

Mid-cycle Meeting Summary

Application type and number: Biological Licensure Application (BLA), Original Submission (OS)

Product name: (b) (4) , Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, *Haemophilus b* Conjugate and Recombinant Hepatitis B Vaccine

Proposed Indication: Active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive *Haemophilus influenzae* type b disease in infants and children 6 weeks through 4 years of age (prior to fifth birthday)

Applicant: MCM Vaccine Company

Meeting date & time: January 23, 2015 11:00AM-1:00PM

Committee Chair: Rana Chattopadhyay, Ph.D.

RPM: Kelsy Hoffman, Ph.D./ Katie Rivers, M.S.

CBER/FDA Attendees:

Rana Chattopadhyay, Ph.D., Chair, DVRPA/OVRR

LCDR Kelsy Hoffman, Ph.D., Regulatory Project Manager, DVRPA/OVRR

Katie Rivers, M.S., Regulatory Project Manager, DVRPA/OVRR

CAPT Ann Schwartz, M.D., Medical Officer, DVRPA/OVRR

Jennifer Bridgewater, M.P.H., Regulatory Coordinator, DBPAP/OVRR

Freyja Lynn, B.S., Serology Assay Reviewer, DBPAP/OVRR

Brian Mocca, Ph.D., Serology Assay Reviewer, DBPAP/OVRR

Leslie Wagner, B.S., Serology Assay Reviewer, DBPAP/OVRR

Juan Arciniega, Ph.D., CMC Reviewer, DBPAP/OVRR

Mustafa Akkoyunlu, M.D., Ph.D., Serology Assay Reviewer, DBPAP/OVRR

Tod Merkel, Ph.D., CMC Reviewer, DBPAP/OVRR

Michael Schmitt, CMC Reviewer, DBPAP/OVRR

Wei Wang, CMC Reviewer, DBPAP/OVRR

Sara Gagneten, Drug Product CMC Reviewer, DVP/OVRR

Marian Major, Ph.D., Serology Assay Reviewer, DVP/OVRR

Dmitry Volokhov, Ph.D., Serology Assay Reviewer, DVP/OVRR

Dino Feigelstock, Ph.D., Serology Assay Reviewer, DVP/OVRR

Alla Kachko, Ph.D., CMC Reviewer, DVP/OVRR

Diana Kouivaskaia, Ph.D., CMC Reviewer, DVP/OVRR

Karen Campbell, M.S., CMC/Lot Release, DBSQC/OCBQ

Mridul Chowdhury, Ph.D., Biostatistics Reviewer, DB/OBE

Kristine Khuc, Labeling Reviewer, DCM/OCBQ

Nancy Waites, CMC/Facility Reviewer, DMPQ/OCBQ

Erin McDowell, BiMo Reviewer, DIS/OCBQ

Patricia Rohan, M.D., Epidemiology Reviewer, DE/OBE

Steve Kunder, Ph.D., Toxicology Reviewer, DVRPA/OVRR

Julienne Vaillancourt, R.Ph., M.P.H., Team Leader, DVRPA/OVRR

Paul Richman, Ph.D., Branch Chief, DVRPA/OVRR

Jay E. Slater, M.D., Director, DBPAP/OVRR

Dale Horne, Ph.D., Branch Chief, DB/OBE

Carolyn Renshaw, Branch Chief, DMPQ/OCBQ

Lisa Stockbridge, Ph.D., Branch Chief, DCM/OCBQ
 Lucia Lee, Team Leader, DVRPA/OVRR
 Lihan Yan, Ph.D., Team Leader, DB/OBE
 Laurie Norwood, Deputy Director, DMPQ/OCBQ
 Gilliam Conley, Director, DIS/OCBQ
 John Eltermann, Jr., R.Ph., M.S., Division Director, DMPQ/OCBQ
 Drusilla Burns, Ph.D., Deputy Division Director, DBPAP/OVRR
 Douglas Pratt, M.D., M.P.H., Associate Director for Medical Affairs, DVRPA/OVRR
 Jay Slater, M.D., Division Director, DBPAP/OVRR
 Karen Farizo, M.D., Associate Office Director for Medical Policy and Vaccine Safety, OVRR
 Theresa Finn, Ph.D., Associate Office Director for Regulatory Policy, OVRR
 Philip Krause, M.D., Deputy Office Director, OVRR
 Marion Gruber, Ph.D., Office Director, OVRR

