionable results and retesting of clinical samples for IND-1016 has not been validated.
4) Notebooks do not identify ~~all~~ each technician~~s~~ performing each task.

MRK-KRA01649971 (original underline removed, underline added).

218.2. An FDA report dated August 6, 2001, stated:

Summary of Findings:
This limited sponsor inspection of a vaccine manufacturer was in response to a directed FACTS [Field Accomplishments and Compliance Tracking System] assignment 227598.[516] This inspection was to assure that raw data from IND 1016, MMR Vaccine, Protocol 007 … was accurate and reliable. …

D. Bennett and K. Carbone wrote this report unless otherwise noted.

MRK-KRA02021754 (emphasis added).

218.3. The FDA report also stated:

[516] *See* RELATOR_00001044 (Merck Workbook 31688 Pages 217-218 stated: "Purpose: To enter into the Merck archives that I contacted the FDA several times during June-July 2001 and was responsible for the FDA's raid of Dave Krah's lab on Aug. 6, 2001. ¶ Procedure: In July 2001 I notified Bob Suter, Human Resources, and Emilio Emini, Vice President of Vaccine Research, that I intended to call the FDA to report Merck for falsifying data. At the time, I had already contacted the FDA twice and reported Merck for instituting a policy to fraudulently lower the pre-positive rate in the Mumps anti-IgG neutralization assay. ¶ Dave Krah had been accused by myself and a co-worker during lab meeting, in front of the entire lab, that he was intentionally falsifying data in order to lower the pre-positive rate and meet the FDA targeted goal of measuring 95% seroconversion in MMRII vaccinees. ¶ I also reported this fraud to Alan Shaw, executive director of vaccine research. He admitted the policy and responded that our lab was to be compensated with large bonuses. ¶ During my meeting with Emilio Emini, he admitted that the policy was a "business decision" and had no scientific basis. He ordered me repeatedly not to contact the FDA. Bob Suter informed me on two separate occasions that Merck would put me in jail if I contacted the FDA. ¶ On Sep. 6, 2001 Dave Krah gave me a poor performance review and told me that he knows I was responsible for the FDA raid. I told him that yes I did call the FDA. The next day, Sep. 7, 2001, Dave reversed course and told me he didn't know who called the FDA and that he now believed it was a "routine inspection". This stinks of a policy decision higher up. And it is precisely for this reason that I am entering my testimony into the Merck archives under MMRV x331-01. If you destroy this record, you will have to explain its absence from the archives. Also, I have photocopied it for my records. ¶ Stephen A. Krahling [signature] 01 Oct 2001") (emphasis added).

On 8/6/01, credentials and an FDA-482 were presented to Emilio A. Emini, Ph.D., Vice President Vaccine Research because he stated that he was the most responsible person. *Id*.

218.4. MRL's former Vice President, Vaccine Research, Dr. Emilio Emini, testified as follows:

> *Q. Before that date, how often in your career had there been an unannounced visit from the FDA?*
> *A. Well, it would not have happened to me because very rarely would a research laboratory have been put into a position of running the assay the way in which this was done.*
> *Q. I'm only asking about you. Prior to the unannounced visit on August 6, 2001, how often had there been an unannounced visit to one of the labs under your supervision?*
> *A. Under my supervision?*
> *Q. Yes.*
> *A. Never before. This was the first time.*
> *Q. Was this a startling event for you?*
> *Defense Counsel: Objection.*
> *A. Well, it was an event that one remembers. That event I remember clearly associated with that one. Whether it would be startling, probably not because unannounced FDA inspections of ongoing clinical studies and/or of ongoing production facilities are not unusual. It happens all the time because we had a laboratory under my supervision that was involved in the conduct of a clinical assay in support of a clinical study and having an unannounced inspection from the agency was startling only because the agency showed up unannounced, but it was not an unusual event, if that was your question.*
> *Q. Had you ever been -- had any laboratory under your supervision ever before been accused by the FDA of changing data?*
> *Defense Counsel: Objection.*

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

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

A. It would be either an external testing laboratory or another testing laboratory within the facility or a testing laboratory responsible for clinical assays over in the manufacturing division for the studies that they supported. What was unusual, if you want to use that terminology, was the fact that we were running these clinical assays in a laboratory, Dr. Krah's laboratory, that was originally designed to support assay development, to support research. But unannounced -- going back to your previous question, unannounced agency inspections related to any product, product under development, product that was licensed and produced, happens all the time.

Deposition of Emilio Emini, June 6, 2017, 297:18-300:11 (emphasis added).

218.5. The FDA report also stated:

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. This AIGENT assay is described in several Merck documents.

MRK-KRA02021754 at '56 (emphasis added).

218.6. MRL's Principal Investigator, Dr. David Krah testified as follows:

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 for mumps vaccine, 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?

Defense Counsel: Object to the Form.

A. 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.

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?

Defense Counsel: Object to the Form. Misstates prior testimony.

A. 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.

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?

Defense Counsel: Object to the form.

A. 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.

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

Defense Counsel: Objection.

Q. for the efficacy of mumps vaccination?

Defense Counsel: Objection. Asked and answered. We've gone over this, Gordon.

A. 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.

Q. So did the FDA get it wrong here?

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

A. I defer to the FDA and their interpretation. That's beyond my responsibility.

Deposition of David L. Krah, July 12, 2017, 597:12-600:25 (emphasis added).

218.7. A letter from MRL's Vice President, Vaccine Research, Dr. Emilio Emini, to FDA's Director, Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality, CBER, Dr. Steven Masiello, dated August 20, 2001, stated:

> On August 6, 2001, Investigator Debra J. Bennett and Supervising Medical Officer, Dr. Kathryn M. Carbone, conducted an investigation of the Virus and Cell Biology laboratory within Merck Research Laboratories in support of IND-1016. At the conclusion of the inspection, Ms. Bennett presented us with a Form 483, Inspectional Observations. Our response to these observations is enclosed.
>
> As a research laboratory, we are committed to providing information of the highest quality, supported by sound science and well controlled practices and procedures …
>
> We believe these responses will fully address the concerns expressed by the investigators.

MRK-KRA00000481 (emphasis added).

219. In my opinion, Mr. Krahling's account of events, as recorded in the Merck workbook, are serious accusations of fraud in a clinical trial, particularly in light of the public health significance of the issues involved.[517]

[517] *See* Compliance Policy Guide § 120.100, Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities, available at https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073837.htm. *See also* Application Integrity Policy, available at https://www.fda.gov/downloads/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm072631.pdf.

220. In my opinion, the Form 483 observation that "raw data is being changed with no justification" in the Protocol 007 testing rendered that data unreliable. Furthermore, Merck had already relied on that data, "changed with no justification," on at least three instances: (1) in response to the 2001 Warning Letter to "justify the efficacy of lower potency product;"[518] (2) in its Serial 63 submission of the results of the preliminary analysis from Protocol 007; [519] and (3) in Biological Product Deviation Report 01-005.[520]

221. In my opinion, because a reasonable and prudent manufacturer must assure submissions to the FDA are accurate,[521] Merck's prior submissions relying on the Protocol 007 data changed without justification should have been amended. Furthermore, after two Form 483s, a Warning Letter and two BPDRs within twelve months all relating in some way to the mumps potency issue, a reasonable and prudent manufacturer would have described to the FDA that it was unable to assure the mumps end expiry specification in MMRII[522] even after the overfill and while it did not have clinical data to support lowering the end expiry specification.

2. Merck's Use of the Protocol 007 Data After the Form 483

222. In December 2001, Merck senior managers and FDA staff held a teleconference during which [FDA's] Dr. Carbone stated the FDA's position that "the assay results are unacceptable for an end expiry decision."[523] Dr. Morsy's draft notes of the teleconference stated:

[518] MRK-KRA00207690 at '08.
[519] Serial No. 63 was signed by MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy. MRK-KRA00017036 at '39. It included Form FDA 1571 "Investigational New Drug Application" that stated: "(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18 Sec. 1001.)" *Id*. at '041.
[520] MRK-KRA00754233.
[521] *See* MRK-KRA01649598 at '98-99 (Letter from Dr. McKee to FDA to correct an inaccuracy in Merck's response to the Warning Letter because "we feel it is important that our submission be accurate.").
[522] MRK-KRA00562218 (email from Mr. Bennett stated: "expiry dating need[ed] to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry,") and MRK-KRA01977383 at '84 (email from Mr. Schofield stated: Mr. Schofield, "the [stability] plan works with 4.0 but not 4.3.").
[523] MRK-KRA00071082 at '83.

"Henrietta [Ukwu, MRL's Vice President, Worldwide Regulatory Affairs] we would like to respond as soon as possible … we would like [to] salvage the data."[524]

222.1. A memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy and MMD's, Senior Director, Worldwide Good Manufacturing Practices Quality Assurance and Quality Engineering, Beverly Zaber, to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, cc'd to: Katalin Abraham, Joseph Antonello, Dave Blois, Joe Boslego, Joye Bramble, Keith Chirgwin, Emilio Emini, David Krah, Jonathan Hartzel, Joseph Heyse, Holly Matthews, Jerald Sadoff, Michael Severino, Florian Schodel, Timothy Schofield, and Alan Shaw, with the subject "CBER teleconference (December 7, 2001): Mumps Inspection results and discussion," dated December 13, 2001, stated:

> *Detailed Discussion of Three Concerns:*
> *Issue number 1*: deals with the use of a different criteria for retesting than discussed in the November 29, 2000 teleconference. When the interim analysis was discussed, CBER has specifically asked if the assay was ready, since they wanted to be sure that data generated was not used to refine the assay, since that would make it a pilot study, not data for analysis. The issue is timing, since the criteria was established subsequent to testing and was not in the original retest criteria.
>
> It was explained to CBER that the normal operation is to perform the analysis, establish the controls and install them in an appropriate manner. This assay was accelerated in its development, in part to meet CBER expectations but also to support Merck stability evaluations. We had fully intended to follow the norm, and it is unfortunate that acceleration precluded it in this case.[525]

[524] MRK-KRA00019434 at '36.
[525] MRK-KRA00019434 (draft minutes stated: "Timothy Schofield: ... it is unfortunate that the cart came before the horse...").

Additional information was provided regarding the reasons for the analysis for the 600 samples.[526] This occurred following the MMD 2000 inspection, and was needed to assure that marketed product was good and to provide needed product profile information. The acceleration was to salvage product and get a sense of the data.[527]

[CBER's] Dr. Carbone briefly discussed the titer issue and that the data was generated because the titer had been raised to 5.0 and we were asking for a reduction. Her concern is the lack of stability data information on the product.[528] Although they have requested this information, they have not received it.[529]

It was clarified that Merck is poised to meet and discuss the data with CBER, as well as the general stability program issues. The license label requirement of 4.3 were briefly reviewed, and a reminder to CBER of the need to show the vaccine is immunogenic at the lower dose was, emphasizing that Merck wants to support a titer of 4.7 [sic] and needs to determine appropriate release specification.[530] [CBER's] Dr. Carbone agreed that all of these things were important from a public health prospective [sic]. She commented that Merck has been at 4.3 or above for two years during study, and that is amazing with a product of this age that such issues as stability, end expiry and release specification still come up.

The discussion was redirected to the issue of data integrity. A description was provided of how extravariability is done as part of the validation and then a workbook is created to implement the rules. It was emphasized that there was no change in the operation itself.

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[526] Merck obtained FDA's approval to run the preliminary subset analysis of the Protocol 007 children. That study enrolled approximately 1800 children divided into three groups. The preliminary subset analysis evaluated approximately 600 of the children, 200 from each subgroup.

[527] MRK-KRA00019434 (draft minutes stated: "Henrietta [Ukwu] – I would like to take down memory line [sic] – you had expressed no intereset [sic] in seeing the interim data – but we wanted to salvege [sic] the product – and take that peak that we were not going down an lane [sic] that would not lead to – alternative was a product recall – to provide reassurance that the product was appropraite [sic] for use.").

[528] *Id.* (draft minutes stated: "Kathy [Carbone] – ... what we wanted was stability").

[529] MRK-KRA01977383 (July 18, 2001 email from Cynthia Morrisey stated: "can we try to schedule the next meeting in the Sept timeframe? This would be strongly preferred, since we can't meet 1 of the 2 FDA objectives for our annual program until the expiry spec is lowered to 4.0") (emphasis added).

[530] MRK-KRA00019434 (draft minutes stated: "Tim [Schofield] ...we were disperate [sic] to establish 4.0 or 3.7 so that we can support shelf life based on stability.").

> CBER stressed that the retesting of sera was done using rules not previously stated and added that although the rules may be good, they were not established before data was generated.[531]

MRK-KRA00071082 at '85-86 (emphasis added).

222.2. Dr. Morsy's December 13, 2001 memo also stated:

> Because official communication of the three points would need to be reviewed through CBER channels before being sent, Dr. Carbone summarized the three points as follows:
>
> 1. Changes were not done in the correct timing sequence, and were in variance with the discussion of how the assay would be run as detailed in the November 29 letter. Basically, we said we would not change how the assay was done and then did (CBER includes analysis of data as part of the assay process.)
>
> 2. There was no documented mechanism for retesting or review of data. The use of alcohol to erase original raw data from the plates raised questions and there are QA issues with the way reasons for changes were recorded (or in many cases not documented).
>
> 3. Because of the use of alcohol on the plates might allow changes to data to be made which would not appear in the notebook, the integrity of the data for this subset is questionable. (Implication is that not even the unchanged data could have been a retest and no one would know, therefore all the data is questionable.)

Id. at '88 (emphasis added).

223. In my opinion, in December 2001, Merck still could not ensure the mumps end expiry specification of 4.3 that continued to be on the MMRII label because, according to Mr. Bennett, the "expiry dating need[ed] to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry," and, according to Mr. Schofield, "the [stability]

[531] *Id.* (draft minutes stated: "Alan [Shaw] keep in prospective [sic] that throughout the course – there have not been a change in the operation of the assy [sic] … Kathy [Carbone] "we would consider that a change...").

plan works with 4.0 but not 4.3."[532] Furthermore, according to Merck's summary of the December 7, 2001 teleconference, FDA's Dr. Carbone raised the potency/stability issue with Mr. Schofield and other recipients of Mr. Bennett's email on the call.[533] A reasonable and prudent manufacturer would have described to FDA's Dr. Carbone and other FDA personnel on the call that Merck was unable to assure the mumps end expiry specification in MMRII even after the overfill and it did not have clinical data to support lowering the end expiry specification because of the deficiencies cited in the Protocol 007 testing.

3. Merck Proposed a Way to "Salvage the Data" from Protocol 007

224. In February 2002, Merck submitted Serial 80, the written response to the December 7, 2001 teleconference in which the FDA communicated its preliminary conclusion that the Protocol 007 data could not be used for end expiry regulatory decision-making.[534] In Serial 80, Merck represented that there was a reliable record of the "originally"[535] recorded assay results and proposed using this data for the mumps end expiry analysis.[536]

224.1. A letter marked "Serial No. 80" from MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to FDA's Director, Office of Vaccines Research & Review, Division of Vaccines and Related Products Application, CBER, Dr. Kathryn Zoon, with the subject: "BB-IND 1016 GENERAL CORRESPONDENCE," dated February 4, 2002, stated:

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[532] MRK-KRA00562218 (email from Mr. Bennett stated: "expiry dating need[ed] to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry,") and MRK-KRA01977383 at '84 (email from Mr. Schofield stated: Mr. Schofield, "the [stability] plan works with 4.0 but not 4.3.").
[533] Katalin Abraham, Timothy Schofield, Dr. Jonathan Hartzel, Dr. Keith Chirgwin, Dr. Jerald Sadoff, Dr. Henrietta Ukwu, Dr. Emilio Emini, Dr. Manal Morsy and Dr. Joye Bramble all received Mr. Bennett's March 14, 2001 email and were in attendance on the December 7, 2001 teleconference. *Compare* MRK-KRA00071082 *with* MRK-KRA00562218.
[534] MRK-KRA00000410.
[535] Following Merck's submission of Serial 80, Merck referred to the Protocol 007 data that it changed without justification as "corrected" data. As proposed in Serial 80, the "original" data was the handwritten counting sheet once all the changes were discarded.
[536] *Id.*

> Merck Research Laboratories (MRL), a division of Merck & Co., is submitting the following information as an amendment to the subject Investigational New Drug Application.
>
> This communication is in follow up to a teleconference on December 7, 2001 during which CBER communicated three concerns regarding the suitability of the data from the mumps plaque reduction neutralization assay as a basis for regulatory decision making. During this teleconference, [CBER's] Dr. Katherine Carbone indicated that it would be appropriate for Merck to provide written clarification relevant to the concerns voiced by CBER.

Id. at '411 (emphasis added).

224.2. Serial 80 also stated:

> Although we believe changes were made for appropriate reasons, we understand CBER's concerns regarding the lack of documented justifications. Therefore, we propose, and seek CBER's concurrence with, the use of the original PRN assay results in the evaluation of the 007 trial. ...

Id. at '421 (emphasis added).

224.3. Serial 80 also stated:

> Summary and Recommendations: …
>
> - A reliable record of the originally recorded assay results exists, i.e. results before recounting. These originally recorded results were generated using only SOP criteria prior to application of acceptance criteria.
> - Therefore, we propose using the originally recorded results from the mumps PRN assay for analysis. The evaluation of these data will strictly follow that specified in the original SOP except for the inclusion of the assay validity criteria on the mock and positive control samples as requested by CBER on November 29, 2000. We seek CBER's concurrence with this proposal.

Id. at '423 (original bold removed, underline added).

224.4. A Merck memo from MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, with the subject: "M-M-R®II (BB-IND 1016); Summary of discussion with CBER (03/22/02) regarding acceptability of mumps PRN assay data," dated March 23, 2002, stated:

> Summary:
> CBER has accepted the mumps plaque reduction neutralization … assay data for submission to support the change in the mumps expiry claim.
>
> Background:
> On 8/6/01, during an inspection of the laboratory where the mumps PRN assay was being performed in support of the Mumps Expiry Trial, G[ood]M[anufacturing]P[ractices] concerns were raised by CBER. During a teleconference on 12/7/01, CBER communicated their specific concerns with the mumps PRN data…
>
> In response to these concerns, Merck submitted clarifying responses on 2/4/02. … On 2/25 and 3/14, I spoke with [FDA's] K[athy] Carbone and indicated that there was some urgency in resolving this issue. On 3/14/02 K. Carbone indicated that she had submitted her report and recommendations to N[orman] Baylor who was responsible for making the final decision based on input from the Medical Reviewers and the Compliance Office. On 3/14 I spoke with N[orman] Baylor, and he indicated that CBER would proceed as quickly as possible… A decision to accept Merck's proposal was reached ... and communicated to Merck on 3/22/02. …

MRK-KRA00064005 at '12 (original bold removed, underline added).[537]

224.5. An email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to Deitra Arena, Keiko Simon, David Krah, Jonathan Hartzel, Holly Matthews,

[537] *See also* MRK-CHA00779484 (BB-IND 1016, Serial 82, April 19, 2002 communication to FDA stated: "… We understand that CBER has accepted … the proposal submitted by Merck on February 4, 2002 … to CBER which is to use the originally recorded results from the mumps PRN assay for analysis …") (emphasis added).

Joye Bramble, and Luwy Musey with the subject: "What CBER concurred with in terms with the mumps end expiry," dated March 27, 2002, stated:

> Dave please let me know as soon as possible if there are any sera that need to be tested – a timing we are on a very constrained time line to file this year as we are out of compliance.

MRK-KRA00064005 (original bold removed, underline added).

224.6. A high-importance email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to David Krah, Mary Yagodich, Joseph Antonello, and Karen Hinckley, cc'd to Alan Shaw, Keiko Simon, Jonathan Hartzel, Keith Chirgwin, Henrietta Ukwu, Patrice Benner, Joye Bramble, Holly Matthews, Timothy Schofield, MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, and Dr. Florian Schodel with the subject "Timing for Analysis of mumps neutralization assay data," dated April 10, 2002, stated:

> As I highlighted in my MVX, filing the mumps end expiry and label change is the highest priority from a regulatory and compliance standpoint - every day delay in the PRN assay transfer to [Biostatistics and Research Decision Sciences] is a problem for the rest of the team and our ability to resolve this compliance issue which is a concern not only for the US but also for the EU and the rest of the world where variations must be filed - we currently are targeting the already very late timeline for filing of December this year - considering that CBER provided its resolution in March an eight month timing for a single study filing is quite considerable.
>
> PRN at this point is the critical path and bottleneck. …

MRK-KRA00561310 (emphasis added).

225. In my opinion, Merck continued to be unable to assure compliance with its end expiry specification in the MMRII label in April 2002 and the Protocol 007 AIGENT data was necessary to resolve the compliance issue.[538]

M. Merck Needed Protocol 007's AIGENT Data to "Justify" the Cutoff Merck Proposed to Use in Its WT ELISA

226. As discussed above, Merck developed a new wild-type ELISA ("WT ELISA")[539] to use in clinical studies, including to support its application for a license to sell ProQuad.[540] Before it could use the WT ELISA in any of its clinical trials, FDA required Merck to demonstrate a correlation between the WT ELISA and a neutralization assay. Merck planned to use the AIGENT data generated in Dr. Krah's lab to support the use of the WT ELISA. After FDA issued the August 2001 Form 483 for deficiencies in the AIGENT testing in Dr. Krah's lab, Merck obtained FDA's agreement to use data from the AIGENT preliminary subset testing[541] to conduct a comparison between the AIGENT and the WT ELISA. Thereafter, Merck prepared and submitted Serial 86, including a correlation analysis comparing the AIGENT and WT ELISA assays.

1. Merck Needed to Justify the WT ELISA Cutoff by Correlating the WT ELISA to the AIGENT, or Using a Four-Fold Rise Criterion

227. Merck and FDA held a teleconference regarding Merck's mumps WT ELISA assays in October 2001. An internal Merck memo from Dr. Morsy to Dr. Ukwu summarizing

[538] MRK-KRA00064005 (Dr. Morsy's March 27, 2002 email stated: "we are out of compliance") and MRK-KRA00561310 (Dr. Morsy's April 10, 2002 email stated: "PRN at this point is the critical path and bottleneck.").
[539] *See* Section III.A. above discussing the WT ELISA using JL-135 (the same virus in the AIGENT test) as the indicator virus. Merck had used a different ELISA with JL™ (the vaccine strain) as the indicator virus in its "Legacy" ELISA.
[540] Merck also proposed to use the WT ELISA in the clinical study to support its application to change from HSA to rHA under BB-IND 10076, and if it could obtain FDA approval, for the additional testing at one-year that FDA added to the Protocol 007 study. MRK-KRA00001467 at '467- 69.
[541] *See* Section III.C above describing testing Dr. Krah conducted on 600 children in December 2000-January 2001 to provide data to respond to FDA's concerns about low potency product following the October 2000 Form 483.

the call stated: "CBER requested additional justification for the cutoff[542] for the mumps [WT] ELISA. The observation that the assay cutoff is sufficiently high[543] to accurately classify pre-vaccination sera as negative is useful, but insufficient by itself as it does not relate to seroprotection."[544] "CBER pointed out that in absence of a reference standard … an acceptable biologically relevant cutoff is that of the P[laque]R[eduction]N[eutralization] assay."[545] CBER also "request[ed] that individual titers are identified in the relative range around the cutoff in the P[laque]R[eduction]N[eutralization] and ELISA in order to confirm that these two assays are categorizing sera in a comparable fashion."[546] The summary memo also documented that "[i]f … 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."[547] Merck was given a choice; it could try to correlate the ELISA cutoff to PRN data, or it could use a four-fold rise criterion[548] in setting the ELISA cutoff.[549] Following the October 2001 teleconference, Dr. Morsy inquired whether the correlation analysis had to wait until the investigation of the Form 483 regarding deficiencies in the testing in Dr. Krah's lab was complete. Dr. Morsy's summary stated: "Dr. Carbone suggests we conduct the correlation with the data on file – she has no real sense yet for when the

[542] *See* Section III.B.3.b.(1)(a) above describing the role of the serostatus cutoff in the assay.
[543] *See* MRK-KRA00233626 at '78 (a serostatus cutoff of 10 Ab was recommended as "the lowest antibody concentration that can be reliably distinguished from a panel of negative samples."). Merck had set the cutoff at the lowest concentration that would allow it to distinguish a negative sample from a positive one. If a sample had an antibody concentration that was equal to or less than a known negative sample, it was classified as negative. *See id.* If the sample had an antibody concentration that was higher than the negative sample, it was classified positive. *Id.*
[544] MRK-KRA00561452.
[545] *Id*. at '53.
[546] *Id.*
[547] *Id*. at '54.
[548] A four-fold rise criteria would require a "four-fold" increase in antibody titer between the child's pre-vaccination and post vaccination blood samples. For example, if the child's antibody titer before vaccination was 10 Ab, the post-vaccination titer would have to be four times that number (10x4), or 40. In that instance, the "cutoff" using a four-fold criterion would be 40 Ab.
[549] Deposition of Keith Chirgwin, January 26, 2017, 316:16-318:10.

investigation/evaluation in her lab will be completed."[550] In January 2002, Dr. Patrick Brill-Edwards, an attendee to the October 2001 teleconference with FDA,[551] in a draft memo to Dr. Chirgwin discussing the ProQuad filing strategy, identified the cutoff for the mumps ELISA assay as a "Key Regulatory Issue" and stated: "CBER would like the rationale for the new cutoff to be linked to a biologically relevant reference standard."[552] The memo further stated: "CBER requested that the [WT] ELISA results be compared to the mumps Plaque Reduction Neutralization (PRN) assay."[553]

227.1. An internal Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, cc'd to MRL's Associate Director, Vaccine Biometrics Research, Dr. Joe Antonello, MRL's Senior Director, Project Planning and Management/Vaccine Integration, Dr. Joye Bramble, MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL's Vice President, Vaccine & Biologics Research, Emilio Emini, MRL's Senior Vice President, Clinical & Regulatory Development, Dr. Doug Greene, MRL's Principal Investigator, Dr. David Krah, MRL's Biometrician, BARDS Dr. Jonathan Hartzel, MRL's Senior Director, Health & Economic Statistics, Joseph Heyse, MRL's Senior Vice President, Project & Vaccine Integration, Dr. Dorothy Margolskee, MRL's Executive Director, Vaccine Integration, Dr. Florian Schodel, MRL's Director, BARDS, Timothy Schofield, MRL's Executive Director, Virus & Cell Biology, Dr. Alan Shaw, among others, with the subject: "CBER teleconference (October 16, 2001): Measles, Mumps, and Rubella ELISAs," dated October 19, 2001, stated:

[550] MRK-KRA00561452 at '54.
[551] MRK-KRA00561452
[552] MRK-KRA00818776 at '78 (emphasis added).
[553] *Id.*

> Executive Summary: …
>
> 2. Mumps ELISA assay….
>
> CBER requests additional justification for the cutoff 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 the cutoff in the PRN and ELISA in order to confirm that these two assays are categorizing sera in a comparable fashion.[554]

MRK-KRA00561452 (emphasis added).[555]

227.2. The memo also stated:

> Summary Discussion: …
>
> Wild type mumps ELISA cutoff: …
>
> - Biological relevance of the 10 Ab ELISA cutoff:
>
> CBER pointed out that in 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

[554] *See* Section VII.B above. Because ELISA is more sensitive than a neutralization test, it will return false positive and false negative results. If the assays are "categorizing sera in comparable fashion," then a negative measured in one assay would also be scored as negative in the other. Similarly, a positive in one assay, should be positive in the other. If they are not categorizing the samples in the same way, the results are "discordant." Where the cutoff is set impacts whether the assays will score the results in the same way. As Merck's document shows, FDA's request was focused on samples around the cutoff. This would include children whose results were just above, or just below, the cutoff being considered. If the cutoff was too low, the assays would not score the samples in the same way. *See also*, Section VIII above, discussing Merck's testing of the samples in the preliminary subset with titers "around the cutoff" (low level responders and non-responders).

[555] A document titled "Minutes M-M-R®II Data Management TEAM CSR Tracking Meeting, dated May 8, 2002, stated: "Joe Antonello, Jonathan [Hartzel] and Manal [Morsy] are creating a document to justify the mumps wild-type ELISA cutoff. The document will show a comparison of ELISA data to PRN data using PRN as the gold standard." MRK-KRA01521665 at '67.

cutoff, an acceptable biologically relevant cutoff is that of the PRN assay. CBER requires a comparison between the PRN and the ELISA cutoff. …

Merck Response: …

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 legacy ELISA assay is consistent with the outcome of this new assay. …

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.

MRK-KRA00561452 at '53 (emphasis added).

227.3. The memo also stated:

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. …

Id. at '54 (emphasis added).

227.4. MRL's former Vice President, Worldwide Regulatory Affairs, Dr. Keith Chirgwin testified as follows:

> *Q. And so, back to my original question. In this teleconference, CBER gave Merck a choice with regard to setting the serostatus cutoff for its ELISA assay used in Protocol 7, it could either correlate the cutoff to the PRN assay or use a fourfold criteria for setting the serostatus cutoff, correct?*
>
> *A. Correct.*

Deposition of Keith Chirgwin, January 26, 2017, 316:15-23.

227.5. A draft Merck memo from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Patrick Brill-Edwards, to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, with the subject "Filing Strategy for ProQuad, dated January 31, 2002, stated:

> Key Regulatory Issues …
> Alternate cutoffs for … mumps assays:
> CBER has indicated … specific assay criteria would be necessary in Phase III studies.
> The outstanding issues are … Justification is required for the new mumps cutoff of 10 ELISA antibody 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. ... This comparison should provide the evidence that the ELISA cutoff correlates the PRN.

MRK-KRA00818776 at '78 (emphasis added).

228. Dr. Morsy's October 19, 2001 memo, the testimony of Dr. Chirgwin and Dr. Brill-Edwards' January 31, 2002 memo evidence the information the FDA required Merck to provide to justify the WT ELISA cutoff. It can be summarized as follows:

- an ELISA cutoff that correctly classified a sample as negative or positive was insufficient because it did not relate to seroprotection.[556]
- the rationale for the cutoff in the new WT ELISA assay needed to be linked to a biologically relevant reference standard.[557]
- In the absence of a reference standard for a sero-protective level for mumps, the best surrogate, or substitute, was to relate the WT ELISA assay cutoff to a neutralization assay cutoff which the FDA viewed as an acceptable biologically relevant cutoff.[558]
- an analysis comparing Merck's WT ELISA assay to Merck's AIGENT would be acceptable.[559]
- after conducting the comparison between the WT ELISA assay and AIGENT assay, if there continued to be uncertainty about the biological relevance of the WT ELISA cutoff Merck proposed, a cutoff would be set using a four-fold rise criteria.[560]
- Merck had a choice of either demonstrating a biologically relevant cutoff with its comparison between the WT ELISA assay and the AIGENT, or using a four-fold criteria for setting the serostatus cutoff as a measure of a significant response to the vaccination.[561]

2. Merck Wanted to Use Protocol 007's AIGENT to Support the WT ELISA 10 Ab Cutoff, Not Have the Four-Fold Rise Criterion

229. In January 2002, while Merck's ability to use Protocol 007's AIGENT data for the end expiry decision was still uncertain, Merck's Dr. Chirgwin contacted FDA's Dr. Carbone to discuss the WT ELISA cutoff issue. Dr. Chirgwin "reminded her that the mumps ELISA cutoff issue was linked to the mumps PRN assay"[562] because FDA "required [justification] for the new

[556] MRK-KRA00561452 at '53.
[557] MRK-KRA00818776 at '78.
[558] MRK-KRA00561452 at '53.
[559] *Id.*
[560] MRK-KRA00561452 at '54.
[561] *Id.*; Deposition of Keith Chirgwin, January 26, 2017, 316:16 -318:10.
[562] MRK-KRA00071388 (emphasis added).

mumps cutoff of 10 ELISA antibody units."[563] Merck was "in the process of writing study reports for MMRV [ProQuad] and therefore it [was] becoming increasingly urgent that we reach closure on the issue."[564] According to Dr. Chirgwin's record of the conversation, from Dr. Carbone's perspective, "'there [was] nothing really scientifically wrong' with our mumps P[laque]R[eduction]N[eutralization] assay and she would be willing to use the mumps PRN data as they currently exist as a basis for discussion on the mumps ELISA cutoff."[565] Thereafter, as Merck prepared the submission for FDA review, Dr. Antonello prepared a presentation to the Vaccine Advisory Committee[566] that stated a 10 Ab cutoff in the WT ELISA assay was "desirable from Merck's perspective."[567] Merck personnel also prepared a "Risk Table" for the impact to ProQuad if 10 Ab was not accepted as the WT ELISA cutoff. The "risk impact" would be "high" because "Mumps seroconversion rates will be lower than what is claimed in the label."[568]

229.1. A Merck memo from MRL's Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, with the subject: "M-M-R®II (BB-IND 1016) and [ProQuad] (BB-IND 7068): Summary of discussion with [FDA's] Dr. Kathryn Carbone about the mumps PRN assay and the measles ELISA cutoff, dated January 18, 2002, stated:

[563] MRK-KRA00818776.
[564] MRK-KRA00071388.
[565] *Id.*
[566] The Vaccine Assay Committee (VAC) was formed in 2002 as a technical peer review committee with the objective and scope "to provide a forum for the in-depth review of all data used to support clinical assays and approve proposals/plans for these analytical assays to support clinical endpoint evaluations. MRK-KRA00279983 (Revised Vaccine Assay Committee scope statement); MRK- KRA00279981 (October 8, 2002 cover email). The VAC was co-chaired by Dr. Emilio Emini (Vaccine Research) and Dr. Florian Schodel (Vaccines Clinical Research). *Id*. at '84.
[567] MRK-KRA01583397 at '18.
[568] MRK-KRA00544510 (emphasis added).

> On January 11, 2002 I spoke with Dr. Kathryn Carbone …
>
> I reminded her that the mumps ELISA cutoff issue was linked to the mumps PRN assay. CBER had suggested that we justify the mumps ELISA cutoff with the mumps PRN data. We are now in the process of writing study reports for [ProQuad] and therefore it is becoming increasingly urgent that we reach closure on the issue. Dr. Carbone stated that in her opinion there was no reason not to pursue the mumps ELISA cutoff discussion in parallel before we have reached closure on the mumps compliance issue.[569] From her perspective, "there is nothing really scientifically wrong" with our mumps PRN assay and she would be willing to use the mumps PRN data as they currently exist as a basis for discussion on the mumps ELISA cutoff. …

MRK-KRA00071388 (emphasis added).

229.2. A presentation by MRL's Statistician, Dr. Joseph Antonello, to the Vaccine Advisory Committee titled, "Assessment of the Mumps WT ELISA Cutoff," dated April 14, 2002, stated:

> Conclusions
>
> - Mumps WT ELISA Cutoff of 10 Ab units is desirable from Merck perspective
> - The AIGENT assay supports the WT ELISA cutoff of 10Ab units …

MRK-KRA01583397 at '18 (emphasis added).[570]

229.3. An email from MRL's Project Planning Manager, Joan Staub, to MRL's Executive Director, Biologics/Vaccines Clinical Research, Dr. Florian Schodel, Dr. Barbara Kuter, Dr. Patrick Brill-Edwards, Dr. Keith Chirgwin, John Hennessey, Christopher Petroski, and Dr. Alan Shaw, among others, with the subject: "ProQuad Risk Table," dated April 16, 2002, stated: "I

[569] *See* Section VIII.L above. In January 2002, following the Form 483 in Dr. Krah's lab, the FDA was still considering whether to allow the data to be used for an end expiry decision.
[570] *See also* MRK-KRA01583396 (cover email circulating the memo).

have been working on this Risk table all morning – now I'm thoroughly depressed!" MRK-KRA00544509 (emphasis added).

229.4. An email from John Hennessey replying to all recipients of Ms. Staub's April 16, 2002 email attached "ProQuad Risk Assessment APR02.doc." *Id.* The attachment stated:

Outstanding Issues/risks for ProQuad® FROZEN CTD Submission and Licensure

Function	Risk	Probability of Occurrence	Programs Affected	Impact	Risk Minimization	Contingency Plans
	CBER does not accept our proposed Mumps WT ELISA cut-off	Moderate	ProQuad® FROZEN ProQuad® REFRIGERATED	High: Mumps seroconversion rates will be lower than what is claimed in the label	• Engage CBER in discussions	• Amend Data Analysis Plan to account for higher Mu cut-off and impact to power.

MRK-KRA00544510.

230. In my opinion, FDA's Dr. Carbone's statement documented in Dr. Chirgwin's record of conversation that "'there is nothing really scientifically wrong' with our mumps PRN assay"[571] is consistent with Dr. Carbone's notes from the unannounced inspection to Dr. Krah's lab in August 2001 that resulted in the Form 483 in which she stated: "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."[572] Furthermore, according to Merck's documents, if Merck's proposed WT ELISA cutoff of 10Ab was not accepted by the FDA, the seroconversion rates Merck would report in clinical studies using the WT ELISA would be lower than the seroconversion rates on the MMRII label.

3. Merck Prepared a Comparison of the AIGENT and the WT ELISA

231. After obtaining FDA approval to conduct the correlation analysis,[573] Merck statisticians compared the results of the children in the Protocol 007 preliminary subset analysis

[571] MRK-KRA00071388.
[572] MRK-KRA02021754 at '56 (emphasis added).
[573] MRK-KRA00561452 at '54.

by the AIGENT and the WT ELISA to support Merck's recommendation of 10 Ab as the WT ELISA cutoff. This would allow Merck to use the WT ELISA as a substitute for the AIGENT or another neutralization assay in the future. As Merck came close to finalizing the submission to send to the FDA with its correlation analysis, "things … got[] stuck with regard to the table that Joe [Antonello] presented at the VAC [Vaccine Advisory Committee] …showing the breakdown by ELISA strata of the discordant PRN neg[ative]/ELISA pos[itive] sera. The large majority of these discordants had ELISA titers <40 and one concern is that presenting the data in this fashion may prompt CBER to request that the ELISA cutoff be raised."[574] "If we are unable to provide sufficient reassurance about the clinical relevance of the ELISA cutoff (which in Kathy [Carbone]'s mind means linking this to the PRN) then we may end up with some type of a fold-rise criterion which I assume we would rather avoid if possible."[575] "If CBER required a fourfold rise in titer (defined as less than 10 to greater than or equal to 40), the seroconversion rates for these studies would range from 80.9 percent to 85.2 percent."[576] Dr. Morsy removed two tables from Dr. Antonello's analysis as "too distracting."[577]

231.1. An email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to MRL's Biostatistician, BARDS, Dr. Jonathan Hartzel, MRL's Associate Director, BARDS, Joseph Antonello, MRL's Clinical Monitor, Protocol 007, Dr. Luwy Musey, MRL's Principal Investigator, Dr. David Krah and MRL's Executive Director, Virus & Cell Biology, Dr. Alan Shaw, cc'd to: Keith Chirgwin, Joye Bramble, Keiko Simon, Florian Schodel,

[574] MRK-KRA00544296. *See also* MRK-KRA00561452 ("CBER had "request[ed] that individual titers [be] identified in the relative range around the cutoff in the PRN and ELISA in order to confirm that these two assays are categorizing sera in a comparable fashion.").
[575] *Id*.
[576] MRK-KRA00561418 (email attachment titled, "Distribution of 6-week Mumps Titers Using the Mumps Wildtype ELISA Assay"); MRK-KRA00561416 (September 28, 2001 cover email from Jonathan Hartzel to Joseph Antonello).
[577] MRK-KRA00544296.

Holly Matthews, and Timothy Schofield, with the subject: Draft – Mumps cutoff document," and attachments "Attachment 1.doc,"[578] "Attachment 2.doc,"[579] "Attachment 2 – Original Data Listings 19 Mar2002.xls,"[580] "Deleted Section from Attachment 2.doc," and "DRAFT 4-25 Mumps cutoff document for CBER submission,"[581] dated April 25, 2002, stated:

> Please review the document attached. …
>
> The document must go out for final review tomorrow … so that … we can submit next week to meet both MMRII and ProQuad hostage timelines!
>
> I have expanded the CC list to allow those who will be reviewing this document to get a head start before the weekend.

MRK-KRA00544512 (emphasis added).

231.2. Dr. Morsy's April 25, 2001 email also stated:

> Joe [Antonello] also please confirm that the attachments enclosed are in fact the audited documents (I have deleted as you know tables 6c and 6d[582] and their corresponding text from attachment 2 [April 8, 2002 memo from Antonello to Shaw, 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'[583] AIGENT Results"] – I have attached the tables and text

[578] MRK-KRA00544540 (March 18, 2002 memo from Dr. Antonello to Dr. Shaw with subject "Testing the Mumps Wild Type ELISA Standard and Control Samples in the Mumps Anti-IgG Enhanced Plaque Reduction Neutralization Assay.").
[579] MRK-KRA00544529 (April 8, 2002 memo from Antonello to Shaw, 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").
[580] MRK-KRA00544539 (Excel file titled "MMRII Data Listing Comparison between Mumps WT ELISA and AIGENT Assays").
[581] MRK-KRA00544515 ("DRAFT" General Correspondence Response to CBER Comments").
[582] MRK-KRA00544514.
[583] Following the August 2001 Form 483 regarding "changes being made without justification" in the AIGENT testing, Merck referred to the changes in the assay results as "corrected" and the data before those changes as "original" results. MRK-KRA00064005 at '12; *id.* at '09 (BB-IND 1016, Serial 80, "Although we believe changes were made for appropriate reasons, we understand CBER's concern regarding the lack of documented justifications. Therefore, we propose, and seek CBER's concurrence with the use of the original PRN assay results in the evaluation of the 007 trial.") (emphasis added). FDA accepted Merck's proposal to use the "original" results.

> deleted for your reference – which I would like to replace as we discussed with a table showing discrepancies within std ranges instead of cutoffs) …

MRK-KRA00544512 (emphasis added). .

231.3. An email from MRL's Senior Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin to MRL's Executive Director, Biologics/Vaccines Clinical Research, Dr. Florian Schodel, cc'd to Joan Staub, with the subject: "FW: Draft document Mumps cutoff," attached four documents: "DRAFT Mumps cutoff document for CBER submission.doc," "Attachment 1.doc," "Attachment 2.doc," and "CBER communication 10-16-01 ELISA teleconference minutes.doc," dated May 7, 2002, stated:

> Joe I removed tables 6 c and 6 d and information referring to them from the 007 ELISA and PRN comparison document (Attachment 2) – too distracting. …
>
> Thanks mm

MRK-KRA00544296 (emphasis added).

231.4. The May 7, 2002 email from Chirgwin incorporating the forwarded email also stated:

> This is the latest version of the mumps cutoff CBER response from Joe [Antonello]. As per the previous email message, it appears that things have gotten stuck with regard to the

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MRK-KRA00779484. There were different numbers of subjects with reportable post-vaccination titers in the "original" and "corrected" data sets. *Compare* MRK-KRA00126468 at '510 ("Comparison Between the Mumps Wild Type (WT) ELISA (SOP910.0096) and the Anti-IgG Mumps Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489) Using the "Original" Results" stated: "Of the 565 subjects tested in the AIGENT assay … 513 had reportable post-vaccination titer.") (emphasis added) *with* MRK-KRA00759120 at '21 ("Comparison Between the Mumps Wild Type (WT) ELISA (SOP 910.0096) and the Anti-IgG Mumps Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489) Using the "Corrected" Results," stated: "Of the 565 subjects tested in the AIGENT assay … 555 had a reportable post-vaccination titer.") (emphasis added). *See also* MRK-KRA00544820 (Email from Dr. Antonello with the subject "Comparison of the WT ELISA and AIGENT results from the MMRII 007 Trial stated: "Having performed these analyses, my sense was that on the whole, the 'corrected' AIGENT results are 'cleaner/closer to the truth' than are the 'original' results and provide for a more accurate comparison between assays. . . . While for the post-vaccination samples there is little difference between 'original' and 'corrected' results, for the pre-vaccination samples, the ELISA titers suggest that the 'corrected' results are more accurate than the 'original' results.").

> table that Joe presented at the VAC several weeks ago showing the breakdown by ELISA strata of the discordant PRN neg/ELISA pos sera. The large majority of these discordants had ELISA titers <40 and one concern is that presenting the data in this fashion may prompt CBER to request that the ELISA cutoff be raised.
>
> I agree that CBER did not specifically indicate that we would be required to demonstrate concordance, however, in reviewing the meeting minutes from last October (attached below), it is also clear that they are going to look closely at how sera with values around the cutoff are classified in the two assays.[584] At least based on October's discussion, if we are unable to provide sufficient reassurance about the clinical relevance of the ELISA cutoff (which in [FDA's] Kathy [Carbone]'s mind means linking this to the PRN) then we may end up with some type of a fold-rise criterion which I assume we would rather avoid if possible.[585]

Id. (emphasis added).

231.5. The document titled "Deleted Section from Attachment 2.doc," attached to Morsy's April 25, 2002 memo, stated:

[584] *See* MRK-KRA00561452 ("CBER requests that individual titers are identified in the relative range around the cutoff in the PRN and ELISA in order to confirm that these two assays are categorizing sera in a comparable fashion") (emphasis added).

