



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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STN #: 125563/0

Application Type: BLA (Original Application)

Subject: Summary of Late Cycle Meeting, held May 5, 2015

Dear Ms. Carrington:

Please find attached a summary of our Late Cycle meeting for STN 125563, held May 5, 2015. Please feel free to contact Katie Rivers, MS or myself if you have any questions.

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LATE-CYCLE MEETING SUMMARY

Memo Date:	June 5, 2015
Late Cycle Meeting Date:	May 5, 2015
Late Cycle Meeting Time:	1:00 pm – 2:30 pm
STN #:	125563/0
Submission Type:	BLA (Original Application)
Product:	(b) (4) Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, <i>Haemophilus b</i> Conjugate and Recombinant Hepatitis B Vaccine
Proposed Indication:	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive <i>Haemophilus influenzae</i> type b disease in infants and children 6 weeks through 4 years of age (prior to fifth birthday)
Applicant:	MCM Vaccine Company

I. ATTENDEES

A. CBER

Juan Arciniega, Ph.D., CMC Reviewer	OVR/DBPAP
Jennifer Bridgewater, M.P.H., Regulatory Coordinator	OVR/DBPAP
Drusilla Burns, Ph.D., Deputy Division Director	OVR/DBPAP
Karen Campbell, M.S., Regulatory Coordinator	OCBQ/DBSQ
Rana Chattopadhyay, Ph.D., Chair	OVR/DVRPA
Al Delgrosso, Ph.D., Assay Reviewer	OCBQ/DBSQ
John Eltermann, Jr., R.Ph., M.S., Division Director	OCBQ/DMPQ
Karen Farizo, M.D., Associate Office Director for Medical Policy and Vaccine Safety	OVR
Sarah Gagneten, Ph.D., Drug Product CMC Reviewer	OVR/DVP
Marion Gruber, Ph.D., Office Director	OVR
LCDR Kelsy Hoffman, Ph.D., RPM	OVR/DVRPA
Hyesuk Kong, Ph.D., Assay Reviewer	OCBQ/DBSQ
Diana Kouivskaia, Ph.D., CMC Reviewer	OVR/DVP
Philip Krause, M.D., Deputy Office Director	OVR
Freyja Lynn, B.S., Serology Assay Reviewer	OVR/DBPAP
Marion Major, Ph.D., Laboratory Chief	OVR/DVP
Erin McDowell, B.S., B.A., BiMo Reviewer	OCBQ/DIS
Loris McVittie, Ph.D., Deputy Division Director	OVR/DVRPA
Laurie Norwood, B.S., Deputy Division Director	OCBQ/DMPQ
Carolyn Renshaw, Branch Chief	OCBQ/DMPQ
Katie Rivers, M.S., RPM	OVR/DVRPA
Jeff Roberts, M.D., Branch Chief	OVR/DVRPA
Patricia Rohan, M.D., Epidemiology Reviewer	OBE/DE

Tina Roecklein, M.S., CMC Reviewer	OVRR/DBPAP
Michael Schmitt, Ph.D., Laboratory Chief	OVRR/DBPAP
CAPT Ann Schwartz, M.D., Clinical Reviewer	OVRR/DVRPA
Jay Slater, M.D., Division Director	OVRR/DBPAP
Wellington Sun, M.D., Division Director	OVRR/DVRPA
Willie Vann, Ph.D., Laboratory Chief	OVRR/DBPAP
Leslie Wagner, B.S., Serology Assay Reviewer	OVRR/DBPAP
Nancy Waites, B.S., CMC/Facility Reviewer	OCBQ/DMPQ
Lihan Yan, Ph.D., Team Leader	OBE/DB

- B. Eastern Research Group (ERG)
Christopher Sese, Independent Assessor

- C. MCM Vaccine Company
Sanofi Pasteur
Krissy Carrington, Deputy Director, Regulatory Affairs
Juthika Menon, Senior Scientist, Analytical Process & Technology
Susan Nelson, Director, Analytical Process & Technology
Olivier Faure, Director, Quality Operations
Maureen Barbalinardo, Deputy Director, RA CMC Conformance
William Flounders, Senior Director, Project Leadership
Liane Smith, Director, IO/Manufacturing Technology
Erin Keyes, Deputy Director, IO/Manufacturing Technology
Ellen Snell, Deputy Director, R&D Project Management
Trevor Aldridge, Compliance Expert, Compliance
Jason Yip, Deputy Director, Biostatistics, Quality Operations
Nitin Bhardwaj, Attending Veterinarian, QC BioResources

Merck
Paul Koser, Director, Regulatory
Charles Kline, Associate Director, CMC Regulator
Andrew Wen-Tseng Lee, Director, Clinical Research
Annie Chen, Executive Director, Clinical Research
Steve Dziennik, Director, Manufacturing Division
Victoria Town, Director, Vaccine Analytical

II. BACKGROUND

On February 6, 2015, CBER and MCM Vaccine Company agreed to hold the late-cycle meeting for STN 125563/0 on May 5, 2015. On April 23, 2015, CBER sent the Late Cycle Memo (see Appendix A) to Merck. The memo provided an overview of significant review issues identified to date. On May 4, 2015, CBER provided an updated Late Cycle Meeting Memo (see Appendix B) to MCM Vaccine Company that incorporated the Applicant's proposed discussion items.