Review Committee

Name, Certifications/Degree	Review Role	Module Assignment
Reviewer: Rana Chattopadhyay, PhD BC: Paul Richman, PhD	Chair	All Modules
Reviewer: Katie Rivers, MS BC: Paul Richman, PhD	Co-Regulatory Project Manager	All Modules
Reviewer: LCDR Kelsy Hoffman, PhD BC: Paul Richman, PhD	Co-Regulatory Project Manager	All Modules
Reviewer: Jennifer Bridgewater, MPH DD: Jay Slater, MD	Regulatory Coordinator	All Modules
Reviewer: Ann Schwartz, MD BC: Jeff Roberts, MD	Clinical	Modules 1, 2 & 5
Reviewer: Mridul Chowdhury, PhD BC: Dale Horne, PhD	Biostatistics	Modules 1, 2 & 5
Reviewer: Patricia Rohan, MD BC: Christopher Jankosky, MD, MPH	Pharmacovigilance/ Epidemiology	Modules 1 & 2
Reviewer: Michael Schmitt, PhD DD: Jay Slater, MD	CMC/Product	Modules 2 & 3
Reviewer: Tod Merkel, PhD LC: Michael Schmitt, PhD	CMC/Product	Modules 2 & 3
Reviewer: Wei Wang, PhD LC: Willie Van, PhD	CMC/Product	Modules 2 & 3
Reviewer: Juan Arciniega, PhD LC: Michael Schmitt, PhD	CMC/Product	Modules 2 & 3
Reviewer: Alla Kachko, PhD LC: Marion Major, PhD	CMC/Product	Modules 2 & 3
Reviewer: Diana Kouivaskaia, PhD DD: Jerry Weir, PhD	CMC/Product	Modules 2 & 3
Reviewer: Sara Gagnetten, PhD	CMC/Product	Modules 2 & 3

Name, Certifications/Degree	Review Role	Module Assignment
DD: Jerry Weir, PhD		
Reviewer: Freyja Lynn, BS DD: Jay Slater, MD	Serology Assay	Module 5
Reviewer: Leslie Wagner, BS LC: Michael Schmitt, PhD	Serology Assay	Module 5
Reviewer: Brian Mocca, MS LC: Willie Vann, PhD	Serology Assay	Module 5
Reviewer: Mustafa Akkoyunlu, MD, PhD LC: Willie Van, PhD	Serology Assay	Module 5
Reviewer: Marian Major, PhD DD: Jerry Weir, PhD	Serology Assay	Module 5
Reviewer: Dmitry Volokhov, DVM, PhD LC: Konstantin Chumakov, PhD	Serology Assay	Module 5
Reviewer: Dino Feigelstock, PhD LC: Steven Rubin, PhD	Serology Assay	Module 5
Reviewer: Nancy Waites, CSO BC: Carolyn Renshaw	CMC/Facility	Modules 2 & 3
Reviewer: Karen Campbell, MS BC: William McCormick, PhD	CMC/Lot Release	Modules 2 & 3
Reviewer: Erin McDowell, BS, BA BC: Patricia Holobaugh, MS	Bioresearch Monitoring	Modules 2 & 5
Reviewer: Oluchi Elekwachi, PharmD, MPH BC: Lisa Stockbridge, PhD	APLB/Promotional Labeling	Modules 1 & 2
Reviewer: Steve Kunder, PhD BC: Dave Green, PhD	Toxicology	Modules 2 & 4

Background

BLA STN#125563/0 was submitted by Sanofi Pasteur Limited on August 12, 2014 (applicant subsequently changed to MCM Vaccine Company) and received by CBER on August 12, 2014. The proposed indication is active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b (Hib) as a three dose series in children from 6 weeks through 4 years of age.

We are referring to the vaccine as PR5I, the proposed proprietary name is (b) (4). The vaccine is manufactured for MCM Vaccine Company, a joint venture between Merck Sharp and Dohme Corp. (Merck) and Sanofi Pasteur Limited (Sanofi). MCM Vaccine Company is the applicant and a new license number has been issued.

Sanofi vaccine components include DTaP and IPV; Sanofi will manufacture the final drug product. Merck components include Hib and HepB; Merck will provide bulk intermediates to Sanofi. Merck has submitted For Further Manufacturing Use (FFMU) BLAs, STN125580/0 and STN125581/0 regarding the manufacture of the bulk intermediates.