[585] *See also* MRK-KRA00561418 (document titled "Distribution of 6-week mumps titers using the Mumps Wild-type ELISA assay" attached to email from Jonathan Hartzel to Joseph Antonello stated: "If CBER required a fourfold rise in titer (defined as less than 10 to greater than or equal to 40), the seroconversion rates for these studies would range from 80.9% to 85.2%.") and Deposition of Joseph Antonello, August 3, 2017, 249:6-11 (*Q. Is that a correct statement? A. To the extent that Jon is correct, yes. I mean, it's Jon's message. Q. And you have no reason to doubt his math, do you? A. Jon? No.*).

A further analysis of the post-vaccination titers is provided in Tables 6c and 6d. Table 6c shows the frequency distribution of AIGENT titers for (a) all AIGENT positive post-vaccination samples, and (b) the subset of ELISA negative and AIGENT positive discordant post-vaccination samples. The relative distributions of Table 6c indicate that, given a sample has tested positive in the AIGENT assay, the likelihood that that sample will test negative in the ELISA decreases with increasing AIGENT titer. Table 6d shows the frequency distribution of ELISA titers for (a) all ELISA positive post-vaccination samples, and (b) the subset of ELISA positive and AIGENT negative discordant post-vaccination samples. The relative distributions of Table 6d indicate that, given a sample has tested positive in the ELISA, the likelihood that that sample will test negative in the AIGENT assay decreases with increasing ELISA titer.

Table 6c

M-M-R®II 007 Frequency Distribution of AIGENT Post-vaccination Positive Titers

AIGENT Titer	Subset of ELISA Negative Samples	All Samples	Percent
≤256	3	17	17.6%
512	4	59	6.8%
1024	1	98	1.0%
2048	3	128	2.3%
>4096	0	175	0.0%
	11	477	

Table 6d

M-M-R®II 007 Frequency Distribution of ELISA Post-vaccination Positive Titers

ELISA Titer	Subset of AIGENT Negative Samples	All Samples	Percent
10<=titer<20	6	25	24.0%
20<=titer<40	8	68	11.8%
40<=titer<80	5	146	3.4%
80<=titer<160	2	161	1.2%
160<=titer<320	1	74	1.4%
320<=titer	0	14	0.0%
	22	488	

MRK-KRA00544514 (highlight added).

231.6. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

Q. If you flip the page to Table 6c and 6d, what are those tables?

A. It says it's frequency distribution for Table 6c AIGENT post-vaccination positive titers. So there's a subset of ELISA negative samples and all samples. So post-vaccination positive. Here we are. So I'm just trying to piece it together. So here there are 511, at least I'm looking in the "All Samples" column. So there are 511 samples listed in Table 6c. And that corresponds to the 511 post-vaccination positive samples in Table 3. So that 511 refers to the 511 in Table 3 that were positive, post-vaccination samples positive in the AIGENT. And then the left-most column, the AIGENT titer, shows how many samples of that 511 that were positive, 17 were less than 256, 62 were 512 and so on.

That gives you the 511. So that shows you the distribution of the post-vaccination positive titers. So you might look at that and say 1, 2, 200, 300, 400, you know, maybe look at it the other way, 90 out of 50 is less than 10 percent. You know, 90 percent of your – I shouldn't say that. 90 out of 50 is closer to 20 percent. Over 80 percent of your samples had a titer greater than 1,024 that were positive, I mean. So that's just the distribution of the results, post-vaccination results. Then in the column that says, "Subset of ELISA Negative Samples," it's just telling you of those post-vaccination samples that were positive in the AIGENT, there were 17, three of those were negative in the ELISA. Of those that were 512, there were 62, four were negative in the ELISA. And so on. The last column are the percentages. In this case it's the three divided by the 17, will give you that 17.6 percent. Four divided by 62, 6.5 percent and so on. So what this is kind of telling you is that where there are discordances, where it's post-vaccination positive in the AIGENT, that the highest percentage of discordances are occurring with the low titered AIGENT samples. So that percentage moves down as you get to the higher tittered samples. So you're less likely to have a misclassification for a low titered sample than a high titered sample between the two assays, which makes sense. That if they're -- you're going have a misclassification, it's more likely to occur for a low titered sample than a high titered sample.

Q. So that the likelihood of a misclassification which is also the same as a discordant pair --

A. Yes.

Q. -- is more likely to happen around the cutoff than it is when you get farther away from the cutoff. Is that correct?

A. Yes.

Deposition of Deposition of Joseph Antonello, August 3, 2017, 201:17-204:9 (emphasis added).

232. Table 6c evidences that there was 17.6% disagreement between the two assays where the sample was AIGENT positive/ELISA negative at the titer closest to the cutoff. Table 6d evidences that there was 24% disagreement between the two assays when the sample was

AIGENT negative/ELISA positive at the titer closest to the cutoff. Furthermore, according to Dr. Antonello's testimony, the two assays are more likely to classify samples around the cutoff differently. The higher the cutoff the less disagreement there is between the results.

4. Merck Submitted Serial 86 Requesting FDA Concurrence With Merck's Use of a 10 Ab Cutoff in its WT Mumps ELISA Assay

233. Merck submitted BB-IND 1016, Serial 86, on June 10, 2002, seeking FDA concurrence with Merck's choice of 10 Ab as the WT ELISA cutoff.[586] Dr. Antonello's Tables 6c and 6d were not included in his report. The conclusions in Serial 86 stated: "There is good agreement between the AIGENT and Mumps WT ELISA assays with regard to performance of controls and Standards" and "There is good agreement between the Mumps WT ELISA and the AIGENT assay 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."[587] A separate attachment, in another part of the submission included the same data as Table 6d, organized differently, to address the question of the expected mismatch classification rates due to assay variability.[588]

233.1. A letter marked "Serial No. 86," from MRL's Associate Director, Worldwide Regulatory Affairs, Manal Morsy, to FDA's Director, CBER, Office of Vaccines Research & Review, Division of Vaccines and Related Products Applications, Kathryn Zoon, regarding "BB-IND 1016, Response to FDA Request for Information," dated June 10, 2002, stated:

> 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 cutoff and specifically to provide: …

[586] MRK-KRA00126468 at '474.
[587] *Id.*; *see also* Section III.B.3.b.(1)(a) above discussing the role of the serostatus cutoff.
[588] *Id.*; Deposition of Joseph Antonello, August 3, 2017, 306:10-309:23.

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.

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 (SOP910.0096) and the Anti-IgG Mumps Plaque Reduction Neutralization (AIGENT) Assay for Mumps (SOP 874.3489) Using the "Original"[589] AIGENT Results (Attachment 2).
3. Expected Mismatch Classification Rates Due to Assay Variability (Attachment 3).

…

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

[589] *See* footnote 582 above describing the "original" and the "corrected" data from the AIGENT preliminary subset analysis.

1016, protocol 007 – secondary objective – sent to CBER simultaneously with this submission).

MRK-KRA00126468 at ’68-69 (emphasis added).

233.2. MRL’s Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello testified as follows:

Q. Did you perform these correlation studies because CBER wanted Merck to justify that the 10 Ab serostatus cutoff it was using on the wild type mumps ELISA by comparing it to the AIGENT results?

Defense Counsel: Objection to form.

A. Yeah, I did the comparison. I think it was, if not requested by Merck internally, requested by CBER. So I did the comparison because I was asked to do it.

Q. But do you have any understanding as to why you were asked to do it?

A. The motivation for it? To see how the two assays compared. Beyond that, how that information was going to be used, no.

Deposition of Joseph Antonello, August 3, 2017, 214:3-214:22 (emphasis added).

233.3. Serial 86 also stated:

Merck Responses/Comments:

1. CBER requested additional information regarding the cutoff chosen for the Mumps WT ELISA comparing the ELISA cutoff to the AIGENT 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 reference sera to assist in the comparison of results between the two assays. …

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.[590]

MRK-KRA00126468 at '74 (original bold removed, underline added).

233.4. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

Q. *Do you recall what serostatus cutoff was used in the AIGENT assay?*

A. I believe it was 32. A titer of 32.

Q. Was that serostatus cutoff a protective level above which there was a view that you would be protected from the disease and below which you would not?

A. Yeah, I don't believe any -- they had that information. So I don't think it was ever considered a protective level.

Deposition of Joseph Antonello, August 3, 2017, 32:16-33:1 (emphasis added).

233.5. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, also testified as follows:

Q. Was there any relevance to protection from the disease that came from the serostatus cutoff calculation that you performed?

Defense Counsel: Objection to form.

A. Can you repeat the question?

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

A. No. I don't think we knew -- you know, it's known what a protective level, antibody level is. Even that depends on which assay and which standard, what you need a standard to judge that. So, no, it's not indicative of protection against the virus.

Deposition of Joseph Antonello, August 3, 2017, 150:18-151:12 (emphasis added).

233.6. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, also testified as follows:

Q. So what was the serostatus cutoff that was used for the wild type mumps ELISA?

[590] Merck's Response to 1 (A) is supported by Attachment 1. MRK-KRA00126468 at '83.

A. I believe it was 10 antibody units.

Q. Was that a protective level?

A. No. I don't -- I'm not aware of it being identified as protective level.

Deposition of Joseph Antonello, August 3, 2017, 33:15-22 (emphasis added).

233.7. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, also testified as follows:

Q. Is the 10 Ab serostatus cutoff that you calculated in any way relevant to the seroprotective level?

A. I don't know what the sero – I don't know a seroprotective level for mumps or what the seroprotective level is so...

Q. But in your work in calculating what you thought was the appropriate serostatus cutoff level for the mumps wild type ELISA assay, did seroprotection play any role in that exercise?

A. Not that I'm aware of.

Q. Well, you were the one that calculated it. Right?

A. Yes. Right.

Q. So in your work in calculating it, did you take into account in any way the level of seroprotection that would be measured by the particular serostatus cutoff that you were calculating?

A. I don't believe I did.

Q. Why not?

A. Because I don't believe a seroprotective level was defined for mumps. It was for, I remember, measles and rubella, and we used those for serostatus cutoffs for those assays, but there was not seroprotective level defined for mumps.

Q. And so because of that, you didn't think it was in any way useful to account for seroprotection in setting the serostatus cutoff –

Defense Counsel: Objection.

Q. -- for that assay?

Defense Counsel: Misstates the record.

A. I was not – there was not, to my knowledge, a seroprotective level. So -- for mumps. It so it couldn't be used -- since one did not exist, it couldn't be used to set the serostatus cutoff.

Q. So if the purpose of the serostatus cutoff was irrelevant to seroprotection, what was the purpose in terms of your work in setting it?

Defense Counsel: Objection to the form.

A. What was the purpose in setting it? The purpose of the serostatus cutoff was to do a good job in classifying likely negative samples as negative and likely positive samples as positive.[591]

Deposition of Joseph Antonello, August 3, 2017, 66:19-68:24 (emphasis added).

233.8. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, also testified as follows:

Q. As far as your performing the calculation, did it give you any comfort that the 10 Ab serostatus cutoff that you calculated was relevant to seroprotection?

Defense Counsel: Same Objection.

A. Yeah, I don't know what is protection. I did the comparison that was requested and showed how the two assays relate. What that means beyond that, that's not my area of expertise, how to interpret the results in that sense.

Q. Did you gain any greater confidence in -- that your selection of 10 Ab was the appropriate serostatus cutoff for the wild type mumps ELISA from the correlation you made between the AIGENT and ELISA tests?

Defense Counsel: Objection to the form.

A. Can you repeat the question?

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

A. In the sense that testing that we looked at pre-vaccination samples and post-vaccination samples in the ELISA, that it did a good job discriminating in the ELISA,

[591] *Compare* MRK-KRAA00561452 (Merck's summary of October 2001 meeting stated: "CBER requests additional justification for the cutoff 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.") (emphasis added).

PRN aside, just within the ELISA itself, gives me confidence -- gave me confidence in the wild type ELISA. Not because of how it related to the PRN but how it performed on pre-vaccination and post-vaccination samples.

Q. So is your testimony that it gave you greater confidence because using the 10 Ab serostatus cutoff provided --

A. Was able to discriminate.

Defense Counsel: Let him finish his question.

Q. I'm not following how, if you're putting the AIGENT part of the comparison to the side and you're just focusing on the ELISA, how did that give you greater confidence that the 10 Ab used in the ELISA was the appropriate cutoff?

A. AIGENT aside -- I mean, AIGENT could have been, you know, let's just say nonsense results, everything in the AIGENT comes out negative, pre and post. Everything in the AIGENT comes out positive pre/post. So regardless of what I got in the AIGENT, I tested, you know, 1,000 samples in the wild type ELISA and the pre[positive]s, it called very high percentage of those negative, and the posts it called a high percentage of those positive. So I've got 1,000 samples that I just tested, I knew pre and post, and it performed well in the wild type ELISA. So that gives me confidence in the ELISA. How it performed relative to the AIGENT is a separate question. The AIGENT could have been -- could be truth or it could be off base. That doesn't make the ELISA right or wrong.

Deposition of Joseph Antonello, August 3, 2017, 236:3-238:22 (emphasis added).

233.9. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, also testified as follows:

Q. I'm going to ask the question again, because you gave me the answer with respect to CBER. I'm asking for your opinion, you. Did it give you greater confidence that you had -- that -- start again. Did the comparisons you made between the AIGENT test and the wild type mump ELISA test give you greater confidence that the 10 Ab serostatus cutoff for the wild type mumps ELISA was the proper ELISA -- was the proper cutoff?

Defense Counsel: Objection. Asked and answered. He did answer for himself.

A. I don't know what a protective level is. So for me I can't say that 10 is the correct protective level. I don't know what the protective level is. So it doesn't give me greater confidence in that sense that 10 is a protective level.

Deposition of Joseph Antonello, August 3, 2017, 239:20-240:15 (emphasis added).

233.10. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, also testified as follows:

Q. So is it your opinion that the wild type mumps ELISA assay was a more reliable assay than the AIGENT assay?

Defense Counsel: Objection to form.

A. In my opinion, it's a less variable assay. I think it will produce more consistent results than the AIGENT assay. And in that regard -- in that sense it's a preferred assay.

Q. Which assay, if either, do you believe offers a better measure of actual protection from the disease?

Defense Counsel: Objection to the form.

A. I couldn't answer that. I don't know.

Deposition of Joseph Antonello, August 3, 2017, 170:6-24 (emphasis added).

233.11. Serial 86 also stated:

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 assays are categorizing sera in a comparable fashion. …

MRK-KRA00126468 at '76 (emphasis added).

233.12. Serial 86, in response to CBER Request 1 (B) stated:

> … Merck conducted comparison between the Mumps WT ELISA (SOP 910.0096) and the AIGENT assay for Mumps (SOP 874.3489) Using the "Original"[592] AIGENT Results (Attachment 2).[593]

MRK-KRA00126468 at '76.

233.13. Serial 86, in response to CBER Request 1 (B) stated:

> 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).

MRK-KRA00126468 at '78 (emphasis added).

233.14. Serial 86, in response to CBER Request 1 (B) stated:

> Conclusion:
> There is good agreement between the Mumps WT ELISA and the AIGENT assay 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 the cutoffs of both assays confirms that both assays are categorizing sera in a comparable fashion.

MRK-KRA00126468 at '78 (original bold removed, underline added).

233.15. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

> *Q. Did the correlation that you performed between the wild type mump ELISA assay and the AIGENT assay results provide, in your opinion, any support that the 10 Ab serostatus cutoff was relevant to seroprotection?*
>
> *Defense Counsel: Object to the form.*

[592] *See* footnote 582 above describing the difference between the "original" and the "corrected" results from the AIGENT preliminary subset analysis.
[593] The "Data for Attachment #2" included the 600 subjects from the Protocol 007 preliminary subset testing. MRK-KRA00126468 at '20. This was the same subset used to support the validation submitted in Serial 63. *See* Section VIII.H above.

A. I don't know what a protective level is. So I don't -- I can't address what a protective level is and whether that's protective or not protective. It just showed the relationship between the two assays. CBER inferred that to mean that that's good. That's not my role.

Deposition of Joseph Antonello, August 3, 2017, 235:11-236:1 (emphasis added).

233.16. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

Q. Do you recall doing the same kind of comparison between the wild type ELISA assay and the AIGENT assay that we just discussed by using a 16 Ab cutoff instead of a 10 Ab cutoff?

A. I don't have that recollection, but I think I looked at it. It's, you know, maybe evaluated, we could evaluate using different cutoffs. And here it says, this is from me, that I did look at the 16 and you had better overall agreement between the two assays with 16 than you did with 10.

Deposition of Joseph Antonello, August 3, 2017, 216:20-217:6 (emphasis added).

233.17. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

Q. And is it your understanding that if Merck had selected for its wild type mumps ELISA assay a serostatus cutoff higher than 10 Ab, then the seroconversion rates that it measured in the assay would have decreased?

A. Yes. The higher you set the serostatus cutoff, the lower seroconversion rate.[594] *If you define seroconversion rate as a fourfold rise, the lower the seroconversion rate would have gone the higher you said set the cutoff.*

Deposition of Joseph Antonello, August 3, 2017, 251:16-252:1 (emphasis added).

233.18. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

[594] MRK-KRA00544510 at '11 (If FDA did not accept Merck's choice of 10 Ab for ELISA, the "high" impact would be "Mumps seroconversion rates will be lower than what is claimed in the label.").

Q. Now, we -- I showed you a document earlier in the day where you had discussed with CAS, C-A-S, [Clinical Assay Subcommittee] *a 16 Ab serostatus cutoff and the decision was -- with CAS was to go with the 10 Ab instead.*

A. Right.

Q. Do you know if what weighed into CAS's decision was the relative seroconversion rates that would have resulted between using the 10 Ab and the 16 Ab as the cutoff?

A. I don't know, can't speak for CAS, but for myself the 16 that we discussed, that made better agreement between the wild type ELISA and the AIGENT assay. It gave better overall agreement between the two assays. For me, the goal in setting the 10 Ab cutoff wasn't to choose the cutoff that gave the best agreement with the AIGENT assay. It was to choose the right cutoff, I don't want to say the right, but based on the wild type ELISA, not based on how the wild type ELISA compared to the neutralization assay. So I think, my opinion, don't change the cutoff for the ELISA to 16 so that it agrees with the AIGENT. I would think the decision would be to keep it at 10 because that's the cutoff that was -- that seems appropriate for that assay in and of itself.

Deposition of Joseph Antonello, August 3, 2017, 257:19-258:21 (emphasis added).

233.19. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello also testified as follows:

Q. But don't you run the risk if the serostatus cutoff is two low of classifying a true negative as a positive?

A. Absolutely.

Q. So why does increasing a serostatus cutoff make it more reliable when you're increasing the possibility of coming up with a false positive?

A. Increasing the cutoff doesn't make it more likely that you'll get a false positive. Increasing the cutoff decreases the probability that you'll get a false positive.

Q. And how does it do that?

A. So we're talking false positive. So a sample is really negative. So if I increase the cutoff from -- let's say I have a cutoff of 10, the sample is really negative. If I increase the

cutoff from 10 to 20, that sample is less likely to test positive. So increasing the cutoff reduces the probability of a false positive.

Deposition of Joseph Antonello, August 3, 2017, 259:23-260:18 (emphasis added).

233.20. Serial 86, Attachment 2, included the following tables:

Table 1 Serostatus Cross-Classification for M-M-R®II Pre and Post Vaccination Samples

Table 2 Sero-status Cross-Classification for M-M-R®II Pre Vaccination Samples

Table 3 Sero-status Cross-Classification for M-M-R®II Post Vaccination Samples

Table 4 Sero-Conversion Cross-Classification for M-M-R®II 007

Table 5a M-M-R®II 007 Pre-Vaccination Discordant Pairs AIGENT Negative and WT ELISA Positive Samples

Table 5b M-M-R®II 007 Pre-Vaccination Discordant Pairs AIGENT Positive and WT ELISA Negative Samples

Table 6a M-M-R®II 007 Post-Vaccination Discordant Pairs AIGENT Negative and WT ELISA Positive Samples

Table 6b M-M-R®II 007 Post-Vaccination Discordant Pairs AIGENT Positive and WT ELISA Negative Samples

Tabble 7a M-M-R®II 007 Sero-Conversion Discordant Pairs AIGENT Converters and WT ELISA Non-Converters

Table 7b M-M-R®II 007 Sero-Conversion Discordant Pairs WT ELISA Converters and AIGENT Non-Converters

MRK-KRA00126468 at '514-18.

233.21. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

Q. And then if you look at the tables that are attached, it goes up to 6b, but 6c and 6d were omitted. Do you know why?

A. No. They should not have been omitted.

Q. Can you think of any reason why they were omitted?

A. No. Is all the data still part of it? Like Table 7. What page was that again?

Q. Table 7 and (a) and (b) is there.

A. So the data Table 7a and (b). Okay.

Q. So, actually, if you go back and compare the two documents, the one that you had done and the one submitted to CBER, Tables 1, 2, 3, 4, are in both. 5a and (b) are in both. 6a and 6b are in both. And 7a and 7b are in both. Correct?

A. I wasn't checking, but yes.

Q. So the only tables that were omitted in this submission were Tables 6c and 6d. Correct?

A. It appears that way. I would have included those tables. I included them in the report. I think it was specifically to address the CBER comments that we were looking at. I think -- so yeah, I would have included it.

Deposition of Joseph Antonello, August 3, 2017, 272:10-273:14 (emphasis added).

233.22. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

BY DEFENSE COUNSEL:

Q. Dr. Antonello, I have a couple of questions. In response to Mr. Schnell's questions to you regarding Merck's submission of data to CBER, you responded to one of his questions about various charts and testified that charts 6c and 6d should have been submitted to CBER. Do you recall that testimony?

A. Yes.

Q. Are you aware of whether the data reflected in 6c and 6d was, in fact, or were, in fact, submitted to CBER?

A. Yes, they were. They weren't in that submission, but they were in subsequent submissions.

Q. And how were you aware of that?

A. In reviewing the CBER submissions.

Q. With regard to 6c, what, if any, document did you see that reflected the data from 6c being submitted?

A. 6c, I think it's in one of the submissions to CBER. So it's there.

Q. If I could direct your attention to Exhibit 12, which is the June 10, 2002 response. Do you have it in front of you?

A. Yes.

Q. If I could ask you to turn to Attachment 3, Table 2 which is on Bates number 761702.

A. Attachment 12?

Q. Attachment 3.

A. I'm sorry.

Q. Exhibit 12.

A. Exhibit 12, Attachment 3, number?

Q. The Bates number is 761702 right at the end.

A. 761 –

Q. The last page.

A. I'm sorry. Yes.

Q. After reviewing that table, can you tell me what your understanding is of what that data reflects?

A. Okay. This was submitted to CBER. Correct?

Q. Correct.

A. Do you have what was Table 6d so we can look at that?

Q. Exhibit 5.

A. Exhibit 5.

Q. Turn to page 544845.

A. 845. So that's Table 6d and this Table 2 –

Q. Yes, sir.

A. -- on 702 in the CBER submission contains the information that's presented in 6d, contains additional information. But the subset of ELISA positive -- of a subset of AIGENT negative samples that were ELISA positive are indicated here under the column says, "Observe Results," number of mismatched samples. So the only difference -- well, there's additional information, but another difference between the tables is that the ELISA titer groupings, it's a little finer grouping. So each -- one group in Table 6d

corresponds to two groups in Table 2. So if you look at the first two groups in the ELISA titer grouping, 10 to 14 and 14 to 20, that's the 10 to 20. And in Table 6d, it's indicated there were 6 samples that were AIGENT negative. If you look at the observed results, number of mismatched in those first two rows, it sums to 6. The next two rows cover the 20 to 40 titer range. And looking at the number of 6 mismatched samples, it's 8 in that range, and 8 is what's indicated in Table 6d. 40 to 80 are the next two groupings. And there it's five samples, and that corresponds to the five. So although Table 6c and 6d weren't included in that particular submission, they are included in subsequent submissions. The 6c, I think, in its exact form. 6d in just a different breakdown of the ELISA titer grouping, but the same information and -- the same information is there[595]

Deposition of Joseph Antonello, August 3, 2017, 306:10-309:23 (emphasis added).

233.23. Serial 86, Attachment 3, Table 2 stated:

[595] "CBER request[ed] 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: 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." MRK-KRA00126468 at '76. In addition to Dr. Antonello's analysis in Serial 86, Merck performed a similar comparison in March 2001 when it compared AIGENT and WT ELISA results for approximately 60 low level responders and non responders from this preliminary subset. The tables summarizing those results were not in Serial 86 or ever given to FDA. *See* Section VIII.E.2 above, and documents collected, including MRK-KRA00562247. In that analysis:
For the children who received the 4.9 dose, the seroconversion rate by WT ELISA was 81% and 43% by AIGENT.
For the children who received the 4.0 dose, the seroconversion rate by WT ELISA was 93% and 26% by AIGENT.
For the children who received the 3.7 dose, the seroconversion rate by WT ELISA was 40% and 20% by AIGENT.
Moreover, the results of assay testing outside the protocol in assay 46-01 were also not part of Serial 86.

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%

MRK-KRA00126468 at '37 (highlight added).

233.24. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello testified as follows:

BY PLAINTIFFS' COUNSEL:

Q. Yes.

A. Okay. Or follow up for the whole day?

Q. Just this narrow subject. I'd like to mark as Antonello-16, an e-mail, dated 5/7/2002 from Keith Chirgwin to Florian Schödel, Bates number 544296. And it seems to cut and paste an e-mail that was sent to you, Dr. Antonello, but it's not clear when or how, but it's cut and paste onto this e-mail from Keith Chirgwin. And the sentence that I want you to focus on it says: "Joe, I removed tables 6c and 6d and information referring to them from the 007 ELISA and PRN comparison document (Attachment 2) - too distracting." Do you remember getting this e-mail?

A. I don't remember it.

Q. Is there anything, in your opinion, that is distracting about Table 6c and 6d as you originally intended them to be included in your AIGENT wild type mumps ELISA assay comparison?

Defense Counsel: Objection to form.

A. No, I do not consider those tables distracting.

Q. Isn't it true, Dr. Antonello, that it had been discussed with you about replacing your tables with the table that you just looked at that your counsel showed you, and you still believed that Table 6c and 6d should have been included to any CBER submission?

A. I don't recollect those discussions, but I think that 6c and 6d should have been included in that one submission and happy or comforted in the fact that they were subsequently sent to CBER. So I personally don't find them distracting. And I, at the time, may have argued to include them. And subsequently they were included apparently.

Q. Well, not Table 6c and 6d?

A. Yes, we just went through that.

Q. That wasn't Table 6c and 6d.

A. 6c we looked at, 6d was the same data, the table we looked at contained the same data that is in 6d. I can go through how it's the same thing. We just had different -- not the same ELISA groupings. We just broke each of those levels into two levels. But it's the same data, same result, same thing, just broken out into two levels. So 6d was submitted in that form, two levels, and 6d -- 6c was also submitted. There was another CBER submission. I don't know if you can provide it. I don't have it on me. But there was another CBER submission where I believe we submitted 6c.

Q. Now, you don't know the submission that you are referring to. Right?

A. No, not offhand I can't state it.

Q. And the table that you're saying the same information was submitted in was not attached to your comparison memo that you had originally intended it to be attached to. Correct?

A. I'm confused by that question.

Q. Well, in the document you were just looking at where -- this is Exhibit – I apologize. Exhibit 12. Now, Attachment 2 to this Exhibit 12 which is where your comparison analysis is –

A. Right. That corresponds to -- the observed results in that table corresponds to the results in 6d. What was I just looking at? I was just looking at something else where it matched up. Yeah, but four and two is six. That's -- oh, this might be for uncorrected or

versus corrected. The original versus corrected. Maybe that's where that is not matching up. So where I was saying we had the wild type ELISA compared to the corrected results and wild type ELISA compared to the uncorrected, that's why it wasn't aligning. I wasn't looking at the wild type versus original results. I was looking at wild type versus corrected. So 6d here, what's here in 6d is here in Table 2 that was submitted to CBER. It's there.

Defense Counsel: Where are we with time?

Videographer: 30 seconds.

Plaintiffs' Counsel: So this is redirect. This is different. I'm almost done.

Q. So the Table 6c and 6d was put in a different form in a different part of the submission. Is that correct?

A. Apparently, Manal didn't submit it with my report when she did that submission that we looked at, but then it was submitted in a later submission. 6c was, I believe, in the same form. 6d is submitted in a form where these ELISA titer groups are just, instead of one group, it's just split into two. So, each group is split into two. So where you have ELISA titers between 10 and 20, how many samples there were, 25, six of those were negative in the AIGENT. Those six samples are identified in this table. You have ELISA titers between 10 and 20 in the first two rows. There were six mismatched samples in the AIGENT. The 20 to 40 are the next two rows, rows 3 and 4. There are eight samples identified in Table 2. There are eight samples identified in 6d. The next two rows are between 40 and 80 in this table. Between 40 and 80 there are five samples that were -- had ELISA titers between 40 and 80 that were mismatched in the AIGENT, that gave negative results in the AIGENT. And there's five listed here. So this table, although it wasn't in the original submission to CBER, was -- this data and the results of the mismatches in relation to the ELISA titer was given to CBER in this submission, June 10, 2002, in this Table 2.

Q. Now, you knew -- you had been -- discussed this issue with Manal Morsy. Isn't that correct?

Defense Counsel: This is the last question.

Plaintiffs' Counsel: No, it's not. You don't get to limit my time on the issue you opened up.

Defense Counsel: It's your time on the record.

A. From here it looks like Manal made the decision to exclude those 6c and 6d from that submission because she felt it was too distracting. She would have final say, and so that appears to have been what happened. And then it also appears that in subsequent submissions, they were provided to CBER. So although it wasn't in that original submission, it was provided to CBER in subsequent submissions, 6c and the data 6d.

Deposition of Joseph Antonello, August 3, 2017, 310:13-316:17 (emphasis added).

233.25. MRL's former Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, testified as follows:

Q. So during this '99 to 2002 time frame that you were the associate director of worldwide regulatory affairs, who would you go through within your management to get approval before something was submitted to the FDA?

A. Definitely Henrietta [Ukwu] *and Keith* [Chirgwin] *because of also his original background and knowledge in depth of the product. Because, again, I was still entering, I had absolutely no background.*

Deposition of Manal Morsy, August 5, 2016, 31:2-11 (emphasis added).

233.26. Merck's Response to CBER Request 2 in Serial 86 stated:

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 ...

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 … if a comparison between the Mumps WT ELISA and the AIGENT assay show acceptable agreement between the two assays.

MRK-KRA00126468 at '82 (emphasis added).

233.27. A letter marked "Serial No. 87," from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to FDA's Director, CBER, Office of Vaccines Research & Review, Division of Vaccines and Related Products Applications, Dr. Kathryn Zoon, regarding "BB-IND 1016: PROTOCOL AMENDMENT – CHANGE IN PROTOCOL," dated June 11, 2002, stated:

> Merck Research Laboratories (MRL), a division of Merck & Co., Inc. is submitting the following information as an amendment to the subject Investigational New Drug Application: …
> 4. Description of Information Submitted: …
>
> One year persistence serology samples will not be tested in the mumps plaque reduction neutralization (PRN) assay. The PRN assay correlates well with the mumps ELISA and therefore only the ELISA testing will be conducted for this time point. Revaccinations will be based solely on ELISA results.

MRK-KRA00126540 at '40-41 (emphasis added).[596]

233.28. A letter marked "Serial No. 89," from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to FDA's Director, CBER, Office of Vaccines Research & Review, Division of Vaccines and Related Products Applications, Dr. Kathryn Zoon, regarding "BB-IND 1016: GENERAL CORRESPONDENCE," dated August 8, 2002, stated:

> This response is to confirm our understanding regarding the outcome of the teleconference conducted between CBER and Merck on Friday, August 2, 2002:
>
> 1. We understand that CBER confirmed the acceptance of the WT Mumps ELISA assay cutoff of 10 Ab units.[597]

[596] *See also* Proposed Protocol Amendment attached including identical language. *Id*. at '546.
[597] Communications between Merck and FDA in 2004 reflect that FDA did not confirm acceptance of the 10Ab cutoff in 2002. *See* Section IX.B below.

> 2. We understand that CBER agreed with our request to use the WT Mumps 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 …

MRK-KRA00000561.

234. In my opinion, based on Dr. Antonello's testimony that neither the 1:32 cutoff in the AIGENT nor the 10 Ab cutoff used in the WT ELISA reflected a protective level, the 10 Ab WT ELISA cutoff did not meet the FDA's requirement that it "relate to seroprotection."

235. In my opinion, if the cutoff in Merck's WT ELISA had been set higher (i.e. 40 ab using a four-fold rise criterion),[598] the seroconversion rates Merck would have reported by its WT ELISA would have been lower than those reported using 10 Ab.[599]

236. In my opinion, in response to FDA's request to identify individual titers "in the relative range around the cutoff in the P[laque]R[eduction]N[eutralization] and ELISA in order to confirm the AIGENT and WT ELISA are categorizing sera in a comparable fashion," I would expect Merck to provide the FDA with the following information relevant to samples with titers around the cutoff:

- The tables Merck prepared in March 2001[600] comparing the results of the approximately 60 low level responders and non responders in the preliminary subset by AIGENT and WT ELISA broken out by potency dose showing seroconversion rates as follows:

  The 4.9 dose: seroconversion rate by WT ELISA was 81% and 43% by AIGENT.

  The 4.0 dose: seroconversion rate by WT ELISA was 93% and 26% by AIGENT.

  The 3.7 dose: seroconversion rate by WT ELISA was 40% and 20% by AIGENT.

[598] MRK-KRA00561418 ("If CBER required a fourfold rise in titer (defined as less than 10 to greater than or equal to 40), the seroconversion rates for these studies would range from 80.9% to 85.2%.").
[599] Deposition of Joseph Antonello, August 3, 2017, 250:25-252:1; MRK-KRA00544510 (If CBER did not accept Merck's choice of 10 Ab for ELISA, the "high" impact would be "Mumps seroconversion rates will be lower than what is claimed in the label.").
[600] MRK-KRA00562247.

- The results of assay testing outside the protocol in assay 46-01, showing the following results for the ten children retested:
  None of the ten responded in a standard neutralization assay using JL-135.
  Seven of the ten responded in the WT ELISA (also using JL-135).[601]

N. Merck Did Not Have Adequate Assurance of the Mumps Potency of MMRII Until the End Expiry Claim on the MMRII Label Was Lowered in 2007

237. As described below, from 2002 until 2007, Merck still could not assure that MMRII lots would meet the end expiry claim of "not less than 4.3" for mumps, even after the overfill.

1. Merck Estimated 7% of MMRII lots "were expected to be below 4.3 at end expiry" and "with some creative math" shelf life could be improved from 12 to 15-16 months

238. In January 2002, MRL's Statistician, BARDS, Philip Bennett again[602] documented Merck's inability to ensure compliance with the "not less than 4.3" mumps end expiry claim on the MMRII label for 24 months. His prior estimate of less than 12 months' shelf life[603] could be improved "with some creative math."[604] Mr. Bennett further estimated as many as 7% of MMRII lots "were expected to be below 4.3 at end expiry."[605] Merck's Clinical Regulatory Review Committee was kept informed of Mr. Bennett's potency calculations and the inability to assure "not less than 4.3" through end expiry for mumps in MMRII. A power point presentation

[601] *See* paragraph 195 above (summary of the results of the ten children in assay 46-01); Deposition of David L. Krah, July 12, 2017, 708:3 to 714:9.
[602] *See* MRK-KRA01896072 at '72-73 (February 27, 2001 Memo: "Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry") and MRK-KRA00562218 (March 14, 2001 email: "Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.").
[603] MRK-KRA00562218.
[604] MRK-KRA00024008.
[605] MRK-KRA00561350.

to the Clinical Regulatory Review Committee stated: "Product still not compliant with labeled potency.[606]

238.1. An email from MRL's Statistician, BARDS, Philip Bennett, to MRL's Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrissey, cc'd to MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky, MRL's Associate Director, Timothy Schofield, Chris Petroski, Sally Wong and MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, with the subject "Re: Mumps End Expiry," dated January 18, 2002, stated:

> The picture does not look good if we must short date Mumps to assure … (4.3 per dose) at expiry with 95% confidence for release at 5.0.
>
> With some creative math and the updated stability data for fills made 1995-1999, the shelf life is about 15-16 months.

MRK-KRA00024008 (emphasis added).

238.2. An email from MMD's Christopher Petroski to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL's Vice President, Infectious Disease and Vaccine Clinical Research, Dr. Jeffrey Chodakewitz, cc'd to MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky, MRL's Vice President, Worldwide Regulatory Affairs, Dr. Henrietta Ukwu, MRL's Senior Director, Project Planning and Management/Vaccine Integration, Dr. Joye Bramble, MRL's Executive Director, Vaccine Integration, Dr. Florian Schodel, MRL's Vice President, Vaccine & Biologics Research, Dr. Emilio Emini, and MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, with the subject "RE: CRRC Agenda – 22January02," dated January 21, 2002, stated:

[606] MRK-KRA00019085 at '010.

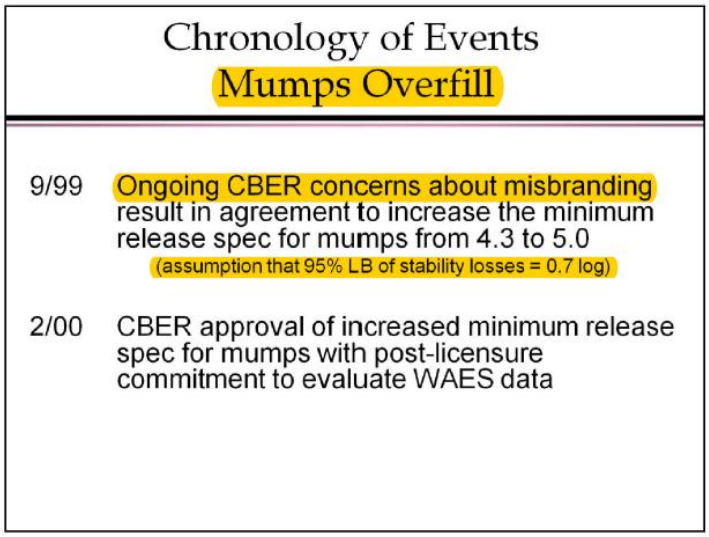
> I reviewed the BPDRs that have been filed since the Team Bio inspection. We filed 14 so far, but only 2 of them are related to failure to meet mumps potencies of 4.3. (I recalled, incorrectly, that there were more). In 1 case we make mention of the Warning Letter response and recent clinical data as low as 4.0/dose. In both cases, we stated that we implemented a new mumps release specification (5.0/dose) to ensure lots at expiry would meet 4.3/dose at expiry. Therefore, from CBER's point of view, they may be expecting all recent lots (after increasing the mumps content and increasing the release specification) to meet 4.3/dose through expiry. That may explain the fact that there has been no negative feedback in response to the BPDRs.
>
> I spoke with Cindy Morrisey (Stability) and Phil Bennet (Biometrics). Even at the current release specification, approx. 7% of the lots are expected to be < 4.3 at expiry. If we were to short date the product to achieve a 95% confidence of meeting 4.3/dose through expiry, we would have to date the product to approx. 16 months. This would impact our ability to supply the market.
>
> If we can not get approval for an end-expiry titer of 4.0, there is still a risk that we will obtaining out-of-specification potency values for mumps at expiry. CBER has not made us take any market action in the past relative to potency values below 4.3/dose. However, the difference now would be the fact that our corrective actions (adding more mumps and increasing the release specification) did not ensure we meet 4.3/dose at expiry as previously indicated.
>
> If CBER rejects the clinical study data and forces us to repeat a portion of it, we should get their concurrence in advance on our planned course of action if an OOS result is obtained, prior to revising the label.

MRK-KRA00561350 (emphasis added).

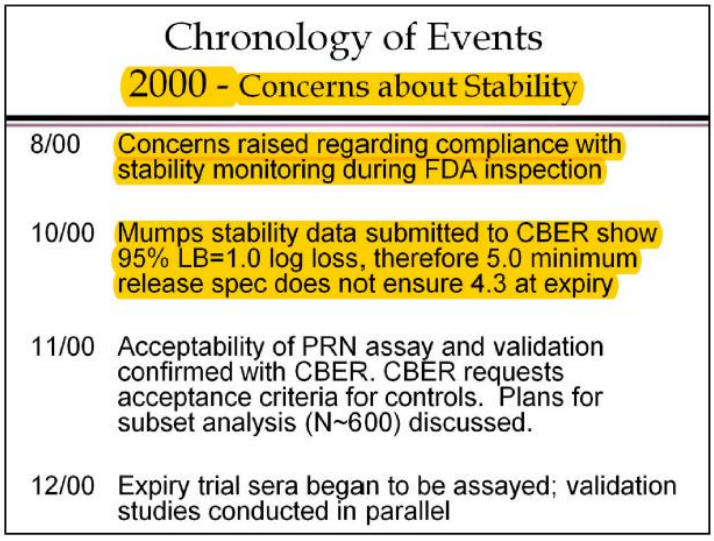
238.3. An email from MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy,

with the subject "CRRC overheads on mumps expiry" dated January 22, 2002 attached a document "CRRC mumps expiry 01-22-022." MRK-KRA00019084.

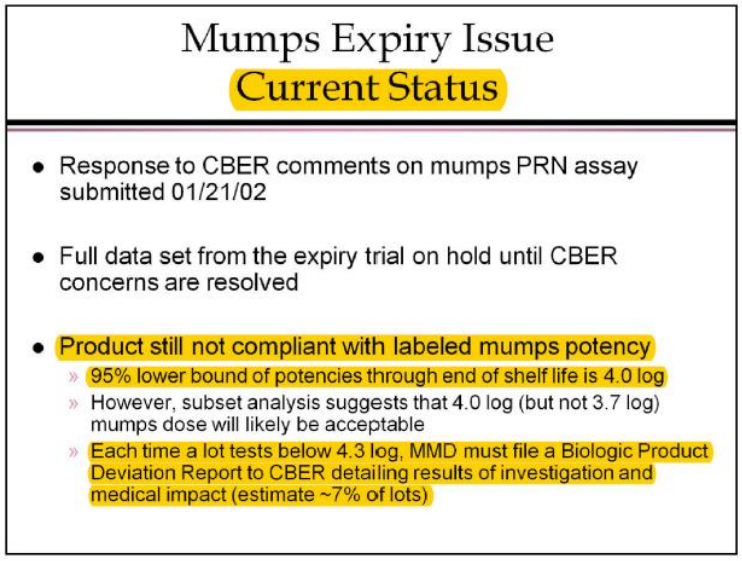
238.4. The attachment to Dr. Chirgwin's January 22, 2002 email stated:



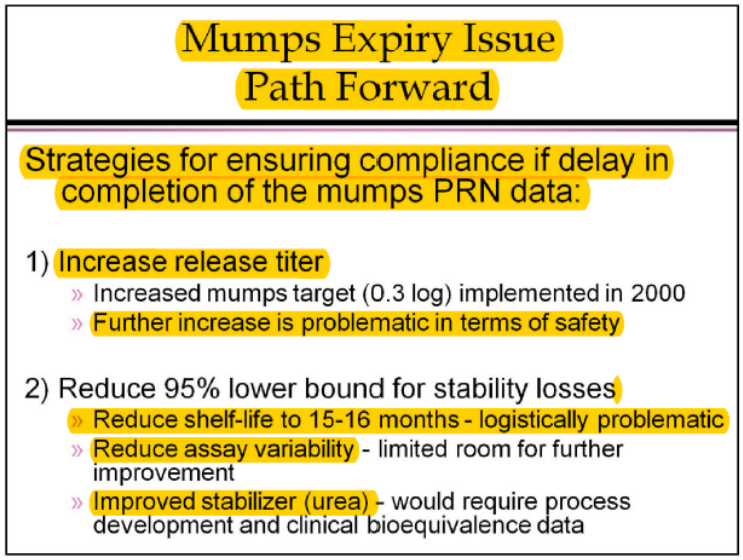
Slide 04



Slide 05



Slide 10



Slide 14

MRK-KRA00019085 at '004, 005, 010, 014 (highlight added).[607]

[607] The reference to WAES in Slide 004 is Merck's Worldwide Adverse Experience System, an internal reporting system established in June 1989. It is a single repository of safety information for Merck products and is intended to allow the company to be aware of the safety profiles of their drugs and be in compliance with regulatory

238.5. The Clinical Regulatory Review Committee overheads can be summarized as follows: (1) FDA had concerns about MMRII being misbranded; (2) the overfill amount was calculated on the assumption that the total loss over the shelf life was 0.7 log; (3) FDA raised concerns about stability monitoring during the October 2000 Team Biologics inspection; (4) the total loss estimate was 1.0 log, not 0.7 log, so that even after the overfill Merck could not ensure 4.3 log at end expiry; (5) Merck was still not in compliance with its label in 2002; (6) a further overfill was problematic because of safety; (7) reducing the shelf life was problematic; (8) there was little room to improve release potency testing to reduce variability; (9) a new stabilizer would require development and more clinical data. The Path Forward options presented included the same options considered by the same committee in December 2000.[608]

238.6. A Merck document titled "M-M-R®II PRODUCT DEVELOPMENT TEAM MEETING," dated March 7, 2002, stated:

> II. PRODUCT SUPPORT
>
> A. New Stabilizer Development – Status J. Bramble
>
> Missbranded – stability continues to be an issue, even with the increase in mumps and reduction of end expiry of 4.0.