III. DISCUSSION SUMMARY

Discussion was limited to status updates of items provided in the May 4, 2015 Late Cycle Memo, and to topics requiring discussion to work toward resolution.

1. Current status of pending issues that will require resolution prior to Action Date:

- A. CBER stated that there are unresolved facility-related issues regarding the companion For Further Manufacturing Use (FFMU) BLA from Merck, STN 125581/0. MCM stated that they are committed to working with Merck to resolve all open Information Requests (IR) for the FFMU BLAs and any outstanding cross-referenced supplement(s) in time for the PR5I BLA action due date. MCM thanked CBER for the open-communication and questioned whether this issue would affect the (b) (4) BLA, CBER indicated that the FFMU BLA is still under review.
- B. CBER reiterated that comments regarding the lot release protocol (LRP) will be sent to the Applicant in the near future. In addition, a determination regarding what samples are required for in-support testing will be communicated to the Applicant shortly.
- C. CBER acknowledged receipt of the April 30, 2015, e-mail response to the April 17, 2015, information request regarding additional information required to evaluate the proposed change in (b) (4) specification. MCM confirmed that an official amendment to the BLA is scheduled for the week of May 11, 2015. CBER stated that this is a very serious concern based on the information that has been provided and asked that the Applicant provide any information available regarding this issue as soon as possible, to include the status of any ongoing investigation to determine a cause of the out of specification (b) (4) results if it has not been determined thus far. MCM stated that they understand the concern and highlighted the key manufacturing and testing findings including:
- i. MCM stated that the US clinical studies did not show increased adverse events over time, which suggests that there are no product stability related safety concerns.
 - ii. MCM stated that an in-depth investigation did not reveal a specific root cause. The antigen concentrates for the (b) (4) lots were manufactured during the same time frame as those antigens used for other acellular Pertussis combination licensed products for which all were within specification. MCM also stated that the drug substance and drug product were manufactured per the defined critical process parameters and met critical quality attributes as defined by the release test specifications. MCM indicated that the results of this investigation support product safety and stability for the proposed commercial shelf-life.
 - iii. MCM stated that a temporal association was observed with a higher frequency of mouse deaths noted in the latter half of 2014, and that the data to date suggest that the cause is likely multi-factorial:
 - a) (b) (4) location change (in mid May 2014)
 - b) (b) (4)

(b) (4)

iv. MCM concluded that

- a) They consider the (b) (4) an appropriate test for (b) (4) although some refinement in the test specification is required for (b) (4)
- b) There is some non-specific interference from mock PR5I matrix with the test.
- c) (b) (4) is different than other acellular pertussis toxoid containing licensed products.

MCM stated that they have provided all information available to date regarding the investigation. Additional information regarding the ongoing investigation will be provided by the end of June 2015. MCM's overall position is that the (b) (4) test and the proposed change in specification are appropriate; however, refinements to the assay may be necessary.

CBER reiterated that the review of the submitted information is still in-progress and that this issue is of major concern. CBER stated that we may not reach the same conclusion as the Applicant. Additional requests for information or further discussions may be necessary as the review progresses.

Note: Following the Late Cycle Meeting, the information submitted in the April 29, 2015 e-mail was officially submitted as an amendment to the BLA on May 19, 2015.

2. Current assessment of the need for risk management actions:

CBER does not anticipate the necessity for Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) at this time. MCM questioned whether Post Marketing Commitments (PMCs) will be required and CBER responded that requests for PMCs are possible as the review is ongoing, and clarified that PMCs are not considered risk management actions.

3. Information requests sent, for which a response has not yet been received:

MCM stated that it was their intent to provide responses to information requests on rolling basis as responses become available. All responses are planned to be submitted no later than May 29, 2015.

Note: As of June 3, 2015, CBER has received responses to all outstanding information requests (please see Section 3 of Appendix 2), with the exception of the IR dated April 17, 2015, which concerns product-related testing/CMC-Hib Drug Substance/Final Drug Product, for which only a partial response was received.

4. New information requests to be communicated:

- A. CBER reiterated that that comments regarding the lot release protocol (LRP) will be sent to the Applicant in the near future.

- B. CBER stated that the Applicant's request for data exclusivity is under review and that additional information will be required and will be requested in the near future.

5. MCM Vaccine Company discussion items provided April 30, 2015

MCM provided three discussion items for the late cycle meeting (see Appendix B for details). All discussions are documented above.

IV. ACTION ITEMS

A. MCM Action Items

- MCM will respond to all outstanding information requests no later than May 29, 2015.
- Additional information regarding the ongoing investigation into the (b) (4) results will be provided no later than the end of June 2015.

B. CBER Action Items

- CBER will send MCM comments on the lot release protocol and samples, and a request for additional information regarding the request for data exclusivity as soon as possible.

V. APPENDICES

- A. Late Cycle Memo, sent to MCM on April 23, 2015
- B. Late Cycle Meeting updated with MCM discussion items, sent to MCM on May 4, 2015