There are two pivotal studies that were completed to support licensure in the US, including:

- Study V419-005 – 981 subjects received and 484 were in the control group. The primary endpoint was immunogenicity, the analysis included response rates for all antigens.
- Study V419-006 - 2399 subjects received PR5I and 401 were in the control group. This was a lot to lot consistency study.

A total of 3380 subjects received at least one dose of PR5I in the US studies.

Report and Discuss:

1. Reviewer Reports

1.1 **Clinical**/Ann Schwartz- The clinical review is currently ongoing and no substantive issues have been identified.

1.2 **Statistical**/Mridul Chowdhury- The statistical review is currently ongoing. A request for additional information will be sent to the sponsor regarding summary information including, the age of the subjects (in days) at the time of vaccine dosing and the raw analyses for primary endpoints without covariates, such as the brand of HepB given at birth.

1.3 **Epidemiology**/Patricia Rohan – The epidemiology review is currently ongoing and no substantive issues have been identified.

1.4 **BiMo**/Erin Mcdowell- The BiMo review is currently ongoing and no substantive issues have been identified. A total of six BIMO inspection assignments were issued for studies V419-005 and V419-006. Five inspections have been completed; EIRs are pending for five sites. One site (Study V419-006, Site #00038) was classified as NAI. Study V419-006, Site#0044 was issued a 483, items included Adverse Events (AEs) recorded in source documents not transcribed or transcribed with incorrect dates into the Case Report Forms (CRFs). The findings will be reviewed and communicated to the committee upon completion of all inspections and after final review.

1.5 **Labeling**/Oluchi Elekwachi - The review is currently ongoing and no substantive issues have been identified.

1.6 **Toxicology**/Steve Kunder- The toxicology review is currently ongoing and no substantive issues have been identified.

1.7 **Product/CMC**

- 1.7.1 **Drug Substance CMC (DT)**/Michael Schmitt- The review is currently ongoing and no substantive issues have been identified.
- 1.7.2 **Drug Substance CMC (aP)**/Tod Merkel- The review is currently ongoing. Drafted request for additional information will be sent to the sponsor regarding (b) (4) evaluation for the stability testing of the pertussis bulk adsorbed antigens and stability studies in (b) (4) containers. The latter is proposed as a Post Marketing Commitment (PMC).
- 1.7.3 **Drug Substance CMC (Hib)**/Wei Wang- The review is currently ongoing. Stability studies for Amorphous Aluminum Hydroxyphosphate Sulfate Adsorbed Polyribosylribitol Phosphate - Outer Membrane Protein Complex (PRP-OMPC) were performed at (b) (4) . However, the (b) (4) . There are concerns of (b) (4) the bulk substance, and an information request will be sent to the sponsor requesting comment on this discrepancy.
- 1.7.4 **Drug Product CMC (DTaP)**/Juan Arciniega-The review is currently ongoing. The proposed changes to the (b) (4) specification are not justified based on the information provided in the submission and a request for additional information will be sent to the sponsor.
- 1.7.5 **Drug Substance CMC (HepB)**/Alla Kachko- The review is currently ongoing and no substantive issues have been identified. Requests for additional information are anticipated and will be sent to the sponsor when available.
- 1.7.6 **Drug Substance CMC (IPV)**/Diana Kouivskaia- The review is currently ongoing and no substantive issues have been identified. Requests for additional information are anticipated and will be sent to the sponsor when available.
- 1.7.7 **Drug Product CMC**/Sara Gagnetten- The review is currently ongoing and no substantive issues have been identified.
- 1.7.8 **Serology Assay (aP)**/Freyja Lynn- The review was completed on December 9, 2014, no substantive issues have been identified.
- 1.7.9 **Serology Assay (DTaP)**/Leslie Wagner- The review is currently ongoing and a request for additional information will be sent to the sponsor regarding assay stability data for tetanus and diphtheria assays used in pivotal studies V419-005 and V419-006.