MRK-KRA00205854 (emphasis in original).

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requirements around the world. Included in it are adverse experiences (AEs) from investigational studies, clinical-development studies, local subsidiary studies, post-marketing surveillance, and spontaneous reports. *See* Judith A. Sromovsky, *WAES*NET — Mercks International AE Reporting System*, 26 Drug Information Journal 545–548 (1992) available at http://journals.sagepub.com/doi/abs/10.1177/009286159202600411?journalCode=dijb (Judith A. Sromovsky, MS, was the Manager Worldwide Product Safety and Epidemiology, Merck & Co. in 1992). Merck agreed to monitor the WAES system for adverse events associated with the overfill of the mumps component of MMRII implemented in September 1999. Merck was cited in the October 2000 Form 483 for failing to implement the tracking until the data was requested as part of the inspection. *See* MRK-KRA00071265 (Observation 2).

[608] *See* MRK-KRA00562323 (December 2000 presentation to the Clinical Regulatory Review Committee listing short dating, stabilizer change).

239. In my opinion, until Merck had clinical data from an adequate and well-controlled study and FDA's approval to lower the mumps end expiry claim on the MMRII label, Merck remained obligated to ensure that all product met the "not less than 4.3 log [20,000]" mumps end expiry claim. Furthermore, Mr. Bennett's analysis documents Merck's ongoing inability to ensure all MMRII products complied with that label specification even after the overfill. Merck continued to have inadequate assurance that MMRII met the label specification for mumps through end expiry in March 2002.

2. FDA Issued a Form 483 for Failure To Expand the Investigate Of Mumps Potency Failures Related to the Biological Deviation Product Report Merck Filed in March 2001

240. In April 2002, Team Biologics returned to Merck for another inspection.[609] As in the previous inspection,[610] the inspectors noted deficiencies related to reporting out of specification lots of MMRII.[611] The reporting deficiencies included potency failures for the measles and mumps components of MMRII.[612] Team Biologics issued another Form 483, including Observation #5 relating to deficiencies in the Biological Product Deviation Report (BPDR) 01-003 Merck submitted in March 2001 reporting MMRII Lot 0628706 as out of specification for the mumps component.[613] Observation #5 stated that "lot 0628706 represented MMR II single-dose lots manufactured in 1998" and the investigations "were incomplete in that they did not include a documented assessment of potential impact of other lots manufactured."[614] Merck's draft response to the Form 483 Observation #5 stated that: "[c]orrective actions have

[609] *See* MRK-KRA00784057.
[610] *See* MRK-KRA01978905 (Team Biologics inspection August and October 2000).
[611] *See* MRK-KRA00784057.
[612] *Id*. at '59; MRK-KRA00784067 at '70; MRK-KRA00784076, at '79.
[613] MRK-KRA00783949 at '64; *see* Section VIII above.
[614] *Id*.

been implemented in all cases."[615] Merck's draft referenced an update to the Standard Operating Procedure to conduct an expanded investigation in the future, but made no reference of an investigation to evaluate the lots similar to Lot 0628706[616] that had not been investigated in 2001.[617]

240.1. A Merck memo from MMD staff, Kellee Salber and Ryan Starr with the subject: dated "FDA West Point GMP Inspection – Day 2," dated April 10, 2002, stated:

> Executive Summary
>
> … Investigator Schofield continued her review of Recall and Biological Process Deviation Records (BPDRs) with specific questions regarding out-of-specification potency results for stability testing for M-M-R®II. Investigator Schofield expressed concern with regard to BPD 01-002[618] and the justification not to recall products that fail to meet release specification when tested on stability. Both Cindy Morrisey and Roberta McKee provided follow-up explanation in this regard to indicate that although the stability time point potency values did not meet release specifications, that strong medical evidence was available to indicate that efficacy of the vaccine had not been compromised at the indicated potency values. In addition, it was further explained that potency expiration values have been the topic of ongoing discussion with CBER as they were also a part of the previous Team Biologics inspection.
>
> While reviewing BPDRs the investigator expressed concern that there was no recall for an M-M-R®II lot that failed to meet Measles potency expiry specifications on stability.

[615] MRK-KRA00783949 at '67.
[616] *Id.*
[617] I have been unable to identify a final response to Form 483 Observation #5. I have also been unable to identify any documents evidencing an investigation of lots manufactured in 1998 that would have been similar to Lot 0628706. I note that since Lot 0628706 was manufactured in 1998, the same year as at least some of the low potency lots listed on Attachment #4 to Dr. Margolskee's February 23, 2001 email to Drs. Scolnick and Greene, I would expect those lots to be among those identified in an investigation. *See* MRK-KRA00549510; MRK-KRA00549518.
[618] BPDR 01-002 reported out of specification measles potency in MMRII Lot 0627419. It did not report mumps potency failures. MRK-KRA00754221. *See also* Schedule 24 (summarizing BPDRs).

> The investigator also expressed concern that there was no recall for an M-M-R®II lot that failed to meet Measles release specifications as a result of a LIMS rounding error.

MRK-KRA00784057 at ’58-59 (emphasis added).

240.2. A memo from MMD Personnel with the subject “FDA West Point GMP Inspection – Day 5,” dated April 15, 2002, stated:

> Daily Activity Summary
>
> Investigator Schofield, after a review of the listing of Stability Test Failures, questioned why no BPDR was issued for international Grifols-containing M-M-R®II Lots. It was explained that these lots were international lots and further they were “Grifols” lots[619] manufactured prior to the Mumps improvements to extend product specification through expiry, and the only “Grifols” lots in the US were High Mumps. However Investigator Schofield expressed a concern that these lots were representative of all Low Mumps lots in the US regardless of the albumin vendor and therefore a BPDR should have been issued. This issue will be discussed further tomorrow.

MRK-KRA00784067 at ‘70 (original bold removed, underline added).

240.3. A Merck memo from MMD Personnel with the subject “FDA West Point GMP Inspection – Day 6,” dated April 16, 2002, stated:

> Daily Activity Summary
> Team Biologics
> Investigator Schofield also re-iterated her concerns for the Mumps out-of-specification results on stability and the need to extend stability investigative testing to retains of other lots manufactured in that year.[620]

[619] Grifols was a manufacturer of human serum albumin. Merck selected Grifols as a demonstration vendor in 1999. MRK-KRA00262316 at ‘24. *See also* MRK-KRA01649698 (memo from Bridget McArdle dated August 29, 2001 with the subject “Minutes of the M-M-R®II, Single Fill # 0631655, 0631656 & 0632464, 24-Month Mumps Potency and Mumps Reconstitute and Store Potency OOS Fact Finding Meeting,” discussing the “Grifols lots”).

[620] *See also* MRK-KRA00239179 at ‘88 (A document titled “Proposed New Stabilizer for M-M-R®II” prepared by the M-M-R®II PDT [Product Development Team], dated July 12, 2002, stated: “In 2002, M-M-R®II stability failures also came under close scrutiny during this year’s Team Biologics inspection. This inspection yielded another 483 observation related to M-M-R®II potency failures on stability. Although the observation itself was due

MRK-KRA00784076 at ‘79 (original bold removed, underline added).

240.4. A draft Merck document with the header “Merck & Co, Inc. Response to FDA 483 Team Biologics Inspection 4/9-12, 15-18, 29-30/02, West Point, PA CBER/ OCBQ, FEI Number 2510592,” dated May 20, 2002, stated:

> Observation #5
> Stability failure investigations … ST100-S027 dated 1/10/01 (MMR II lot 0628706 – 24 months mumps potency) … were incomplete in that they did not include a documented assessment of potential impact of other lots manufactured that were representative of the stability lots. … lot 0628706 represented MMR II single-dose lots manufactured in 1998…
>
> > *Merck Response to Observation #5*
> > We understand the concern raised during your review to focus on the need to include documented rationale regarding the impact assessment of stability out-of-specification results on all related material represented by these stability lots. Therefore, our procedure SOP 261-SU303, “Stability Test Investigation”, has been updated and was approved as of May 2, 2002 to explicitly require the inclusion of documented rationale and impact assessment of stability failures on marketed product and/or material that is representative of marketed product. The updated procedure will be implemented with training performed by May 24, 2002.

MRK-KRA00783949 at ‘64 (original bold removed, underline added).

240.5. The draft response to the Form 483 also stated:

> *Corrective Actions*

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to the lack of documented assessment of potential impact on other lots manufactured that were represented by the stability lots, during the inspection the lead investigator questioned why Merck continued to distribute product following these stability failures.”) (emphasis added).

> Several common factors contributed to the observed out-of-specification results in the subject stability test investigations. Corrective actions have been implemented in all cases. As noted previously, release specifications have been revised based on stability analyses to improve the probability that product meets release specification through expiry. …
>
> Representatives from Merck & Co. and CBER met in April of 2001 to discuss the stability program for M-M-R II family products. Topics discussed at that meeting included House Standard adjustment, evaluation of individual stability interval results versus the entire stability profile of the lot, and the appropriate number of lots to be monitored to effectively study the stability of live virus vaccines. The Active Stability Monitoring program was also discussed as both a predictive tool for ongoing stability lots and as an investigation tool for evaluating lots with results below the prescribed potency specification limits. CBER representatives requested that a follow-up meeting be held to finalize decisions regarding these proposals. Merck & Co., Inc. made a written request for this meeting on August 1, 2001. Scheduling of the meeting by CBER is pending.

Id. at '68 (original bold removed, underline added).

241. In my opinion, in response to the April 2002 Form 483, finding a deficiency in the underlying report from March 2001, a reasonable and prudent manufacturer would have investigated other single-dose vial MMRII lots manufactured in 1998. A reasonable and prudent manufacturer would have also reported that it did not have adequate assurances that future lots would meet the mumps potency specification of 4.3 TCID50/dose at expiry.

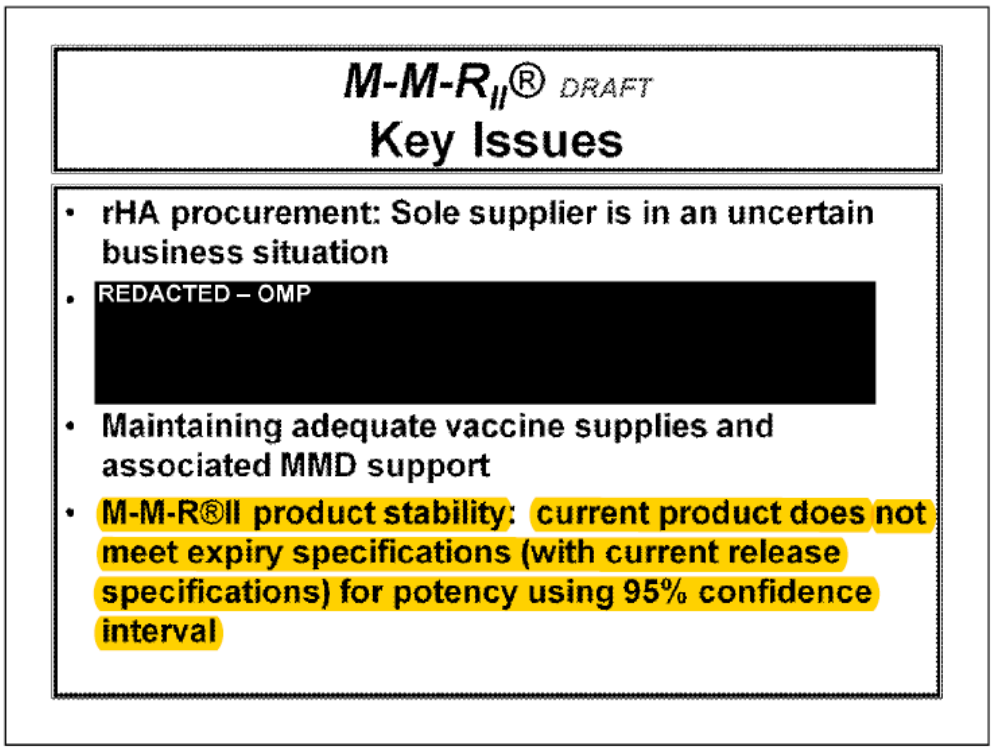
3. Merck Considered Options to Address The "Issues and Concerns with the Current Product Stability"

242. In July 2002, a "key issue" within Merck continued to be "MMRII product stability: current product does not meet expiry specifications (with current release specifications)

for potency using 95% confidence interval."[621] To address this "issue," the MMRII Product Development Team requested permission from the Tactical Product Approval Committee to "charter a team" to support a proposed initiative to develop a new stabilizer for MMRII.[622] The introduction to the Product Development Team's proposal stated: "Since the early 1990's, the M-M-R®II franchise has been challenged with issues and concerns with the current product stability and tolerability profile that has led to numerous short-term program fixes to maintain the product on the market" and "the short-term programs have not addressed in totality the original issues identified in 1996."[623] "The ultimate goal of the new stabilizer for M-M-R®II [was] to protect the franchise by improving the product stability profile and to comply better with minimum potency requirements through shelf-life (typical shelf-life of 24 months)."[624]

242.1. A power point presentation titled "M-M-R®II MRL Planning 2002 DRAFT revised 7/11," for MRL's Vaccine Coordination Committee meeting on July 16, 2002 focusing on key issues and 2003 objectives[625] stated:

[621] MRK-KRA00498914 at '17.
[622] MRK-KRA00207690.
[623] *Id.* at '93.
[624] *Id.* at '94.
[625] *See also* MRK-KRA00498912 (July 15, 2002 email from MRL's Project Manager, Keiko Simon, stated: "Attached below are slides sent for review at VCC [Vaccine Coordination Committee] tomorrow. They will be focusing on key issues and 2003 objectives.").



MRK-KRA00498914 at '17 (highlight added).

242.2. A memo from the M-M-R®II PDT [Product Development Team] to Vaccine TPAC [Tactical Product Approval Committee] with the subject "New Stabilizer for M-M-R®II," dated July 26, 2002, stated:

> This new stabilizer program is being proposed to address continued stability issues for the measles[626] and mumps components of M-M-R®II that have most recently been the focus of an intensive investigation in MMD. …
>
> Based upon the regulatory and marketing drivers described in the background document, we are requesting that Vaccine TPAC charter a team to support this proposed new initiative.

[626] *See* MRK-KRA00494158 at '58-59 (discussing "S[enior] M[ana]g[e]m[en]t Review of Findings and Path Forward" for Measles stability); MRK-KRA00754221 (BPDR 01-002 reporting measles potency out of specification). I understand that discovery in this case has been limited to issues regarding the mumps component of MMRII and that documents relating to the measles component were produced only if the document also related to the mumps component.

MRK-KRA00207690 (emphasis added).

243. The background document attached to the Product Development Team's July 26, 2002 memo stated:

> I. INTRODUCTION
>
> Since the early 1990's, the M-M-R®II franchise has been challenged with issues and concerns with the current product stability and tolerability profile that has led to numerous short-term program fixes to maintain the product on the market. …
>
> … Also, as the short-term programs have not addressed in totality the original issues identified in 1996, a new approach to solving these issues is required. To further complicate the existing situation, issues with product stability have recently been exacerbated dues to concerns raised by FDA inspectors regarding continued failures of measles and mumps in annual stability studies and questions regarding why Merck continued to distribute M-M-R®II product following these stability failures. …
>
> The ultimate goal of the new stabilizer for M-M-R®II is to protect the franchise by improving the product stability profile and to comply better with minimum potency requirements through shelf-life (typical shelf-life of 24 months).

Id. at '93-94 (emphasis added).

244. In my opinion, as of July 2002, Merck still did not have adequate assurances that that all MMRII product met the "not less than 4.3 log [20,000]" potency claim for mumps on the label, even after the overfill implemented in September 1999. Furthermore, until Merck actually implemented any of the proposed "fixes" it contemplated, it remained obligated to ensure compliance with its label.

4. Merck Did Not Have Adequate "Controls to Ensure" that Mumps Potency in MMRII Would Be At or Above 4.3 at End Expiry

245. Following the Team Biologics yearly inspection and the Form 483 for failure to investigate mumps stability failures completely, Merck personnel continued to document that

"current [MMRII] product does not meet expiry specifications (with current release specifications) for potency using 95% confidence.[627] MRL's Statistician, BARDS, Mr. Bennett continued to report "shelf life of 12 months."[628] In response, MRL's Director, Worldwide Regulatory Affairs, Dr. Morsy, stated: "We have [a] much larger problem … if we can only support 12 month."[629] Senior Merck management, in the context of a measles potency investigation, "decided that we needed to wait until the expiry spec[ification] of 4.0 was approved for mumps before we do anything else to follow up on mumps potency or stability. …"[630] Merck "ran the risk of having new mumps potency stability failures without an adequate corrective action to put on the B[iological]P[roduct]D[eviation]R[eport] (compliance notification to the FDA for stability failures). We've been lucky with mumps so far, but it's only a matter of time, since we can statistically predict that a certain number of lots will fail on stability."[631] While Merck prepared to report the measles potency failure, it "[had] not forwarded the stability plans to CBER" as part of its measles corrective action because "translating the same logic today to mumps would mean 'no product' since shelf life estimates reduce to less than 12 month."[632] On September 17, 2002, MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, stated: "I understand and agree that the probability of all of these extremes being realized on a single lot is very low. However, there are no controls to ensure that they do not occur. Do you think CBER would have considered anything less? I don't believe the Compliance Office would have."[633]

[627] MRK-KRA00498914 at '17.
[628] MRK-KRA01562819 at '20.
[629] *Id*.
[630] *Id*. at '19.
[631] *Id*.
[632] MRK-KRA00501762 at '64 (emphasis added).
[633] *Id*. at '62.

245.1. An email from MRL's Statistician, BARDS, Philip Bennett, to MMD's Quality Assurance, Biological Stability Unit, Bioanalytical Development, Mary Macchi, cc'd to MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, MRL's Director, BARDS, Timothy Schofield, MRL's Executive Director, BARDS Joseph Heyse, MRL's Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrissey, among others, with the subject "MMR Mumps Expiry Dating," dated September 5, 2002, stated:

> As you requested, we performed analyses of the mumps stability data in order to estimate the maximum shelf life for Kaketsukan[634] …
>
> These yield the maximum … shelf life of 12 months.

MRK-KRA01562819 at '20 (emphasis added).

245.2. An email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, replying to Mr. Bennett, Ms. Macchi, Mr. Schofield, Dr. Heyse, Ms. Morrisey, and copying MVD's Senior Director, International Sales, Marketing & Operations, Robert Verdugo, MMD's Senior Director, Bioprocess R&D, Dr. Joye Bramble, MRL's Project Manager, Keiko Simon, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL's Executive Director, Virus & Cell Biology, Dr. Alan Shaw, MRL's Executive Director, Biologics/Vaccines Clinical Research, Florian Schodel, among others, dated September 5, 2002, stated:

> This is what I was fearful of – 12 months will be unacceptable – I am copying marketing on this also so that they can weigh on this

[634] Merck had an agreement with Japan's Kaketsukan to seek regulatory approval to sell MMRII in Japan. The agreement ultimately ended without Merck obtaining approval to sell MMRII in Japan. *See also* Schedule 23 (describing Merck MMRII program elsewhere in the world).

We have much larger problem than just [Japan] if we can only support 12 month

Id. at ’19-20 (emphasis added).

245.3. An email from MRL’s Manager, Vaccine Regulatory and Analytical Sciences, Cynthia Morrissey, replying to MRL’s Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, MRL’s Statistician, BARDS, Philip Bennett, MMD’s Quality Assurance, Biological Stability Unit, Bioanalytical Development, Mary Macchi, MVD’s Senior Director, International Sales, Marketing & Operations, Robert Verdugo, MMD’s Senior Director, Bioprocess R&D, Biologics Pilot Plant, Dr. Joye Bramble, MRL’s Project Manager, Keiko Simon, MRL’s Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL’s Executive Director, Virus & Cell Biology, Dr. Alan Shaw, MRL’s Executive Director, Biologics/Vaccines Clinical Research, Dr. Florian Schodel, and MMD’s Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, cc’d to Timothy Schofield, Joseph Heyse, and Mark Rosolowsky among others, dated September 5, 2002, stated:

> We also discussed this during the measles investigation,[635] and decided that we needed to wait until the expiry spec. of 4.0 was approved for mumps before we do anything else to follow up on mumps potency or stability (such as set an upper release spec. or adjust the min. release spec), since this analysis would compel us to increase the manufacturing target yet again. …
>
> Manal: What is the current status of the 4.0 expiry spec.? If it’s not “pretty soon”, we run the risk of having new mumps potency stability failures without an adequate corrective action to put on the BPDR (compliance notification to the FDA for stability failures). We’ve been lucky with mumps so far, but it’s only a matter of time, since we can

[635] MRK-KRA00494158 at ‘58-59 (discussing “S[enior] M[ana]g[e]m[en]t Review of Findings and Path Forward” for Measles stability).

> statistically predict that a certain number of lots will fail on stability.[636] And if we increase the number of annual lots that we test, like we committed to do, then the probability increases. Not to put the pressure on, but it's probably worthwhile to touch base on this, and make sure that we are aligned. Thanks!!

Id. at '19 (emphasis added).

245.4. A Merck memo from MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, to MRL's Vice President, Vaccine & Sterile Quality Operations Dr. Roberta McKee, MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky, MMD's Director, Vaccine Technology and Engineering, Rahul Singhvi, MRL's Director, BARDS, Timothy Schofield, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, and MRL's Executive Director, Biologics/Vaccines Clinical Research, Dr. Florian Schodel, with the subject: "CBER Teleconference to Discuss Measles PAS September 6, 2002," dated September 13, 2002, stated:

> Roberta McKee stated that the purpose of this discussion was to get a concurrence as to the various aspects that should be included in the PAS [Prior Approval Supplement]. She further stated issues with mumps, and the mumps expiry study should be deferred for later discussion.

MRK-KRA00498772 at '73 (emphasis added).

245.5. A high importance email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to MRL's Vice President, Vaccine & Sterile Quality Operations Dr. Roberta McKee, and MRL's Executive Director, Biologics/Vaccines Clinical Research, Florian Schodel, cc'd to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin,

[636] The out of specification lots that Merck reported in 2001 as failing mumps potency at expiry were all manufactured before the overfill. In 2002, Merck statistically predicted that 7% of overfilled lots would fail; although it had not yet happened. Moreover, although Merck had agreed with FDA to increase how many lots Merck would monitor on its stability program, it had not implemented the change. Increasing the number of lots Merck monitored would have increased the probability of finding a lot that failed.

MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, and MMD's Senior Director, Bioprocess R&D, Biologics Pilot Plant, Dr. Joye Bramble, with the subject: "RE: measles PAS," dated September 17, 2002, stated:

> All - currently all loss estimates for variables are based on "worst case scenario"[637] - also we absolutely have to have an end expiry of 4.0 to be viable or minimum fill for mumps at 5.2 which may not be manufacturely [sic] possible - there is room to question weather "worst case scenario" loss estimates are in fact practical especially with the uncertainty of mumps or if there is room to explore average losses if that would even buy us anything … translating the same logic today to mumps would mean "no product" since shelf life estimates reduce to less than 12 month.
>
> my concern is that CBER may tag on the approach and ask that we apply to mumps and to stability monitoring - even though it is our plan to use that logic in the stability model it is still our internal decision we have not forwarded the stability plans to CBER[638] - so there maybe room to re- evaluate considering the uncertainties pertaining to mumps expiry especially in terms of log loss estimates.

MRK-KRA00501762 at '64 (emphasis added).

245.6. Another email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to MRL's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, and MRL's Executive Director Biologics/Vaccines, Clinical Research, Dr. Florian Schodel, cc'd to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin,

[637] Potency is defined as the "ability of the product ... to effect a given result." 21 CFR 600.3 (s). "Dating period" is defined as: "the period beyond which the product cannot be expected beyond a reasonable doubt to yield the specific results." 21 CFR 600.3 (l). Dr. Morsy appears to question Merck's calculation which would ensure "beyond a reasonable doubt" that it could meet the specification.

[638] In 2002, Merck learned that the measles component, like the mumps component was falling out of specification before the end of the expiry period. Merck proposed to file a Prior Approval Supplement to overfill the measles component the same way it had overfilled the mumps component in 1999. Merck had a corrective action for the measles component in 2002; it did not have a corrective action for mumps. If Merck provided its stability model for MMRII as part of addressing the measles issue, applying the model to mumps would require Merck to short date MMRII, as Mr. Bennett's analysis had been stating.

MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, and MMD's Senior Director, Bioprocess R&D, Biologics Pilot Plant, Dr. Joye Bramble, with the subject: "RE: measles PAS," dated September 17, 2002, stated:

> 'worst case scenario' meaning that the assumptions are compounded by building up compound losses such that we are basing our assumption on the least potent lot released (which is not a reflection of what the potency of the majority of lots is), keeping lots at max T[ime]O[ut]R[efrigerator] 40 hours (which I am led to believe that only a few lots only use up 40 hours of T[ime]O[ut]R[efrigerator] and certainly the possibility of the least potent lot being the exact same lot that uses up 40 hours of T[ime]O[ut]R[efrigerator] is not calculated but rather it is assumed that the least will use up 40 hours T[ime]O[ut]R[efrigerator] and will be reconstituted for 8 hours at rm temp and will be stored at -20 for a whole year and will be used only at end of shelf life at 24 month), etc - all these worst case scenario conditions are then compounded by variability at each parameter and further compounded by 95% lower bound estimates - so we assume releasing at lowest potency with max T[ime]O[ut]R[efrigerator], max - 20C storage, max reconstitution loss Plus max variability - all compounded - and although that is the most conservative and provides possibly 99.999 % that we will never fail a lot on stability the key issue here is that by using these stringent and compounded criteria[639] we assure ourselves a non viable mumps containing product if 4.0 is not achieved as the end expiry potency[640]
>
> alternatively one can propose that average / mean estimates rather than max can be used which would reflect possibly the more practical reality or even median …[641]

[639] These stringent criteria were reinforced by FDA, according to Merck's minutes of the April 4, 2000 meeting with FDA's Dr. Carbone. The minutes stated: "CBER wants, with 95% confidence, that lots be at or above 4.3 log10 TCID50 mumps/dose at expiry. She explained that 4.3 is the lower bound of the expiry potency and that CBER calculations indicated that the expiry titer should be 4.6." MRK-KRA00049238 at '39 (emphasis added).

[640] If Merck strictly applied the parameters Mr. Bennett had set forth in his analysis, the maximum shelf life for MMRII was only 12 months. The CDC contract required delivery with at least twelve months left on the shelf life. *See* Schedule 16 (CDC contracting).

[641] *See* MRK-KRA00501762 above. Dr. Morsy's alternative appears to be to an alternative to the calculations Merck made to establish assurance "beyond a reasonable doubt."

MRK-KRA00501762 at '62-63 (emphasis added).

245.7. An email from MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee to MRL's Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, and MRL's Executive Director Biologics/Vaccines, Clinical Research, Dr. Florian Schodel, cc'd to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, and Senior Director, BPR&D, Biologics Pilot Plant, Joye Bramble, with the subject: "RE: measles PAS," dated September 17, 2002, stated:

> I understand and agree that the probability of all of these extremes being realized on a single lot is very low. However, there are no controls to ensure that they do not occur. Do you think CBER would have considered anything less? I don't believe the Compliance Office would have.

Id. at '62 (emphasis added).

246. In my opinion, with regard to FDA requirements, a vaccine is adulterated if a manufacturer does not have procedures that are designed to assure that the product has the identity, strength, purity or potency it purports or represents it to have.[642] Merck had to have procedures to assure that MMRII vaccine had "not less than 4.3 log10 [20,000] TCID50" per dose through end expiry. In September 2002, according to Merck's documents, Merck did not have adequate procedures to assure that MMRII met that standard, even after the overfill implemented in September 1999.

[642] 21 USC § 351 (a)(2)(B) states: "A drug or device shall be deemed to be adulterated … if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." (emphasis added).

247. In my opinion, with regard to MMRII lots manufactured from September 1999 – September 2002, Merck never informed the FDA that "approx[imately] 7% of the lots [we]re expected to be < 4.3 at expiry"[643] or that Merck could "statistically predict that a certain number of lots will fail on stability,"[644] even after the manufacturing change implemented in September 1999 to "overfill" the mumps component to ensure Merck could "provide a high level of assurance that the minimum titers would be maintained through expiry."[645] Furthermore, since this was never reported to the FDA, to the best of my understanding, no one has investigated which lots released were the 7% Merck that would fail to have 4.3 log10 [20,000] TCID50/dose at end expiry. Moreover, with regard to children immunized in the United States with vaccines manufactured from September 1999- September 2002, no one can determine which of the children, who are now young adults (approximately 17-22 years old), were immunized from the 7% of lots Merck predicted would fail to have 4.3 log10 [20,000] TCID50/dose at end expiry to evaluate whether they have been sufficiently immunized because the end expiry potency fell below Merck's specification.[646]

5. Merck Identified Corrective Actions to Ensure Compliance With the Mumps End Expiry Claim on the MMRII Label

248. In October 2002, Merck's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, stated that because "mumps does not support the current label claim, Merck was required to report this finding to the FDA."[647] She further stated the report needed to be

[643] MRK-KRA00561350.
[644] MRK-KRA01562819.
[645] MRK-KRA00756233 at '35-36.
[646] *See* Section XI below discussing the resurgence of mumps cases and outbreaks in the United States among fully vaccinated young adults.
[647] MRK-KRA00094134.

made by December 6, 2002.[648] Between October and December 2002, Merck identified a series of corrective actions to ensure compliance with the mumps end expiry claim on the MMRII label. The corrective action "agreed upon" was to lower the shelf life for MMRII.[649] Merck considered proceeding with the application to lower the end expiry label claim, but the success of the study was put at risk when Merck invalidated the results of a portion of the study.[650] Merck's MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky telephoned FDA's Dr. Phil Krause in the Office of Vaccines Research and Review to notify him that Merck would submit a Product Application Supplement (PAS) to reduce the shelf-life.

248.1. A memo from the Product Development Team for M-M-R®II to the Clinical Regulatory Review Committee[651] with the subject: "Background Document: M-M-R®II Protocol #007 – Mumps End Expiry Study: AIGENT Assay Issues and Impact on Study Criteria," dated October 2, 2002, stated:

> 1. Executive Summary[652]
>
> During communications with CBER in 1996-98, it became evident that the agency did not agree with our proposal that the specifications noted in our label were the minimum release potencies for M-M-R®II. Instead, they defined these specifications as end-expiry potencies, since the language in the label stated "... each 0.5 ml dose contains not less than..." Arguments for the demonstrated immunogenicity at lower potencies of the monovalents and the apparent effectiveness of Merck's release strategy, due to the virtual eradication of disease in the US and Finland where the product was used exclusively were further rejected, because of the small number of children used in the studies and the

[648] *Id.*
[649] MRK-KRA00560717 at '19-20.
[650] MRK-KRA00615152 at '56-57.
[651] *See also* MRK-KRA00615147 (cover email from MRL's Project Manager, Keiko Simon, circulating the memo to distribution list).
[652] A Memo titled "MMRII Mumps End Expiry Study: AIGENT Assay Issues Impact on Study Criteria Regulatory Implications Global Strategic Review Committee, Presenter Manal Morsy" dated October 11, 2002 included the same "Executive Summary." MRK-KRA00094161 at '63-64.

circumstantial nature of the justification. CBER asked Merck to demonstrate that the mumps "expiry" specification could be met as per their interpretation.

To address this issue the following actions were taken by Merck:

1. Merck committed to a clinical study to evaluate lower end expiry potencies and a new functional antibody assay was developed at the request of CBER to be used for that study. This study was initiated in February 1999 with LPO (day 42) in September 2000.

2. To maintain the product on the market while the end expiry study was in progress, CBER specified that the mumps minimum release potency be increased to 5.0 log TCID50/dose to support an end expiry claim of 4.3 log TCID50/dose. This change was implemented in September 1999.

Subsequent to completion of the end expiry study, a series of issues arose with the serology assay and samples that have now put the success of this [Protocol 007] study at risk.[653] …

Based upon these evolving issues … M-M-R®II may have to remain at the current expiry dose of 4.3 log TCID50/dose which would only support < 12 months expiry using current data in the stability model.

As a result of these issues the team is now proposing the following recommendations:

1. Accelerate the new stabilizer program for M-M-R®II in order to improve the stability and the tolerability of the vaccine. …

2. The team is also evaluating other options to be considered as short-term fixes, since a new stabilizer program would require approximately three years before being implemented. The options and risks are outlined below:

[653] *See* MRK-KRA00018369 at '73, 76 (BB-IND 1016, Serial 90, General Correspondence from Dr. Morsy to Dr. Zoon stated: "CBER concurrence requested: Merck therefore conclude[s] that the data from the testing carried out in June-August 2002 on ~ 300 pairs of samples … are invalid. … Merck proposes that the primary immunogenicity analyses for the mumps PRN assay exclude subjects whose mumps PRN samples were tested during June-August 2002 and declared invalid…").

- … evaluation underway to define conditions to achieve a shelf-life of 18 months if possible…

- Change label to reflect lower than 96% protection - this would require negotiating with CBER to relax the criteria of success; however, this would lower the bar for the competition.

- Repeat Mumps End Expiry Study - issues include … time to completion with no assurance that we would succeed the second time...

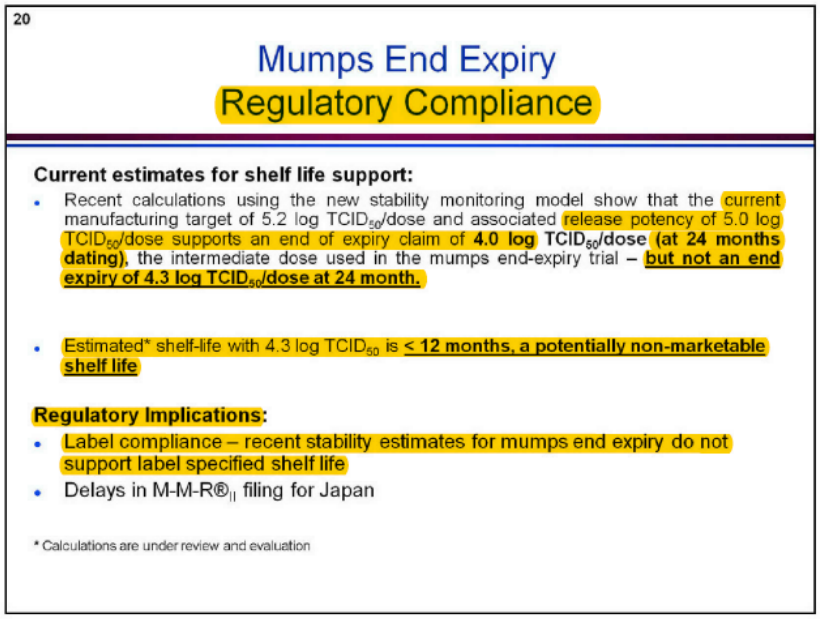
- Increase overfill level of mumps - issues include manufacturing capacity limitations and lack of adequate safety data to support overfill.

Decision Requested: Concurrence on the PDT recommendation to accelerate development of the New Stabilizer for M-M-R®II in order to improve the stability and tolerability of the vaccine...

MRK-KRA00615152 at ’55-56 (original underline removed, underline added).[654]

248.2. A powerpoint presentation titled “M-M-R®II Mumps End Expiry study status & Regulatory implications” with Dr. Manal Morsy Presenter, dated “GRSRC [Global Regulatory Strategic Review Committee] October 11, 2002,” stated:

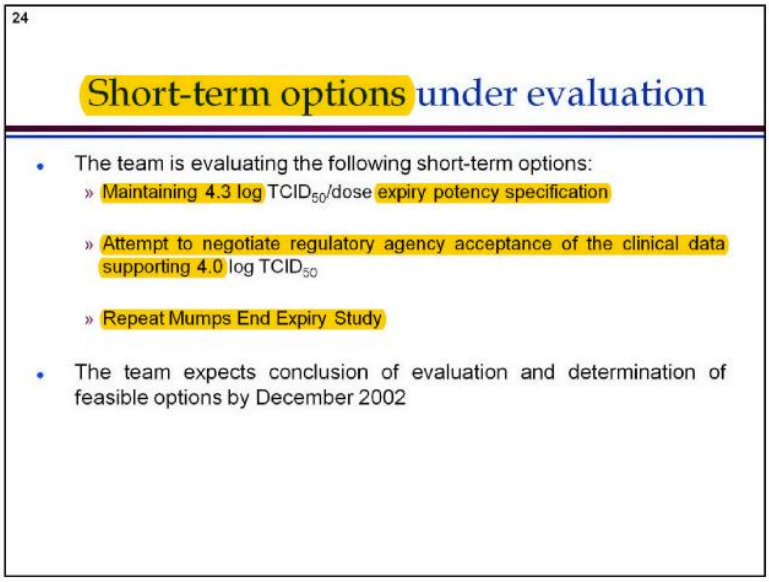
[654] *See also* MRK-KRA00207690 (July 2002 Product Development Team proposal to Tactical Product Approval Committee to approve team to develop the new stabilizer).



MRK-KRA00040705 at '00020.[655]

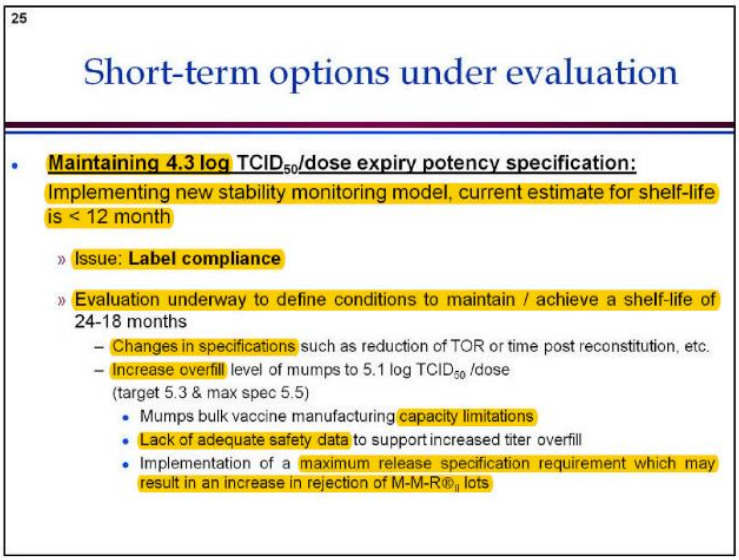
248.3. The presentation titled "M-M-R®II Mumps End Expiry study [Protocol 007] status & Regulatory implications" also stated:

[655] Dr. Morsy's presentation slide sets forth the same information conveyed in Mr. Bennett's analysis in February and March 2001. *See* MRK-KRA01896072 at '72-73 (February 27, 2001 email: "Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry"); MRK-KRA00562218 (March 14, 2001 email: "Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.").



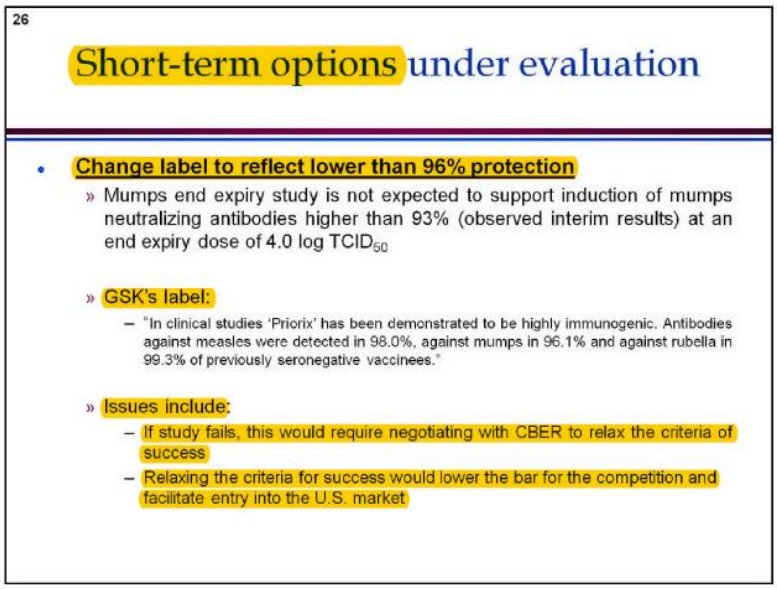
Id. at '00024 (highlight added).

248.4. The presentation titled "M-M-R®II Mumps End Expiry study [Protocol 007] status & Regulatory implications" also stated:



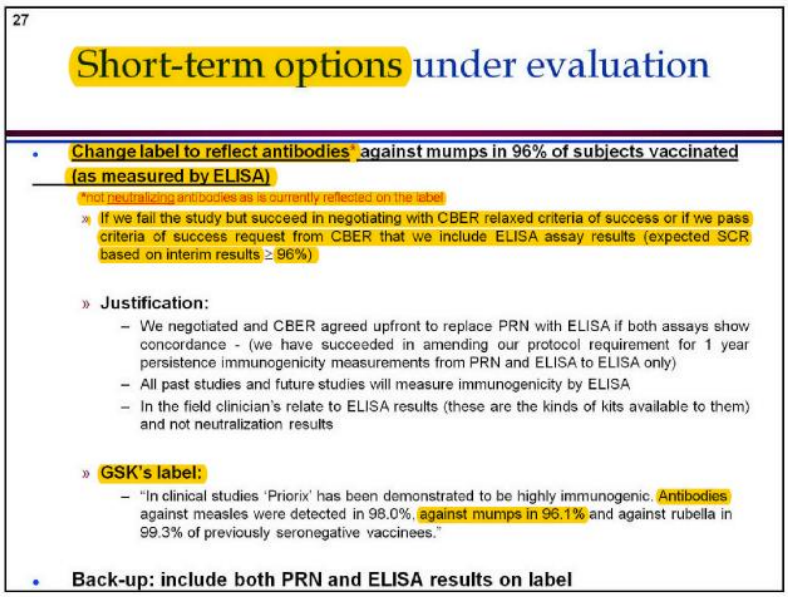
Id. at '00025 (highlight added).

248.5. The presentation titled "M-M-R®II Mumps End Expiry study [Protocol 007] status & Regulatory implications" also stated:



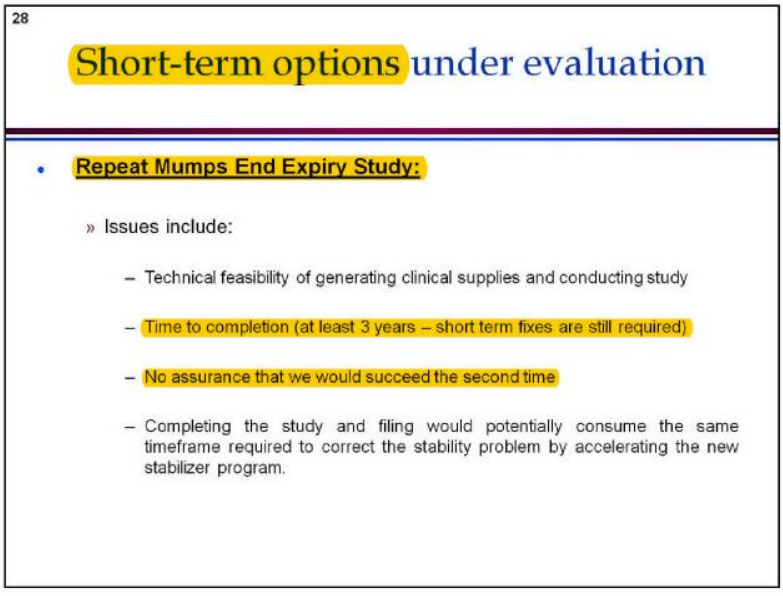
Id. at '00026 (highlight added).

248.6. The presentation titled "M-M-R®II Mumps End Expiry study [Protocol 007] status & Regulatory implications" also stated:



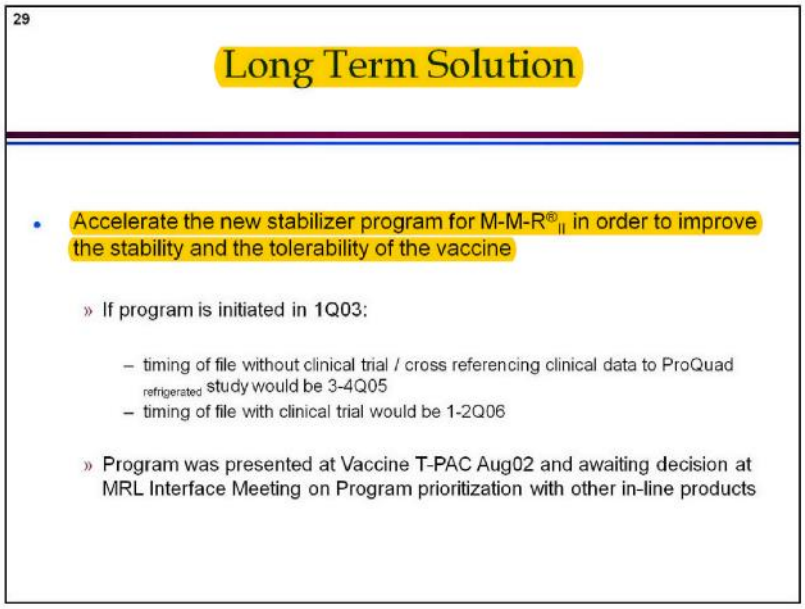
Id. at '00027 (highlight added).

