



FIRST COMMITTEE/FILING MEETING SUMMARY

Date and Time:	September 30, 2014, 12:00 p.m. – 12:45 p.m.
Location:	WO-Bldg 71 - 2244
STN #:	125563/0
Submission Type:	Biological Licensure Application (BLA), Original Submission (OS)
Applicant:	MCM Vaccine Company
Product:	(b) (4) Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), Inactivated Poliovirus (IPV), Haemophilus b Conjugate (Hib) and Recombinant Hepatitis B Vaccine (HepB)
Meeting Chair:	Rana Chattopadhyay, PhD
Meeting Recorder:	LCDR Kelsy Hoffman, PhD/ Katie Rivers, MS

Meeting:

CBER/FDA Attendees

Rana Chattopadhyay, PhD, Chair, DVRPA/OVRR
LCDR Kelsy Hoffman, PhD, Regulatory Project Manager, DVRPA/OVRR
Katie Rivers, MS, Regulatory Project Manager, DVRPA/OVRR
CAPT Ann Schwartz, MD, Medical Officer, DVRPA/OVRR
Jennifer Bridgewater, MPH, Regulatory Coordinator, DBPAP/OVRR
Freyja Lynn, Serology Assay Reviewer, DBPAP/OVRR
Brian Mocca, PhD, Serology Assay Reviewer, DBPAP/OVRR
Leslie Wagner, Serology Assay Reviewer, DBPAP/OVRR
Juan Arciniega, PhD, CMC Reviewer, DBPAP/OVRR
Mustafa Akkoyunlu, MD, PhD, Serology Assay Reviewer, DBPAP/OVRR
Tod Merkel, PhD, CMC Reviewer, DBPAP/OVRR
Michael Schmitt, PhD, CMC Reviewer, DBPAP/OVRR
Wei Wang, PhD, CMC Reviewer, DBPAP/OVRR
Sara Gagneten, PhD, Drug Product CMC Reviewer, DVP/OVRR
Marian Major, PhD, Serology Assay Reviewer, DVP/OVRR
Dmitry Volokhov, PhD, Serology Assay Reviewer, DVP/OVRR
Alla Kachko, PhD, CMC Reviewer, DVP/OVRR
Diana Kouivaskaia, PhD, CMC Reviewer, DVP/OVRR
Karen Campbell, MS, CMC/Lot Release, DBSQC/OCBQ
Mridul Chowdhury, PhD, Biostatistics Reviewer, DB/OBE
Oluchi Elekwachi, PharmD, MPH, Labeling Reviewer, DCM/OCBQ
Nancy Waites, CMC/Facility Reviewer, DMPQ/OCBQ
Erin Mcdowell, BiMo Reviewer, DIS/OCBQ
Patricia Rohan, MD, Epidemiology Reviewer, DE/OBE
Paul Richman, PhD, Branch Chief, DVRPA/OVRR

Dale Horne, PhD, Chief, DB/OBE
 Willie Vann, PhD, Chief, DBPAP/OVRR
 Carolyn Renshaw, PhD, Chief, DMPQ/OCBQ
 Steven Rubin, PhD, Chief, DVP/OVRR
 Wellington Sun, M.D., Division Director, DVRPA/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 (DT)	Modules 2 & 3
Reviewer: Tod Merkel, PhD LC: Michael Schmitt, PhD	CMC/Product (aP)	Modules 2 & 3
Reviewer: Wei Wang, PhD LC: Willie Van, PhD	CMC/Product (Hib)	Modules 2 & 3
Reviewer: Juan Arciniega, DSc LC: Michael Schmitt, PhD	CMC/Product (DTaP)	Modules 2 & 3
Reviewer: Alla Kachko, PhD LC: Marion Major, PhD	CMC/Product (HepB)	Modules 2 & 3
Reviewer: Diana Kouivaskaia, PhD DD: Jerry Weir, PhD	CMC/Product (IPV)	Modules 2 & 3
Reviewer: Sara Gagneten, PhD DD: Jerry Weir, PhD	CMC/Product	Modules 2 & 3
Reviewer: Freyja Lynn, BS DD: Jay Slater, MD	Serology Assay (Hib)	Module 5
Reviewer: Leslie Wagner, BS LC: Michael Schmitt, PhD	Serology Assay (DTaP)	Module 5
Reviewer: Brian Mocca, MS LC: Willie Vann, PhD	Serology Assay (Hib)	Module 5
Reviewer: Mustafa Akkoyunlu, MD, PhD LC: Willie Van, PhD	Serology Assay (Pneumococcal)	Module 5

Name, Certifications/Degree	Review Role	Module Assignment
Reviewer: Marian Major, PhD DD: Jerry Weir, PhD	Serology Assay (HepB)	Module 5
Reviewer: Dmitry Volokhov, DVM, PhD LC: Konstantin Chumakov, PhD	Serology Assay (IPV)	Module 5
Reviewer: Dino Feigelstock, PhD LC: Steven Rubin, PhD	Serology Assay (Rotavirus)	Module 5
Reviewer: Nancy Waites 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

1.0 PURPOSE

- To discuss the milestones, roles and responsibilities of each member of the review team.
- To discuss the completeness of the BLA submission and ensure it is acceptable to file.