- 1.7.10 **Serology Assay (Hib)**/Brian Mocca- The review is currently ongoing and no substantive issues have been identified.
- 1.7.11 **Serology Assay (Pneumococcal)**/Mustafa Akkoyunlu- The review is currently ongoing and no substantive issues have been identified.
- 1.7.12 **Serology Assay (Heb B)**/Marian Major- The review is currently ongoing and no substantive issues have been identified.
- 1.7.13 **Serology Assay (IPV)**/Dmitry Volokhov- The review is currently ongoing and no substantive issues have been identified.
- 1.7.14 **Serology Assay (Rotavirus)**/ Dino Feigelstock- The review is currently ongoing and no substantive issues have been identified.
- 1.8 **CMC Lot Release**/Karen Campbell- The review of the draft lot release protocol is currently ongoing, and no substantive issues have been identified.
- 1.9 **CMC/Facility**/Nancy Waites- The review is currently ongoing and no substantive issues have been identified. Requests for additional information are anticipated and will be sent to the sponsor when available.
2. Will Discipline Review Letters be issued (for PDUFA V Program submissions)? Information requests will be sent to the sponsor as needed.
3. If the application will be discussed at an Advisory Committee, potential issues for presentation. This application will not be presented to VRBPAC.
4. Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REM.S.) are needed. As previously noted, at this time, on CMC related PMC is anticipated. The review team does not anticipate the need for any PMRs or REM.S. at this time.
5. National Drug Code (NDC) assignments to product/packaging. The NDC number has been provided on the product packaging.
6. Proper naming convention. The currently proposed proper name is: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, *Haemophilus b* Conjugate and Recombinant Hepatitis B Vaccine. Additional discussion regarding the proper name will take place during labeling discussions.

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. The review is currently ongoing, however, at this time, there have been issues that could prevent approval have not been identified.

Confirm

8. Components Information Table was obtained and notification to the Data AB.S.traction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed. The process for obtaining the components information table and identifying potential deficiencies has been initiated.
9. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not complete, indicate date it will be completed. Facility information is up-to-date in RMS-BLA.
10. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan. As previously noted, the review of the lot release protocol and lot testing plan is currently ongoing.
11. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information. The process for acquiring UNII codes was initiated September 23, 2014. *Following the Mid-cycle meeting, UNII codes have been issued and are currently under review.*
12. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision. PeRC is scheduled for June 17, 2015. PeRC forms will be submitted two weeks in advance of scheduled PeRC meeting.
13. Reach agreement on information to be included in the Mid-cycle communication with the applicant (see section below). The Mid-cycle communication is only for applications that qualify under the PDUFA V Program. Information to be included in the Mid-cycle communication was agreed upon by the review committee members and management present at the meeting.

Review

14. Major target and mile stone dates from RMS/BLA
Submitted: August 12, 2014
Received: August 12, 2014

Committee Assignment: September 1, 2014
First Committee Meeting: September 30, 2014
Filing Meeting: September 30, 2014
Filing Action: October 11, 2014
Deficiencies Identified: October 25, 2014
VRPAC Determination: October 26, 2014
PeRC Determination: December 25, 2014
SWG Determination: June 8, 2015
Mid-cycle Communication: February 11, 2015
Late-cycle Briefing Package: April 16, 2015
First Draft Reviews Due: January 19, 2015
Final Reviews Due: March 20, 2015
Final Review Addendum Due: July 12, 2015
Action Due: August 12, 2015
Action Packing for Posting Due: August 12, 2015

Meetings

First Committee Meeting: September 30, 2014
Filing Meeting: September 30, 2014
Monthly Team Meetings: Fourth Wednesday of every month 11:00AM to 12:00PM
Mid-cycle Review Meeting: January 23, 2015
Mid-cycle Communication with Sponsor: February 6, 2015
Late-cycle Meeting: April 14, 2015
Late-cycle Communication with Sponsor: May 5, 2015
PeRC: June 17, 2015
VRBPAC: N/A
SWG: TBD by June 8, 2015
Labeling Meetings: TBD by June 11, 2015

15. The status of the review for each discipline, inspection, EIR. If any primary reviews have not met the target date, provide the date the review will be completed. Include any consult disciplines. *Discussed above (#1 in the Report and Discuss section)*
16. Discuss pending dates of targets and milestones. *Discussed above (#14 in the Review section)*
17. Establish a labeling review plan and agree on future labeling meeting activities. The first labeling meeting will be scheduled to take place no later than June 11, 2015.

Action items

1. Requests for additional information will be drafted and sent to the sponsor.

2. The Mid-cycle Communication will be drafted and sent to the sponsor two days prior to the communication, which is scheduled on February 6, 2015.
3. Labeling meetings will be scheduled to be held no later than June 11, 2015.