248.7. The presentation titled "M-M-R®II Mumps End Expiry study status & Regulatory implications" also stated:



Id. at '00028 (highlight added).

248.8. The presentation titled "M-M-R®II Mumps End Expiry study status [Protocol 007] & Regulatory implications" also stated:


29

Long Term Solution

- Accelerate the new stabilizer program for M-M-R®II in order to improve the stability and the tolerability of the vaccine
  - » If program is initiated in 1Q03:
    - – timing of file without clinical trial / cross referencing clinical data to ProQuad refrigerated study would be 3-4Q05
    - – timing of file with clinical trial would be 1-2Q06
  - » Program was presented at Vaccine T-PAC Aug02 and awaiting decision at MRL Interface Meeting on Program prioritization with other in-line products

Id. at '00029 (emphasis added).

248.9. Dr. Morsy's presentation slides can be summarized as follows:

- Merck could not support the "not less than 4.3" mumps specification on the MMRII label, and shelf life was estimated to be less than 12 months, which would impair Merck's ability to supply its customers.[656]
- The short term options for Merck included keeping the 4.3 claim on the label, or lowering it to 4.0, which would require either FDA's acceptance of the Protocol 007 data which Merck expected to fail, or a repeat of the end expiry study.
- If Merck kept the 4.3 claim on the label, it would need to make adjustments to ensure label claim compliance. Options that it was considering included short-

[656] *See also*, MRK-KRA01896072 at '72-73 (February 27, 2001 memo: "Given our current minimum release specification limit of 5.0, we have 95% confidence that each lot released will be at or above 4.0 through expiry"); MRK-KRA00562218 (March 14, 2001 email: "Our expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry.").

dating the product, changing specifications related to manufacturing process, or increasing the overfill a second time.

- Increasing the overfill a second time presented problems both for Merck's ability to implement it, but also for safety implications of adding more mumps virus to each dose.
- If Merck wanted to proceed with the label change to 4.0 and did not have the Protocol 007 results from the AIGENT to support the change, Merck could use ELISA data only and change its label to remove the word neutralizing in the representation of "96% protection." If Merck succeeded in using ELISA only, it would "lower the bar" for GSK to come to the United States. GSK's label stated 96.1% regarding mumps but did not make a claim that it measured "neutralizing" antibodies.
- Merck also considered repeating the mumps end expiry study and developing a better stabilizer for MMRII that would reduce the amount of potency lost over the shelf-life. Both those options required additional time and would still require interim corrective actions.

248.10. A letter from MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee to "Mike," dated October 17, 2002,[657] stated:

> Mike,
> From my perspective the highest priority is ensuring compliance to the label claim.
>
> It is CBER's understanding (as was ours) that Merck took temporary measures in 1999 to accomplish this (add more mumps and change release spec). Based on recent stability analyses using the revised stability model we now believe that we do not have adequate (95%) confidence that the current manufacturing process supports the 4.3 log TCID50/dose label claim. As such, an immediate corrective action must be taken. I see we have at least two options:

[657] Deposition of Roberta McKee, March 30, 2017, 276:9-13 (Mike is MMD's Senior Vice President, Global Quality, Michael Angelo). Metadata for this document is October 17, 2002.

1. Pursue the 4.0 log TCID50/dose end-expiry claim based on the recent clinical trial.

- Probable that we will not meet the pre-established criteria for success of the trial.
- Would have to argue and gain CBER concurrence that the criteria were arbitrarily set and the response rates are still satisfactory.
- May have to change label claim highlighting the lower response rate. This is expected to put us at a competitive disadvantage. Previous discussion with Jeff C[hodakewitz, MRL's Vice President, Infectious Disease and Vaccine Clinical Research][658] indicated that this may not be necessary.
- Would have to communicate to CBER that the steps taken in 1999 were not temporary and we intend to continue to manufacture at the higher mumps titers

2. Modify the product profile (add more mumps/change release spec/shorten expiry dating, etc.)

- Based on discussion with Manal Morsey, [sic] Clinical would likely not support another doubling (add 0.3 log -- the amount needed to preserve 24 month shelf-life) of the mumps content due to lack of experience at these high titers. As such, the shelf-life would have to be shortened to no more than 18 months (maybe less).
- Based on discussion with Rahul Singhvi, manufacturing options to improve stability … do not afford much benefit.
- Such action would be going in the opposite direction that CBER expects. Norman Baylor has commented to me on numerous occasions that the additional mumps in the product was expected to be temporary.

Given what we know today, we must make a decision ASAP. Both options would bring us into compliance with the label. The path forward really is a business one. …We must weigh the pros and cons of each option and make a decision.

[658] Deposition of Roberta McKee, March 30, 2017, 280:18-20 ("I think that's Jeffrey Ch[o]adakewitz.").

> If however Option (1) is not viable and we must move forward with Option (2), I think the stabilizer is critical to our long-term success. Only under these circumstances do I feel the program is critical.

MRK-KRA01649892 at '92-93 (emphasis added).

248.11. A letter from MMD's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee to FDA's Director, Office of Compliance and Biologics Quality, CBER, regarding "Biological Product Deviation Report [BPD 02-007] Measles, Mumps, Rubella Virus Vaccine Live [M-M-R®II]," dated October 18, 2002, stated:

> Merck & Co., Inc. is filing a Biological Product Deviation Report to document investigation into the 24-month out-of-specification measles potency and measles reconstitute and store potency results obtained during testing of M-M-R®II.
>
> Please reference the attached Biological Product Deviation Report Form for the complete investigation and contact me should you require any additional information.

MRK-KRA00754322 (emphasis added).

248.12. BPD 02-007 attached to McKee's October 18, 2002 letter stated:

> B7. Follow Up
>
> Based on this analysis, Merck & Co., Inc. has concluded that no market action is necessary for the M-M-R®II family of products containing measles vaccine. However, based on the findings of the recent stability profile analysis, changes to the product profile are required to provide adequate assurance that the manufacturing process produces product that meets specification through expiry. To address this issue, Merck & Co., Inc. filed a Prior Approval Supplement (PAS) with FDA on September 16, 2002, outlining changes to the measles filling target, release specifications and assay testing scheme. These changes are based upon the comprehensive assessment of stability losses and will ensure compliance to the label claim with 95% confidence. Merck & Co., Inc. is awaiting CBER review of the PAS.

Id. at '27 (original bold removed, underline added).[659]

248.13. A background package for Pediatric Measles, Mumps, Rubella and Varicella-containing Vaccines Franchise: Integrated Vaccine T-PAC Review, dated October 28, 2002, stated:

> I. Executive Summary …
>
> C. New Stabilizer for M-M-R®II …
>
> - Label out of Compliance: Recent evaluations of M-M-R®II show that the current end expiry potency claims for measles and mumps at 24 months will not be met with the current release potency targets. By current calculation models, the end-expiry potency claims would justify a shelf life of less than 12 months, a potentially non-marketable product profile. The recent Prior Approval Supplement (PAS) for the measles component provided a partial remedy to this compliance issue, but at the cost of using approximately 20% more measles bulk to make a lot of vaccine and creating a narrower potency window to target during manufacture. We will be at our maximum manufacturable window will no room for additional process/assay variability. A mumps end expiry study was conducted to support lowering the mumps end expiry potency to 4.0 log TCID50 in the package circular to address this concern. Recently, has been concern that the study has the potential to fail[660] the pre-established immunogenicity criteria due to the decrease in evaluable sample size and the uncertainty in the mumps Plaque Reduction Neutralization (PRN) assay performance. To address this issue the team is considering several short-term options to address mumps expiry potency in the package circular.

MRK-KRA00233586 at '92-93 (emphasis added).

[659] The language in this BPDR is consistent with FDA's expectation of assurance with 95% confidence. While Merck's proposed corrective action for the measles component assured the measles component would meet the measles specification with 95% confidence, it is silent regarding the mumps component of the same product.

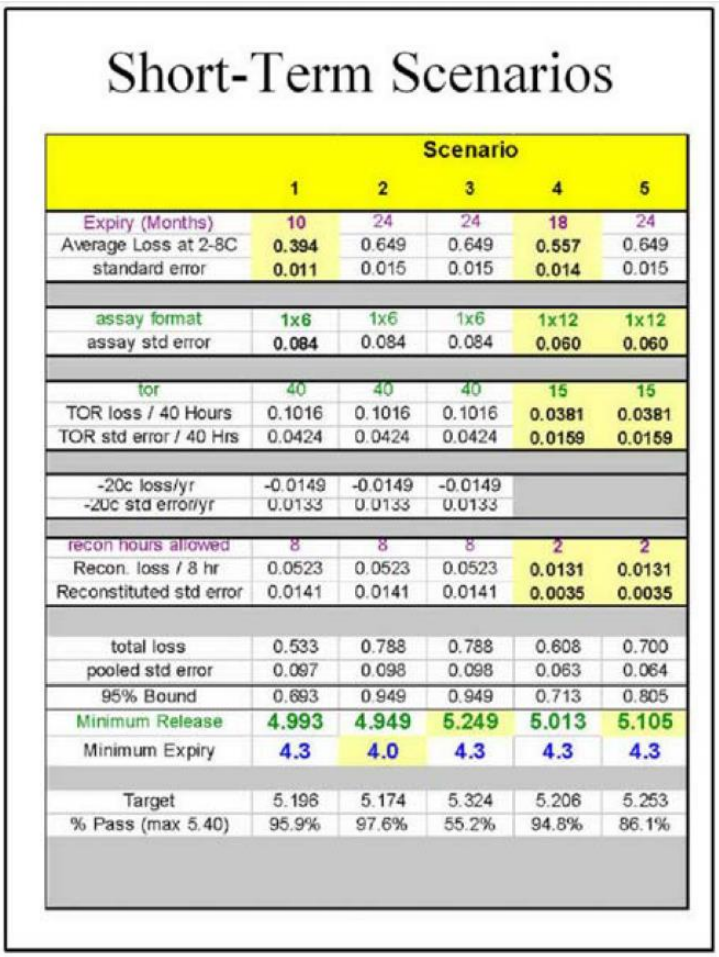
[660] *See* MRK-KRA00018369 (Serial 90); MRK-KRA00621796 at '97 (BB-IND 1016, Serial 92, General Correspondence from Dr. Morsy to Dr. Zoon stated: "We understand that CBER concurred that the 300 samples tested outside the assay SOP are invalid and agreed that Merck invalidated these results" during the teleconference on October 25, 2002.) (emphasis added).

248.14. An email from MRL's Project Manager, Keiko Simon, to MVD's Senior Director, International Sales, Marketing & Operations, Robert Verdugo, MVD's Associate Director, Product Marketing Vaccines, Phil Maher, MVD's Vice President, Vaccines Worldwide Marketing, David Ross, and Mark Twyman, cc'd to MMD's Senior Director, Bioprocess R&D, Biologics Pilot Plant, Dr. Joye Bramble, with the subject "Mumps stability/shelf life assessment," dated October 29, 2002, stated:

> Attached below is a file that T[imothy] Schofield presented at the Friday morning (Oct[ober] 25) meeting with M[erck]M[anufacturing]D[ivision] regarding the technical options to address mumps expiry. ... P[roduct]D[evelopment]T[eam] has proposed (in a preliminary analysis) a series of "fixes" to maximize the shelf life of the vaccine. These now have to enter the phase of a more rigorous evaluation of impact from each of the stakeholder areas. The table (2nd page of the file) contains these options in the form of different scenarios. The table is complicated but basically outlines several different scenarios, [sic] Each scenario uses different "levers" that impact the shelf life of the product. The definition of the scenarios is found on slide 3. …
>
> I have highlighted the options that impact marketing/end user in purple and the ones that impact M[erck]M[anufacturing]D[ivision] in green.

MRK-KRA00561103 (emphasis added).

248.15. Slide 3 [original highlights] stated:



Short-Term Scenarios

	Scenario				
	1	2	3	4	5
Expiry (Months)	10	24	24	18	24
Average Loss at 2-8C	0.394	0.649	0.649	0.557	0.649
standard error	0.011	0.015	0.015	0.014	0.015
assay format	1x6	1x6	1x6	1x12	1x12
assay std error	0.084	0.084	0.084	0.060	0.060
tor	40	40	40	15	15
TOR loss / 40 Hours	0.1016	0.1016	0.1016	0.0381	0.0381
TOR std error / 40 Hrs	0.0424	0.0424	0.0424	0.0159	0.0159
-20c loss/yr	-0.0149	-0.0149	-0.0149		
-20c std error/yr	0.0133	0.0133	0.0133		
recon hours allowed	8	8	8	2	2
Recon. loss / 8 hr	0.0523	0.0523	0.0523	0.0131	0.0131
Reconstituted std error	0.0141	0.0141	0.0141	0.0035	0.0035
total loss	0.533	0.788	0.788	0.608	0.700
pooled std error	0.097	0.098	0.098	0.063	0.064
95% Bound	0.693	0.949	0.949	0.713	0.805
Minimum Release	4.993	4.949	5.249	5.013	5.105
Minimum Expiry	4.3	4.0	4.3	4.3	4.3
Target	5.196	5.174	5.324	5.206	5.253
% Pass (max 5.40)	95.9%	97.6%	55.2%	94.8%	86.1%

MRK-KRA00561105 (highlight in original).

248.16. The scenarios described in the slide and the summary in Ms. Simon's October 29, 2002 can be summarized as follows:

Definition of the scenarios in MRK-KRA00561103	Summary of the scenarios in MRK-KRA00561105
– Scenario 1 is based on the current stability losses for mumps and having to meet the current 4.3 log TCID50/dose.	– Scenario 1: "short date" from 24 months to "10 month shelf life"
– Scenario 2: is if the mumps end expiry study is successful and we get 4.0.	– Scenario 2: Reduce end expiry specification from 4.3 to 4.0 log using [Protocol 007] leaving other specifications un-changed
– Scenario 3: increase the amount of mumps vaccine put into the vaccine to 5.25 minimum at release (however, this is unacceptable from the MMD stand point as the projection is that 55% lots would fail release)	– Scenario 3: Implement a second overfill to increase the minimum release to 5.25. (However, this posed problems for manufacturing as lots with very high amount would be rejected for safety reasons)[661]
– Scenario 4: work the levers: change assay format, TOR[662], recon...and get to 18 months	– Scenario 4: Change label- In order to have 18 month shelf life (rather than the 12 estimated) Merck also needed to adjust other specifications, including the "time out the refrigerator during manufacturing and the time it could be held out at a doctor's office once prepared for use
– Scenario 5: same as scenario 4 but with added overfill of vaccine (not that overfill is 5.1 minimum release).	– Change label as in Scenario 4 but shelf-life at 24 months by increasing the overfill from 5.0 log to 5.1 log.

[661] In the manufacturing process, in order to ensure a release potency of 5.0, Merck set the target as 5.2. Some lots would be filled above 5.2 and other below, but all had to be released above 5.0. If Merck increased the minimum release to 5.25, the target would also have to increase. Because Merck had limited safety data for fills at this higher amount, lots with higher fills would have to be rejected.

[662] "Sealing, inspection and packaging times are included in Time-Out-of-Refrigeration," or TOR. MRK-KRA01894982 at '89.

248.17. A high priority email on behalf of MRL's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee to MMD's Sr. Director, Sterile Process Technology & Engineering, Regulatory & Analytical Sciences, Susan Behrens, MRL's Vice President, Infectious Disease and Vaccine Clinical Research, Dr. Jeffrey Chodakewitz, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MMD's Vice President, Vaccine Technology & Engineering, Barry Garfinkle, Donna Gulbinski, Robert Dolan, MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky, MMD's Director, Vaccine Technology and Engineering, Rahul Singhvi, MRL's Associate Director, Timothy Schofield, and Mark Twyman, with the subject: "Updated: HIGH PRIORITY! Mumps Label Claim/FDA communication – R. McKee (Behrens, Chodakewitz, Chirgwin, Dolan, Garfinkle, Gulbinski, Rosolowsky, Singhvi, Schofield)," dated October 31, 2002, stated:

> Below is background on the issue from Roberta McKee:
>
> Given that our most recent stability analysis for mumps does not support the current label claim, Merck is required to report this finding to FDA. The Biological Product Deviation Reporting regulation[663] requires that this report be made within 45 days of knowledge of the event. I consider Tim's presentation last Friday as "Day 1" which means that the final report must be submitted by Friday, December 6th.
>
> A cross-functional team must convene to develop our path forward and communication plans with the FDA and other agencies. The following items must be resolved:
>
> - Confirm the accuracy of the stability analysis (have the data been audited? any potential for errors here?)

[663] The final rule on "Reporting of Biological Product Deviations in Manufacturing" issued on November 7, 2000 stated: "the final rule more clearly describes the types of events, now termed 'biological product deviations' … are events [that must be reported to FDA] which may affect the safety, purity, or potency of a distributed biological product and which represent either a deviation from CGMP, applicable regulations, applicable standards, or established specifications, or are unforeseen or unexpected." Biological Products: Reporting of Biological Product Deviations in Manufacturing, 65 Fed. Reg. at 66622 (emphasis added).

- Identify any immediate actions that can be taken to minimize impact (reduction in TOR, etc.)
- Develop the proposal for path forward

To that end, I am setting up a one-hour teleconference meeting for 8:00AM on Friday, November 1st to identify and assign specific activities to achieve resolution of the issue. Senior management leadership is critical to provide appropriate guidance and direction on the path forward. Therefore your attendance is important. I appreciate your accommodation of this request.

MRK-KRA00094134 at '34-35 (emphasis added).

248.18. A high-importance email from MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, to MRL's Associate Director, Worldwide Regulatory Affairs, Dr.Manal Morsy, cc'd to Alok Ghosh, Michael Fleming, Kunio Kageura, Roberta McKee, Florian Schodel, Elizabeth Stoner, Mark Twyman, Timothy Schofield, Mark Rosolowsky, Keiko Simon, Ercem Attilasoy, Carlo Russo, and Brian White-Guay, with the subject "Path forward for mumps end expiry," dated November 26, 2002, stated:

In the discussion today with Roberta [McKee]'s working group, agreement was reached on the path forward to support 4.3 mumps through end shelf-life. The agreed upon changes are:

18 mo[nth] shelf life
38 hours maximum T[ime] O[out of] R[efrigeration]
12 mo[nth] -20C storage
4 hours reconstitution
1x12 two-stage testing format.[664]

[664] The agreed upon changes do not match any of the five scenarios presented in Mr. Schofield's presentation (MRK-KRA00561105 at '05) but appear to be a variation on "working the levers," scenario 4. Merck would reduce the total potency loss by reducing the "time out of refrigeration," changing the length of time the vaccine could be

> This translates into the same minimum release spec[ification] for mumps as currently in place (5.0) with same target (5.2); will impose for the first time a max[imum] release spec[ification] (5.4) for mumps. ...
>
> Path forward for communicating and filing this proposal:
> US: FDA background document draft to be circulated this evening will describe this proposal and the submission target is next week. MMD will call next week to let CBER know that the background document describing this proposal will be submitted shortly, with a request a [sic] follow-up teleconference after CBER has time to review the background ... at this point I do not expect that there will be any major contentious issues given that we are basically following the same approach that they have agreed with in concept for measles.

MRK-KRA00560717 at '19-20 (emphasis added).[665]

248.19. MMD's former Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, further testified as follows:

> *Q. And for the record, Exhibit 32 is a document that bears Bates stamp number 560717 through 720. It's a series of e-mails. And I will direct your attention to the e-mail on 719 through 720 which was from Keith Chirgwin to Manal Morsy and, Dr. McKee, you are cc'd on this. Subject: Path forward for mumps end expiry. Do you see that?*
> *A. Uh-huh.*
> *Q. And so in the first paragraph, it says: In discussion today with Roberta's working group – do you see that?*
> *A. Yes.*
> *Q. -- agreement was reached on the path forward to support 4.3 mumps through end of shelf life. Do you see that?*

---

stored frozen, changing the assay used to measure potency at release, and reducing the time a doctor's office could leave the vaccine out after preparing it for use. Even with those changes, the maximum shelf life would need to be reduced from 24 months to 18 months.

[665] MRK-KRA00560717 at '18-19. Multiple replies to this email are redacted as privileged.

A. Yes, I do.

Q. And it says: The agreed upon changes are 18 months shelf life, 38 hours maximum TOR, 12 months at negative 20C storage, four hours reconstitution and a 1 by 12 two-stage testing format. Do you see that?

A. Uh -huh.

Q. Do you recall reaching agreement on November 26, 2002, to change the label for the mumps product to decrease the shelf life from 18 months -- from 24 months to 18 months and make other changes to the manufacturing of the product?

Defense Counsel: Object to form.

A. I don't recall this. Again, this is 15 years ago and there were, you know, many discussions, so I don't recall this specific discussion that's described here, no.

Q. In order to change the shelf life and reduce the reconstitution time on the product, a label change would be required; correct?

A. What do you mean by label change?

Q. Well –

A. Or can you clarify what you mean by label change?

Q. What is the reconstitution that's referenced here? Is that at the doctor's office?

A. Or the administrator.

Q. Whoever is preparing the shots be given to kids; correct?

A. Correct.

Q. And so if that's a change from previously -- do you understand before that the reconstitution was eight hours; correct?

A. Yes.

Q. Okay. To change it from eight hours to four hours would require a label change; correct?

A. I don't believe it requires a label change.

Q. Doesn't the label instruct the doctor how to prepare?

A. Oh, excuse me. You're right. You're right. It does in the when I'm thinking of a label, I'm not -- I'm thinking -- I think you're using a different interpretation of label than I am.

Q. Okay.

A. Okay.

Q. What do you understand the label to be?

A. The physical label on the vial.

Q. Okay. But you understand that the label may also include the package insert; correct?

A. I accept now that you're referring to the more -- to the holistic scope of label.

Q. Okay. And so –

A. When you work in manufacturing for many years and you put labels on things, that's what you think about first, so I apologize for not appreciating the scope of what you're describing.

Q. And so it's commonly understood that the label at Merck is a representation of not just the physical label on the vial –

A. Sure.

Q. -- but, actually, it includes all the packet inserts describing the product and its pharmacology and safety and how to use the product; correct?

A. Instructions for use, correct. Yes.

Q. And so do you recall -- so at this point a decision was made by your working group to change the label; correct?

Defense Counsel: Object to form.

A. At this -- again, I don't recall this meeting, so I can only take at face value what was stated here, so these are agreed upon changes to -- I would say to the process.

Defense Counsel: I'm sorry. Can I just put on the record, too, that I want to object to foundation, as well, to that last question. I apologize.

Q. Do you recall discussions at Merck regarding changing the label to decrease the shelf life claim and to change the reconstitution time?

A. I don't recall. Again, it was 15 years ago and there were -- it's just a long time ago.

Q. So based on the current -- the most recent stability data that we had discussed earlier in Exhibit 28, the path forward was to change the label and reduce the shelf life; correct?

Defense Counsel: Object to form and foundation.

Q. Amongst other manufacturing changes?

Defense Counsel: Same objections.

A. Again, I don't recall those meetings specifically. I can only read what – this note written by Keith Chirgwin reflecting that.

Deposition of Roberta L. McKee, March 30, 2017, 306:19-311:5 (emphasis added).

248.20. An email from MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky, to MRL's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee, MMD's Vice President, Vaccine and Sterile Operations, Robert Dolan, MMD's Vice President, Vaccine Technology & Engineering, Barry Garfinkle, MMD's Sr. Director, Sterile Process Technology & Engineering, Regulatory & Analytical Sciences, Susan Behrens, MRL's Associate Director, Timothy Schofield, Mark Twyman, MVD's Vice President, Vaccines Worldwide Marketing, David Ross; MRL's Vice President, Infectious Disease and Vaccine Clinical Research, Jeffrey Chodakwitz, MRL's Executive Director, Vaccine Integration, Florian Schodel, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, Carlo Russo, and MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, dated December 4, 2002, with the subject "Conversation with Phil Krause re: MMRII," stated:

> I spoke with Phil Krause [Senior Investigator, CBER, Office of Vaccines Research and Review, Laboratory of DNA Viruses] this afternoon on the following topics: ... b) notification of results of applying the enhanced stability model to mumps viruses...
>
> <u>Mumps...PAS</u>
>
> I mentioned that we had ... applied the same enhanced stability model to mumps ... and I proposed that we have a teleconference to discuss our findings, as we had done previously. Of course, a background package would be submitted in advance of the meeting. Phil replied that he didn't think it was necessary to have a teleconference since it was the same general idea that had been agreed to ... My response was that while it was true <u>we were applying the same statistical principles for stability losses</u>, including upper

> release potency specifications, and the same changes to the assay (i.e. house standard calibration and 2-stage testing format), the difference in the case for mumps was that expiry dating and reconstitution/store times would have to be shortened in order to meet the label claim of 4.3 log TCID50 with 95% confidence. For example, shelf life would be shortened from 24 to approx 18 months and reconstitution/store times from 8 to 4 hours. However, we were keeping the current filling target for mumps... I also stated that we had not observed out-of-specification results on stability for mumps .... Phil again did not believe that we needed to convene a teleconference to discuss these changes and recommended that we submit a supplement for these changes. He added that this amount of shelf life would be adequate for us to continue to supply the market. I responded that this was our belief, also...
>
> Phil asked when we would be submitting the mumps ... supplement, and I responded that we would possibly be able to submit by the end of the year, but due to the holidays and a shorter month for most Merck employees, that it would probably be submitted in January.
>
> In closing I asked Phil to contact me if questions come up during review that would apply to mumps ... to ensure that any issues would be addressed prior to submitting the mumps ... supplement. He said he would keep that in mind and would contact us if anything came up. I also mentioned that if he believed that a teleconference was warranted to discuss the mumps ... change to contact me. He said he would.

MRK-KRA00560682 at '82-83 (underline "Mumps ... PAS" original, emphasis added).

248.21. An email from MRL's Vice President, Infectious Disease and Vaccine Clinical Research, Dr. Jeffrey Chodakewitz, to Barry Gertz, Elizabeth Stoner, and Vera Byrnes forwarding Rosolowsky's December 4, 2002 email, dated December 5, 2002, stated:

> FYI, an update re our ability to support the mumps component of MMR prior to resolution of the mumps expiry study. Sounds like a conversation between MMD and CBER indicates good agreement with the approach being used... along with shortening of shelf life and time the vaccine can be held post-reconstitution.

MRK-KRA00560682 (emphasis added).

249. In my opinion, Dr. Rosolowsky's telephone conversation with FDA's Dr. Phil Krause apparently notifying Dr. Krause of Merck's intention to file a Prior Approval Supplement as a corrective action for the mumps potency issue, as documented in a December 2002 email, does not change Merck's obligation to ensure the products that it releases to the market are safe and effective and meet the specifications on the label. Furthermore, a verbal notification to FDA personnel of a corrective action that will take place in the future does not change the manufacturer's obligation to implement an immediate corrective action to correct the problem identified and prevent its recurrence. It is the manufacturer's responsibility to ensure that its products meet the specifications on the label and to comply with all provisions of the Federal Food, Drug, and Cosmetic Act, the Public Health Services Act, and all applicable regulations.

250. In my opinion, in December 2002, Merck still did not have adequate controls to ensure that mumps potency of MMRII would be "not less than 4.3" at end expiry, even the overfill.

6. Merck Did Not Implement the Corrective Action Identified to Ensure Compliance with the "Not Less Than 4.3" on the Label

251. After communicating to FDA's Dr. Phil Krause that Merck could not ensure compliance with mumps end expiry in MMRII and would file the Prior Approval Supplement ("PAS") in January 2003 to change the shelf-life, Merck did not follow through and implement the corrective action. In June 2003, Dr. Roberta McKee sent an internal email that stated that Merck "set the expectation" that the PAS would be filed in the first quarter. In June, it still had not been filed.[666] Also in June, a Clinical Regulatory Review Committee document stated: "there

[666] MRK-KRA01481838.

is potential for the [Protocol 007] study to fail the primary immunogenicity analysis."[667] A draft of a Prior Approval Supplement in July 2003 stated: "the current release titers of 5.0 log10 TCID50/dose for mumps ... are also insufficient to meet the current minimum potencies at expiry of 4.3 ... for a twenty-four month shelf life at 2-8ºC storage."[668] A Prior Approval Supplement to reduce the shelf life for mumps and ensure it met its end expiry specification was never filed. Instead, when results of Protocol 007 showing "similarity of neutralizing antibody and ELISA responses between 4.0 log $TCID_{50}$ and 4.9 log $TCID_{50}$ mumps doses," Merck pursued an "alternative strategy" that again had Merck using the Protocol 007 data to submit a supplemental Biologics License Application to reduce the end expiry claim on the MMRII label.[669] An email from Dr. Keith Chirgwin to himself dated September 22, 2003 stated that Dr. McKee "got a call" from FDA's Dr. Baylor. Dr. Chirgwin's email stated Dr. Baylor "would be comfortable with Merck providing a filing plan that lays out the issues and risk assessment – why the risk is low based on clinical data."[670] Dr. Chirgwin's email also stated: "Need to get this down there ASAP – sooner this happens the sooner we minimize the compliance risk."[671]

251.1. A memo from MRL's Executive Director, Vaccine Integration, Dr. Florian Schodel, to MRL's Vice President, Infectious Disease and Vaccine Clinical Research, Jeffrey Chodakewitz, with the subject "Summary of Monthly Highlights – Biologics, Clinical Research," dated January 16, 2003, stated:

[667] MRK-KRA00190427 at '93.
[668] MRK-KRA01894982 at '85-86.
[669] MRK-KRA00254730.
[670] MRK-KRA00096313.
[671] *Id*. The compliance risk would be lots would fall out of specification while the label continued to state "not less than 4.3 log" for mumps end expiry. Merck could not assure compliance with that specification and had not implemented a corrective action such as short-dating to remediate the risk. *See* MRK-KRA01562819 ("We've been lucky with mumps so far, but it's only a matter of time, since we can statistically predict that a certain number of lots will fail on stability.").

> M-M-R®II
> PRN assay testing of the retain samples from the mumps expiry trial is complete. Final audited data should be available 15JAN03. ... A background document is being drafted to support a change in the M-M-R®II stabilizer ... and will be proposed to CBER in JAN03.

MRK-KRA00525669 at '70.

251.2. An email from MRL's Vice President, Vaccine & Sterile Quality Operations, Dr. Roberta McKee to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, MRL's Vice President, Infectious Disease and Vaccine Clinical Research, Dr. Jeffrey Chodakewitz, MMD's Vice President, Vaccine Technology & Engineering Barry Garfinkle, MRL's Project Manager, Pediatric Combination Vaccine Program, Dr. Alison Fisher, MRL's Executive Director, BARDS Vaccines, MRL's Executive Director, BARDS Vaccines, Joseph Heyse, Ann Lee, Scott Reynolds, MRL's Senior Director, PR&D Vaccine siRNA Group, Carl Burke, MMD's Senior Director, Regulatory & Analytical Sciences, Mark Rosolowsky, MRL's Executive Director, Vaccine Integration, Florian Schodel, MRL's Statistician, BARDS, Philip Bennett, and cc'd to Robert Sitrin, John Hennessey, Linda Lou Johnson, Pete DePhillips, Scott Reynolds, and Jonelle Rittenhouse, with the subject "Follow-Up: M-M-R®II House Standard Assignment," dated June 11, 2003, stated:

- Quickly prepare and submit the mumps supplement to reduce expiry to 18 months and include the upper specs for mumps and rubella. Note that Phil Krause was informed of the mumps issue last December and we set an expectation that we would file this in 1Q.

MRK-KRA01481838 (emphasis added).

251.3. A document titled "CRRC [Clinical Regulatory Review Committee] Development Projects," dated June 17, 2003, stated:

> Due to the reduction in the number of evaluable subjects, and uncertainty in the performance of the mumps PRN assay, there is potential for the study to fail the primary immunogenicity analysis.

MRK-KRA00190427 at '93 (original bold removed, underline added).[672]

251.4. A draft version of a Prior Approval Supplement (PAS) titled "Mumps and Rubella Formulation and Potency Assay Format Changes to Support Potency through Twenty-four Month Expiry," dated July 28, 2003, stated:

> Introduction….
> A similar evaluation of the mumps ... components has been performed using the enhanced release model and is the subject of this document. The results of these analyses indicated that the current release titers of 5.0 $\log_{10}$ $TCID_{50}$/dose for mumps ... are also insufficient to meet the current minimum potencies at expiry of 4.3 ... for a twenty-four month shelf life at 2-8ºC storage.
>
> In order to apply our comprehensive statistical model to the mumps component in M-M-R®II, manufacturing and testing changes are required, including the establishment of a higher minimum release specification for the mumps virus component and a reduction in TOR. In addition, a maximum release specification for the mumps component will be implemented to ensure that the product does not exceed historically observed release potencies. Potency assay format changes are also necessary to ensure that the proposed minimum and maximum specification window can be met for release of the final product.
>
> Together these changes will ensure, with 95% confidence, that any lot will maintain a mumps potency of at least 4.3 log10 TCID50/dose at expiry.

MRK-KRA01894982at '85-86 (original bold removed, underline added).

[672] *See also* MRK-KRA00615152 at '55, '70 (October 2, 2002 background document prepared by Product Development Team for MMRII stated: "[T]here are now several outstanding risks for the successful completion of the end expiry study. First, [t]he study may not meet the 5% equivalence criteria …and/or lower 95% CI for 90% seroconversion rate. Second, M-M-R®II may have to remain at the current expiry dose of 4.3 log TCID50/dose which would only support <12 months expiry using current data in the stability model.") (emphasis in original).

251.5. A memo from MRL's Project Manager, Keiko Simon, to Distribution, with the subject "Proposed filing strategy for M-M-R®II activities," listing meeting attendees MMD's Senior Director, Bioprocess R&D, Biologics Pilot Plant, Dr. Joye Bramble, MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinksi, MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, MRL's Director, Clinical Research, Barbara Kuter, MRL's Executive Director, Vaccine Integration, Florian Schodel, MRL's Senior Director, Bioprocess Development, Mike Washabaugh, and MRL's Project Manager, Keiko Simon, dated August 19, 2003, stated:

> A meeting was held to discuss the strategies for the various planned filings for M-M-R®II in light of the recently released positive clinical data for ... #007 (demonstrated similarity of neutralizing antibody and ELISA responses between 4.0 log $TCID_{50}$ and 4.9 log $TCID_{50}$ mumps doses)...
>
> US filing strategy: An alternative strategy was discussed and proposed for further evaluation.
>
> This strategy lays down the foundation for House standard calibration, upper (& lower) release specifications, and mumps expiry in the filing; as well as maintaining product expiry at 24 months. ...
>
> Strategy is as follows...
> 1. House standard calibration PAS for mumps, rubella, and responses to CBER questions for measles: file T-Oct03. The team's working assumption is that since protocol #007 was successful, the mumps PAS will not include the proposal to add an additional 0.1 log TCID50 mumps to increase expiry to 24 months (end expiry – 4.3 log TCID50), 8h recon/store time, and 40h TOR. The assumption will be confirmed in discussions with MMD and MVD.

2. Mumps end expiry study (sBLA): File as soon as possible. Timing to be established at a subsequent meeting.

3. rHA replacement[673] (sBLA): file concurrently (or soon after) mumps expiry sBLA. Note that this strategy could delay the rHA submission due to the need to wait for mumps expiry submission.

MRK-KRA00254730 (original bold removed, underline added).

251.6. A memo from Mandie Lyon and MRL's Project Manager, Keiko Simon, dated November 23, 2003, with the subject "Notes from September 9, 2003 meeting," listing attendees Joye Bramble, Peggy Fahnestock, Mark Galinski, Jonathan Hartzel, J. Liptock, V. Liska, Mandie Lyon, P[ ]. Maher, Manal Morsy, Luwy Musey, Alan Shaw, and Keiko Simon, stated:

II. Overall Filing Strategy for M-M-R®II Programs

A. Planned Submissions for M-M-R®II

- The strategy and timing of submission for the US and E.U. planned submissions is the outcome of cross divisional discussions between MMD, Regulatory, Marketing and Clinical.
- House Standard (HS) Calibration and Upper Specifiactions [sic] for measles, mumps, and rubella (US): ...
  - Mumps and rubella upper specifications will be combined into a PAS and submitted simultaneously with the Mumps End Expiry Supplemental Biologics License Application (sBLA).
- Mumps End-Expiry (US): Timing of the rHA sBLA has been tentatively scheduled for JAN04. A 1 y[ea]r review period is expected, however CBER may accelerate this process due to compliance issues. A request to CBER to not shorten the product shelf-life during the review period will be made.

[673] Merck planned to replace human serum albumin used in the bulk manufacturing process with a recombinant human albumin to address ongoing safety and sourcing concerns related to human-blood derived products. *See* MRK-KRA00137854. "CBER and European regulatory agency officials [had] requested and recommended the removal of HSA derived from plasma in the manufacture of MMRII." MRK-KRA00262316 at '18.

MRK-KRA01568581 (original bold removed, underline added).

251.7. An email from MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin to himself, with the subject: Mvx 9/22," dated September 22, 2003, stated:

> 9/23
>
> R[oberta] McKee - got a call from N[orman] Baylor [CBER] re[garding] mumps expiry path [forward]. N[orman] B[aylor] would be comfortable with Merck providing a filing plan that lays out the issues and risk assessment – why the risk is low based on clinical data. Filing strategy would be as follows: lay out what CMC mod[ification]s we would make; upper spec[ification]s for mu[mps], ru[bella]; timing for filing expiry trial. From his perspective by having this filing plan submitted with risk assessment this allows CBER to just come back and say that they would concur with plan and allows them to be silent on the label noncompliance issue. This notifies them of the issue and provides a plan for how to address – allows them to come back and agree with us. We would need to meet whatever commitment we make. N[orman] B[aylor] somewhat nervous and we will need to do some negotiation internally. Agrees that interim filing (i.e. shorter shelf-life) does not really do anyone much good. Need to get this down there ASAP – sooner this happens the sooner we minimize the compliance risk.

MRK-KRA00096313 (emphasis added).

252. In my opinion, Merck did not execute the corrective action it represented to FDA's Dr. Krause that it would take in January 2003, or any time thereafter. Merck's "alternative strategy" was to use Protocol 007 data instead of changing the MMRII label to reduce the shelf-life and ensure currently marketed product met the label specification of "not less than 4.3" for mumps at end expiry.

253. In my opinion, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin's September 2003 email regarding "a call" from FDA's Dr. Baylor did not change Merck's obligation to ensure the products that it releases to the market are safe and

effective.[674] It is the manufacturer's responsibility to ensure that its products meet the specifications on the label and to comply with all provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Services Act, all applicable regulations, including reporting when the manufacturer cannot assure the product will meet its specification throughout its shelf-life. In my opinion, through the end of 2003, Merck still could not ensure that MMRII vaccine had "not less than 4.3 log10 [20,000] TCID50" of mumps virus per dose through end expiry.

7. Merck Continued to be "Out of Compliance" and its MMRII Label was "Wrong" in 2004

254. In 2004, Merck's Philip Bennett provided analysis of stability and potency data for the mumps component of MMRII dated February, March, and November 2004. Mr. Bennett's 2004 analyses continued to document Merck's inability to ensure the 4.3 $\log_{10}$ [20,000] TCID50 at expiry with a 24-month shelf life, even after the overfill. Also in 2004, Merck regulatory affairs personnel continued to document that Merck's stability model "does not support an expiry of 20,000 [4.3 log] after storage for 24 months"[675] and that the MMRII label with an end expiry specification of "not less than 4.3 log10 TCID50" was "wrong."[676]

254.1. A memo from MRL's Statistician, BARDS, Philip Bennett, to MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, dated February 9, 2004, with the subject "Determination of Minimum Release Specifications for Mumps and Rubella in M-M-

[674] *See* MRK-KRA00560682 at '82-83.
[675] MRK-KRA01564065 at '67 (emphasis in original).
[676] MRK-KRA01574732 at '32-33.

R®II," and with a reference to "Memo Bennett to Morrissey 'Stability of Mumps Virus Vaccine at 2-8ºC ... and Determination of Minimum Release Specification' January 2, 2003,"[677] stated:[678]

> SUMMARY
>
> The above referenced memos report the stability and minimum release specifications for mumps and rubella components of M-M-R®II. This report uses the same stability determinations with slightly different shelf life storage conditions, a reduced minimum expiry of 4.1 $\log_{10}$ $TCID_{50}$ per dose for mumps,[679] and 1 x 12 release assay[680] to calculate the required minimum release specifications for mumps and rubella.[681]

Storage	Maximum
2-8°C Shelf Life	24 months
-20°C Storage (Pre-Packaging)	12 months
TOR (Packaging Operations)	40 hours
Reconstituted (End User)	8 hours
Calculated Minimum Release Spec ($\log_{10}$ $TCID_{50}$ per Dose)	Mumps: 5.0 Rubella: RED

MRK-KRA01580008 (emphasis added).

254.2. The February 9, 2004 Bennett memo also stated:

> MINIMUM RELEASE SPECIFICATION DETERMINATION:

[677] MRK-KRA00720264 at '64, '68 (January 2, 2003 Bennett to Morissey. The memo lists a "Proposed" 18 month 2-8ºC shelf life. The memo calculated a 5.0 $\log_{10}$ $TCID_{50}$ minimum release specification using a 4.3 $\log_{10}$ $TCID_{50}$ end expiry specification and an 18 month 2-8ºC shelf life.).

[678] The link referenced in the table to additional information on the 5-year weekly average calculation is no longer accessible at http://www.cdc.gov/ncphi/disss/nndss/phs/files/5yearweeklyaverage.pdf. As of March 14, 2017, the information is available at https://wwwn.cdc.gov/nndss/document/5yearweeklyaverage.pdf.

[679] All measurements were raised by 0.1 log when Merck adjusted its house standard making a measure of "4.0 log" a measurement of "4.1 log." *See* MRK-KRA00000315 at '37; *see also* MRK-KRA01971197 ("Calibration of potency results to a reference standard was approved by CBER on May 18, 2004."); Schedule 5 (describing house standard).

[680] In 2004, Merck requested and gained FDA approval to change its release potency assay from a 1x6 assay to a 1x12 assay. *See* MRK-KRA01926962; MRK-KRA01971200; MRK-KRA01971199; MRK-KRA01971197; MRK-KRA01971196.

[681] In 2004, 5.0 log [100,000] was the minimum release specification that Merck implemented to ensure not less than 4.3 log [20,000] at end expiry. Mr. Bennett's February 2004 analyses showed that in order to ensure 4.1 log at end expiry, the minimum release needed to be 5.0. The 5.0 minimum specification was inadequate to ensure compliance with 4.3 at end expiry given the known potency loss.

The loss estimates and standard errors that are used to determine the minimum release potency specification limits needed to ensure with 95% probability that the minimum expiry potency would be met at the end of the shelf life are listed below. The calculations are summarized in the following tables, and described below:

			Mumps			Rubella
Storage	Loss Estimate	Std Error	Duration	Loss[1]	Var[2]	REDACTED – OMP
Release Potency Assay Variability [3]						
Mumps		0.060			0.00356	
Rubella		REDACTED – OMP				
Room Temperature (Sealing/Inspection/Packaging)						
Mumps	0.10163 / 40 Hr	0.04244	40 Hrs	0.10163	0.00180	
Rubella	REDACTED – OMP					
-20°C Storage						
Mumps	-0.01493 / Yr [4]	0.01325	1 Yr	-0.01493	0.00018	
Rubella	REDACTED – OMP					
2-8°C Storage						
Mumps	0.54338 / 2 Yrs	0.02671	2 Yrs	0.54338	0.00071	
Rubella	REDACTED – OMP					
Reconstituted storage by physician						
Mumps	0.05272 / 8 Hr	0.01411	8 Hrs	0.05272	0.00020	
Rubella	REDACTED – OMP					
			Total :	**0.6828**	**0.00645**	

1. Loss is the loss estimate for the duration at each step in the product profile.
2. Var (variance) is the square of the duration x the standard error per time:

   *Variance = (std err * duration)*^{2}
3. The values for the release assay variability represent the standard error of a 1 x 12 assay (one vial assayed in each of the 12 independent tests calibrated to the concurrently tested house standard).
4. A negative loss estimate for -20ºC storage reflects the observed increase in the data.

The minimum release potency is calculated using the minimum potency at expiry (4.1 $\log_{10}$ [12,500] $TCID_{50}$ / dose for Mumps ...) and adding the total loss plus a factor of 1.65 times the square root of the total variance. This gives the minimum release potency that will provide 95% probability of meeting the expiry limit.

	Minimum Expiry	+ Total Loss	+ 1.65 x $\sqrt{TotalVariance}$	=	Minimum Release
Mumps	: 4.1 $\log_{10}$TCID$_{50}$	+ 0.6828	+ 1.65 x 0.0803	=	4.92 $\log_{10}$TCID$_{50}$
Rubella	REDACTED – OMP				

Potency units are per 0.5 mL dose.

Since release potency determinations are reported to 0.1 $\log_{10}$, the minimum release estimates are conservatively rounded up to provide the proposed minimum release specifications of 5.0 $\log_{10}$ TCID$_{50}$/dose for mumps...

Id. at '009 (emphasis added).