2.0 BACKGROUND

BLA STN#125563/0 was submitted by Sanofi Pasteur Limited on August 12, 2014 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 supplements, STN103237/5498 and STN101066/5653 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.

3.0 DISCUSSION TOPICS

3.1 Milestones

Review timelines and important upcoming milestones. This product is on a 12-month review clock.

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: TBD ASAP

Mid-Cycle Review Meeting: TBD by October 16, 2015

Late-Cycle Meeting: TBD by December 25, 2014

PeRC: TBD by December 25, 2014

VRPAC: TBD by October 26, 2014

SWG: TBD by June 8, 2015

Labeling Meetings: TBD by June 11, 2015

3.2 Filing Review by Discipline

3.2.1 **Clinical/Ann Schwartz** – The BLA is acceptable to file.

3.2.2 **Statistical/Mridul Chowdhury** - The BLA is acceptable to file.

3.2.3 **Epidemiology**/Trish Rohan - The BLA is acceptable to file.

3.2.4 **BiMo**/Erin McDowell - The BLA is acceptable to file. Six clinical sites from clinical studies V419-005 and V419-006 will be inspected.

3.2.5 **Labeling**/Oluchi Elekwachi - The BLA is acceptable to file.

3.2.6 **Product/CMC**

3.2.6.1 **Drug Substance CMC**/Michael Schmitt - The BLA is acceptable to file.

3.2.6.2 **Drug Substance CMC**/Tod Merkel - The BLA is acceptable to file.

3.2.6.3 **Drug Substance CMC**/Wei Wang - The BLA is acceptable to file; however, there is concern that the transport temperature stated in a cross-referenced submission (STN 103237/5498) (b) (4) . CBER will request that the shipping temperature be the (b) (4) storage temperature for PRP-OMPC (b) (4)

3.2.6.4 **Drug Product CMC**/Juan Arciniega – The BLA is acceptable to file; however, the sponsor is proposing an acceptance criterion for the (b) (4) test that differs from other vaccines containing a Sanofi pertussis component of similar composition (same detoxified pertussis toxin at the same or lower concentration per dose). The current acceptance criterion for other vaccines containing pertussis toxoid is (b) (4) when injected with one human dose of vaccine. The proposed criterion for PR5I is (b) (4) per dose of vaccine. CBER will discuss this further in the context of the clinical safety results obtained using product lots C3145A, C3146B, C3147A, and C3886A.

3.2.6.5 **Drug Substance CMC**/Alla Kachko - The BLA is acceptable to file.

3.2.6.6 **Drug Substance CMC**/Diana Kouivaskaia - The BLA is acceptable to file.

3.2.6.7 **Drug Product CMC**/Sara Gagneten - The BLA is acceptable to file. It was noted that the sponsor is requesting a waiver from the general safety test (GST) and the review team does not currently disagree with this approach as long as the specific toxicity test for residual diphtheria and tetanus toxin toxicity continues to be in place for release and a stability test for final (b) (4) drug product. The reviewers for each bacterial drug substance should review the drug product for that same antigen and include this information in their review memo.

3.2.6.8 **Serology Assay**/Freyja Lynn - The BLA is acceptable to file.

- 3.2.6.9 **Serology Assay**/Leslie Wagner - The BLA is acceptable to file.
- 3.2.6.10 **Serology Assay**/Brian Mocca - The BLA is acceptable to file.
- 3.2.6.11 **Serology Assay**/Mustafa Akkoyunlu - The BLA is acceptable to file.
- 3.2.6.12 **Serology Assay**/Marian Major - The BLA is acceptable to file.
- 3.2.6.13 **Serology Assay**/Dmitry Volokhov - The BLA is acceptable to file.
- 3.2.6.14 **Serology Assay**/Kelsy Hoffman for Dino Feigelstock - The BLA is acceptable to file.
- 3.2.7 **CMC/Lot Release**/Karen Campbell - The BLA is acceptable to file. CBER will request that the sponsor submit a draft lot release protocol.
- 3.2.8 **CMC/Facility**/Nancy Waites - The BLA is acceptable to file. DMPQ recommended that CMC facility inspections be waived. CBER will request clarification from the sponsor regarding if there is a shared manufacturing agreement in place or if the manufacturing is considered contract manufacturing.

3.3 Administrative Details

- 3.3.1 The review team agreed that it is not currently necessary to hold a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to discuss this application.
- 3.3.2 The review team was reminded that the first draft reviews are due January 19, 2015 and the final reviews are due March 20, 2015.
- 3.3.3 The review team was reminded that every review must be 508 compliant.
- 3.3.4 The review team was asked to send notifications for documents uploaded to the EDR to K. Hoffman and K. Rivers.
- 3.3.5 The review team was reminded to keep their outlook calendars up-to-date.

4.0 CONCLUSION

During the Filing Meeting the committee agreed that the application could be filed.

5.0 SUMMARY OF ACTION ITEMS

- 5.1** Discipline reviewers that would like to request additional information should provide comments to K. Hoffman and K. Rivers.
- 5.2** The filing letter will be drafted by K. Hoffman and K. Rivers for circulation and sign-off for issuance before or on October 10, 2014. At this point no deficiencies have been identified; therefore there are no plans for issuing a deficiencies identified (DI) letter.
- 5.3** The monthly meetings and mid-cycle meeting will be scheduled as soon as possible.