254.3. A memo from MRL's Statistician, BARDS, Philip Bennett to MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, dated March 29, 2004, with the subject "Determination of Minimum Release Specifications for Mumps in MMRII, and also referencing "Memo Bennett to Morrisey 'Stability of Mumps Virus Vaccine at 2-8ºC... and Determination of Minimum Release Specification' January 2, 2003," stated:

SUMMARY

The above referenced memo reports the stability and minimum release specifications for mumps components of M-M-R®II. This report uses the same stability determinations with different shelf life storage (24 mos. v. 18 mos.) and a lower minimum expiry specification (4.1 log10 TCID50 per dose v. 4.3) to calculate the required minimum release specification.

Storage	Maximum
2-8°C Shelf Life	24 months
-20°C Storage (Pre-Packaging)	12 months
TOR (Packaging Operations)	35 hours
Reconstituted (End User)	8 hours
Minimum Expiry Specification:	4.1
Calculated Minimum Release Spec: ($\log_{10}$ TCID$_{50}$ per Dose)	4.9

MRK-KRA01580010 (emphasis added).[682]

254.4. An email from MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, to MRL Associate Director, Alison Fisher, and Merck Sharpe Dohme (New Zealand) Regulatory Affairs Manager, J. Margaret Relph, with the subject: "MMRII (HSA) Updates," dated August 20, 2004, stated:

> The... stability model[683] that was constructed for predicting the mumps minimum release specification to expiry (dose-claim) window **does not** support an expiry of 20,000 after storage for 24 months at 4-8 ˚C. This potency window is adequate for 18 months. This is why the Mumps End Expiry Study is important as it supports an expiry potency of 12,500 for the full 24 months.

MRK-KRA01564065 at '67 (bold original emphasis, underline added).

254.5. An email from MRL's Associate Director, Worldwide Regulatory Affairs, Alison Fisher, to Merck, Sharp & Dohme, Regulatory Affairs/ Europe/ Vaccines, Guy Demol, cc'd to Keiko Simon, Heather Joseph, Mary Macchi and Mark Galinski, with the subject: "RE: EU submission MMRII Mumps End Expiry and rHA," dated September 18, 2004, stated:

> Today Ercem [Attilasoy], Keith [Chirgwin], and others met to discuss path forward with respect to MMRII and updating the mumps end expiry in our label for the H[uman]S[erum]A[lbumin] product that will be on the market longer than we thought.

[682] The only difference between the February 2004 and March 2004 memos is the maximum time out of refrigeration (TOR) for sealing, inspection, and packaging operations. *Id*. at '11. In March 2004, Mr. Bennett's analyses still showed that the current release specification of 5.0 together with the known potency loss supported a 4.1 end expiry, not the 4.3 log on the MMRII label.

[683] These calculations are consistent with Mr. Bennett's calculations in his February and March 2004 memos.

> As we discussed yesterday, there will be a delay in the launch of MMRII with rHA, which means there is a compliance gap for our current H[uman]S[erum]A[lbumin] product in some of the countries in the EU.[684]
>
> Some of those countries have a mumps end expiry of 20,000 in their labels (4.3 log TCID50), which is wrong as we cannot guarantee this potency in our product, and some countries have 5000 as mumps end expiry, the wrong number, but at least we can guarantee this amount of mumps in our product).
>
> Kieth [sic] stressed to work to remediate labels in countries who are out of compliance with respect to mumps end expiry potency first, that would be countries with 20,000 TCID50 (4.3 log) in the MMRII label.

MRK-KRA001574732 at '32-33 (emphasis added).

254.6. A memo from MRL's Statistician, BARDS, Philip Bennett, to MMD's Quality Assurance, Biological Stability Unit, Bioanalytical Development, Mary Macchi, with the subject "Determination of Minimum Release Specifications for Mumps in M-M-R®II," dated November 4, 2004, referencing "Memo Bennett to Galinski 'Determination of Minimum Release Specification for Mumps in M-M-R®II' March 29, 2004"[685] stated:

> SUMMARY
>
> The above referenced memo reports the stability and minimum release specifications for mumps components of M-M-R-®II. This report uses the same stability determinations with different scenarios for shelf life storage (18 and 24 months) and TOR (35 and 40 hours) with a minimum expiry specification 4.3 $\log_{10}$ $TCID_{50}$ per dose to calculate the required minimum release specification.[686]

[684] In June 2004, Merck submitted a Supplemental Biologics License Application for a manufacturing change from Human Serum Albumin to Recombinant Human Albumin. *See* Sections IX.A.5.b, A.6.b, A.7.b below describing the sBLA.
[685] *See* MRK-KRA01580010; *see also* paragraph 253.3 above discussing the March 29, 2004 memo.
[686] The fourth column in Mr. Bennett's memo depicts Merck's label specification in 2004. According to Mr. Bennett's analysis, the minimum release specification required to assure "not less than 4.3" for the 24 month dating

Storage				
2-8°C Shelf Life	18 months	18 months	24 months	24 months
-20°C Storage (Pre-Packaging)	12 months	12 months	12 months	12 months
TOR (Packaging Operations)	35 hours	40 hours	35 hours	40 hours
Reconstituted (End User)	8 hours	8 hours	8 hours	8 hours
Release Assay Format	1 x 12	1 x 12	1 x 12	1 x 12
Calculated Minimum Release Spec: (log_{10} $TCID_{50}$ per Dose)	5.1	5.1	5.1	5.2

MRK-KRA01580012 (emphasis added).

254.7. The November 4, 2004 Bennett memo also stated:

> MINIMUM RELEASE SPECIFICATION DETERMINATION: …
> The minimum release potency is calculated using the minimum potency at expiry (4.3 log_{10} $TCID_{50}$/dose for Mumps) and adding the total loss plus a factor of 1.65 times the square root of the total variance. This gives the minimum release potency that will provide 95% probability of meeting the expiry limit.
>
> For example, for 35 Hours TOR and 24 Months at 2-8°C:

	Minimum Expiry	+	Total Loss	+	1.65	x	$\sqrt{TotalVariance}$	=	Minimum Release
Mumps :	4.3 $log_{10}TCID_{50}$	+	0.6701	+	1.65	x	0.0777	=	5.1 $log_{10}TCID_{50}$

> Potency units are per dose.

Id. at '13 (emphasis added).

255. Mr. Bennett's memos evidence Merck's continued inability to ensure the mumps component of MMRII would meet the "not less than 4.3" log10 TCID50/dose expiry specification on the label.[687] Furthermore, Merck's regulatory affairs officers continued to

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period and the TOR specification in place at that time was 5.2, not the 5.0 minimum specification implemented with the start of the overfill in 1999. FDA approved a minimum release of 5.0, not 5.2. MRK-KRA01897091 ("The Supplements to your License Applications … to include an increase in the minimum release titer for the mumps component to 5.0 log10 [100,000] TCID50 …have been approved.") (emphasis added).

[687] *See also* MRK-KRA00561103 describing attempts to "work the levers" in October 2002 to ensure compliance with not less than 4.3 at expiry for mumps; MRK-KRA00561105 (Slides: "Short Term Scenarios").

document that Merck's label stating "not less than 4.3" was "wrong" and that Merck had a "compliance gap" until the end expiry potency for mumps was reduced. Moreover, Merck's regulatory officers identified the Protocol 007 end expiry trial as "important," as it "supports an end expiry specification of 12,500 [4.1 log10] TCID50/dose."

256. In my opinion, it is the manufacturer's responsibility to ensure that its products meet the specifications on the label and to comply with all provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Services Act, all applicable regulations, including the reporting when the manufacturer cannot assure the product will meet its specification throughout its shelf-life. In my opinion, through the end of 2004, Merck still could not ensure that MMRII had "not less than 4.3 log10 [20,000] TCID50" mumps virus per dose through end expiry.

8. Merck's Continued Inability to Ensure Compliance Until the MMRII Mumps Potency Claim Was Lowered in 2007

257. While I am a professor of biostatistics and trained in pharmacology, in my regulatory and medical experience, I have regularly relied on statisticians and biopharmaceutical scientists to provide me information to support my work. Furthermore, it is customary in my fields of expertise to rely on such subject matter experts. In this section of my report, I have taken into consideration the expert opinions of Dr. Phillip Stark and Dr. Mark A. Schenerman, as discussed below.

258. In June 2004, Merck filed a Supplemental Biologics License Application ("sBLA") to support the change from HSA (Human Serum Albumin) to rHA (Recombinant Serum Albumin) in the manufacture of MMRII (the "sBLA for rHA").[688] The sBLA for rHA included a section on

[688] MRK-KRA00137854.

MMRII stability data.[689] The stability calculations Merck submitted in the sBLA for rHA did not ensure MMRII's mumps component contained "not less than 4.3 $\log_{10}$ TCID/$_{50}$" at expiry as specified on the label.[690] In June, 2005, FDA requested information regarding the stability calculations in the still-pending sBLA for rHA.[691] In response, Merck modified the "Comprehensive Statistical Release Model" it used to project minimum release specifications for MMRII. The updated stability model used all the time points in the model, from time zero through time approximately 30 months, in the calculation of the loss rate for storage at 2-8˚C over 24 months.[692] The 2005 modification of the stability model time period had the effect of decreasing the overall average loss rate of the model.[693] Merck submitted the modified stability model in a July 2005Amendment to the sBLA for rHA.[694] The modified stability model submitted to FDA in 2005 represented that Merck could ensure compliance with the "not less than 4.3 $\log_{10}$ TCID/$_{50}$" mumps end expiry specification on the MMRII label.[695]

[689] MRK-KRA00138585 (sBLA for rHA, Module 3 "Quality," Section 3.2.P "Drug Product – M-M-R™II with rHA," Subsection 3.2.P.8.3, "Stability Data.").
[690] The June 2004 sBLA for rHA included a stability calculation demonstrating compliance with an end expiry specification of not less than 4.1 log. *See* MRK-KRA00138585 at '705 (The "Basis for the Label Claim" states, "[E]nd-expiry specification for... mumps... for M-M-R™II with rHA will be defined as... ≥12 5000... $TCID_{50}$/dose ... translating to log scale potency values of... ≥4.1 ... log $TCID_{50}$/dose").
[691] As discussed in Section IX.A.5 below, Merck submitted two sBLAs in 2004 seeking approval to change MMRII. The first sBLA, filed in January, was to change the mumps end expiry potency from 4.3 log to 4.1 log. Merck followed with the sBLA to change from HSA to rHA in June 2004. In June 2005, after FDA denied the sBLA to change the mumps end expiry potency, and while the rHA application was still pending, the potency claim on the MMRII label continued to state "not less than 4.3." *See* Sections IX.A, B and C below (discussing the two sBLAs).
[692] *See* MRK-KRA00689798 (excel spreadsheet entitled "Mumps 5C updated lots TSchofieldjun05.xlx"); MRK-KRA00722667 (Philip Bennett to Mary Macchi memo dated November 4, 2004 with subject, "Determination for Minimum Release Specification for Mumps in M-M-R®II"); MRK-KRA00048712 at '13 (June 22, 2005 "[Table 3.2.P.8.3-mmr; 35] Calculation of Mumps Overall Stability Profile...").
[693] I have read the expert reports of Dr. Mark A. Schenerman and Dr. Phillip Stark regarding the modification to the stability model and the impact on average loss rates discussed in this section. *See also*, MRK-KRA00138585 at '707; MRK-KRA00141789 at '885.
[694] MRK-KRA00125553 (July 13, 2005 letter from Allison Fisher to Norman Baylor (CBER) (Serial No. 089, BB-IND 10076, "INFORMATION AMENDMENT - CHEMISTRY, MANUFACTURING AND CONTROL"); MRK-KRA00141789 (July 13, 2005 letter from Allison Fisher to Norman Baylor (CBER) (STN 101069/5068, "Amendment to Supplemental Biological Licensing Application - June 30, 2004").
[695] MRK-KRA00141789 at '871.

258.1. The sBLA for rHA, 3 Quality, Quality Overall Summary, Section 8.3 Stability Data, 8.3.6.3, "Basis for Minimum Release Potency Specification, stated:

> The 24-month shelf-life claimed includes potency losses occurring at room temperature during sealing, inspection, and packaging, -20˚C storage before packaging, loss during 2-8˚C storage after packaging for up to 24 months, and up to 8 hours at 2-8˚C following reconstitution immediately prior to use.

MRK-KRA00138585 at '706 (emphasis added).

258.2. The sBLA for rHA, Stability Data Section 8.3.6.3, also stated:

8.3.6.3.2 Minimum Release Potency Limit for Mumps

The loss estimates and standard errors for mumps potency were used to determine the minimum post-lyophilization release specification limit needed to ensure, with 95% probability, that the minimum expiry potency of 4.1 log $TCID_{50}$/dose, following reconstitution and up to 8 hours at 2–8 °C, would be met. These variables are summarized in [Table 3.2.P.8.3-mmr; 35].

[Table 3.2.P.8.3-mmr; 35] Calculation of Mumps Overall Stability Profile Using the Comprehensive Statistical Release Model

Storage	Loss Rate (log $TCID_{50}$/ unit time)	Standard Error (SE) (log $TCID_{50}$)	Duration
Storage at 23–27 °C *(Sealing/Inspection/Packaging)*	0.10163/40 hours	0.04244	40 hours
Storage at ≤ –20 °C	–0.01493/year	0.01325	1 year[a]
Storage at 2–8 °C	0.54338/24 months	0.02671	24 months
Storage at 2–8 °C following Reconstitution	0.05272/8 hours	0.01411	8 hours
Release Potency Assay (1x12) Variability *(Std. Deviation)*	N/A	0.060	N/A

N/A: Not applicable.
[a] A transfer study is in progress to extend storage at ≤ –20 °C to 18 months.

The release potency required to guarantee minimum mumps potency at expiry of ≥4.1 log $TCID_{50}$/dose is calculated utilizing the total loss (0.6828) and the total variability (square root of the total variance, $\sqrt{0.00645}$). Using the one-sided 95% critical value from a standard normal distribution (1.65) the minimum release potency needed to ensure a 95% probability of exceeding the expiry potency is:

Minimum Release Potency = Minimum Expiry + total loss + (1.65 x $\sqrt{TotalVariance}$)
= 4.1 log $TCID_{50}$/dose + 0.6828 + (1.65 x 0.0803)
= 4.92 log $TCID_{50}$/dose

Id. at '707 (emphasis added).

258.3. An original appointment invitation from MRL's Senior Administrative Assistant, Heather Sinsel, to herself with the subject: "Updated: URGENT (see enclosed): M[umps] E[nd] E[xpiry] Potency of 4.3 TCID 50 requested for rHA MMRII – Pathforward," dated June 13, 2005, stated:

> Urgent Meeting:
> Emerging issue- Alison Fisher received a call from Daryll Miller (FDA) on Friday, June 10th. Daryll Miller mentioned that in order to approve the rHA file, the Mumps End Expiry potency in the label needs to be moved from log10 4.1 TCID50 to log10 4.3 TCID50 because the Mumps End Expiry file is not yet approved.[696] She also mentioned that the stability model in the drug product section would need to be changed to support the potency of log10 4.3 TCID50 in the label. ... [T]he stability model in the drug product section would suggest that we can not support an e[nd] e[xpiry] potency of 4.3[697]...
>
> Ms. Daryll Miller also asked if there was any difference in terms of minimum release potency for the currently marketed product and the rHA product. I mentioned that there is no difference in the minimum release potency. Therefore, Daryll Miller is confused by the fact that the HSA product would seem to have a .7 log loss in Mumps End Expiry

[696] As part of the sBLA for rHA, Merck submitted proposed labeling. Since it submitted the sBLA for rHA after the sBLA to change mumps end expiry, the proposed new label submitted with the sBLA for rHA had a 4.1 log mumps potency claim in the Description section of the label. *See* Section IX.A.5.a and b.

[697] The sBLA for rHA included potency specifications in Section 2.3 "Quality Overall Summary," Subsection 2.3.P.8.3, "Stability Data." *See* MRK-KRA00137934 at '7994 ("Since the two products [M-M-R™II with rHA and the currently licensed M-M-R™II with HSA] have similar stability profiles for infectivity titration, the same loss model developed for the currently licensed product will be applied to M-M-R™II with rHA. … …The loss model and end-expiry study results support the mumps minimum release specification of 5.0 and expiry claim of ≥4.1 log TCID50/dose, respectively. The loss model also supports a 24-month shelf life at 2-8˚C for M-M-R™II manufactured with rHA.") (emphasis added); *id.* at '8015 ("The potency specifications for M-M-R™II with rHA filled container product have been derived from the M-M-R™II with HSA product. …[T]he expiry potency limit for mumps was based on clinical experience with commercially released lots of M-M-R™II with HSA. Minimum potencies at release are calculated using stability data from single dose M-M-R™II with HSA lots manufactured between January 1995 and June 2001.").

> Potency over 24 months but the rHA product would appear to have a .9 log loss in Mumps End Expiry potency over 24 months.[698]
>
> This is an URGENT issue please be prepared to discuss today at the meeting. Please plan to attend if at all possible.

MRK-KRA00256875 (emphasis added).

258.4. An email from MMD's Regulatory Coordinator, Quality Assurance, Biological Stability Unit, Bioanalytical Development, Mary Macchi, to MRL's Director, BARDS, Timothy Schofield, Subject "Stability Models," dated June 22, 2005, stated:

> As per our conversation earlier today, could you please provide the data to complete a mumps stability model table similar to the table on page 123 of P.8.3 (attached below). The calculations should be based on the new loss calculation at 2-8 C (with standard rounding). I am assuming that the loss rates and standard errors for the storage at 23-27 C, storage at 2-8 C following reconstitution, and the release potency assay variability will not change.

MRK-KRA00560284 (emphasis added).[699]

258.5. A letter marked "Serial No. 89" from MRL's Associate Director of Worldwide Regulatory Affairs, Alison Fisher to FDA's Office of Vaccines Research and Review, CBER, Norman Baylor, with the subject: "BB-IND 10076: Measles, Mumps, and Rubella Virus Vaccine Live with Recombinant Human Albumin (*S. cerevisiae*, Aventis Behring) Excipient,"

[698] The confusion would appear to be because both the HSA and rHA product had a minimum release specification of 5.0 log, but the loss model submitted with the sBLA to approve the new formulation represented MMRII with rHA as having 0.9 log loss (5.0-0.9 = 4.1). Since the currently marketed HSA product had a label claim of 4.3 log, it would appear Ms. Miller reconciled the difference by assuming the average loss for the HSA product was different (5.0 – 0.7 = 4.3). Ms. Miller, it would appear, did not understand that Merck could not ensure not less than 4.3 log for the currently marketed product; it could only ensure not less than 4.1 log according to Mr. Bennett's analyses. *See* MRK-KRA01580008 (February 9, 2004 Philip Bennett memo to Mark Galinski with the subject, "Determination of Minimum Release Specifications for Mumps and Rubella in M-M-R®II"); MRK-KRA01580010 (March 29, 2004 Philip Bennett memo Mark Galinski with the subject, "Determination of Minimum Release Specification for Mumps in M-M-R®II", calculating the minimum specification to support the 4.1 expiry).

[699] MRK-KRA00560284 at '284-285 (Tim Schofield's reply to Mary Macchi, including a table titled "Calculation of Mumps Overall Stability Profile Using the Comprehensive Statistical Release Model").

"INFORMATION AMENDMENT-CHEMISTRY, MANUFACTURING AND CONTROL," dated July 13, 2005, stated:

> Merck Research Laboratories (MRL), a division of Merck & Co., Inc. is submitting the following information as an amendment to the subject Investigational New Drug application in response to a telephone conversation with Daryl Miller on June 28, 2005 and an email on July 1, 2005.
>
> As per CBER's request this information amendment clarifies that mumps infectivity Titers of 4.1 log $TCID_{50}$ should be expressed as log 4.3 log $TCID_{50}$ because the Mumps End Expiry File (STN 101069/5061, Jan 29, 2004) has not yet been approved.

MRK-KRA00125553 (emphasis added).

258.6. A letter from MRL's Associate Director of Worldwide Regulatory Affairs, Dr. Alison Fisher, to FDA's Office of Vaccines Research and Review, CBER, Dr. Norman Baylor, with the subject: "MMRII (Measles, Mumps, and Rubella Virus Vaccine Live) STN 101069/5068, "Amendment to Supplemental Biological Licensing Application – June 30, 2004," dated July 13, 2005, stated:

> In these sections, the mumps end expiry potency has changed from 4.1 log $TCID_{50}$ to 4.3 log $TCID_{50}$ (12,500 $TCID_{50}$ to 20,000 $TCID_{50}$ or 12,500 $TCID_{50}$ to 20,000 $CCID_{50}$ [*sic*]) because the Mumps End Expiry File (STN: BL 10176/5061) has not been approved. Also, any reference to STN: BL 10176/5061 in these sections has been removed for the same reason.
>
> In Attachment 2, please note updates to 3.2.P.8.3 Drug Product section, page 123.[700] The loss rate and standard error for storage at 2-8 °C were updated using additional stability data from mumps containing vaccines manufactured with either HSA or rHA. The

[700] *See* MRK-KRA00138585 at '707 (sBLA for "Measles, Mumps, and Rubella Virus Vaccine - Live — Replacement of Human Serum Albumin with Recombinant Albumin," Module 3 Quality, 3.2.P.8.3 Drug Product — M-M-R II with rHA, page 123 "[Table 3.2.P.8.3-mmr; 35] Calculation of Mumps Overall Stability Profile Using the Comprehensive Statistical Release Model").

> minimum mumps release potency was recalculated with the updated measurements, together with a change of assignment of loss rate at -20 °C. An estimated increase in potency at -20 °C was originally used in the calculation. This was changed to 0 (zero) in order to eliminate the artificial deflation of the minimum release potency by a predicted increase of potency at -20 °C over time.

MRK-KRA00141789 (emphasis added).

258.7. The July 2005 "Amendment to Supplemental Biological Licensing Application – June 30, 2004" included Attachment 2 (consisting of "revised mumps end expiry potency text in Module 3, Quality, 3.2.P Drug Product Section" for M-M-R II with rHA), which contained Subsection 3.2.P.5.6 "Justification of Specifications" stated:

> 5.6 Justification of Specifications[701]
>
> ...Minimum potencies at release were determined using a statistical stability loss model that ensures, with 95% confidence, that the potencies of the measles, mumps, and rubella components do not fall below their end-expiry titer. The expiry potency limits are based on historical expiry potencies assigned to the measles, mumps, and rubella virus components of M-M-R™II with HSA.

MRK-KRA00141789 at '865 (emphasis added).

258.8. Attachment 2 to the July 2005 Amendment to the sBLA also stated:

> Conclusions on Mumps Stability[702]
>
> Stability studies on final container vaccine at 2-8 °C, -20 °C, 8 hours storage after reconstitution, and 25 °C demonstrate the equivalency of mumps stability profile between

[701] Subsection path: Module 3, Section 3.2P, "Drug Product – M-M-R™II with rHA, Subsection 3.2.P.5 "Control of Drug Product," Subsection 3.2.P.5.6 "Justification of Specifications." *See* MRK-KRA00138548 (Table of Contents), at '52 (the sBLA for rHA had referenced the Protocol 007 end expiry study as the basis of the specification: "The expiry potency limits are based on historical expiry potencies assigned to the measles, mumps, and rubella virus components of M-M-R™II with HSA; the expiry potency limit for mumps was based on the mumps end expiry study associated with M-M- R™II with HSA.") (emphasis added).

[702] sBLA Subsection path: Module 3, Section 3.2.P - Drug Product M-M-R™II with rHA, Subsection 3.2.P.8.3 - Stability Data, Subsection 3.2.P.8.3.5 - Results of Stability Tests on the Filled Container, Subsection 3.2.P.8.3.5.2 - Mumps Infectivity Titrations, Subsection 3.2.P.8.3.5.2.5 - Conclusions on Mumps Stability. *See* MRK-KRA00138585 (Table of Contents), at '661.

M-M-R™II manufactured with rHA and the currently licensed M-M-R™II with HSA product. Since the two products have similar stability profiles, the same loss model developed for the currently licensed product will be applied to M-M-R™II with rHA... The loss model supports the mumps minimum release specification of 5.0 log $TCID_{50}$/dose, expiry claim of ≥4.3 log $TCID_{50}$/dose, and a 24-month shelf life at 2-8 °C for M-M-R™II with rHA.

MRK-KRA00141789 at '871 (original bold removed, emphasis added).

258.9. Attachment 2 to the July 2005 Amendment to the sBLA also stated:

Minimum Release Potency Limits for Mumps

The loss estimates and standard errors for mumps potency were used to determine the minimum... release specification limit needed to ensure, with 95% probability, that the minimum expiry potency of 4.3 log TCID50/dose, following reconstitution and up to 8 hours at 2-8ºC, would be met. These variables are summarized in [Table 3.2.P.8.3-mmr; 35].

8.3.6.3.2 Minimum Release Potency Limit for Mumps

The loss estimates and standard errors for mumps potency were used to determine the minimum post-lyophilization release specification limit needed to ensure, with 95% probability, that the minimum expiry potency of 4.3 log $TCID_{50}$/dose, following reconstitution and up to 8 hours at 2–8 °C, would be met. These variables are summarized in [Table 3.2.P.8.3-mmr; 35].

[Table 3.2.P.8.3-mmr; 35] Calculation of Mumps Overall Stability Profile Using the Comprehensive Statistical Release Model

Storage	Loss Rate (log $TCID_{50}$/ unit time)	Standard Error (SE) (log $TCID_{50}$)	Duration
Storage at 23–27 °C *(Sealing/Inspection/Packaging)*	0.10163/40 hours	0.04244	40 hours
Storage at ≤ –20 °C	0/year[a]	0.01325	1 year[b]
Storage at 2–8 °C	0.4397/24 months	0.01788	24 months
Storage at 2–8 °C following Reconstitution	0.05272/8 hours	0.01411	8 hours
Release Potency Assay (1x12) Variability *(Std. Deviation)*	N/A	0.060	N/A

N/A: Not applicable.
[a] Predicted increase in potency over time set equal to 0-loss.
[b] A transfer study is in progress to extend storage at ≤ –20 °C to 18 months.

The release potency required to guarantee minimum mumps potency at expiry of ≥4.3 log $TCID_{50}$/dose is calculated utilizing the total loss (0.5491) and the total variability (square root of the total variance, $\sqrt{0.0060996}$). Using the one-sided 95% critical value from a standard normal distribution (1.65) the minimum release potency needed to ensure a 95% probability of exceeding the expiry potency is:

Minimum Release Potency = Minimum Expiry + total loss + (1.65 x $\sqrt{TotalVariance}$)
= 4.3 log $TCID_{50}$/dose + 0.5941+ (1.65 x 0.0781)
= 5.02 log $TCID_{50}$/dose

The minimum release potency for mumps of 5.0 log TCID50/dose ensures, with 95% confidence, that the vaccine will meet or exceed the end-expiry dose at the end of the 24 month shelf life.

Id. at '885 (original bold removed, underline added) (highlight added).

259. Comparing the "Comprehensive Statistical Release Model" Merck submitted in the sBLA for rHA in June 2004 and the Amendment to the sBLA for rHA in June 2005 there is a decline in the average loss rate for storage at 2-8˚C over a "duration" of "24 months" and "standard error." In June 2004, the average loss was .54338/24 months with a standard error of

.0267. In July 2005, the average loss was .43971/24 months with a standard error of .01788.[703] Neither the sBLA, nor the Amendment to the sBLA describe how the model was "updated using additional stability data" nor how the "minimum mumps release potency was recalculated with the updated measurements."[704]

259.1. Dr. Stark's report stated that he "investigate[d] how Merck estimated the rate at which the potency of mumps vaccines decreases with time, as reported in MRK-KRA00689798…."[705]

259.2. Dr. Stark opined:

> The estimated rate of change in vaccine potency (adjusted for the "house standard") per day is -0.0006969 units per day, with a standard error of 0.00003031 units per day. This estimated rate of change in vaccine potency (adjusted for the "house standard") is approximately 15.5 percent larger than Merck's corresponding estimate, which includes data on vaccines older than 24 months.[706]

259.3. Dr. Stark also opined:

> Evidently, the difference in slopes results from fitting a straight line to data that do not follow a straight line. Rather than decreasing at a constant rate, the potency measurements tend to decrease more rapidly shortly after production and then less rapidly after a year or two.[707]

259.4. Dr. Stark also opined:

> Using all the data in the spreadsheet, which span vaccines from age 0 to 931 days (approximately 30.6 months), I found an estimate of the rate of change in vaccine

[703] *See* MRK-KRA00138585 at '707; MRK-KRA00141789 at '885.
[704] MRK-KRA00141789.
[705] Expert Report of Phillip B. Stark, Ph.D. ¶77.
[706] *Id*. at ¶80.
[707] *Id.*

potency (adjusted for the "house standard") of -0.0006036 units per day, with a standard error of 0.00002083 units per day.[708]

259.5. Dr. Stark opined:

In summary, Merck's inclusion of data beyond 24 months in its regression estimates of the rate of vaccine potency loss decreased the estimated rate at which vaccines lost potency from 0 to 24 months by approximately 15.5 percent and did not correctly account for the non-linear slope of vaccine potency loss (assuming Merck was attempting to calculate the rate of vaccine potency loss from 0 to 24 months).[709]

259.6. Dr. Schenerman's report stated that he also "performed a recalculation of the potency release specification that was done in June 2005"[710] and calculated its effect on Merck's ability to represent that it can assure compliance with its end expiry potency label claims.

259.7. Dr. Schenerman opined:

I have reviewed Merck's November 4, 2004 "Determination for Minimum Release Specification for Mumps in M-M-R®II" and supporting documentation and the June 22, 2005 Calculation of Mumps Overall Stability Profile and supporting data. These two calculations suggest that from November 2004 to June 2005 the mumps minimum release potency for MMR-II necessary to assure an end-expiry potency of 4.3 log10 TCID50/dose (which was the label specification) somehow decreased from 5.2 to 5.0. The reasons for this claimed decrease in minimum release potency are not valid.[711]

259.8. Dr. Schenerman also opined:

In my recalculation, the same assumptions in the 2004 submission for stability model and loss calculation and were used (with 24 months of data only) but applied to 2005 data:

[708] *Id.* at ¶79.
[709] *Id.* at ¶82.
[710] Report of Potency Expert Expert Report of Mark A. Schenerman, Ph.D., p.33.
[711] *Id*. at 32 (citations omitted).

Assumptions:

- Storage at 23-27˚C = 0.10163/40 hours
- Storage at ≤20˚C = 0/year
- Storage at 2-8˚C: slope = (-0.0006969/day x 2 x 365) =0.508737/24 months (based on only 24 months data)
- Variance = (0.00003031/day x 2 x 365) =0.0221263/24 months (based on only 24 months data)
- Storage at 2-8˚C following Reconstitution = 0.05272/8 hours

Calculations:

Minimum Release Potency = Minimum Expiry + total loss + (1.65 x √(Total Variance))

Minimum Release Potency = 4.3 + 0.663087 + (1.65 x √(0.0221263))

Minimum Release Potency = 5.2

Based on this calculation, the 2005 potency specification for minimum release should have been 5.2. The actual minimum release potency remained at 5.0, based in part on this biased analysis of the available data.[712]

259.9. Dr. Schnerman opined that:

The rationale for my recalculation is that it is not scientifically justifiable to include data beyond the shelf life (24 months) when calculating overall slope because the time points beyond 24 months were known to decrease further in slope and their use would bias the overall calculation. The amount of mumps potency vaccine losses <u>after</u> its 24 month shelf life is irrelevant to calculating how much potency will be lost during the 24-month

[712] *Id.* at 33-34 (bold in original, citations omitted).

shelf life. I note the [sic] Merck's prior calculation of the minimum release specification in November 2004 only used data from 0 to 24 months."[713]

259.10. Dr. Schenerman also opined: "This means Merck did not have data to show that mumps vaccine with rHA released at the approved Minimum Release Potency of 5.0 log TCID50/dose would be sufficient to support the label expiry potency of 4.3 log TCID50/dose."[714]

259.11. Dr. Schenerman also opined: "Applying the same numbers to a variation of the formula; release potency – (loss + variance) = end expiry, equates to 5.0 – (0.663087 + (1.65 X √(0.22163))) = 4.0914, which means the lower bound expiry potency is 4.09, or 4.1."[715]

260. In my opinion, consistent with the reports of Dr. Stark and Dr. Schenerman, Merck used data time points from 0 to 931 days (i.e., 30.587269 months) to calculate the slope of loss for storage at 2-8˚C over a "duration" of "24 months." Furthermore, the use of 0 to 30.58 months to calculate the slope of loss for storage at 2-8˚C over a "duration" of "24 months" is not discussed in the Amendment to the sBLa for rHA. Moreover, this information was relevant to the evaluation of the product's stability and Merck's ability to ensure MMRII with rHA met the end expiry potency claim for mumps.

261. In my opinion, Attachment 2 of the 2005 Amendment to the sBLA for rHA (consisting of "revised mumps end expiry potency text in Module 3, Quality, 3.2.P Drug Product Section" for M-M-R II with rHA) is misleading because it represents that the loss rate for storage at 2-8˚C is calculated over a "duration" of "24 month," not over a duration of 30.58 months.

[713] *Id.* at 33.
[714] *Id*. at 34.
[715] *Id*. at 34, fn. 63.

262. In my opinion, it is the manufacturer's responsibility to ensure that its products meet the specifications on the label and to comply with all provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Services Act, all applicable regulations, including reporting when the manufacturer cannot assure the product will meet its specification throughout its shelf-life. Furthermore, consistent with Dr. Stark and Dr. Schenerman, from July 2005-2007 Merck could not ensure that MMRII met its mumps end expiry potency specification of "not less than 4.3."

9. Merck Did Not Have Adequate Assurances of the Mumps Potency of MMRII From 1998 Until 2007 When the End Expiry Claim on the MMRII Label Was Lowered

263. In my opinion, as described above, with regard to FDA requirements, a vaccine is adulterated if a manufacturer does not have procedures that are designed to assure that the product has the identity, strength, purity or potency it purports or represents it to have. Merck had to have procedures to assure that MMRII vaccine had "not less than 4.3 log10 [20,000] TCID50" per dose through end expiry as long as that was the potency specification on the MMRII label.

264. In my opinion, as described above, from at least 1998 – September 1999, Merck did not have adequate procedures to assure that MMRII vaccine had "not less than 4.3 log10 [20,000] TCID50" per dose through end expiry. Merck's actions with regard to the identification of product manufactured before the overfill for which it could not assure "not less than 4.3 log10 [20,000]" at end expiry can be summarized as follows:

– Merck identified 225 lots it predicted could not meet the end expiry specification of "not less than 4.3" on the MMRII label	MRK-KRA00549518
– Merck identified six of the lots with predicted lowest potency identified on the list of 225 lots	MRK-KRA00616007 at '08

– Merck tested five of the six lots, 0538J, 0539J, 0926J, 1070J and 1071J, and reported the results in BPDR 01—005: – Lot 0538J (117,970 doses) was out of specification – Lot 0539J (115,320 doses) was out of specification – Lot 1070J (118,040 doses) was out of specification – Lot 1071J (117,550 doses) was out of specification – Lot 0926J (57,720 doses) was within specification	MRK-KRA00754233; MRK-KRA00549518
– The sixth lot, Lot 0517J (115,400 doses) was not tested or reported to the FDA. Merck documents indicate it was exported outside the United States.	MRK-KRA00548824; MRK-KRA00548114

With regard to the remaining 219 lots (225-6= 219), Merck could not assure those lots met the end expiry claim of 4.3 log10 [20,000] TCID50/dose, and never informed the FDA. Moreover, with regard to children immunized in the United States with vaccines from lots Merck manufactured from May 1998 – September 1999 for which Merck did not have adequate assurance, no one can determine whether these children who are now young adults (approximately 18-23 years old) have been sufficiently immunized because the end expiry potency fell below Merck's specification.

265. In my opinion, as described above, as of the end of 2000, Merck could not ensure MMRII lots manufactured after September 1999, after the overfill, met the label potency specification of "not less than 4.3 log" for mumps. Furthermore, Merck could not ensure MMRII lots manufactured before the overfill and still within the 24-month shelf life, met the label potency specification of "not less than 4.3" for mumps. Moreover, in December 2000 Merck did not have clinical data to support lowering the end expiry claim on the MMRII label, or adequate data to provide reassurance of the efficacy of lower potency product.

266. In my opinion, as described above, as of April 2001, Merck still did not have adequate assurance that MMRII would have "not less than 4.3" mumps potency at the end of the 24 month shelf life. Furthermore, Mr. Bennett's conclusion that "expiry dating needs to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry" was relevant to the April 4, 2001 discussion with FDA about the ongoing questions of mumps stability/potency in MMRII that started with the Section 314 Review in 1996. A reasonable and prudent manufacturer would have described the results of Mr. Bennett's analysis to the FDA personnel in attendance. Moreover, a reasonable and prudent manufacturer would have updated its response to the Warning Letter four weeks earlier that had stated: "we believe that the actions taken to date comprehensively address all concerns raised during the referenced inspection as well as in the subsequent Warning Letter."

267. In my opinion, as described above, as of August 2001, Merck could not assure the end expiry potency of the mumps component of MMRII [4.3 log10/20,000 TCID50], even after the overfill initiated in September 1999, because Merck's stability data only supported an end expiry potency of 4.0. With an end-expiry potency of 4.3, Mr. Bennett calculated that MMRII's shelf life was less than 12 months, not the 24 months in MMRII's labeling. A reasonable and prudent manufacturer would have described this issue to the FDA, and not waited for "the clinical efficacy data that was being generated."

268. In my opinion, as described above, as of December 2001, Merck still could not ensure the mumps end expiry specification of 4.3 that continued to be on the MMRII label because, according to Mr. Bennett, the "expiry dating need[ed] to be 12 months in order to provide 95% confidence that a lot released at 5.0 will be above 4.3 at expiry," and, according to Mr.

Schofield, "the [stability] plan works with 4.0 but not 4.3." Furthermore, according to Merck's summary of the December 7, 2001 teleconference, FDA's Dr. Carbone raised the potency/stability issue with Mr. Schofield and other recipients of Mr. Bennett's email on the call. A reasonable and prudent manufacturer would have described to FDA's Dr. Carbone and other FDA personnel on the call that Merck was unable to assure the mumps end expiry specification in MMRII even after the overfill and it did not have clinical data to support lowering the end expiry specification because of the deficiencies cited in the Protocol 007 testing.

269. In my opinion, as described above, until Merck had clinical data from an adequate and well-controlled study and FDA's approval to lower the mumps end expiry claim on the MMRII label, Merck remained obligated to ensure that all product met the "not less than 4.3 log [20,000]" mumps end expiry claim. Furthermore, Mr. Bennett's analysis documents Merck's ongoing inability to ensure all MMRII products complied with that label specification even after the overfill. Merck continued to have inadequate assurance that MMRII met the label specification for mumps through end expiry in March 2002.

270. In my opinion, as described above, as of July 2002, Merck still did not have adequate assurances that that all MMRII product met the "not less than 4.3 log [20,000]" potency claim for mumps on the label, even after the overfill implemented in September 1999. Furthermore, until Merck actually implemented any of the proposed "fixes" it contemplated, it remained obligated to ensure compliance with its label.

271. In my opinion, in September 2002 according to Merck's documents, as described above, Merck did not have adequate procedures to assure that MMRII met that standard, even after the overfill implemented in September 1999.

272. In my opinion, as described above, with regard to MMRII lots manufactured from September 1999 – September 2002, Merck never informed the FDA that "approx[imately] 7% of the lots [we]re expected to be < 4.3 at expiry"[716] or that Merck could "statistically predict that a certain number of lots will fail on stability,"[717] even after the manufacturing change implemented in September 1999 to "overfill" the mumps component to ensure Merck could "provide a high level of assurance that the minimum titers would be maintained through expiry."[718] Furthermore, since this was never reported to the FDA, to the best of my understanding, no one has investigated which lots released were the 7% Merck that would fail to have 4.3 log10 [20,000] TCID50/dose at end expiry.[719]

273. In my opinion, as described above, in December 2002, Merck still did not have adequate controls to ensure that mumps potency of MMRII would be "not less than 4.3" at end expiry, even the overfill.

274. In my opinion, as described above, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin's September 2003 email regarding "a call" from FDA's Dr. Baylor did not change Merck's obligation to ensure the products that it releases to the market are safe and effective.[720] It is the manufacturer's responsibility to ensure that its products meet the specifications on the label and to comply with all provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Services Act, all applicable regulations, including reporting when the manufacturer cannot assure the product will meet its specification throughout its shelf-

[716] MRK-KRA00561350.
[717] MRK-KRA01562819.
[718] MRK-KRA00756233 at '35-36.
[719] *See* Section XI below discussing the resurgence of mumps cases and outbreaks in the United States among fully vaccinated young adults.
[720] *See* MRK-KRA00560682 at '82-83.

life. In my opinion, through the end of 2003, Merck still could not ensure that MMRII vaccine had "not less than 4.3 log10 [20,000] TCID50" of mumps virus per dose through end expiry.

275. In my opinion, as described above, through the end of 2004, Merck still could not ensure that MMRII had "not less than 4.3 log10 [20,000] TCID50" mumps virus per dose through end expiry.

276. In my opinion, as described above, consistent with Dr. Stark and Dr. Schenerman, from July 2005-2007 Merck could not ensure that MMRII met its mumps end expiry potency specification of "not less than 4.3."

277. In my opinion, from May 1998-December 2007, MMRII was adulterated because Merck was unable to assure the potency specification for mumps of not less than 4.3 log10 [20,000] TCID50 for the shelf life of the vaccine.

278. In my opinion, with regard to children immunized in the United States with vaccines manufactured from 1998-2007, no one can determine which of the children, who are now young adults, were immunized from the lots of MMRII for which Merck did not have adequate assurances of the potency.

IX. MERCK STATEMENTS IN APPLICATIONS TO FDA WERE MISLEADING BECAUSE THEY OMITTED THAT ASSAYS MERCK USED DID NOT RELATE TO PROTECTION. MMRII AND PROQUAD LABELS ARE MISLEADING BECAUSE THEY OMIT THAT ASSAYS USED DID NOT RELATE TO PROTECTION

279. As described below, Merck submitted three applications to the FDA in 2004.

280. In January 2004, Merck submitted a Supplemental Biologics License Application (sBLA) to support a change to the MMRII mumps end expiry specification from "not less than

4.3" to "not less than 4.1" log10 TCID50 ("sBLA for Mumps End Expiry").[721] In order to support this change to the label's end expiry potency specification, Merck performed one clinical study, Protocol 007, to demonstrate that M-M-R®II with a mumps potency of 4.1 log10 TCID50 would afford the same level of protection as M-M-R®II at its release potency of ~4.9 log10 TCID50.[722]

281. In June 2004, Merck submitted an sBLA to support a change from Human Serum Albumin to Recombinant Serum Albumin in the M-M-R®II manufacturing process ("sBLA for rHA").[723] In order to support this manufacturing change, Merck performed one clinical study, Protocol 009, to demonstrate that M-M-R®II manufactured with Human Serum Albumin (HSA) was as safe and effective as M-M-R®II manufactured with Recombinant Serum Albumin (rHA).[724]

282. In August 2004, Merck submitted a Biologics License Application seeking FDA approval to sell ProQuad ("BLA for ProQuad").[725] The BLA for ProQuad was supported by five clinical studies; three of the studies supporting the ProQuad application are discussed below. Protocol 012 compared Proquad in terms of immunogenicity, safety and tolerability to MMRII and Varivax administered separately.[726] Protocol 013 was conducted to show that the concomitant use of ProQuad, Tripedia and Comvax did not impair the safety or antibody response to each vaccine component compared with separate administration of ProQuad followed by Tripedia and Comvax or separate administration of MMRII and Varivax followed

[721] *See* Section IX.A.5.a below.
[722] *See* Section IX.A.6.a below.
[723] *See* Section IX.A.5.b below.
[724] *See* Section IX.A.6.b below.
[725] *See* Section IX.A.5.c below.
[726] MRK-KRA00162963 at '2995-96.

by Tripedia and Comvax.[727] Protocol 014 was conducted to show ProQuad could be used in place of the recommended second dose of MMRII administered to children at 4 to 6 years of age who were previously administered MMRII and Varivax separately.[728]

283. Each of the three submissions was supported by clinical studies using the WT ELISA with a 10 Ab cutoff for measuring mumps immunogenicity. All three submissions were approved by FDA.

A. FDA Permitted Merck to Use the WT ELISA Assay for Mumps Immunogenicity Testing If Merck Correlated the WT ELISA to a Neutralization Assay as a Link to Protection Against Disease.

1. When Merck Designed the Clinical Studies to Support its Three Applications, the "Gold Standard" for Testing Mumps Immunogenicity and Protection Was a Plaque-Reduction Neutralization Assay.

284. As discussed above,[729] Merck documented its understanding in 1998 that "CBER considers the WT neutralizing antibody assay to be the 'gold standard.'"[730]

2. Merck Used ELISA Assays in Large Studies Because They Are Highly Sensitive and Less Labor Intensive Than Neutralization Assays

285. As stated above, Merck used ELISA assays "in large protocols because they are highly sensitive and far less labor intensive compared with neutralization assays."[731]

3. FDA Requirements For Use of the WT ELISA Assay in Merck's Clinical Studies

286. As stated above,[732] FDA required that the cutoff chosen for the WT ELISA be "linked" to a "biologically relevant reference standard," and requested "that individual titers

[727] MRK-KRA00164918 at '4946.
[728] MRK-KRA00166846 at '6867.
[729] *See* Section VII.A.1.
[730] MRK-KRA01731773 at '79.
[731] MRK-KRA00666494 at '58; *see also* Section VII.A.1 above.

[were] identified in the relative range around the cutoff in the PRN and ELISA in order to confirm that these two assays [were] categorizing sera in a comparable fashion."[733] The requirement to compare to a functional assay is "[b]ecause neutralization assay results were correlated with seroprotection in early efficacy trials …"[734]

287. As stated above,[735] FDA stated the following with regard to Merck's WT ELISA assay and the 10 Ab cutoff chosen for the WT ELISA assay:

- An ELISA cutoff that correctly classified a sample as negative or positive based only on a detectable difference between pre-vaccination and post-vaccination samples was insufficient because it did not relate to seroprotection.[736]
- The rationale for the cutoff in the WT ELISA had to be linked to a biologically relevant reference standard.[737]
- The cutoff employed in the WT ELISA needed to be supported by data demonstrating it was appropriate which meant some relevance with protective levels of antibody.[738]

288. As stated above, according to FDA, Merck could use the WT ELISA assay if Merck did the following:

- In the absence of a reference standard for a protective level of mumps antibodies, relate the ELISA cutoff to the cutoff in a neutralization assay as the best

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[732] *See* Section VIII.M.1.
[733] *Id.*
[734] MRK-KRA00561452; *see also* Schedule 7 (summarizing early studies) and MMRII label, Clinical Pharmacology: "Efficacy of … mumps … vaccine was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components. These studies also established that seroconversion in response to vaccination against … mumps … paralleled protection from these diseases." (internal citations omitted).
[735] *See* Section VIII.M.1 above.
[736] MRK-KRA00561452.
[737] MRK-KRA00818776 at '78.
[738] MRK-KRA00846451.

surrogate, or substitute, for a reference standard because FDA viewed a neutralization assay as a biologically relevant assay that is linked to protection.[739]

- Compare the WT ELISA assay to the AIGENT[740] assay to confirm samples were being classified the same way in the two assays.[741]
- Showed in the WT ELISA and AIGENT comparison analysis that no more than 10% of WT ELISA low positive sera score negative in the PRN.[742]

289. As stated above, if there continued to be uncertainty about the biological relevance of the cutoff Merck proposed after it conducted the comparison between the WT ELISA and AIGENT assays, the following alternative would be acceptable to FDA:

- implement a four-fold rise criteria[743] to measure seroconversion in the WT ELISA.[744]

4. Merck Comparison of the AIGENT and WT ELISA to Satisfy FDA Requirements to Use WT ELISA

290. After FDA set forth the requirements summarized above, Merck submitted an analysis in Serial 86, comparing the performance of the WT ELISA and the AIGENT assay.[745] In BB-IND 1016 (Mumps End Expiry), Serial 86, Merck asserted a correlation between the AIGENT and the WT ELISA.[746] Merck referred back to Serial 86 and the analysis comparing the AIGENT and the WT ELISA in subsequent regulatory submissions to FDA, including: BB-

[739] MRK-KRA00561452 at '53.
[740] The FDA report from the inspection of Dr. Krah's lab that resulted in the August 2001 Form 483, documented FDA's understanding that the AIGENT had been developed as "the immunological correlate for efficacy of mumps vaccination." MRK-KRA01649971 at '56. *See* Section VIII.L.1 above.
[741] *Id.*
[742] MRK-KRA0079315 at '18.
[743] MRK-KRA00561452 at '54; *see also* MRK-KRA00544296 ("If we are unable to provide sufficient reassurance about the clinical relevance of the ELISA cutoff (which in [FDA's] Kathy [Carbone]'s mind means linking this to the [AIGENT]) then we may end up with some type of a fold-rise criterion which I assume we would rather avoid if possible.").
[744] MRK-KRA00561418 ("If CBER required a fourfold rise in titer (defined as less than 10 to greater than or equal to 40), the seroconversion rates for these studies would range from 80.9 percent to 85.2 percent.").
[745] MRK-KRA00126468 (BB-IND 1016 (Mumps End Expiry), Serial 86) (June 10, 2002); *see also* Section VIII.M.1-4 above discussing FDA's requirements and Merck's submission of Serial 86.
[746] *See* Section VIII.M.4 above.

IND 1016 (Mumps End Expiry), Serial 89;[747] BB-IND 10076 (rHA), Serial 53;[748] BB-IND 7068 (ProQuad), Serial 221;[749] and BB-IND 1016 (Mumps End Expiry), Serial 102.[750]

5. Merck Filed Applications Utilizing the WT ELISA

291. In 2004, Merck filed two Supplemental Biologics License Applications for M-M-R®II and a Biologics License Application for ProQuad.

a. The sBLA for Mumps End Expiry

292. Merck submitted the sBLA for Mumps End Expiry to FDA in January 2004, seeking regulatory approval to lower the M-M-R®II mumps end expiry specification from "not less than 4.3" to "not less than 4.1" log10 TCID50. The Mumps End Expiry sBLA stated that the "data presented here indicate with a high level of assurance that decreasing mumps end-expiry titer … will ensure that M-M-R™II remains a highly effective vaccine."[751]

292.1. The sBLA for Mumps End Expiry included a letter from MRL's Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to FDA's Director, Office of Vaccines Research and Review, CBER, titled "SUPPLEMENTAL BIOLOGICS LICENSE APPLICATION," dated January 29, 2004.[752]

292.2. The sBLA for Mumps End Expiry also included "Form FDA 356h"[753] titled "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" (Title 21,

[747] MRK-KRA00000561 (BB-IND 1016 (Mumps End Expiry), Serial 89) (August 8, 2002).
[748] MRK-KRA00124554 at '588 (BB-IND 10076 (rHA), Serial 53) (June 28, 2004).
[749] MRK-KRA00155481 (BB-IND 7068 (ProQuad), Serial 221) (November 12, 2004).
[750] MRK-KRA00126963 (BB-IND 1016 (Mumps End Expiry), Serial 102) (November 17, 2004).
[751] MRK-KRA00000032 at '127.
[752] MRK-KRA00135652.
[753] Form FDA 356h also identified Merck's "Responsible Officer or Agent," as Dr. Manal Morsy, Director of Worldwide Regulatory Affairs/Vaccine Biologics, who certified: "the data and information in this submission has been reviewed and to the best of my knowledge are certified to be true and accurate." MRK-KRA00135657 at '58.

Code of Federal Regulations, Part 314 and 601). Merck checked the following boxes on the Form 356h:

- Biologics License Application (21 CFR Part 601)
- Type of Submission-Efficacy Supplement

MRK-KRA00135657 at '57-58 (emphasis added).

292.3. MRL's former Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, testified as follows:

> *Q. A couple of boxes down it says, "TYPE OF SUBMISSION" and it says, quote, and it's you checked off the box, "EFFICACY SUPPLEMENT." Do you see that?*
> *A. Yes.*
> *Q. So this was an efficacy supplement?*
> *A. That's what it says.*
> *Q. What do you understand that to mean?*
> *A. It means that an efficacy supplement in general means that you have data that shows that your product was efficacious based on whatever the FDA has defined to be the basis of having that kind of claim.*

Deposition of Manal Morsy, August 5, 2016, 97:10-98:2 (emphasis added).

292.4. MRL's former Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, testified as follows:

> *Q. And if you had learned after filing this BLA, I understand if you learned it the next day and I know you left soon thereafter, that the PRN assay that was part of Protocol 007 was unreliable, do you believe you would have been obligated to tell the FDA that?*
> *A. Absolutely. Merck would have been obligated and Merck would have picked the phone and talked with the FDA and discussed it. That's the common practice.*
> *Q. Did they? Did they?*
> *A. I have no idea.*

Deposition of Manal Morsy, August 5, 2016, 110:19-111:7 (emphasis added).

293. The sBLA for Mumps End Expiry included Module 2, "Common Technical Document Summaries."[754] Section 2.5 in Module 2 summarized the "Clinical Overview" of the submission.

293.1. The Module 2's Clinical Overview in the sBLA for Mumps End Expiry, stated:

> Overview of Clinical Development Program[755]
>
> The purpose of this application is to obtain approval to lower the mumps end-expiry potency of M-M-R®II from 4.3 $\log_{10}$ to 4.1 $\log_{10}$ $TCID_{50}$ per dose (20,000 and 12, 500 $TCID_{50}$, respectively).
>
> The clinical data described here demonstrate that M-M-R®II with a mumps virus potency of 4.1 log10 TCID50 per dose is immunogenic and well tolerated as M-M-R®II with a mumps virus potency within the release range (based on a vaccine lot containing a mumps virus potency of 4.8 log10 TCID50 per dose). Lowering the mumps virus potency to 4.1 log10 TCID50 per dose maintains >90% seroconversion rate using a mumps neutralization assay, thus preserving the excellent safety and efficacy profile of the vaccine.

MRK-KRA00135723 at '29 (original bold removed, underline added).

293.2. Module 2's Clinical Overview in the sBLA for Mumps End Expiry also stated:

> Study Endpoints[756]
>
> Mumps neutralizing antibodies were measured immediately prior to vaccination and 6 weeks postvaccination using the plaque-reduction neutralization (PRN) assay. The PRN assay was used as the primary endpoint because it is a functional assay that measures the

[754] A Biological License Application is a compilation of the evidence supporting the proposed application. FDA's Guidance identifies 5 modules that should be included in a Biologics Licensing Application or a Supplemental Biologics Licensing Application. Module 1 contains the "Administrative and prescribing information" (i.e., labeling); Module 2 contains "Summaries and overview" (Common Technical Document Summaries); Module 3 contains "Information on product quality;" Module 4 contains "Nonclinical study reports;" and Module 5 contains "Clinical study reports." *See* Guidance for Industry Submitting Marketing Applications According to the ICH-CTD Format-General Considerations- Draft Guidance (August 2001) at 3, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073308.pdf.
[755] Module 2, Subsection 2.5.1.5.
[756] Module 2, Subsection 2.5.1.5.3.

> ability of the vaccine-induced immune response to inhibit viral replication in vitro, and can, therefore, be considered a surrogate for vaccine effectiveness.

Id. at '30-31 (original bold removed, underline added).

293.3. MRL's former Vice President, Clinical Research, Dr. Florian Schodel, testified as follows:

> *Q. What do you understand surrogate of vaccine effectiveness to mean, Doctor?*
> *A. I think that's a bit of a surrogate for vaccine. I mean, it's supportive data that the vaccine has not changed in that context of the comparison. You can use it as vaccine effectiveness because the vaccine has shown effectiveness. The immunogenicity to it has not changed and, therefore, you would expect the same effectiveness does not mean that it directly correlates with effective.*
> *Q. I see. But isn't Merck representing –*
> *A. The surrogate simply means that you can't measure the original, so it means it stands in for.*
> *Q. Because you couldn't do an efficacy study today, that's unethical?*
> *A. That's correct.*
> *Q. So the best assay that you can use is a surrogate of vaccine effectiveness. Correct?*
> *A. Any assay that you can use you would try to use as a surrogate for vaccine effectiveness showing that the vaccine hasn't changed since it's been started to use and looking at the field effectiveness data that you constantly get. So it doesn't necessarily have to be the best. It is what the best effort that you can make. And in that regard both ELISA and both the PRN were used to support that the vaccine had not changed.*

Deposition of Florian Schodel, December 22, 2016, 368:4 – 369:13 (emphasis added).

293.4. Module 2's Clinical Overview also stated:

> Efficacy...[757]
> … In agreement with CBER/FDA, the mumps-specific PRN assay was developed and used as a surrogate for vaccine effectiveness. In addition … mumps specific antibodies

[757] Module 2, Subsection 2.5.4.1

> were evaluated at 6 weeks and 1 year postvaccination by ELISA to assess the immune response by a standard assay and to confirm persistence of antibodies...

MRK-KRA00135723 at '34-35 (original bold removed, underline added).

293.5. Module 2's Clinical Overview in the sBLA for Mumps End Expiry also stated:

> Benefits and Risk Conclusions[758] …
>
> The analysis of the clinical data presented in this application confirms that M-M-R™II with a candidate mumps end-expiry potency of 4.1 $\log_{10}$ $TCID_{50}$ per dose is generally well tolerated and highly immunogenic in healthy children 12 to 18 months of age. Importantly, the safety and immunogenicity profile was shown to be generally comparable to the profile found in healthy children 12 to 18 months of age who are routinely vaccinated with M-M-R™II with a mumps virus potency typical of the product at release.
>
> There are no significant known risks associated with the use of M-M-R™II. The data presented here indicate with a high level of assurance that decreasing the mumps end-expiry titer from 4.3 to 4.1 $\log_{10}$ $TCID_{50}$ per dose in children 12 to 18 months of age will ensure that M-M-R™II remains a highly effective vaccine. The change in mumps end expiry does not confer any additional benefit to the subject, but rather supports the continued production of a medically important vaccine.

Id. at '46 (original bold removed, underline added).

294. In sum, Merck submitted a Supplemental Biological License Application that was an efficacy supplement to change the potency of MMRII's mumps component. The information contained in the sBLA was certified as accurate and Merck had an ongoing obligation to update the sBLA with any new information that it later learned. The "Clinical Overview" in Module 2 of sBLA for mumps end expiry included the following statements:

[758] Module 2, Subsection 2.5.6

- Merck submitted the sBLA for Mumps End Expiry to obtain approval to lower the MMRII mumps end-expiry potency from "not less than 20,000 [4.3 $\log_{10}$]" to "not less than 12,500 [4.1 $\log_{10}$]" $TCID_{50}$ per dose.
- Merck used a neutralization assay[759] that measured mumps neutralizing antibodies to support the application.
- The neutralization assay was developed and used as a surrogate for vaccine effectiveness.
- The neutralization assay could be considered a surrogate of vaccine effectiveness.
- The neutralization assay was used to support Merck's claim that the vaccine had not changed since the time it was licensed.
- Analysis of the data confirmed that M-M-R®II with potency of 4.1 $\log_{10}$ [12,500] $TCID_{50}$ was highly immunogenic.
- The data indicate with a high level of assurance that M-M-R®II with a mumps end expiry specification of not less than 4.1 $\log_{10}$ $TCID_{50}$ per dose would remain a highly effective vaccine. [760]

b. The sBLA for MMRII manufactured with Recombinant Human Albumin (rHA)

295. Merck submitted the sBLA for rHA in June 2004[761] to support the use of recombinant serum albumin ("rHA") instead of pooled human derived serum albumin ("HSA") as a viral growth media in the bulk manufacturing process and as a component of the bulk diluents at the formation of the final product.[762] The sBLA for rHA stated that the replacement of HSA with rHA in the bulk manufacturing of MMR™II was not expected to affect the efficacy of the vaccine.[763]

[759] The neutralization assay that Merck used to support the application was the AIGENT assay. *See* Section IX.A.6.a.
[760] *See* MRK-KRA00135723 at '29, 30, 35, 46; Deposition of Florian Schodel, December 22, 2016, 368:4 – 369:13.
[761] MRK-KRA00137854.
[762] *See* footnote 672 above describing the rationale for changing to rHA.
[763] MRK-KRA00138137 at '47.

295.1. The SBLA for rHA included a letter from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, to FDA's Acting Director, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, Dr. William Egan, titled "SUPPLEMENTAL BIOLOGICS LICENSE APPLICATION" dated June 30, 2004. As with the sBLA for Mumps End Expiry, the sBLA for rHA was supported by several modules.[764]

295.2. 14.2. The sBLA for rHA also included "Form FDA 356h" titled "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" (Title 21, Code of Federal Regulations, Part 314 and 601).[765] Form FDA 356h also identified Merck's "Responsible Officer or Agent," as Dr. Alison Fisher, Associate Director, Worldwide Regulatory Affairs/Vaccine Biologics, who certified: "the data and information in this submission has been reviewed and to the best of my knowledge are certified to be true and accurate."[766]

295.3. Like the sBLA for Mumps End Expiry, the sBLA for rHA included Module 2, "Common Technical Document Summaries," and included a "Clinical Overview" of the submission in Section 2.5, which stated:

> Overview of the Clinical Development Program[767]
>
> The purpose of the clinical development program described in this application was to compare the safety and immunogenicity profiles of M-M-R™II for bulks manufactured with rHA versus HAS. ... This application supports the replacement of HSA with rHA in the bulk manufacturing of M-M-R™II as the [Protocol 009 clinical] study[768] results demonstrated that M-M-R™II with rHA induced acceptable antibody response rates for

[764] *See* footnote 753 above describing the modules included in an sBLA.
[765] MRK-KRA00137874.
[766] *Id.*
[767] Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.1 "Product Development Rationale," Subsection 2.5.1.5.
[768] *See* Section IX.A.6.b below discussing Protocol 009.

measles, mumps, and rubella that are similar (noninferior) to those induced by M-M-R™II ...

MRK-KRA00138137 at '44 (emphasis added, internal citations omitted).

295.4. The "Clinical Overview" Section of Module 2 of the sBLA for rHA stated:

Immunogenicity[769]

The immunogenicity data presented in this application were derived from a single clinical trial (Protocol 009) [770] [Ref. 5.3.5.1; P009]. All assays used in support of this study were conducted at MRL. Antibody responses to... mumps... were assessed using ELISAs. Endpoints for these assays are defined as the proportion of initially seronegative subjects who developed serum antibody levels... ≥10.0 ELISA antibody units/mL for mumps... following vaccination ...

Id. at '47 (emphasis added).

295.5. Module 2's "Clinical Overview" in the sBLA for rHA also stated:

Study Endpoints[771]

The primary endpoints used to assess immunogenicity were the antibody response rates to measles, mumps, and rubella 6 weeks postvaccination...

All immunogenicity endpoints in Protocol 009 were assessed using measles, wild-type mumps,[772] and rubella ELISAs, respectively. Specific levels of serum antibodies to measles, mumps, and rubella as measured by hemagglutination inhibition [HI] and serum neutralizing antibody assays in field efficacy studies have been shown to correlate with protection against these diseases, and thus immunogenicity data can be used as a surrogate marker for vaccine efficacy [Ref. 5.4; 13; 14]. [773] Correlation between the

[769] Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.4.2.
[770] *See also* MRK-KRA00138137 at '41, '44, '45, '47.
[771] Module 2, Section 2.5, Subsection 2.5.1.5.1, "Study Endpoints."
[772] *See also* MRK-KRA00138137 at '47 ("Antibody responses to … mumps … were assessed using ELISAs. Endpoints for these assays are defined as the proportion of initially seronegative subjects who developed serum antibody levels … ≥10.0 ELISA antibody units/mL for mumps … following vaccination.") (Emphasis added).
[773] *See* MRK-KRA00138137 at '60 (Ref. 5.4: 13 - Chen RT, Markowitz LE, Albrecht P, Stewart JA, Mofenson LM, Preblud SR, et al. "Measles antibody: reevaluation of protective titers" J Infect Dis 1990; 162:1036-42 and Ref. 5.4:

current assays (enzyme linked immunosorbent assay [ELISA]) and the assays used in the field efficacy studies (i.e., HI assay and serum neutralizing antibody assay) has been established [Ref. 5.4; 15; 16].[774]

Id. at '44-45 (emphasis added).

295.6. Module 2's "Clinical Overview" in the sBLA for rHA also stated:

Efficacy and Effectiveness[775]

The efficacy of the monovalent measles, mumps, and rubella vaccines was previously established through blinded, controlled field studies and in outbreak situations [Ref. 5.4; 22; 23]. A single dose of monovalent vaccines has proven to be very effective in preventing the development of measles (91% to 100% efficacy) [Ref. 5.4; 24; 25], mumps (75% to 96% efficacy) [Ref. 5.4; 26; 27],[776] and rubella (93% to 100% efficacy) [Ref. 5.4; 28; 29] after exposure to wild-type virus... The effectiveness of M-M-R™II has been further demonstrated by the significant reduction (>99%) in the incidence of these diseases and their associated complications and virtual elimination of endogenous measles, mumps, and rubella following the implementation of routine vaccination programs in several countries [Ref. 5.4; 9; 32; 33].

No studies of the efficacy of M-M-R™II with rHA or M-M-R™II were performed in support of this application. The clinical study included in this license application was

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14 - Ratnam S, Gadag V, West R, Burris J, Oates E, Stead F, et al. "Comparison of commercial enzyme immunoassay kits with plaque reduction neutralization test for detection of measles virus antibody" J Clin Microbiol 1995; 33(4):811-5). This study does not address mumps.

[774] MRK-KRA00138137 at '60. (Ref. 5.4: 15 - Weigle KA, Murphy MD, Brunell PA. "Enzyme-linked immunosorbent assay for evaluation of immunity to measles virus" J Clin Microbiol 1984; 19(3):376-9 and (Ref. 5.4: 16 - Cremer NE, Cossen CK, Shell G, Diggs J, Gallo D, Schmidt NJ "Enzyme immunoassay versus plaque neutralization and other methods for determination of immune status to measles and varicella-zoster viruses and versus complement fixation for serodiagnosis of infections with those viruses" J Clin Microbiol 1985; 21(6):869-74). These studies do not address mumps.

[775] Module 2, Section 2.5, Subsection 2.5.4, "Overview of Efficacy and Immunogenicity," Subsection 2.5.4.1, "Efficacy and Effectiveness."

[776] MRK-KRA0141562 (Ref 5.4:26 - J.E. Lewis, M.A. Chernesky, M.L. Rawls, W.E. Rawls, *Epidemic of Mumps in a partially immune population*, 121 Canadian Medical Association Journal 751-754 (1978); MRK-KRA00141567 (Ref 5.4:27 - Maurice R. Hilleman et al., *Live, Attenuated Mumps-Virus Vaccine, 4. Protective Efficacy as Measured in a Field Evaluation*, 276 New England Journal of Medicine 252-258 (1967).

> aimed at evaluating the safety and immunogenicity of M-M-R™II with rHA and MMR™II. Given the structural and genetic similarities of HSA and rHA, as well as the excellent and high level of vaccine-induced immune responses observed for both treatment groups in Protocol 009, the replacement of HSA with rHA in the bulk manufacturing of MMR™II was not expected to affect the efficacy of the vaccine.[777]
>
> Specific levels of serum antibodies to measles, mumps, and rubella as measured by HI and serum neutralizing antibody assays in field efficacy studies have been shown to correlate with protection[778] against these diseases, and thus immunogenicity data can be used as a surrogate marker for vaccine efficacy [Ref. 5.4; 13; 14].[779]

Id. at '47 (emphasis added).

295.7. The "Clinical Overview" Section of Module 2 in the sBLA for rHA stated:

> Immunogenicity[780]
>
> The immunogenicity data presented in this application were derived from a single clinical trial (Protocol 009) [Ref. 5.3.5.1; P009]. All assays used in support of this study were conducted at MRL. Antibody responses to... mumps... were assessed using ELISAs. Endpoints for these assays are defined as the proportion of initially seronegative subjects who developed serum antibody levels... ≥10.0 ELISA antibody units/mL for mumps[781]... following vaccination.

Id. (emphasis added).

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[777] *See also* MRK-KRA01386177 (September 13, 2002 email from MRL's Assoc. Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, to Kaketsuken's Yoichiro Kino "RE Katetsuken Questions regarding mumps end expiry potency," stated: "[I]n terms of why PRN and ELISA in the mumps end expiry and only ELISA in the MMRII/rHA – and this [is] CBER's explanation because we asked the same question regarding the need for a PRN – CBER considers a neutralization assay essential for establishing efficacy where you need to define effectiveness for a product –the mumps end expiry trial is comparing release to expiry within the same product – however when you are comparing equivalence between two products – CBER considers ELISA sufficient.").

[778] "The Food and Drug Administration (FDA) defines a correlate of protection as 'A laboratory parameter that has been shown from adequate and well-controlled studies to be associated with protection from clinical disease.'" MRK-KRA0133955 at slide '61 (powerpoint presentation titled "PRINCIPLES OF VACCINOLOGY" by MMD's Director, Bio/Sterile Validation, Vaccine Technology & Engineering Mike Dekleva, June 2003).

[779] *See* footnote 742 above. References 5.4; 13 and 14 cite to measles studies only. There is no citation to support this statement as to mumps.

[780] Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.4.2.

[781] *See also* MRK-KRA00138137 at '41, 44, 45, 47.

295.8. In sum, the sBLA for rHA stated that, based on similarity in structure and genetic similarity between HSA and rHA, MMRII with rHA was expected to be as immunogenic and to display safety and tolerability profiles similar to that of MMRII manufactured with HSA.[782] The Protocol 009 clinical study was conducted to confirm this hypothesis.[783] Module 2's "Clinical Overview" of the sBLA to change to rHA in MMRII included the following statements regarding the clinical program supporting the Application:

- The Protocol 009 clinical study was conducted to support the application.
- The purpose of the clinical development program described in this application was to compare the safety and immunogenicity profiles of MMRII for bulks manufactured with rHA versus HSA.[784]
- The primary objectives of the study were to demonstrate that the antibody response rates to measles, mumps, and rubella among children who receive MMRII with rHA would be acceptable and similar to the antibody response rates among children who receive MMRII and to demonstrate that MMRII with rHA would be generally well tolerated.[785]
- Protocol 009 measured mumps immunogenicity using the WT ELISA with the 10 Ab cutoff.
- Given the structural and genetic similarities of HSA and rHA, as well as the excellent and high level of vaccine-induced immune responses observed for both treatment groups in Protocol 009, the replacement of HSA with rHA in the bulk manufacturing of MMRII was not expected to affect the efficacy of the vaccine.

[782] *Id.* at '47
[783] *Id.* at '41. Module 2, Section 2.5.1 "Product Development Rationale," Subsection 2.5.1.3 "Current and Targeted Indications."
[784] *Id.* at '44. Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.1.5 "Overview of the Clinical Development Program."
[785] MRK-KRA00138137 at '44. Module2, Section 2.5 "Clinical Overview," Subsection 2.5.1.5.1 "Study Design and Objectives."

c. The BLA for ProQuad

296. Merck submitted a Biologics License Application in August 2004 for FDA approval to sell ProQuad, a new measles, mumps, rubella and varicella vaccine. The BLA for ProQuad stated that the clinical studies demonstrated that the immunogenicity of the mumps component of ProQuad was generally comparable to that of MMRII.

296.1. A letter from MRL's Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, to FDA's Office of Vaccines Research and Review, CBER, Dr. William Egan, with the subject: "ORIGINAL BIOLOGICS LICENSE APPLICATION," dated August 27, 2004, stated:

> Pursuant to Section 351 of the Public Health Services Act and in accordance with 21 CFR 601.2, we submit for your approval an Original Biologics License Application for Measles, Mumps, Rubella and Varicella ... Virus Vaccine Live (STN 125108, ProQuad) ...
>
> The protective efficacy of M-M-R®II... has been demonstrated through a series of double-blinded controlled field trials. In these studies seroconversion in response to vaccination against... mumps... paralleled protection from these diseases. In a series of randomized, controlled clinical trials ... ProQuad was demonstrated to have comparable... immunogenicity profiles as the component vaccines (M-M-R®II plus VARIVAX).

MRK-KRA00157572 (emphasis added).

297. The BLA for ProQuad also included "Form FDA 356h" titled "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" (Title 21, Code of Federal Regulations, Part 314 and 601).[786] Form FDA 356h also identified Merck's "Responsible Officer or Agent," as Dr. Michael Dekleva, Director, Worldwide Regulatory Affairs/Vaccine

[786] MRK-KRA00157539 at '40.

Biologics, who certified: "the data and information in this submission has been reviewed and to the best of my knowledge are certified to be true and accurate."[787]

298. Like the two Supplemental Biological Applications for MMRII, the BLA for ProQuad was organized into "Modules" containing the information supporting the application.[788] The ProQuad BLA included Module 2, "Common Technical Document Summaries," which included a "Clinical Overview" of the submission.[789]

298.1. The BLA for ProQuad Module 2 "Clinical Overview" stated:

> Overview of the Clinical Development Program[790]
>
> … A formal efficacy trial was not conducted with ProQuad. The efficacy of the product was determined through the use of serologic correlates of protection previously established in the evaluation of the efficacy of the monovalent measles, mumps, rubella and varicella vaccines. Each of these studies demonstrated a high degree of protective efficacy and established that seroconversion in response to vaccination parallels protection from disease [Ref. 5.4: 31, 32, 33, 34]…[791]

MRK-KRA00158126 at '30 (emphasis added).

298.2. The BLA for ProQuad Module 2 "Clinical Overview" also stated:

> Regulatory Guidance and Advice [792]

[787] *Id.*
[788] The complete ProQuad BLA was produced in multiple documents with the bates range MRK-KRA00157532-MRK-KRA00172512.
[789] "Clinical Overview" is Section 2.5.
[790] Module 2, Section 2.5, Subsection 2.5.1.5.
[791] *See also* MRK-KRA00158320 at '338- 39. ("No formal evaluation of the efficacy of ProQuad™ was conducted. A trial to evaluate the efficacy of ProQuad™ would no longer be considered ethical in view of the availability of effective vaccines to prevent measles, mumps, rubella, and varicella. Therefore, the efficacy of ProQuad™ was determined through the use of serologic correlates of protection previously established in the evaluation of the monovalent measles, mumps, rubella, and varicella vaccines... The use of serologic correlates for this purpose was done with the concurrence of the Center of Biologics Evaluation Research (CBER), United States Food and Drug Administration (FDA), and through informal discussions with other regulatory agencies." (Emphasis added).)
[792] Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.1, "Product Development Rationale," Subsection 2.5.1.7, "Regulatory Guidance and Advice."

> The protocols for all of the clinical trials conducted in support of this Application were submitted to the Centers for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA). CBER concurrence was obtained on the following items with regard to the design and conduct of the clinical studies: (1) Evaluation of immunogenicity using validated assays [sic] could be used as a surrogate measure of efficacy; (2) Seroconversion and GMTs were evaluated for all studies supporting licensure; (3) Non-inferiority or equivalence margins were implemented to establish the similarity of ProQuad™ with M-M-R™II and VARIVAX™ administered concomitantly at separate injection sites ... ; and (4) Definition of the minimum clinically acceptable dose of varicella virus in ProQuad. [793]

Id. at '35 (emphasis added, internal reference omitted).

298.3. The BLA for ProQuad Module 2 "Clinical Overview" also stated:

> Efficacy[794]
>
> The efficacy of ProQuad™ was established through the use of immunological correlates for protection against measles, mumps, rubella and varicella. The specifications for measles, mumps, and rubella in ProQuad™ are the same as those for M-M-R™II. Antibody response was used to confirm that the immunogenicity of the measles, mumps and rubella components remained unchanged between the 2 products. The efficacy of the monovalent measles, mumps and rubella vaccines had been established through blinded, controlled field studies and in outbreak situations. The presence of serum antibody was established in these studies as a serological correlate of protection for measles, mumps,

[793] MRK-KRA00170981 at '982 (Ref. 5.4: 35, a memo from Dr. Manal Morsy to Dr. Henrietta Ukwu, dated February 16, 2000, with the subject "BB-IND 7068: MMRV pre-phase III meeting minutes received from CBER 2-15-00" stated: "One main discrepancy is that CBER outlines that Merck will conduct a correlation between wild type mumps neutralization PRN assay and a wild type ELISA for use in MMRV related mumps immune responses. Our understanding is that we not only have to conduct a correlation study, and that CBER agreed that we used ELISA for mumps in MMRV (only – not in M-M-R®II) provided that we use a wild type mumps and not our current vaccine strain based ELISA assay.") (emphasis added). *See also* MRK-KRA00170981 at '83, '86 (official Telephone Conversation Record dated January 31, 2000, stated: "CBER discussed concerns associated with the use of the ELISA assay to measure seroconversion to mumps. CBER requested that Merck utilize a wild-type virus strain in this assay and to also provide a correlation between a plaque reduction neutralization assay (PRN).")

[794] Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.4, "Overview of Efficacy," Subsection 2.5.4.1, "Efficacy."

> and rubella. These immunological correlates were then used to show that the immune response to the combination measles, mumps, and rubella vaccine was comparable to the immune response following receipt to the monovalent vaccines. The monovalent ...mumps... vaccine[] and M-M-R™II have proven to be very effective in preventing the development of ... mumps (75 to 96% efficacy) ... after exposure to wild-type virus. The effectiveness of M-M-R™II has been confirmed by the significant reduction (>99%) in the incidence and virtual elimination of endogenous measles, mumps, and rubella following the implementation of routine vaccination programs in several countries. As described in [Sec. 2.5.4.2], the immunogenicity of the measles, mumps, and rubella components of ProQuad™ is generally comparable to that of M-M-R™II.

Id. at '36 (emphasis added, internal citations omitted).

298.4. The BLA for ProQuad "Clinical Overview" also stated:

> Key Serologic Endpoints[795]
>
> Comparison of antibody response rates and/or GMTs ~ 6 weeks following vaccination were used as the primary serologic endpoints in each study. … Levels of antibody for each assay were evaluated by an appropriately sensitive and reliable method and each assay was rigorously validated... For Protocol 012, 013, and 014, a mumps ELISA based on the wild-type mumps virus was used. The response rate for mumps in these 3 studies was the percent of subjects with a post vaccination mumps antibody titer ≥10 ELISA units ...[796]

MRK-KRA00158320 at '37-38 (emphasis added).

298.5. The BLA for ProQuad's Module 2 also included Section 2.7, "Clinical Summary," Subsection 2.7.3, "Summary of Clinical Efficacy – prophylaxis,"[797] which stated:

[795] Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.4, "Overview of Efficacy," Subsection 2.5.4.2 "Immunogenicity," Subsection 2.5.4.2.1.
[796] *See also* MRK-KRA00158320 at '370-71 ("In Protocols 012, 013, and 014, a low passage of the Jeryl-Lynn™ strain virus was used as the antigen; this passage level is considered to be representative of wild-type virus... Sera with responses equal to or above the cutoff of 10.0 mumps Ab units were considered positive while sera with responses below the cutoff were considered negative ...").
[797] *See* Section III.B above discussing vaccines as prophylaxis.

> The efficacy of ProQuad™ was established through the use of immunological correlates for protection against measles, mumps, rubella, and varicella. Results from efficacy studies or field effectiveness studies that were previously conducted for the component vaccines were used to define levels of serum antibodies that correlate with protection against measles, mumps, rubella, and varicella. No formal efficacy trial was conducted with ProQuad™ ...
>
> The clinical efficacy of the monovalent measles, monovalent mumps, and monovalent rubella vaccines was established in a series of double-blind, controlled clinical trials performed in the 1960s-1970s. Each of these studies demonstrated a high degree of protective efficacy against the virus studied. These studies also established that seroconversion in response to vaccination parallels protection from these diseases ...
>
> [Sec 2.7.3.1.2-prophylaxis][798] summarizes the details of the efficacy trials and the field effectiveness studies that were conducted for measles, mumps, rubella, and varicella vaccines (in monovalent or combination form) and the levels of serum antibodies established as correlates of protection for each. [799]

MRK-KRA00158320 at '39-40 (emphasis added).

298.6. The BLA for ProQuad's Module 2's "Summary of Clinical Efficacy – prophylaxis" also stated:

> Overview of Clinical Development Program[800]
>
> The principal objective of the clinical development program for ProQuad™ was to demonstrate that ProQuad™ was as immunogenic and generally well tolerated in healthy

[798] Section 2.7.3.1.2 Summary of Results of Individual Studies "The details of the studies performed to establish the efficacy/effectiveness of measles, mumps, rubella, and varicella vaccines are described in [Sec. 2.7.3.1.3-prophylaxis]."
[799] Module 2, Section 2.7, "Clinical Summary," Subsection 2.7.3, "Summary of Clinical Efficacy – prophylaxis," Subsection 2.7.3.1, "Clinical Efficacy/Effectiveness," Subsection 2.7.3.1.1 "Background and Overview."
[800] ProQuad BLA, Module 2, Section 2.7, "Summary of Clinical Efficacy," Subsection 2.7.3, "Summary of Clinical Efficacy-prophylaxis," Subsection 2.7.3.1, "Clinical Efficacy/Effectiveness" Subsection 2.7.3.1.3 "Comparison and Analyses of Results Across Studies," Subsection 2.7.3.1.3.2.2, "Efficacy/Effectiveness of Mumps Virus-Containing Vaccines."

children, 12 months of age and older, as the concomitant administration of M-M-R™II and VARIVAX™ at separate injection sites. Concomitant administration of M-M-R™II and VARIVAX™ at separate injection sites to children is standard practice in the United States. ...

The clinical summary summarizes the safety and immunogenicity information from all clinical trials performed with ProQuad™... Four (4) of these studies evaluated the immunogenicity and safety of ProQuad™ as compared with the licensed products, M-M-R™II and VARIVAX™, in children 12 months of age and older, and 1 study evaluated the immunogenicity and safety of ProQuad when administered to children 4 to 6 years of age in place of the routinely administered second dose of M-M-R™II. Data on the efficacy of measles, mumps, rubella, and varicella vaccines and the effectiveness of M-M-R™II and VARIVAX™ also are presented in this clinical summary. The data summarized in this clinical summary demonstrate that ProQuad™ is immunogenic and generally well tolerated in healthy children and is as efficacious as its parent products.

MRK-KRA00158320 at ‘38-39 (emphasis added).

298.7. The BLA for ProQuad’s Module 2’s “Summary of Clinical Efficacy – prophylaxis” also stated:

Clinical Efficacy/Effectiveness... [801]

Table 2.7.3-prophylaxis: 2

Efficacy and Effectiveness Studies of Jeryl Lynn™ Mumps Vaccine[802]

[801] Module 2, Section 2.7.3, Subsection, Subsection 2.7.3.1, “Clinical Efficacy/Effectiveness,” Subsection 2.7.3.1.1 “Background/Overview.”

[802] Table 2.7.3 describes two kinds of studies supporting the efficacy and effectiveness. The two clinical trials cited are the studies supporting the efficacy of Mumpsvax. *See* Schedule 7 (Schedule of Efficacy Studies). The remaining studies are “outbreaks” studies. *See* Schedule 6 (Schedule of Epidemiological Studies). *See also* Section III.B.3.a discussing efficacy studies.

Study Reference	Study Type	Study Location	Interval Between Vaccination and Exposure (Months)	Vaccinated Group			Unvaccinated Group			Vaccine Efficacy/ Effectiveness (%) (95% CI)
				Number of Cases	Number at Risk	Attack Rate (%)	Number of Cases	Number at Risk	Attack Rate (%)	
Hilleman MR, 1967 [Ref. 5.4: 34]	Clinical Trial	Philadelphia	0 to 20	3†	113	2.7	80‡	129	62	95 (NA)
Sugg WC, 1968 [Ref. 5.4: 95]	Clinical Trial	North Carolina	0 to 6	5	1004	0.5	13	115	11.3	95.6 (NA)
MMWR, 1973 [Ref. 5.4: 96]	Outbreak	New York	NA	6§	178	3.4	115	721	16.0	79 (53, 91)
Lewis JE, 1979 [Ref. 5.4: 41]	Outbreak	Canada	48 to >156	8	145	5.5	76	350	21.7	75 (49, 87)
Sullivan KM, 1985 [Ref. 5.4: 97]	Outbreak	Ohio	NA	31	375	8.3	26	59	44.1	81.2 (70.8, 88.0)
Kim-Farley R, 1985 [Ref. 5.4: 98]	Outbreak	Ohio	NA	2	30	7	30	69	43	85 (39, 94)
Chaiken BP, 1987 [Ref. 5.4: 99]	Outbreak	New Jersey	NA	5	122	4	19	43	24	91 (77, 93)
Wharton M, 1988 [Ref. 5.4: 100]	Outbreak	Tennessee	NA	31	184	16.8	97	201	48.3	75 (65, 86)
Hersh BS, 1991 [Ref. 5.4: 101]	Outbreak	Kansas	<48 to >120	135	1713	7.9	3	8	37.5	83 (57, 94)

Study Reference	Study Type	Study Location	Interval Between Vaccination and Exposure (Months)	Vaccinated Group			Unvaccinated Group			Vaccine Efficacy/ Effectiveness (%) (95% CI)
				Number of Cases	Number at Risk	Attack Rate (%)	Number of Cases	Number at Risk	Attack Rate (%)	
Toscani L, 1996 [Ref. 5.4: 102]	Outbreak	Switzerland	NA	6	41	14.6	19	44	43.2	66.1 (29.0, 83.8)
Schlegel M, 1999 [Ref. 5.4: 103]	Outbreak	Switzerland	NA	5	36	14	5	8	63	78 (64, 82)

† Two (2) cases were laboratory-confirmed mumps; 1 case was based on clinical diagnosis only.
‡ Sixty-one (61) cases of laboratory-confirmed mumps; 19 cases were based on clinical diagnosis only.
§ Three (3) of the 6 children who developed mumps after vaccination had received live mumps vaccine; however, at least 1 of the remaining 3 had killed mumps vaccine.
NA = Not available.
CI = Confidence interval.

Correlation of protection with the development of detectable antibody was established in the early mumps efficacy studies using a neutralization assay [Ref 5.4: 34].[803] The development of any detectable antibody in the neutralization assay was found to correlate strongly with protection against wild-type infection. More recently, Merck & Co., Inc has assessed the correlation between neutralizing antibody (as measured in a plaque reduction neutralization [PRN] assay) and a wild-type enzyme-linked immunosorbent assay (ELISA) [Ref. 5.4: 107,[804] 108[805]]. The overall agreement rate was 93.6%

[803] Reference 5.4:34 is a 1967 study by Dr. Maurice Hilleman. *See* Table 2.7.3-prophylaxis: 2, above, row one, identified as [Ref.5.4:34].

[804] MRK-KRA00171829 (Ref. 5.4:107, "Memo to Shaw A. From Antonello JM: Comparison between the mumps wild type (WT) ELISA (SOP 910.0096) and the anti-IgG enhanced plaque reduction neutralization (AIGENT) assay for mumps (SOP 874.3589) using the 'corrected' AIGENT results, 08-Apr-2002"); *see* footnote 582 above (explaining that Merck agreed to use "original" data after the August 2001 Form 483 for deficiencies in the AIGENT testing.) Merck could not rely on the comparison of the "corrected" data. *See also* Section IX.A.6.a below (describing the submission of the "corrected" analysis in the Protocol 007 Clinical Study Report in support of the sBLA for Mumps End Expiry).

[805] Ref. 5.4:108, "Memo to Shaw A from Antonello JM: Examination of the twenty-two WT ELISA positive and AIGENT negative samples from the subset of post-vaccination samples tested in the MMRII 007 trial, [June 5,] 2002," stated: "… Of the 565 subjects tested in the AIGENT assay, … 513 had a reportable post-vaccination titer ..." MRK-KRA00171851 at '51-53.

(480/513). These data support the use of the results of a wild-type ELISA as a correlate for protection.

MRK-KRA00158320 at '47-48, '50 (emphasis added).

298.8. The BLA for ProQuad's Module 2's "Summary of Clinical Efficacy – prophylaxis" also stated:

Clinical Trials with ProQuad[806]

Five (5) clinical trials were conducted from 1998 to 2002 using ProQuad™ [Ref.5.3.5.1: P009, P011, P012, P013, P014]... These 5 studies... form the basis of the clinical database in support of licensure of this product.

Id. at '75.

298.9. The BLA for ProQuad "Summary of Clinical Efficacy – prophylaxis" in Module 2 also stated:

Conclusions Regarding Immunogenicity[807]

The immunogenicity data from the... clinical trials of ProQuad™ support the following conclusions:

1. A single dose of ProQuad™ is highly immunogenic. The immune response to ProQuad™ is similar (noninferior) to that obtained following administration of the component vaccines by concomitant administration of M-M-R™II and VARIVAX™ at separate injection sites...

Id. at '76.

299. In sum, Module 2 of the BLA for ProQuad included the following statements:

- The efficacy of ProQuad was determined through the use of correlates of protection established in the evaluation of the efficacy of the mumps monovalent vaccine.

[806] Module 2, Section 2.7.3, Subsection 2.7.3.2 "Immunogenicity," Subsection 2.7.3.2.2 "Summary of Results of Individual Studies," Subsection 2.7.3.2.2.2 "Clinical Trials with ProQuad™."
[807] Module 2, Section 2.7.3, Subsection 2.7.3.2 "Immunogenicity," Subsection 2.7.3.2.6 "Conclusions Regarding Immunogenicity."

- The BLA was supported by five clinical trials.
- For Protocols 012, 013 and 014, a mumps WT ELISA was used with a 10 Ab cutoff.
  - Evaluation of immunogenicity using validated assays could be used as a surrogate measure of efficacy.
  - Antibody response was used to confirm that the immunogenicity of the mumps component did not change from MMRII to ProQuad.
  - Levels of antibody for each assay were evaluated by an appropriately sensitive and reliable method.
  - The data demonstrated that ProQuad is immunogenic and as efficacious as its parent products, including MMRII.
  - Merck assessed the correlation between its neutralization assay and its WT ELISA and the data support the use of the results of the WT ELISA as a correlate for protection.[808]
  - The presence of detectable antibody by neutralization assay or ELISA for mumps has generally been shown to have a strong correlation with protection from disease.[809]

6. Merck Used the WT ELISA in Clinical Studies Supporting Three Applications

a. sBLA for Mumps End Expiry – Protocol 007

300. The sBLA for Mumps End Expiry was supported by one clinical study, Protocol 007. The Protocol 007 Clinical Study Report[810] ("CSR") was submitted in the sBLA's Module 5 ("Clinical Study Reports"). [811] The Clinical Study Report included a description of the assays

[808] Merck witnesses Dr. David Krah and Dr. Florian Schodel testified that there is no correlate of protection for mumps. Deposition of David L. Krah, July 11, 2017, 182:12-20 and Deposition of Florian Schodel, December 22, 2016, 124:18 to 125:12.
[809] *See* MRK-KRA00158126 at '30-31, '35-38; MRK-KRA00158320 at '38-39, '49-50, '65.
[810] The Clinical Study Report is dated December 23, 2003 and is marked "Reference P007 – Clinical Study Report-A Study of M-M-R II at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age (Protocol 007)."
[811] Module 5 also included a document marked "Reference R1" and titled "MRL Report: Comparison of the immunogenicity of M-M-R®II manufactured with GOS stabilizer to M-M-R®II manufactured with oGOS stabilizer, 2003" MRK-KRA00137307 at '08.

used in Protocol 007. With regard to the AIGENT, the Report stated that a "functional plaque reduction neutralization assay was developed and used to measure the ability of the vaccine-induced immune response to inhibit viral replication in vitro, and therefore possibly provide a better indication of immune protection."[812] With regard to the WT ELISA, the Report stated that the "mumps wild-type ELISA used in this study was shown to correlate with the PRN assay, and previous studies have established a strong correlation between the development of mumps-specific neutralizing antibodies and vaccine efficacy."[813]

300.1. The Protocol 007 Clinical Study Report[814] stated:

> The "shelf-life" of M-M-R II, which is defined as the maximum duration of storage allowed at 2 to 8°C (from manufacture to expiration), is 24 months in most countries in the world. "Shelf-life" is based on several factors: (1) the stability of the vaccine or virus potency decay over time,[815] (2) knowledge about the minimum vaccine potency required to ensure successful protection, and (3) the release potency at the time the vaccine is manufactured and its correlate, the targeted or "fill potency."

MRK-KRA00135759 at '5786 (emphasis added).

300.2. The Protocol 007 Clinical Study Report[816] also stated:

> Minimum Immunizing Dose
>
> Studies evaluating the minimum immunizing dose for ... mumps ... were performed at MRL by Hilleman and colleagues using both the monovalent and multivalent preparations of measles, mumps, and rubella vaccines. ... These limited studies suggested

[812] MRK-KRA00135759 at '5813.
[813] MRK-KRA00135759 at '5951-954.
[814] CSR Section 1 "Introduction," subsection 1.2, "Vaccine Shelf-life, Stability and Potency Specifications."
[815] *See* Section III.B.2 above discussing the interconnection between potency, shelf life and the end expiry specification.
[816] CSR Section 1, Introduction, Section 1.2.2 "Measles, Mumps, and Rubella Potency Specifications," Section 1.2.2.1.

> that as little as ... 2.5 $\log_{10}$ $TCID_{50}$/ dose (~317 $TCID_{50}$) of Jeryl Lynn™ mumps virus ... strains provide 100% seroconversion in ... mumps- …naïve individuals ...

Id. at '5787.

300.3. The Protocol 007 Clinical Study Report also stated:

> Minimum End- Expiry Potencies
>
> Based on existing data regarding the minimum immunizing dose for ... mumps ... and the significant amount of stability data gathered at MRL, minimum end-expiry titers for each virus component were determined ... The minimum end-expiry dose insured that vaccine lots released with a titer at or above the minimum release titer could be stored at 2 to 8ºC for as long as 24 months and still provide adequate immunogenicity at the end of the product's shelf life.

Id. (emphasis added).

300.4. The Protocol 007 Clinical Study Report also stated:

> Study Rationale[817]
>
> Although M-M-R™II has been demonstrated to be highly immunogenic and efficacious and previous dilution studies have suggested that lower doses of the vaccine are immunogenic, no specific study of M-M-R™II has been performed at the mumps virus expiry potency. Based on historical data with mumps containing vaccine, it was likely that a potency lower than 4.3 log10 TCID50/dose would prove to be equally immunogenic as higher mumps virus potency.
>
> The objective of this study was to demonstrate that children vaccinated with M-M-R™II at mumps virus end-expiry potency below 4.3 $\log_{10}$ $TCID_{50}$/dose would achieve similar seroconversion rates by neutralization antibody assay at 6 weeks postvaccination as children receiving M-M-R™II containing the targeted mumps release potency.

Id. at '5789.

300.5. The Protocol 007 Clinical Study Report also stated:

[817] Section 1 "Introduction," subsection 1.3.

OBJECTIVES[818]

Primary[819]

1. To demonstrate a similar immune response to mumps virus by neutralization among subjects receiving M-M-R™II containing an expiry dose of mumps virus ... compared to subjects receiving M-M-R™II containing a release dose of mumps virus ...

2. To demonstrate an adequate immune response among subjects receiving M-M-R™II containing an expiry dose of mumps ...

Secondary[820]

1. To demonstrate similar immune responses to ... mumps, and ... (seroconversion rates by ELISA) among children who receive M-M-R™II containing an expiry dose of mumps virus ... compared to children who receive M-M-R™II containing a release dose of mumps virus ...

5. To summarize the persistence of antibody to ... mumps ... (as measured by the mumps PRN assay and by ELISA) 1 year postvaccination in each treatment group.

Id. at '5794.

300.6. The Protocol 007 Clinical Study Report[821] also stated:

The mumps neutralization assay is a plaque reduction neutralization assay (PRN) designed to quantitate mumps neutralizing antibody in prevaccination and post vaccination sera. This assay was developed and validated by MRL. It is not the primary assay used by MRL to evaluate serologic response to a mumps virus-containing vaccine.

[818] The Objectives are pre-defined before the study begins and state the overall purpose of the study. At the conclusion of the study, a clinical study report summarizes the results of the study and the findings of the research conducted.

[819] *See* MRK-KRA00135759 at '5779 ("For the primary objectives of the study, the sera were tested for mumps antibody by a plaque reduction neutralization (PRN) assay.")

[820] *See* MRK-KRA00135759 at '5780 ("For the secondary objectives concerning...mumps... the sera were tested for antibody to each viral component using an enzyme-linked immunosorbent assay (ELISA)."); *see also* MRK-KRA00135759 at '5809. ("...In agreement with CBER, the measurement of mumps neutralizing A[nti]b[odies] by PRN at 1 year post vaccination was later eliminated in view of the excellent correlation between mumps PRN and ELISA.") (emphasis added).

[821] CSR Section 5, Subsection 5.5.2, "Appropriateness of Measurements."

> Typically, the mumps ELISA is used to detect immunoglobulin gamma antibody (IgG) to mumps virus before and after vaccination. However, antibody detection by ELISA does not reveal ability to block viral replication. For the purpose of this study, a functional plaque reduction neutralization assay was developed and used to measure the ability of the vaccine-induced immune response to inhibit viral replication in vitro, and therefore possibly provide a better indication of immune protection.

MRK-KRA00135759 at '5813 (emphasis added).

300.7. The Protocol 007 Clinical Study Report also stated:

> Description of the [Mumps WT ELISA] Assay[822]
>
> …
>
> The serostatus cutoff is the lowest antibody concentration that can be reliably distinguished from a panel of negative samples. A panel of 72 "negative" samples were tested, 12 in each of 6 assay runs. … Based on the results of this panel, a serostatus cutoff of 10 Ab units was recommended.

MRK-KRA00135759 at '5820 (original bold removed, underline added).

300.8. The seroconversion results of Protocol 007 measured by the AIGENT assay and WT ELISA can be summarized as follows:

[822] CSR Section 5, Subsection 5.5.4.3 "Mumps Antibody Enzyme-Linked Immunosorbent Assay (Mumps ELISA)."

Summary of Antibody Responses to Mumps for Protocol 007 Subjects Initially Seronegative to Measles, Mumps, or Rubella (Per-Protocol Analysis)

	Treatment Groups of M-M-R™II						
Antibody (Assay) Parameter	3.8 log10 TCID50/Dose Mumps Virus Potency* (N=663)		4.1 log10 TCID50/Dose Mumps Virus Potency* (N=662)		4.8 log10 TCID50/Dose Mumps Virus Potency** (N=672)		**All Subjects (N=1997)**
	Observed Response	95% CI	Observed Response	95% CI	Observed Response	95% CI	**Observed Response**
42-Day Mumps (AIGENT)							
SCR[823]	**89.3%** (410/459)	(86.1%, 92.0%)	**93.3%** (404/433)	(90.5%, 95.5%)	**92.2%** (403/437)	(89.3%, 94.6%)	**91.5%** (1,217/1,329)
42-Day Mumps (ELISA)							
SCR[824]	**94.1%** (543/577)	(91.9%, 95.9%)	**97.4%** (568/583)	(95.8%, 98.6%)	**98.0%** (576/588)	(96.5%, 98.9%)	**96.5%** (1,687/1,748)
One Year Mumps (ELISA)[825]							
Persistence Rate	**96.7%** 409/423	(94.5%, 98.2%)	**95.4%** 417/437	(93.0%, 97.2%)	**95.7%** 446/466	(93.4%, 97.4%)	**95.9%** (1,272/1,326)

*Two sublots of M-M-R™II derived from the same parent lot as the control 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 vaccinated in each treatment group.
SCR = Seroconversion rate.
[Persistence Rate] = Persistence rate (ratio) proportion of subjects who maintained a positive response at 1 year among those who were initially seronegative and who responded at 6 weeks postvaccination. A positive response … for mumps is antibody titer ≥10 ELISA Ab units, …
Definitions:
ELISA = Enzyme-linked immunosorbent assay.
AIGENT = Anti-IgG Enhanced Neutralization Test.
CI = Confidence interval.

300.9. The "Discussion" Section of the Protocol 007 Clinical Study Report stated:

... Following agreement with CBER and in an attempt to demonstrate that mumps virus at end expiry potency was not only immunogenic but effective in inhibiting viral

[823] *See* MRK-KRA00135759 at '782.
[824] *See* MRK-KRA00135759 at '782.
[825] *See* MRK-KRA00135759 at '889.

replication, a functional assay (Plaque Reduction Neutralization or PRN assay) aimed at measuring mumps-specific neutralizing antibodies, was developed and validated at MRL, and used the evaluate the primary immunogenicity hypotheses of the study. …

This randomized, double-blind (using in-house blinding procedures), multicenter, comparative study ... was conducted in order to demonstrate similarity between M-M-R™II containing a candidate expiry dose of mumps virus and M-M-R™II containing the current release dose of mumps virus with respect to safety, tolerability, and immunogenicity. ...

Selection of M-M-R™II containing no less than 4.1 $\log_{10}$ $TCID_{50}$ mumps virus as the end expiry potency was confirmed by use of an ELISA assay to address the secondary immunogenicity hypothesis for this study. ...

The mumps wild-type ELISA used in this study was shown to correlate with the [AIGENT] assay [2.2.6][826], and previous studies have established a strong correlation between the development of mumps-specific neutralizing antibodies and vaccine efficacy [1.1.10; [827] 1.1.11; [828] 1.1.12[829]]. Therefore, the mumps [AIGENT] assay and [WT] ELISA results from this study support the effectiveness of M-M-R™II containing a mumps virus potency of no more than 4.1 $\log_{10}$ $TCID_{50}$ and the lowering of the mumps virus end expiry potency from the currently assigned potency of 4.3 $\log_{10}$ $TCID_{50}$ to no

In summary, this study has demonstrated that M-M-R™II containing mumps virus at expiry potency of no more than 4.1 $\log_{10}$ $TCID_{50}$ was similar to M-M-R™II containing the current release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$ with respect to safety, tolerability and immunogenicity to measles, mumps, and rubella. ... Overall, the study

[826] *See* Section IX.A.6.b below, Appendix 2.2.6, cited in Section 9 of the Clinical Study Report.
[827] MRK-KRA00135759 at '312 (Appendix 1.1.10 - E. B. Buynak & M. R. Hilleman, *Live Attenuated Mumps Virus Vaccine. 1. Vaccine Development*, 123 EXPERIMENTAL BIOLOGY AND MEDICINE 768–775 (1966)).
[828] MRK-KRA00135759 at '321 (Appendix 1.1.11 - R. E. Weibel et al., *Persistence of Antibody After Administration of Monovalent and Combined Live Attenuated Measles, Mumps, and Rubella Virus Vaccines*, 61PEDIATRICS 5–11 (1978).
[829] MRK-KRA00135759 at '328 (Appendix 1.1.12 - Maurice R. Hilleman et al., *Live, Attenuated Mumps-Virus Vaccine*, 278 New England Journal of Medicine 227–232 (1968).

> results suggest that M-M-R™II containing a release potency of 4.1 $\log_{10}$ $TCID_{50}$ is highly immunogenic, well tolerated, and will be as effective as M-M-R™II containing the current release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$.

MRK-KRA00135759 at '5951-954 (emphasis added).

301. Appendix 2.2.6, as cited in Section 9 of the Protocol 007 Clinical Study Report, "Merck Memo from J. M. Antonello to A. Shaw with the 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 "Corrected"[830] AIGENT Results," dated April 8, 2002, stated:

> Given that the AIGENT titers are measured values and subject to the variabilities inherent in a biological assay, agreement between the ELISA and AIGENT assays is considered quite good, exceeding 90% 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 92.3% (1022/ 1107) with 503 samples classified as positive in both assays and 519 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 (6.9% as compared to 2.0%), and a post-vaccination sample was less likely to be classified sero-positive in the AIGENT assay than in the ELISA (92.1% as compared to 95.7%). 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 92.5% (468/506), with the ELISA being slightly more likely to classify a sample as a seroconverter. Among the set of samples that were evaluable in both assays, the sero-conversion rate was 95.7% (484/506) in the ELISA and 92.1% (466/506) in the AIGENT assay.

MRK-KRA00135759 at '746 (emphasis added).

[830] *See* footnote 582 above. Merck agreed to use "original" data after the August 2001 Form 483 for deficiencies in the AIGENT testing. Merck could not rely on the "corrected" data.

302. MRL's former Vice President, Clinical Research, Florian Schodel, testified as follows:

> *Q. And Merck in the clinical study report stated that it correlated its wild-type ELISA to its PRN assay. Correct?*
>
> *A. That's correct.*

Deposition of Florian Schodel, December 22, 2016, 370:7-11.

b. The sBLA for rHA – Protocol 009

303. The sBLA for rHA was supported by a single clinical study, Protocol 009, with a Clinical Study Report dated March 19, 2004. The Protocol 009 Clinical Study Report was submitted as part of the sBLA for rHA in Module 5, "Clinical Study Reports." Protocol 009 was performed to demonstrate that MMRII manufactured with Human Serum Albumin (HSA) was as safe and effective as MMRII manufactured with Recombinant Serum Albumin (rHA).

303.1. The Protocol 009 Clinical Study Report[831] stated:

> The primary immunogenicity objectives of this study were to demonstrate that (1) M-M-R™II with rHA induces antibody response rates to measles, mumps, and rubella similar to those induced by M-M-R™II with HSA and (2) that M-M-R™II with rHA induces acceptable antibody response rates[832] to measles, mumps, and rubella. To address these objectives, antibody response rates to each antigen were assessed in initially seronegative subjects, based on blood samples obtained prior to and ~42 days following vaccination.

MRK-KRA00140056 at '0119.

303.2. The Protocol 009 Clinical Study Report[833] also stated:

[831] Protocol 009 Clinical Study Report Section 5.7 "Statistical Methods Planned in the Protocol and Determination of Samples Size," subsection 5.7.1 "Statistical and Analytical Plans to Address Study Objectives."
[832] *See also* MRK-KRA00140056 at '0081 ("The primary purposes of this study were ...to demonstrate that M-M-R™II manufactured with rHA induced acceptable antibody responses to measles, mumps, and rubella ~6 weeks postvaccination." (emphasis added)).
[833] Protocol 009 Clinical Study Report Section 5.2 "Discussion of Study Design, Including the Choice of Control Groups."

> This study was conducted to demonstrate that M-M-R™II with rHA was well tolerated and similar to M-M-R™II with HSA with respect to immunogenicity for measles, mumps, and rubella. Since M-M-R™II is currently manufactured with HSA, subjects receiving this formulation served as the control group in this study. ...
>
> The primary endpoints used to assess immunogenicity 6 weeks postvaccination were the antibody response rates to measles, mumps, and rubella, which were defined as the proportion of subjects who developed serum antibody levels... ≥10 ELISA antibody units/mL for mumps ... among subjects initially below the cutoff ...

Id. at '0086 (emphasis added).

303.3. The Protocol 009 Clinical Study Report[834] also stated:

> Serum samples obtained from each subject immediately prior to receiving the study vaccination and ~6 weeks postvaccination were analyzed for levels of antibodies ... to measles, mumps, and rubella viruses using ELISA specific for each virus type. ...

Id. at '0097.

303.4. The Protocol 009 Clinical Protocol, which was submitted as part of the Protocol 009 Clinical Study Report,[835] stated:

> Serum levels of antibodies to measles, mumps, and rubella will be determined by enzyme-linked immunosorbent assays (ELISAs). Protective levels of antibody will be defined as ... ≥10.0 ELISA antibody units for mumps (wild-type) IgG, ...

MRK-KRA00140056 at '0941 (emphasis added).

303.5. The Protocol 009 Clinical Study Report also stated:

> Appropriateness of Measurements[836]

[834] Protocol 009 Clinical Study Report Section 5.5 "Immunogenicity and Safety Variables," subsection 5.5.1 "Measurements Assessed and Timing of Assessment," subsection 5.5.1.1 "Immunological Parameters."
[835] Protocol 009 Clinical Study Report, Appendix 3.3.2.
[836] Clinical Study Report, Section 5.5.2.

> The ELISAs that were used to measure serum levels of antibodies (IgG) to measles, mumps, and rubella antigens are the primary assays used by Merck & Co., Inc. to evaluate antibody responses to vaccines containing these viruses.

Id. at '0104.

303.6. The Protocol 009 Clinical Study Report also stated:

> The assumed response rate [of 95%] to ... mumps [was] based on preliminary results from M-M-R™II Protocol 007... and ProQuad™ Protocol 012 ... as well as clinical experience with M-M-R™II from 1992 to 1997.

Id. at '0121, fn.7 (emphasis added).

303.7. The Discussion section of the Protocol 009 Clinical Study Report stated:

> This randomized, double-blind (using in-house blinding procedures), multicenter comparative study was conducted in healthy children 12 to 18 months of age to demonstrate the tolerability of M-M-R™II to rHA and its similarity to M-M-R™II with HSA with respect to immunogenicity. …
>
> The primary objective of the study was to demonstrate similarity in antibody response rates to measles, mumps, and rubella of subjects who received M-M-R™II with rHA to those who received M-M-R™II with HSA. Another objective of the study was to demonstrate that M-M-R™II with rHA induced acceptable antibody response to measles, mumps, and rubella. ...
>
> The measles, mumps, and rubella antibody response rates were each observed to be ≥97.9% for both treatment groups. ... In addition, study results showed that the acceptability criterion for the antibody response rates induced by M-M-R™II with rHA was also achieved for each of the 3 antigens. The observed antibody response rate[] in recipients of M-M-R™II with rHA for...mumps... [was]... 99.5%...

Id. at '0193-94 (emphasis added).

303.8. The "Discussion" Section of the Protocol 009 Clinical Study Report also stated:

> In summary, this study demonstrated that M-M-R™II with rHA is well tolerated and similar to M-M-R™II with HSA with respect to immunogenicity (i.e. antibody response rates) for measles, mumps, and rubella. ... Overall, the study results suggest that M-M-R™II with rHA is highly immunogenic, well tolerated, and will be as effective as M-M-R™II with HSA in preventing measles, mumps, and rubella.

Id. at '0196 (emphasis added).

c. The BLA for ProQuad – Protocols 012, 013, and 014

304. The BLA for ProQuad was supported by five clinical studies. Protocols 012, 013, and 014 used a WT ELISA with a 10 Ab cutoff to measure mumps immunogenicity.[837]

(1) BLA for ProQuad: Protocol 012

304.1. Protocol 012 compared Proquad in terms of immunogenicity, safety and tolerability to MMRII and Varivax administered separately.[838]

304.2. The Protocol 012 Clinical Study Report stated:

> The current study was conducted to demonstrate similarity among 3 consistency lots of ProQuad™, in terms of their immunogenicity, safety, and tolerability. The 3 lots were compared to each other, then combined, and compared to the responses generated by the concomitant administration of M-M-R™II and VARIVAX™ at separate injection sites, the current standard of care in the United States. This clinical study report (CSR) presents the results of a partially double-blind, multicenter, randomized study to confirm manufacturing consistency of ProQuad™.

MRK-KRA00162963 at '2995-96 (emphasis added).

304.3. The Protocol 012 Clinical Study Report also stated:

> Study Objectives

[837] The ProQuad BLA was supported by five clinical studies, ProQuad Protocol 009, 011, 012, 013, and 014. *See* MRK-KRA00158126 at '131 (ProQuad BLA Module 2, Section 2.5 "Clinical Overview," Subsection 2.5.1.6.1 "Conduct and Design of the Study" "The clinical program to support licensure of ProQuad consisted of 5 randomized, controlled protocols ...")
[838] MRK-KRA00162963 at '2995-96.

1. To demonstrate that the 3 consistency lots of ProQuad™ will elicit similar immune responses to measles, mumps, rubella, and varicella.

2. To determine whether the 3 consistency lots of ProQuad™ combined will elicit an immune response similar to M-M-R™II and VARIVAX™ given concomitantly, but at separate injection sites.

3. To demonstrate that each of the 3 consistency lots of ProQuad™ provides an acceptable immune response to measles, mumps, rubella and varicella.

4. To demonstrate that the 3 consistency lots of ProQuad™ will be well tolerated.

5. To evaluate the persistence of antibodies to all 4 vaccine antigens 1 year postvaccination ...

Id. at '2998-99 (emphasis added).

304.4. The Protocol 012 Clinical Study Report also stated:

Discussion of Study Design, Including Choice of Control Groups

This study was conducted to confirm consistency of the manufacturing process of the current formulation of ProQuad™ (frozen). The 3 consistency lots had varicella potencies ... all within the expected release range for the product. The safety and immunogenicity results of each lot were evaluated, then pooled and compared to those of a control group of M-M-R™II and VARIVAX™ given as separate, concomitant injections, reflecting current immunization practice in the United States. These comparisons were used to demonstrate clinical consistency of manufactured material and similarity to the current standard of care for prophylaxis against measles, mumps, rubella, and varicella. All subjects were followed for adverse experiences for 42 days after the vaccination. At the 42-day follow-up visit, a serological sample was taken and analyzed for immunogenicity, and disease/exposure surveys were completed. All subjects were scheduled for a 1-year postvaccination blood draw to evaluate the persistence of antibodies to all 4 vaccine antigens and to assess disease exposures.

Id. at '3002 (emphasis added).

304.5. The Protocol 012 Clinical Study Report also stated:

Vaccine Antibody Measurements

Serologic testing was performed by MRL, West Point, PA. Levels of measles, mumps, rubella, and varicella humoral antibodies were evaluated by an appropriately sensitive and reliable method (by ELISA or gpELISA, as appropriate). MRL Laboratory personnel were not blinded with respect to the bleed interval, but were blinded as to the treatment group. The decision to revaccinate a study participant was based on MRL's test results.

Id. at '3013 (emphasis added).

304.6. The Protocol 012 Clinical Study Report also stated:

Mumps Enzyme Immunoassay (Mumps ELISA)

The mumps EIA [WT ELISA] was used to detect antibody (IgG) to mumps virus before and after vaccination with a mumps virus-containing vaccine; it was the primary assay used in MRL to evaluate the anti-mumps serologic response. The assay uses and early passage of the Jeryl Lynn™ mumps virus (<12 passages) which is less attenuated than the Jeryl Lynn™ mumps virus used in the Merck mumps virus-containing vaccines, and is considered to be a wild-type (WT)-like strain ...

The serostatus cutoff is the lowest antibody concentration that can be reliably distinguished from a panel of negative samples. A panel of 72 "negative" samples were tested, 12 in each of 6 assay runs. Twelve of the 72 samples were postvaccinated negatives as determined in the historical non-WT EIA, and the remaining were prevaccinated samples. Based on the results of this panel, a serostatus cutoff of 10 Ab units was recommended. Samples with ODs less than or equal to the cutoff were serostatus negative and assigned a titer of less than 10.0 Ab units. Samples with ODs greater than the cutoff were considered serostatus positive and quantified using the standard curve. The quantifiable range of the assay was defined as 0.5 to 64 Mumps Ab

> units/mL. Sera whose titers exceeded this range were retested at greater dilutions until an endpoint titer was obtained.

Id. at '3016-17 (emphasis added).

304.7. The Protocol 012 Clinical Study Report "Discussion" Section stated:

> The results of this study suggest that the immune responses demonstrated by the 3 consistency lots of ProQuad™ appear comparable to one another as well as to the control group for all 4 antigens. Additionally, the 3 consistency lots of ProQuad™ induced acceptable immune responses to measles, mumps, rubella, and varicella.

Id. at '3194 (emphasis added).

(2) BLA for ProQuad: Protocol 013

305. Protocol 013 was conducted to show the concomitant use of ProQuad, Tripedia and Comvax did not impair the safety or antibody response to each vaccine component compared with separate administration of ProQuad followed by Tripedia and Comvax or separate administration of MMRII and Varivax followed by Tripedia and Comvax.[839]

306. The Protocol 013 Clinical Study Report stated:

> This study was conducted to show that ProQuad™, TRIPEDIA™ (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Connaught Laboratories, Inc., Swiftwater, PA), and COMVAX™ can be administered concomitantly at separate injections sites without impairing the safety or the antibody response to each of vaccine components. ... This clinical study report (CSR) presents the results of concomitant administration of ProQuad™, TRIPEDIA™, and COMVAX™ in comparison with the separate administration of ProQuad™ followed 6 weeks later by TRIPEDIA™ and COMVAX™, or the separate administration of M-M-R™II and VARIVAX™ followed 6 weeks later by TRIPEDIA™ and COMVAX™.

MRK-KRA00164918 at '4946 (emphasis added).

[839] MRK-KRA00164918 at '4946.

306.1. The Protocol 013 Clinical Study Report also stated:

Study Hypotheses and Objectives (Cont.)

Primary Objectives

1. To demonstrate that ProQuad™ can be administered concomitantly with TRIPEDIA™ and COMVAX™ without impairing the immune response to measles, mumps, rubella, varicella, diphtheria, tetanus, pertussis PT, pertussis FHA, hepatitis B, or Haemophilus influenzae type B (HiB).

2. To demonstrate that the concomitant administration of ProQuad™ with TRIPEDIA™ and COMVAX™ provides an acceptable immune response to measles, mumps, rubella, and varicella.

3. To show that ProQuad™ is generally well tolerated when administered concomitantly with TRIPEDIA™ and COMVAX™ at the same visit or separated by an interval of 6 weeks.

4. To show that ProQuad™, whether administered concomitantly with TRIPEDIA™ and COMVAX™ at the same visit or separately by an interval of 6 weeks, is generally well tolerated compared to the concomitant administration of M-M-R™II and VARIVAX™.

Id. at '4950 (emphasis added)

306.2. The Protocol 013 Clinical Study Report also stated:

Discussion of Study Design, Including Choice of Control Groups

This study was conducted to show that ProQuad™, TRIPEDIA™ and COMVAX™ can be administered concomitantly at separate injection sites without impairing the immune response to any vaccine component or compromising the safety profile of any of the components. Concomitant administration of ProQuad™, TRIPEDIA™, and COMVAX™ was evaluated for safety ... and immunogenicity in comparison with the treatment group that received ProQuad™ on Day 0 and TRIPEDIA™ and COMVAX™

> on Day 42. Safety ... was also evaluated between the concomitant group and the control group that received M-M-R™II and VARIVAX™ on Day 0 and TRIPEDIA™ and COMVAX™ on Day 42. The control group in this study was included to mimic standard vaccination practices at ~12 months of age.
>
> All treatment groups were followed... for adverse experiences, injection-site reactions, temperature, exposure, and rashes ... All subjects were encouraged to have a baseline blood sample taken before vaccination at Day 0. The concomitant group (Group 1) had a blood sample take on Day 42. The nonconcomitant group (Group 2) had blood samples taken on Days 42 and 84. The control group (Group 3) had the option of having a blood sample taken on Days 42 and 84. All 48 sites randomized subjects to 1 of the 3 treatment groups in a 2:1:1 ratio.

Id. at '4953 (emphasis added).

306.3. The Protocol 013 Clinical Study Report also stated:

> Immunogenicity and Safety Parameters ...
>
> Vaccine Antibody Measurements
>
> Serologic testing was performed by MRL, West Point, PA and CSL, Australia. Levels of measles, mumps, rubella, varicella, HIB, hepatitis B, diphtheria, tetanus, and pertussis antibodies were evaluated by an appropriately sensitive and reliable method. Laboratory personnel who analyzed any clinical samples were blinded with respect to the randomization schedule, but did have access to the protocol and assay testing schedules as well as the time intervals for each subject tested. The decision to revaccinate a study participant was based on MRL's and CSL's test results.

Id. at '4967 (emphasis added).

306.4. The Protocol 013 Clinical Study Report also stated:

> Mumps Enzyme Immunoassay (Mumps [WT] ELISA)

> The mumps [WT ELISA] was used to detect antibody (IgG) to mumps virus before and after vaccination with a mumps virus-containing vaccine; it was the primary assay used in MRL to evaluate the anti-mumps serologic response. The assay uses and early passage of the Jeryl Lynn™ mumps virus (<12 passages) which is less attenuated than the Jeryl Lynn™ mumps virus used in the Merck mumps virus-containing vaccines, and is considered to be a wild-type (WT)-like strain...
>
> The serostatus cutoff is the lowest antibody concentration that can be reliably distinguished from a panel of negative samples. A panel of 72 "negative" samples was tested, 12 in each of 6 assay runs. Twelve (12) of the 72 samples were postvaccinated negatives as determined in the historical non-WT EIA, and the remaining were prevaccination samples. Based on the results of this panel, a serostatus cutoff of 10 Ab units was recommended. Samples with Ods less than or equal to the cutoff are serostatus negative and assigned a titer of less than 10.0 Ab units. Samples with Ods greater than the cutoff are considered serostatus positive and quantified using the standard curve. The quantifiable range of the assay was defined as 0.5 to 64 Mumps Ab units/mL. Sera whose titers exceeded this range are retested at greater dilutions until an endpoint titer was obtained.

Id. at '4970 (emphasis added).

306.5. The Protocol 013 Clinical Study Report also stated:

> Overall Immunogenicity and Safety Conclusions
>
> In healthy children 12 to 15 months of age with a negative clinical history of measles, mumps, rubella, and varicella who received either ProQuad™, COMVAX™, and TRIPEDIA™ administered concomitantly (concomitant group); ProQuad™ followed 42 days later by COMVAX™ and TRIPEDIA™ (nonconcomitant group); or M-M-R™II and VARIVAX™ followed 42 days later by COMVAX™ and TRIPEDIA™ (control group), the following conclusions can be drawn:

1. The antibody responses to measles, mumps, rubella, varicella, Haemophilus influenzae type B, hepatitis B, diphtheria, tetanus, and pertussis PT are similar in the concomitant group compared with the nonconcomitant group; therefore, ProQuad™ and COMVAX™ can be administered concomitantly. ...

3. The immune response rates to measles, mumps, rubella, and varicella ... are acceptable when ProQuad™, COMVAX™, and TRIPEDIA™ are administered concomitantly.

4. In general, the safety and tolerability profile of the concomitant group is comparable to both the nonconcomitant and control groups. ...

Id. at '5173.

(3) BLA for ProQuad: Protocol 014

307. Protocol 014 was conducted to show ProQuad could be used in place of the recommended second dose of MMRII administered to children at 4 to 6 years of age who were previously administered MMRII and Varivax separately.[840]

308. The Protocol 014 Clinical Study Report stated:

This Clinical Study Report (CSR) presents the results of a double-blind, multicenter, randomized study to show that ProQuad™ ... may be used in place of the recommended second dose of M-M-R™II administered to children 4 to 6 years of age who were previously immunized with M-M-R™II and VARIVAX™. In addition, this study evaluated the immune response of a second dose of varicella vaccine administered in the form of ProQuad™ at 4 to 6 years as compared with the administration of a second dose of VARIVAX™ at 4 to 6 years of age.

MRK-KRA00166846 at '6867 (emphasis added).

308.1. The Protocol 014 Clinical Study Report also stated:

Objectives

[840] MRK-KRA00166846 at '6867.

... Primary Objectives

1. To show that the antibody responses to measles, mumps, and rubella following a dose of ProQuad™ at 4 to 6 years will be similar to the antibody responses after the recommended second dose of M-M-R™II.

2. To show that the antibody responses to measles, mumps, rubella, and varicella following a dose of ProQuad™ at 4 to 6 years will be similar to the antibody responses after a second dose of M-M-R™II and VARIVAX™ administered concomitantly at separate injection sites.

3. To show that a dose of ProQuad™ at 4 to 6 years will be generally well tolerated.

4. To summarize the following immunogenicity parameters by treatment group: seroconversion rates to measles, mumps, and rubella in subjects initially seronegative to the respective antigen; seropositivity rates to measles, mumps, and rubella in all subjects; the percent of subjects with post vaccination varicella antibody titer ≥5 gpELISA units/mL in subjects initially seronegative to varicella, in subjects with predose varicella titer <1.25 gpELISA units/mL, and in all subjects; for each of measles, mumps, rubella, and varicella, the percent of subjects achieving ≥4-foldrise in antibody titer.

... Secondary Objective

To show that the antibody response to measles, mumps, and rubella following a dose of M-M-R™II and VARIVAX™ administered concomitantly at separate injection sites at 4 to 6 years will be similar to the antibody responses after a second dose of M-M-R™II and placebo administered concomitantly at separate injection sites.

Id. at '6870 (emphasis added).

308.2. The Protocol 014 Clinical Study Report also stated:

Discussion of Study Design, Including the Choice of Control Groups

This study was conducted to show that ProQuad™ may be used in place of the second dose of M-M-R™II routinely administered to children 4 to 6 years of age who were

previously immunized with M-M-R™II and VARIVAX™. In addition, the study evaluated the immune response of a second dose of varicella vaccine administered in the form of ProQuad™ at 4 to 6 years of age as compared with the administration of a second dose of VARIVAX™ at 4 to 6 years of age. ...

Since subjects entering this study had already received a primary measles, mumps, rubella, and varicella vaccination, the majority of subjects were seropositive to these antigens at study entry. Therefore, a comparison of seroconversion rates between groups would not be meaningful in this setting. Thus, GMTs were chosen as the primary endpoint as this effectively allows for comparison of the distribution of Postdose 2 titers within each group. Since the rise in antibody titer after a second dose may depend upon the predose titer level, predose titer levels were controlled for in the comparisons between post vaccination GMTs.

Id. at '6874-75 (emphasis added).

308.3. The Protocol 014 Clinical Study Report also stated:

Vaccine Antibody Measurements
Serologic testing was performed by MRL, West Point, PA. Levels of measles, mumps, rubella, and varicella antibody were evaluated by an appropriately sensitive and reliable method. Treatment group assignment was not available to MRL serology testing laboratory personnel. The decision to revaccinate a study participant was based on MRL's test results.

Id. at '6888 (emphasis added).

308.4. The Protocol 014 Clinical Study Report also stated:

Mumps Enzyme Immunoassay (Mumps [WT] ELISA)

The mumps [WT] ELISA was used to detect antibody (IgG) to mumps virus before and after vaccination with a mumps virus-containing vaccine; it was the primary assay used in MRL to evaluate the anti-mumps serologic response. The assay uses and early passage of the Jeryl Lynn™ mumps virus (<12 passages) which is less attenuated than the Jeryl

> Lynn™ mumps virus used in the Merck mumps virus-containing vaccines, and is considered by CBER to be a wild-type (WT)-like strain ...
>
> The serostatus cutoff is the lowest antibody concentration that can be reliably distinguished from a panel of negative samples. A panel of 72 "negative" samples was tested, 12 in each of 6 assay runs. Twelve (12) of the 72 samples were post vaccination negatives, as determined in the historical non-WT EIA, and the remaining were prevaccination samples. Based on the results of this panel, a serostatus cutoff of 10 Ab units was recommended. Samples with ODs less than or equal to the cutoff are serostatus negative and are assigned a titer of <10.0 Ab units. Samples with ODs greater than the cutoff are considered serostatus positive and quantified using the standard curve. The quantifiable range of the assay was defined as 0.5 to 64 Mumps Ab units/mL. Sera whose titers exceeded this range are retested at greater dilutions until an endpoint titer is obtained.

Id. at '6891-92 (emphasis added).

308.5. The Protocol 014 Clinical Study Report "Overall Immunogenicity and Safety Conclusions" section stated:

> Overall Immunogenicity and Safety Conclusions
> In healthy children 4 to 6 years of age who were previously vaccinated with M-M-R™II and VARIVAX™ either concomitantly or nonconcomitantly and subsequently received ProQuad™ and placebo, M-M-R™II and placebo, or M-M-R™II and VARIVAX™, the following conclusions can be drawn:
>
> 1. ProQuad™ may be administered in place of a second dose of M-M-R™II administered alone or a second dose of M-M-R™II and VARIVAX™ administered concomitantly based on the following:
>
> - ProQuad™ induces measles-, mumps-, and rubella-specific GMTs comparable (non-inferior) to those induced by M-M-R™II and to those induced by M-M-R™II and VARIVAX™ administered concomitantly.

- ProQuad™ induces varicella-specific GMTs comparable (non-inferior) to those induced by VARIVAX™ administered concomitantly with M-M-R™II.
- ProQuad™ is generally well tolerated; the adverse experience profile of ProQuad™ is comparable to that of M-M-R™II and placebo or that of M-M-R™II and VARIVAX™ administered concomitantly

Id. at ‘7009 (emphasis added).

7. Results Utilizing WT ELISA Assay for Mumps Immunogenicity

a. The sBLA for Mumps End Expiry: Protocol 007

309. The Protocol 007 seroconversion results measured by WT ELISA at 42-days and one year can be summarized as follows:

Summary of Antibody Responses to Mumps for Protocol 007 Subjects Initially Seronegative to Measles, Mumps, or Rubella (Per-Protocol Analysis)

	Treatment Groups of M-M-R™II						
Antibody (Assay) Parameter	3.8 log10 TCID50/Dose Mumps Virus Potency (N=663)		4.1 log10 TCID50/Dose Mumps Virus Potency (N=662)		4.8 log10 TCID50/Dose Mumps Virus Potency (N=672)		**All Subjects (N=1997)**
	Observed Response	95% CI	Observed Response	95% CI	Observed Response	95% CI	**Observed Response**
42-Day Mumps (ELISA)							
SCR[841]	**94.1%** (543/577)	(91.9%, 95.9%)	**97.4%** (568/583)	(95.8%, 98.6%)	**98.0%** (576/588)	(96.5%, 98.9%)	**96.5%** (1,687/1,748)
One Year Mumps (ELISA)							
Persistence Rate[842]	**96.7%** 409/423	(94.5%, 98.2%)	**95.4%** 417/437	(93.0%, 97.2%)	**95.7%** 446/466	(93.4%, 97.4%)	**95.9%** (1,272/1,326)

b. The sBLA for rHA: Protocol 009

[841] *See* MRK-KRA00135759 at '782.
[842] *See* MRK-KRA00135759 at '889.

310. The Protocol 009 seroconversion results measured by WT ELISA at 42-days are stated in the Clinical Study Report as follows:

Table 16

Summary of Antibody Responses to Measles, Mumps, and Rubella at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella (Per-Protocol Analysis)

Antibody (ELISA)	Parameter	M-M-R™II With rHA (N=641) Observed Response	M-M-R™II With rHA (N=641) 95% CI	M-M-R™II With HSA (N=638) Observed Response	M-M-R™II With HSA (N=638) 95% CI
Measles	REDACTED - OTHER MERCK PRODUCTS				
Mumps	% ≥10.0 ELISA antibody units/mL	99.5% (560/563)	(98.5%, 99.9%)	97.9% (522/533)	(96.3%, 99.0%)
	GMT	98.2	(92.5, 104.2)	85.8	(80.1, 92.0)
Rubella	REDACTED - OTHER MERCK PRODUCTS				

N=Number of subjects vaccinated in each treatment group.
rHA=Recombinant human albumin.
HSA=Human serum albumin.
GMT=Geometric mean titer.
CI=Confidence interval.
ELISA=Enzyme-linked immunosorbent assay.

Data Source: [4.3.1]

MRK-KRA00140056 at '0146 (highlight added).

c. The BLA for ProQuad: Protocol 012, 013, and 014

(1) The BLA for ProQuad: Protocol 012

311. The Protocol 012 seroconversion results measured by WT ELISA at 42-days are stated in the Clinical Study Report as follows:

RESULTS:
IMMUNOGENICITY:

Summary of Measles, Mumps, Rubella, and Varicella Antibody Responses at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or Subjects With Prevaccination Varicella Antibody Titer <1.25 gpELISA Units
(Per-Protocol Analysis)

Vaccine Component (Assay)	Parameter	ProQuad™ (Lot 1) (N=985) Observed Response (95% CI)	ProQuad™ (Lot 2) (N=968) Observed Response (95% CI)	ProQuad™ (Lot 3) (N=962) Observed Response (95% CI)	ProQuad™ (Combined Lots†) (N=2915) Observed Response (95% CI)	M-M-R™ II / VARIVAX™ (N=1012) Observed Response (95% CI)
Measles (ELISA)	Response Rate‡	REDACTED - OTHER MERCK PRODUCTS				
	GMT§					
Mumps (ELISA)	Response Rate‡	96.4% (825/856) (94.9%, 97.5%)	96.7% (796/823) (95.3%, 97.8%)	94.9% (788/830) (93.2%, 96.3%)	96.0% (2409/2509) (95.2%, 96.7%)	97.9% (854/872) (96.8%, 98.8%)
	GMT§	100.5 (94.3, 107.2)	102.3 (96.0, 109.0)	85.6 (79.9, 91.8)	95.9 (92.3, 99.6)	89.7 (84.7, 94.9)
Rubella (ELISA)	Response Rate‡	REDACTED - OTHER MERCK PRODUCTS				
	GMT§					
Varicella (gpELISA)	Response Rate†					
	GMT§					

MRK-KRA00162963 at '2988 (highlight added).

(2) The BLA for ProQuad: Protocol 013

312. The Protocol 013 seroconversion results measured by WT ELISA at 42-days are stated in the Clinical Study Report as follows:

RESULTS:
IMMUNOGENICITY: Immunogenicity results are summarized in the following table:

Summary of Antibody Responses to ProQuad™, TRIPEDIA™, and COMVAX™ With Respect to the Primary Endpoints at 6 Weeks Postvaccination (Per-Protocol Population)

Vaccine Component (Assay)	Parameter	Concomitant Group (N=949) N	Concomitant Group (N=949) Observed Response (95% CI)	Nonconcomitant Group (N=485) n	Nonconcomitant Group (N=485) Observed Response (95% CI)
Measles (ELISA)	REDACTED - OTHER MERCK PRODUCTS				
Mumps (ELISA)	% ≥10 ELISA Ab Units	811	95.4% (774/811) (93.8%, 96.8%)	415	95.2% (395/415) (92.7%, 97.0%)
	GMT (ELISA Ab Units)	811	89.4 (83.5, 95.7)	415	84.1 (76.2, 92.8)
Rubella† (ELISA)	REDACTED - OTHER MERCK PRODUCTS				
Varicella (gpELISA)					
Diphtheria	% ≥0.1 IU/mL	452	98.7% (446/452) (97.1%, 99.5%)	252	98.4% (248/252) (96.0%, 99.6%)
Tetanus	% ≥0.1 IU/mL	488	100% (488/488) (99.2%, 100%)	259	100% (259/259) (98.6%, 100%)
Pertussis Toxin (PT)	% ≥4-fold rise in titer	468	80.3% (376/468) (76.4%, 83.8%)	247	90.3% (223/247) (85.9%, 93.7%)
Pertussis FHA	% ≥4-fold rise in titer	468	69.7% (326/468) (65.3%, 73.8%)	248	87.5% (217/248) (82.7%, 91.3%)
Hepatitis B	REDACTED - OTHER MERCK PRODUCTS				
Hib					
REDACTED - OTHER MERCK PRODUCTS					

Percentages were calculated as the number of subjects who met the criterion divided by the number of subjects contributing to the per-protocol analysis.
Concomitant Group = ProQuad™ + TRIPEDIA™ + COMVAX™ at Day 0. Nonconcomitant Group = ProQuad™ at Day 0 followed by TRIPEDIA™ and COMVAX™ 6 weeks later.
N = Number of subjects vaccinated in each treatment group; n = Number of subjects contributing to the per-protocol analysis; gpELISA = Glycoprotein enzyme-linked immunosorbent assay; ELISA = Enzyme-linked immunosorbent assay; CI = Confidence interval; GMT = Geometric mean titer; FHA = Filamentous hemagglutinin.

MRK-KRA00164918 at '4941 (highlight added).

(3) The BLA for ProQuad: Protocol 014

313. The Protocol 014 seroconversion results measured by WT ELISA at 42-days are stated in the Clinical Study Report as follows:

RESULTS:

IMMUNOGENICITY: Immunogenicity results are summarized in the following table:

Summary of Antibody Responses to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination in Subjects Who Had Previously Received M-M-R™II and VARIVAX™ (Per-Protocol Population)

Group Number (Description)	n	GMT (95% CI)	Seropositivity Rate (95% CI)	% ≥ 4-Fold Rise in Titer (95% CI)	Geometric Mean Fold Rise (95% CI)
		Measles†			
[redacted]					
		Mumps‡			
Group 1 (N=399) (ProQuad™ + placebo)	367	206.0 (188.2, 225.4)	99.5% (98.0%, 99.9%)	27.2% (22.8%, 32.1%)	2.43 (2.19, 2.69)
Group 2 (N=205) (M-M-R™II + placebo)	185	308.5 (269.6, 352.9)	100% (98.0%, 100%)	41.1% (33.9%, 48.5%)	3.69 (3.14, 4.32)
Group 3 (N=195) (M-M-R™II + VARIVAX™)	171	295.9 (262.5, 333.5)	100% (97.9%, 100%)	41.5% (34.0%, 49.3%)	3.36 (2.84, 3.97)

MRK-KRA00166846 at '6864.

B. FDA and Merck Communications Regarding Merck'sUse of the WT ELISA Assay with a 10 Ab Cutoff to Support the Pending Applications

314. As stated above, in 2001, FDA required Merck to demonstrate that the WT ELISA was linked to a "biologically relevant reference standard."[843] FDA indicated this requirement could be satisfied by demonstrating a correlation between WT ELISA and a neutralization assay. In 2002, Merck submitted Serial 86, including its correlation analysis, to support the use of WT ELISA in Protocol 007 for the testing at one year for the duration of protection afforded by vaccination with MMRII. In 2004, Merck referred back to Serial 86 to support the use of the WT ELISA in (1) BB-IND 10076 (rHA) Protocol 009, (2) BB-IND 7068 (ProQuad) clinical studies, and (3) BB-IND 1016 (End Expiry).

1. BB-IND 1016: Protocol 007

315. As discussed above, Merck used the WT ELISA for testing the Secondary Objectives in Protocol 007: "to demonstrate similar immune responses to ... mumps, and ...

[843] *See* Section VIII.M above discussing the requirements in more detail.

(seroconversion rates by ELISA) among children who receive M-M-R™II containing an expiry dose of mumps virus ... compared to children who receive M-M-R™II containing a release dose of mumps virus" and to summarize the persistence of antibody to ... mumps ... (as measured by the mumps PRN assay and by ELISA) 1 year postvaccination in each treatment group."[844] The one year persistence follow up was added to the study because FDA had concerns about "long term protection against mumps … by the vaccine, as opposed to natural infection.[845] After submitting Serial 86 to FDA in 2002, Merck requested to use the WT ELISA in place of neutralization testing for measuring "persistence of the mumps immune response at the one year period.[846]

2. BB-IND 10076: Protocol 009

316. As discussed above, Merck used the WT ELISA for testing the primary objectives in Protocol 009: to demonstrate that "MMRII with rHA induces antibody response rates to mumps similar to those induced by MMRII with HSA and that MMRII with rHA induces acceptable immune responses to mumps."[847] In 2003, CBER requested that Merck provide data to support the WT ELISA 10 Ab cutoff for Protocol 009 (BB-IND 10076).[848] In its 2004 response, Merck referenced the analysis submitted in Serial 86 and asserted its understanding that CBER had confirmed the acceptance of the WT ELISA cutoff of 10 Ab units.[849]

[844] MRK-KRA00135759 at '5794. Merck also used the WT ELISA assay with the 10 Ab cutoff in a comparison of the seroconversion rates of the children in Protocol 007, which used MMRII with an experimental stabilizer, to the seroconversion rates of children who received MMRII with the approved stabilizer. *See* MRK-KRA00137307 at '16-17 ("Report: Comparison of the immunogenicity of MMRII manufactured with GOS stabilizer to MMRII manufactured with oGOS stabilizer).
[845] MRK-KRA00001467 at 469. *See also* Section VII.A.2 above.
[846] MRK-KRA00000561 (BB-IND Serial 89).
[847] MRK-KRA00140056 at '0119.
[848] MRK-KRA00124098.
[849] MRK-KRA00124554 at '588, '622.

316.1. A letter from FDA's Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, CBER, Dr. Karen Goldenthal to MRL's Director, Worldwide Regulatory Affairs, Dr. Manal Morsy dated April 28, 2003, in reference to BB-IND 10076, stated:

> We have completed our review of your Investigation new Drug Application (IND) for "Measles, Mumps and Rubella Virus Vaccine, Live with Recombinant Human Albumin..." and your study may proceed. We have the following related comments and questions:..
>
> [] The cut off point for the mumps ELISA assay is currently under discussion with CBER. Please provide AIGENT data on references and/or controls used for this assay (positive and negative) and please provide AIGENT data in support of the ELISA cutoff, as requested by CBER in the teleco[nference] dated October 16, 2001.[850]

MRK-KRA00124098 at '98-99 (emphasis added).

316.2. A letter from MRL's Associate Director, Worldwide Regulatory Affairs, Vaccines and Biologics, Dr. Alison Fisher, to FDA's Director, Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications, CBER, Dr. Jesse Goodman, with the subject "Response to FDA Request for Information" and marked "BB-IND 10076 Serial 53," stated:

> This question addressed previously, in the course of addressing comments to IND 1016, in a Communication to CBER on June 10, 2002 (BBIND 1016 serial no. 086), see attachment 2.[851]
>
> Briefly, AIGENT data for references and/or controls used for this assay (positive and negative) are shown in pages 3-5 of BBIND 1016 serial no. 086, and in a report attached

[850] *See* Section VIII.M.1 discussing the October 16, 2001 teleconference.
[851] *See* MRK-KRA00124554 at '622. BB-IND 10076 Serial 53 included BB-IND 1016 Serial 86 as Attachment 2.

> in BBIND 1016 serial no. 086 entitled "Testing for Mumps Wild Type ELISA Standard and Control Samples in the Mumps Anti-IgG Enhanced Plaque Reduction Neutralization Assay."
>
> AIGENT data in support of the ELISA cutoff are shown on pages 6-9 of BBIND 1016 serial no. 086 and in ... documents that are included with BBIND 1016 serial no. 086....
>
> Also, we understand that CBER confirmed the acceptance of the WT mumps ELISA assay cutoff of 10 Ab units (communication BBIND 1016, August 8, 2002, serial number 089).

MRK-KRA00124554 at '88 (emphasis added).

3. BB-IND 7068: ProQuad Protocol 012, 013, and 014

a. The AIGENT Assay Did Not Measure Protection

317. In 2004, FDA personnel contacted Merck's Dr. Keith Chirgwin regarding the upcoming filing of the BLA for ProQuad. The call included discussion of the WT ELISA and Merck's justification for the cutoff. Thereafter, senior Merck management exchanged emails over several days regarding Serial 86 and the comparison of Protocol 007 AIGENT and WT ELISA data that was submitted to "justify" the WT ELISA 10 Ab cutoff.[852] Merck senior managers "agreed" that they "[did not] know what a clinically protective level" was in either the AIGENT or the WT ELISA.[853] MRL's Executive Director, Biologics/Vaccines Clinical Research, Dr. Schodel ended the exchange stating: "could not overemphasize the weakness of the [AIGENT]."[854]

317.1. An email from MRL's Associate Director, BARDS, Dr. Joseph Antonello to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin cc'd to Dr.

[852] *See* Section VIII.M above (discussing communication with FDA to "justify" the WT ELISA cutoff).
[853] MRK-KRA00791315 at '19.
[854] MRK-KRA00791315.

MRL's Director, Worldwide Regulatory Affairs, Michael Dekleva, MRL's Associate Director, Worldwide Regulatory Affairs,Alison Fisher and MRL's Executive Director, Biologics/Vaccines Clinical Research, Florian Schodel, with the subject: " Comparing Mumps WT ELISA and AIGENT Assay" dated June 29, 2004, stated:

> In response to your MVX, I know that we prepared, and I assume that we sent an extensive response to CBER (Zoon/Carbone). Manal [Morsy] was involved in assembling that response and it should be in the regulatory files. That response contained:
>
> (1) Results of the 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.

MRK-KRA00791315 at '19 (emphasis added).

317.2. An email from Dr. Chirgwin replying to Dr. Antonello and others copied on Dr. Antonello's June 29, 2004 email and adding MRL's Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, stated:

> 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[855] – this seems like a problematic approach as the % "false-positive" would depend on which specific sera are selected for inclusion in such an analysis.

MRK-KRA00791315 at '18 (emphasis added).

317.3. An email from Dr. Dekleva to Dr. Schodel, dated July 2, 2004, with the subject "RE: Comparing Mumps WT ELISA and AIGENT Assay" in response to Dr. Antonello's June 29, 2004 email, stated:

> 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.[856] 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...
>
> I spoke with Joe Antonella [sic] yesterday, and he re-emphasized that the precision with the PRN assay was very poor, and felt that it was really hard to say whether the

[855] *See* Section VIII.E.2 discussing the analysis of non-responders and low-responders in February-March 2001, including the tables showing the cross-classification of the approximately 60 children examined; *see also* MRK-KRA00562216.

[856] *See* Section VIII.M.4 above discussing Serial 89 (Merck's request to confirm FDA's understanding).

> differences in the data sets were significant – influenced to a great extent by the variability in the PRN data.

Id. at '15 (emphasis added).

317.4. An email from Dr. Schodel to Dr. Dekleva, dated July 3, 2004, with the subject "RE: Comparing Mumps WT ELISA and AIGENT Assay" in response to Antonello's June 29, 2004 email, stated:

> 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!!!!!!!).

Id. (emphasis added)

318. Merck witnesses testified about the June-July 2004 email with the subject: "Comparing Mumps WT ELISA and AIGENT Assay" about the specificity of the assay which was part of a validation report Dr. Antonello conducted.

318.1. MRL's former Vice President, Clinical Research, Dr. Florian Schodel, testified that he agreed that "[w]e don't really know what a clinically protective level is in either assay,"[857] that the neutralization assay "had its weaknesses,"[858] that as far as he could tell Merck had not "submitted this PRN assay as support and to be considered as a surrogate of vaccine effectiveness,"[859] that the neutralization assay is "relatively weaker than the ELISA,"[860] and Merck in the clinical study report stated that it correlated its wild-type ELISA to its PRN assay.[861]

[857] Deposition of Florian Schodel, December 22, 2016, 342:21-343:9.
[858] *Id.*, 352:14-22.
[859] *Id.*, 366:6-13.
[860] *Id.*, 369:14 - 370:11.
[861] *Id.*

318.2. MRL's former Vice President, Clinical Research, Dr. Florian Schodel, testified as follows:

Q. Nor [sic] the record, Exhibit 15 is a document bearing Bates stamp number 791315 through 19 which is a series of emails. Doctor, I'd like to direct your attention to the last email on page 791319. This is an email from Joe Antonello to Keith Chirgwin, and you're cc'd on this. The subject is Comparing Mumps wild-type ELISA and AIGENT assay, June 29, 2004. If you want to take a minute to review that.

A. Okay.

Q. Here this is an e-mail – and Keith – Joe was saying, writing to Keith, "In response to your MVX...," that's a voicemail system that Merck had at the time, correct?

A. Yes.

Q. So he got a – this appears to be a voicemail from Keith Chirgwin who he's responding to. In the middle of the page it says In that response, we contended that there was reasonably good agreement between the two assays in terms of serostatus classification when using a cutoff of 10 Ab units in Mumps wild-type and a cutoff of 1 to 32 in the AIGENT assay, so I am concerned when you say that the two assays are discordant around the cutoff. Concluding that the two assays agree reasonably well was important for the purpose of arguing that the ELISA was acceptable substitute for the neutralizing assay. Do you see that?

A. Yes.

Q. Does that lead you to believe that Merck is arguing that they have correlated their plaque reduction neutralization assay to the ELISA assay?

A. No, it means exactly what it says, that a serostatus classification concordance testing was done and that the using the cutoffs of 1 of 10 and 1 to 32 there was reasonable concordance.

Q. And so <u>Merck wanted to use that as a substitute, so to rely upon the ELISA as a substitute for the neutralization assay</u>?

A. <u>Those are Joe's words. I don't know what he means with a substitute</u>.

Q. I see.

A. I mean, there were two assays used in 007. So ultimately the ELISA was important for that particular study and it was also used for the ProQuad filings. So obviously CBER accepted that the ELISA was a reasonable assay to measure mumps activity.

Q. I see. Here he says, "I do agree with your key points...," and he's responding to the Keith Chirgwin, "We don't really know what a clinically protective level is in either assay...." Do you see that?

A. Yes.

Q. He's talking both about the wild-type ELISA and Merck's PRN assay as used in Protocol 0097. [sic] Correct?

A. Probably, yes.

Q. Do you agree with that statement?

A. Yes.

Deposition of Florian Schodel, December 22, 2016, 340:15 – 343:9 (emphasis added).

318.3. MRL's former Vice President, Clinical Research, Florian Schodel, testified as follows:

Q. You say, "Agree with Joe – could not overemphasize the weakness of the PRN (50% specifies [sic] *!!!!!!." Do you see that?*

A. Yes, I see that.

Q. So is it your opinion that the PRN assay was weak and only had 50 percent specificity?

A. I think it had its weaknesses. The 50 percent is a partial misquote. There was not -- as we pointed out earlier, there was not a formal specificity analysis performed, so I couldn't know what the exact specificity was. What I was reacting to was that in a very, very small sample, in half of the samples some of the titers were reduced by unspecific reagents such as measles extracts, rubella extracts and Varicella extracts that summarized in the validation report does not necessarily mean that the overall specificity is only 50 percent because that wasn't formally analyzed. It just means exactly that, that there are other factors that contribute to the variability of the assay. And, again, didn't matter for 007 because it was a comparative study.

Q. Well, Doctor, you seem to be very well versed in the definition of specificity. So here you write 50 percent specificity with six exclamation points. So at this time that you wrote this, you agreed with Joe that the precision was very poor and that you could not overemphasize the weakness of the PRN assay. Is that a fair statement?

A. Yes, but I just explained to you that the specificity of 50 percent here does not refer to a specific specificity analysis as could have been performed that wasn't performed.

Q. I see.

A. So I don't know what the real number was. I didn't know at the time.

Q. So the 50 percent specificity you're talking about is whether or not the neutralization that occurred in this PRN assay was the result of mumps -- I mean, measles or rubella?

A. Not at all. No. What I was reacting to was a data mentioned in the summary of the validation report which essentially states if you reread it, that in a number of sera, in half of them the titer could only be reduced by mumps so that half of them were completely specific. And the other half, some of the plaque reduction, I don't even know whether it's the titer, just the plaque reductions seemed to be reduced by unspecific reagents. That does not yet mean that the assay overall has a 50 percent specificity. I just interpreted that as meaning that half is 50 percent. It is a sloppy expression which I should probably not have used, but it does not reflect on the overall specificity, nor does it matter.

Q. So it's your testimony today when you say specificity, you didn't really mean specificity?

> *Defense Counsel: Object to the form. It's argumentative. He's already addressed this.*

A. My testimony today is that I just translated four out of eight with something that doesn't translate into specificity as 50 percent.

Q. So you're talking about with something in the clinical study report?

A. No, it's in the validation report for the mumps neutralizing assay.

Q. When did you review that?

A. I must have reviewed it around that time, but because that question arose again, I looked it up and that's what it was.

Q. When did you look it up?

A. I looked it up whenever it was, Monday.

Q. So you went back and looked it up that on Monday?

A. Because I wanted to know what I had referred to at the time. I don't –I'm sorry, maybe you're perfect, but I don't remember everything that I said in 2004.

Q. That was after you spoke to your lawyers, correct?

A. No, not at all. It was after I saw this email and they asked me what I meant.

Deposition of Florian Schodel, December 22, 2016, 352:14 – 356:15.

318.4. MRL's former Vice President, Clinical Research, Florian Schodel, further testified as follows:

Q. You understand that the use of these two assays was to show that the vaccine -- to support vaccine effectiveness?

A. Among other data, yes.

Q. So vaccine effectiveness means that the vaccine works in the real world, correct, based on your definition?

A. That's correct, but that's not based on the PRN assay result.

Q. So when you agreed with Joe that the PRN assay that's being used to correlate to the wild-type ELISA is very poor and could not overemphasize the weakness of the PRN assay, you think that's appropriate to submit to CBER that the wild-type assay was correlated to the PRN assay?

A. Yes. It's actually only very weak around this particular definition of a cutoff. It's not overall very poor. That's not what anybody said. And therefore, overall the correlation is pretty good. Most people are vaccinated at very high titers and then it would have an almost perfect correlation.

Q. So if Merck submitted this PRN assay as support and to be considered as a surrogate of vaccine effectiveness, would that cause you concern?

Defense Counsel: Object to the form.

A. It's not what Merck has done as far as I can tell.[862]

[862] *Compare* MRK-KRA00135723 at '30-31 (sBLA to change Mumps End Expiry: "PRN assay … can, therefore, be considered a surrogate of vaccine effectiveness.")

Deposition of Florian Schodel, December 22, 2016, 365:7-366:13.

318.5. MRL's former Vice President, Clinical Research, Florian Schodel, further testified as follows:

> *Q. I see. And so, you're not concerned that any assay that you considered to be -- that you stated you cannot overemphasize the weakness of this assay, you agreed with Joe Antonello that it was very poor with regard to precision is being represented by Merck to CBER as a surrogate for vaccine effectiveness?*
> *A. No, that doesn't concern me because you're taking my statements of its weakness out of context. It's not weak across the board. It's very precise in estimating high titers, for example.*
> *Q. It's just weak around the cutoff?*
> *A. It's relatively weaker than the ELISA.*
> *Q. I see. And Merck in the clinical study report stated that it correlated its wild-type ELISA to its PRN assay. Correct?*
> *A. That's correct.*

Deposition of Florian Schodel, December 22, 2016, 369:14 - 370:11 (emphasis added).

319. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified that (1) "[i]n retrospect, looking at the specificity results in this study, they're peculiar,"[863] (2) the purpose of the validation report as it relates to specificity is to conclude with some level of confidence that the assay is specific to the antigen being measured and "looking back, the results are not strong in that regard" for the neutralization assay[864] and (3) because the neutralization assay "within Merck was accepted and that CBER accepted it" it gave Dr. Antonello "confidence that it was an acceptable assay for its use."[865]

[863] Deposition of Joseph Antonello, August 3, 2017, 115:4-9.
[864] *Id.*, 123:25-124:14.
[865] *Id.*, 136:1-11.

319.1. MRL's Associate Director, Biostatistics and Research Decision Sciences, Dr. Joseph Antonello, testified as follows:

Q. I'd like to mark as Antonello Exhibit 3 a document dated February 27, 2001, from Drs. Wolchko and Antonello titled: "Validation of Anti-IgG Enhanced Mumps Wild Type Plaque Reduction Neutralization Assay," Bates range 16988 through 17023. Dr. Antonello, this is the validation report you did for the AIGENT assay. Is that correct?

A. Yes, Robin and myself.

Q. And if -- on the first and second pages is the summary of your conclusions. Is that correct?

A. It's a summary, yes.

Q. And here you found the 38.7 percent and 42.9 percent precision rate?

A. Yes.

Q. And that was under what you -- your expectation of what a good precision rate, that was -- that met what you set or what you had an expectation as for a good precision rate for this kind of test. Is that correct?

A. Yeah. It was acceptable variability.

Q. Did you later find that the variability was more than you estimated in this validation report?

A. I don't recollect that.

Q. So as far as you recollect, the AIGENT test had a precision rate that was satisfactory to you?

A. In this validation study, the results of this validation study, yes.

Q. And it also had a specificity that you were satisfied with as well?

A. In retrospect, looking at the specificity results in this study, they're peculiar. And I think today I might push back a little more on the lab given these results.

Q. The results that were in the validation report?

A. Yes.

Q. So at the time you found these results, you were satisfied and did not provide any pushback to the lab, but in retrospect you're saying you would have?

A. In retrospect now, yeah, I think I would. At the time probably I didn't have enough experience to know to push back on that.

Q. When did you join Merck?

A. I joined in 1984.

Q. So you had been at Merck, what was that, 17 years at that point and you didn't have enough experience?

A. 16 years. I wasn't doing clinical assay validations at that time.

Deposition of Joseph Antonello, August 3, 2017, 113:20-116:2.

319.2. MRL's Associate Director, Biostatistics and Research Decision Sciences, Joseph Antonello further testified as follows:

Q. Did the results of your specificity experiments give you any confidence that the AIGENT assay was able to reliably distinguish between mumps neutralizing antibodies and non-mumps neutralizing antibodies?

Defense Counsel: Objection to the form.

A. Can you repeat the question? (The court reporter read the pertinent part of the record.) To a degree. I mean, you had general further reduction with the mumps. But in this – from this experiment, it's not -- it's not strong evidence certainly that the response, that there's no response to measles or rubella. Again, it's just an experiment. It doesn't necessarily reflect that if someone actually had measles antibody and not mumps, that that would be a false signal in the mumps assay, in the AIGENT assay.

Q. Isn't the purpose of the validation report as it relates to specificity to conclude with some level of confidence that the assay is specific to the antigen that you're attempting to measure?

A. Yes. And I think that looking back, the results are not strong in that regard. Now, too, these results were submitted to the FDA, the validation was submitted to the FDA. They viewed it as acceptable and approved the assay. You know, perhaps, you know, their understanding, I don't know enough about the biology to say that maybe there is an explanation for this, for this result.

Deposition of Joseph Antonello, August 3, 2017, 122:23-124:14.

319.3. MRL's Associate Director, Biostatistics and Research Decision Sciences, Joseph Antonello further testified as follows:

Q. Do you have any confidence one way or the other that the specificity of the AIGENT assay was sufficient for rendering a reliable result?

Defense Counsel: Objection to the form. Asked and answered.

A. I think for me the fact that, too, that within Merck it was accepted and that CBER accepted it, yes, that gives me confidence that it was an acceptable assay for its use.

Deposition of Joseph Antonello, August 3, 2017, 136:1-11.

320. MRL's former Director, Worldwide Regulatory Affairs, Dr. Manal Morsy, testified that specificity means that "it's specific to whatever it is that you're measuring, and it is not picking a lot of garbage and background" and that, if it's nonspecific, it's going to find things that the assay is not supposed to be looking for.[866]

320.1. MRL's former Director, Worldwide Regulatory Affairs, Manal Morsy, testified as follows:

Q. When you say, "sensitivity and specificity" what's the difference?

A. Specificity means that it's specific to whatever it is that you're measuring, and it is not picking a lot of garbage and background.

Q. So if an assay was only 50 percent specific, what would that mean to you as an example?

A. 50 percent specific.

Q. So that the other 50 percent would be picking up garbage?

A. I don't know. It depends on the assay and what it's picking up.

Q. Right.

A. So yeah.

Q. But you would expect if an assay, for example, that was only 50 percent specific, that would be something that would be -- would that raise an eyebrow to you?

[866] Deposition of Manal A. Morsy, August 5, 2016, 204:12-206:12.

Defense Counsel: Objection.

A. It may be good enough, I don't know. It depends on what the purpose of the assay is.

Q. If the assay is designed to identify neutralizing antibodies and is only 50 percent specific, would that be a concern to you?

Defense Counsel: Objection.

A. It's not an area of my expertise.

Q. Based on your experience.

Defense Counsel: Objection.

A. I haven't worked in that field in my research.

Q. So is it if a -- when you're looking at specificity, specific means that it actually will identify what you're -- that the test is looking to identify. Correct?

A. Yes.

Q. And if it's 50 percent, for example, if it's nonspecific, I mean, it's going to find things that are -- that the assay is not supposed to be looking for. Correct?

A. Yes.

Deposition of Manal A. Morsy, August 5, 2016, 204:12-206:12.

321. MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, testified that she could not recall sending the FDA "any document where you say to the FDA the precision of this assay is really poor."[867]

321.1. MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher testified as follows:

Q. And then Mr. Dekleva is relaying a conversation with Mr. Antonello, I'm at the bottom of the e-mail on the first page, it starts with the word -- the paragraph starts with the word "SO...." "I spoke with Joe Antonello yesterday, and he re-emphasized that the precision with the PRN assay was very poor..." Do you remember having any discussions about that?

A. I'm aware of that.

[867] Deposition of Alison L. Fisher, November 1, 2016, 288:9-13.

Q. Was that your opinion as well?

A. I don't recall having an opinion. I just heard the talk about the assay.

Q. Is there any document where you say to the FDA the precision of this assay is really poor?

A. I don't recall sending them that type of document.

Deposition of Alison L. Fisher, November 1, 2016, 287:18-288:13 (emphasis added).

322. The testimony of Merck's witnesses regarding the AIGENT, including its precision and specificity, can be summarized as follows:

- Dr. Schodel testified: Merck didn't know what the clinically protective level was.[868]
- Dr. Antonello testified:
  - The neutralization assay "had its weaknesses." [869]
  - The specificity results in the study were "peculiar."[870]
  - The results "are not strong" for the specificity of the neutralization assay.[871]
- Dr. Morsy testified: "If an assay is nonspecific, it's going to find things the assay is not supposed to be looking for."[872]
- Dr. Fisher testified: She had no recollection sending a document to the FDA regarding the poor specificity of the AIGENT.[873]

b. Merck Cited Serial 86 to Support Using WT ELISA in ProQuad Clinical Studies

323. In October 2004, while all three applications were pending, FDA requested that Merck provide data to "support the appropriateness of the cutoff employed in the mumps [WT]

[868] Deposition of Florian Schodel, December 22, 2016, 342:21-343:9.
[869] *Id.*, 352:14 -22.
[870] Deposition of Joseph Antonello, August 3, 2017, 115:4-9.
[871] *Id.*, 123:25-124:7.
[872] Deposition of Manal A. Morsy, August 5, 2016, 204:12-206:12.
[873] Deposition of Alison L. Fisher, November 1, 2016, 288:9-13.

ELISA ... relative to the plaque reduction neutralization assay."[874] An FDA memo regarding ProQuad BB-IND 7068 sent to Merck stated that 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)," and that "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."[875] In response to CBER's request, Merck referred FDA to Serial 86.

324. A document titled "Regulatory Liaison FDA Conversation Record" to MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, dated October 5, 2004, stated:

> 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.

MRK-KRA00846405 (emphasis added, original bold removed).

324.1. The memo from FDA's Dr. Steven A. Rubin and Dr. Lev Sirota to FDA's Herbert Smith, cc'd to FDA's Judy Beeler, Phil Krause and Konstantin Chumakov, with the subject: "Review of Merck's 7068-214," dated July 27, 2004, described in Dr. Dekleva's October 5, 2004 Conversation Record stated:

> Summary

[874] MRK-KRA00846405.
[875] MRK-KRA00846451 at '51-52.

CBER had recommended use of a wild type mumps virus strain as the target antigen in the ELISA for assessing 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 the 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 [ProQuad] and [MMRII and Varivax] 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 [ProQuad] 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 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.

MRK-KRA00846451 at '51-52 (section heading underline original, emphasis added).

324.2. An email from MRL's Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, to MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, with the subject: "Mumps ELISA," attaching "File: Mumps ELISA 19 Oct.2004.ppt," dated October 19, 2004, stated "... here's a summary of the CBER memo and what I think they're looking for." MRK-KRA00846454.

324.3. The attachment to Dr. Dekleva's October 19, 2004 email, "File: Mumps ELISA 19 Oct.2004.ppt," stated:

> History
>
> - CBER recommended:
> - Use of wild type mumps virus as target ELISA [antigen]
> - Validation protocol completed by Merck under IND 1016-114 (Serial 62); reviewed by CBER on 02 Feb 2001.
> - However, justification of mumps ELISA seropositive cutoff by [sic] justified via use of known mumps neutralizing and non-neutralizing sera, as requested by CBER, was never provided...
>
> CBER Issues

- The appropriateness of cutoff employed in the ELISA for seropositivity should be supported by data demonstrating some relevance with protective levels of antibody (e.g., neutralizing antibody)
- 93% agreement between ELISA and plaque neutralization assay is encouraging, but is only a point estimate and does not support the chosen ELISA cutoff per se...

What I think they're looking for (?)

- Seems to me like we need to look at the correlation between the assays for plaque neutralization assay (PNA) points above the lower 95% confidence bound (vs. all points).
- Maybe the 93% encompassed the entire gamet, [sic] which CBER doesn't care about. They only care about those points on the curve considered seropositive by the PNA.

MRK-KRA00846460 at '60-62.

324.4. An email from Dr.Fisher replying to Dr. Dekleva's October 19, 2004 email, dated October 26, 2004, stated:

> Thanks for sending the slides.
> In my opinion, I think we need to look at the points just below, at, and above the cutoff and else where [sic] there is disagreement between the two 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.

MRK-KRA00781533 (emphasis added).

324.5. The document attached to Dr. Fisher's October 26, 2004 email replying to Dr. Dekleva stated:

> Possible reasons for imbalance at the cut-off between pre and post vaccination sera:

> … [T]he 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 (%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 cutoff between pre-vaccination and post-vaccination sera.
>
> Driver for use of the WT ELISA in place of the AIGENT assay….
>
> 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.

MRK-KRA00781535 at ‘36 (emphasis added).

324.6. MRL’s Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, testified as follows:

> *Q. Then the next sentence, Alison Fisher writes, "PRN is a functional assay --correlate of protection." You agree with that, don't you?*
>
> *Defense Counsel: Object to Form*
>
> *A. This is, again, I think -- you know, when I look at this exchange, I'm obviously at this time uncomfortable with all of the nomenclature, the language, the terminology and I see in this upper memo, Alison, you know, in her role trying to continue to educate me on what these things are. So PRN is a functional assay correlate of protection, those are Alison's words.*
>
> *Q. I understand. I'm asking you if you agree with them?*
>
> *A. PRN, as I understand it, is a functional assay, yes.*
>
> *Q. And then the next sentence, "ELISA is not a functional assay but an antibody assay." Do you agree with that statement?*
>
> *A. Correct. Yes.*

Q. Okay. Great. Then Alison Fisher says, We need to convince CBER that the ELISA assay will provide equivalent results to PRN and thus equate (bridge) to protection. Do you agree with that statement?

A. I don't know at this point. I mean, in order to -- the equivalent to establish equivalence with PRN. If the ELISA is replacing a PRN assay, then you need to make sure that you maintain a bridge.

Q. Let me say it this way: ProQuad was approved based on ELISA assay data. Right?

A. Right.

Q. Okay. Now, before the FDA did that, did they require you to correlate or bridge that ELISA data to PRN data?

A. Yes.

Q. Okay. What PRN data did you use to make that bridge?

A. I don't know.

Deposition of Michael Dekleva, February 9, 2017, 168:10-170:8 (emphasis added).

324.7. A letter marked "Serial No. 221" from MRL's Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, to FDA's Director, Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications, CBER, Dr. Jesse Goodman, titled "BB-IND 7068 RESPONSE TO FDA REQUEST FOR INFORMATION,"[876] dated November 12, 2004, stated:

> 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

[876] A letter marked "Serial No. 102" from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, to FDA's Director, Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications, CBER, Dr. Jesse Goodman, titled "BB-IND 1016 RESPONSE TO FDA REQUEST FOR INFORMATION," dated November 17, 2004, provided the identical response to BB-IND 1016. MRK-KRA00126963.

> 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.

MRK-KRA00155481 (emphasis added).

324.8. Serial 221 also stated:

> Table 1 provides the sero-status classification for M-M-R®II for Protocol 007 pre-vaccination and post-vaccination samples. …

Id.

325. In March 2005, while all three applications were still pending, FDA's Dr. Rubin requested additional information about BB-IND 7068, Serial 221, the submission Merck made in November 2004 in response to FDA's request for data "demonstrating some relevance with protective levels of antibody" for the WT ELISA 10Ab cutoff used in the supporting clinical studies. Merck responded: "Serial 86 … provided information on the clinical relevance of the chosen ELISA cutoff."[877] This response was consistent with the instructions of MRL's Director Worldwide Regulatory Affairs, Dr. Michael Dekleva, not to provide any "new" information, Merck responded citing back to BB-IND 1016, Serial 86.[878]

325.1. A document titled "Regulatory Liaison FDA Conversation Record" to MRL Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, dated March 30, 2005, stated:

> Merck Participant: Michael Dekleva

[877] MRK-KRA00155481.
[878] MRK-KRA00798644.

> Executive Summary
> Additional CMC information was requested by Drs. Herb Smith and Steve Rubin; …
> All of the results rather than the "most frequently observed results for Table 1 in a 12-Nov-204 [sic] [BB-IND 7068, Serial 221][879] submission to support the serostatus cutoff for the measles, mumps and rubella ELISA assay relative to the plaque reduction neutralization assay. …
>
> Discussion
> … Dr. Rubin appreciated why Merck may have based conclusions on the most frequently observed results, but felt that it is important for them to see all of the run results. In other words, he wanted to [sic] all of the data that was used to generate Table 1. He stressed that the request fell into the "for the sake of completeness" category, and that he didn't anticipate any surprises.

MRK-KRA00763902 (emphasis added).

325.2. An email from MRL's Director, BARDS, Dr. Joseph Antonello to MRL's Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, among others, with the subject: "Responses to CBER Request of 30 March 2005," dated April 22, 2005, stated:

> The response has been revised per our meeting this morning. The updated response is attached for your review and comment. With the exception of the package inserts, all references are restricted to prior communications between Merck and CBER (adheres to Mike's desire that we not provide "new" information to CBER).

MRK-KRA00798644 (emphasis added).

325.3. A letter from MRL's Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, to FDA's Office of Vaccines Research and Review, CBER, Dr. Norman Baylor, dated May 4, 2005, stated:

[879] *See* paragraph 302.8 (BB-IND 7068 Serial 221, Table 1).

> Per a 30-Mar-2005 telephone request from Drs. Herb Smith and Steve Rubin of CBER, Merck is submitting an electronic amendment to the BLA containing information and data to support the validation of the ELISA assays for measles, mumps and rubella. Specifically, Dr. Rubin was interested in evaluating data supporting the specificity and sensitivity of each assay. To address this request we prepared a brief summary of the validation history for those assays, referencing data in reports that had previously been sent to CBER, and which are included in this submission for reviewer convenience. Additionally, CBER requested that a complete data set to support the [mumps] serostatus cutoff from ELISA vs. plaque reduction neutralization assay be submitted. Information in response to both requests is contained in the following document. …

MRK-KRA00846087 at ’87 (emphasis added).

> Sensitivity and Specificity of the Mumps WT ELISA
>
> … The serostatus cutoff in the mumps WT ELISA is 10 Ab units/mL [7, 3] The serostatus cutoff has been evaluated against that of a mumps neutralization assay, and the data show good agreement between assays when using a cutoff of 10 Ab units m/L in the mumps WT ELISA and a cutoff of 1:32 in the mumps neutralization assay. [8,9]

MRK-KRA00846087 at ’87 (emphasis added).

> References:
>
> [3] BB-IND 1016, Serial No. 072, Background Information for Mumps, Measles, Rubella ELISA teleconference Discussion on October 4, 2001, 10Oct2001. …
> [7] BB-IND 7068, Serial No. 214, Response to FDA Request for Information 14Jun2004.
> [8] BB-IND 1016, Serial No. 086, Response to FDA Request for Information, 10Jun2002.
> [9] BB-IND 1016, Serial 102, Response to FDA Request for Information, 17Nov2004.

MRK-KRA00846087 at ’93 (emphasis added).

326. For each of the three applications supported by clinical studies using the WT ELISA with a 10 Ab cutoff, Merck submitted BB-IND 1016 Serial 86 with Dr. Antonello’s analysis of the

correlation between the AIGENT and the WT ELISA in order to demonstrate the "clinical relevance" of the assay and the appropriateness of the 10 Ab cutoff.[880] In BB-IND 7068 Serial 221 and BB-IND Serial 102, Merck stated: "Serial 86 … provided information on the clinical relevance of the chosen ELISA cutoff."[881]

4. Merck's Statements that the WT ELISA could be used as a measure of protection against disease were misleading

327. In my opinion, after conducting the comparison between the AIGENT and WT ELISA, Merck made repeated representations to FDA that the comparison supported the cutoff used in the WT ELISA assay. FDA requested specific, additional information from Merck about the 10 Ab cutoff in the WT ELISA assay after Merck's submission in Serial 86. FDA 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." In response to FDA's request, Merck did not provide additional information. Merck's response stated "Serial 86 … we believe provided information on the clinical relevance of the chosen ELISA cutoff for seropositivity." Merck made this statement in BB-IND 7068[882] and in BB-IND 1016[883]. These statements were misleading for the following reasons:

- Merck's statements suggest that Serial 86 answered FDA's questions regarding the clinical relevance of the WT ELISA assay cutoff when Merck had not determined the clinical relevance of the WT ELISA cutoff to use in the clinical studies to support its three pending applications.

[880] MRK-KRA00000561 (BB-IND 1016 (Mumps End Expiry), Serial 89); MRK-KRA00124554 at '588 (BB-IND 10076 (rHA), Serial 53); MRK-KRA00155481 (BB-IND 7068 (ProQuad), Serial 221); MRK-KRA00126963 (BB-IND 1016 (Mumps End Expiry), Serial 102).
[881] MRK-KRA00155481 (Serial 221) and MRK-KRA00126963 (Serial 102).
[882] MRK-KRA00155481 (Serial 221 signed by Dr. Dekleva dated November 12, 2004).
[883] MRK-KRA00126963 (Serial 102 signed by Dr. Fisher dated November 17, 2004).

- Merck's statements omitted that the AIGENT assay had not been demonstrated to be a reliable measure of the presence of mumps neutralizing antibodies or validated as a sufficiently specific assay to measure mumps neutralizing antibodies.
- Merck's statements omitted that the AIGENT assay had not been shown to be a reliable measure of clinical protection and that Merck senior management "[did not] know what a clinically protective level [was]" using either the AIGENT or WT ELISA. [884]
- Merck's statements omitted that seroprotection had not been considered in determining the WT ELISA assay's 10 Ab cutoff.

328. In my opinion, the AIGENT assay results from Protocol 007 could not be used to provide reliable information about protection from disease. Moreover, according to Merck's documents, if the biological relevance of the chosen cutoff continued to be in question, a four-fold rise criteria may have been required to "demonstrate significant response to the vaccine."[885]

329. As discussed below, Merck subsequently obtained FDA approval to use the WT ELISA with a 10 Ab cutoff in the five clinical studies supporting its three pending applications based on its comparison of AIGENT and WT ELISA Protocol 007 clinical data submitted in BB-IND 1016 Serial 86.[886]

C. Regulatory Approvals Supported by the WT ELISA Assay

330. As described above, the sBLA for Mumps End Expiry was submitted in January 2004; the sBLA for rHA was submitted in June 2004; and the BLA for ProQuad was submitted

[884] MRK-KRA00791315 at '319.
[885] MRK-KRA000561452 (Dr. Morsy's memo documenting the October 19, 2001 teleconference with FDA regarding requirements for the use of the WT ELISA assay stated: ("… a 4-fold rise criteria as that would be necessary to demonstrate significant response to the vaccine.").
[886] *See* Section IX.C below discussing the approval of the three pending applications.

in August 2004.[887] The sBLA for rHA was approved on August 31, 2005, and the BLA for ProQuad was approved shortly after on September 6, 2005.[888] In December 2004, FDA found that the Protocol 007 AIGENT data was insufficient to support the sBLA for Mumps End Expiry.[889] Merck's response, submitted in 2005, was also inadequate for final approval.[890] In 2006, Merck proposed using Protocol 007 WT ELISA data to support the sBLA.[891] In 2007, CBER accepted the use of the WT ELISA data.[892] Thereafter CBER approved the change of the mumps end-expiry specification on the M-M-R®II label from "not less than" 20,000 [4.3 log10] TCID50 to "not less than" 12,500 [4.1 log10] TCID50 based on Protocol 007 WT ELISA data.[893]

1. The sBLA for rHA

331. A letter from FDA's Acting Director, Division of Viral Products, Office of Vaccines Research and Review, CBER, Dr. Philip Krause, to MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, dated August 31, 2005, stated:

> We have approved your request to supplement your biologics license application for Measles, Mumps, and Rubella Virus Vaccine Live, to replace the currently used Human Derived Serum Albumin (HSA) with Recombinant Human Albumin in yeast [Recombumin™] 20% (rHA).

MRK-KRA00141909 (emphasis added).

[887] *See* Section IX.A discussing MRK-KRA00135652 (sBLA for Mumps End Expiry); MRK-KRA00137854 (sBLA for rHA); MRK-KRA00157572 (BLA for ProQuad).
[888] *See* Sections IX.C.1 and IX.C.2 below discussing MRK-KRA00141909 (sBLA for rHA approved) and MRK-KRA00761865 (BLA for ProQuad approved).
[889] MRK-KRA00000315 at '56-59.
[890] MRK-KRA00000479 at '79-80.
[891] MRK-KRA00000393 at '04-05.
[892] MRK-KRA00000383.
[893] MRK-KRA00141976.

2. The BLA for ProQuad

332. A letter from FDA's Director, Office of Vaccines Research and Review, CBER, Dr. Norman Baylor, to MRL's Director, Worldwide Regulatory Affairs, Dr. Michael Dekleva, dated September 6, 2005, stated:

> We have approved your biologics license application (BLA) for Measles, Mumps, Rubella and Varicella Virus Vaccine Live effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Measles, Mumps, Rubella and Varicella Virus Vaccine Live under your existing Department of Health and Human Services U.S. License No. 0002.

MRK-KRA00761865 (emphasis added).

3. The sBLA for Mumps End Expiry

a. AIGENT Data Insufficient to support sBLA for Mumps End Expiry

333. In December 2004, CBER denied the request to change the mumps end expiry claim on the MMRII and requested additional information. Merck prepared its response. In October 2005, CBER determined "the information and data submitted are inadequate for final approval."[894] In November, 2006 Merck responded and proposed to use ELISA data to provide "indirect evidence" to support the study.[895]

333.1. A letter from FDA's Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, CBER, Dr. Karen Goldenthal, to MRL Regulatory Liaison, Dr. Alison Fisher, dated December 3, 2004, stated:

> This letter is in regard to the Supplement to your License Application submitted under Section 351 of the Public Health Service Act.

[894] MRK-KRA00000479.
[895] MRK-KRA00000393 at '04.

> 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 TCID50 to 12,500 TCID50. Our review finds that the information and data submitted are inadequate for final approval at this time based on the deficiencies described below.[896]
>
> 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. ...
>
> 10. ...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 ... Module 5, you show that only 437 of the 672 immunized control group subjects contributed to the per-protocol analyses. Likewise, only 65% (433 out of 662) of the 4.1 $\log_{10}$ $TCID_{50}$ group were included at 69% (449 out of 663) of the 3.8 $\log_{10}$ $TCID_{50}$ group were not 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.

MRK-KRA00000315 at '356-359 (emphasis added).

333.2. An email from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, to MMD's Director, Vaccine Regulatory & Analytical Sciences, Mark Galinski, MMD's Senior Director, Regulatory & Analytical Sciences, Dr. Mark Rosolowsky, MRL's Executive Director, Worldwide Regulatory Affairs, Dr. Keith Chirgwin, cc'd to Mary Maachi,

[896] *See* Schedule 30 (describing history of Protocol 007 and FDA's regulatory decision-making).

Ercem Atillasoy and Joye Bramble with the Subject "M[umps]E[nd]E[xpiry] Q[uestion]1," dated March 28, 2005, stated:

> Here is my attempt at answering question #1 for Mumps end expiry file question #1 given our conversations last week. Correspondence cited will be useful for our discussion with Norman Baylor. …
> 1. Please describe the purpose and underlying rationale for proposing a reduction in potency of the mumps component of the approved product, MMRII.

MRK-KRA00560317 (original bold removed, replaced with underline).

333.3. Dr. Fisher's draft response to question #1 stated:

> Summary
> The purpose and underlying rationale for proposing a reduction in potency of the mumps component of the approved product, M-M-R®II was historically to 1) evaluate the immunogenicity of mumps when administered to children at a targeted expiry titer of 5000 (3.7 log10 TCID50) and titers above this, and submit any proposed change in end expiry potency in the label to CBER for review and approval and based on the current data to 2) provide evidence that a mumps end expiry potency of 12 500 TCID 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].

Id. at '318 (emphasis added).

333.4. A letter from MRL's Associate Director, Worldwide Regulatory Affairs, Dr. Alison Fisher, to FDA's Director, Office of Vaccines Research and Review, CBER, Dr. Norman Baylor, titled: "RESPONSE TO FDA REQUEST FOR INFORMATION" dated April 13, 2005, stated: "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." MRK-KRA00000315.

333.5. Merck's April 13, 2005 letter to FDA's Norman Baylor in response to FDA Comment 1 stated:

> Response [1] …
>
> Summary
>
> 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 log10 TCID50 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].

MRK-KRA00000315 at '20-21 (emphasis added, brackets original).

333.6. Merck's April 13, 2005 letter to FDA's Norman Baylor in response to FDA Comment 5 stated:

> Response [5] …
>
> 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,