

**MID-CYCLE MEETING SUMMARY**

To: The File
From: Kirk Prutzman, Ph.D., RPM
Through: Brenda Baldwin, Ph.D., Chair
Date and Time: May 11, 2015 1:00 PM – 2:30 PM
Location: WO71– Room 3244
STN #: 125510/0
Submission Type: Original BLA
Applicant: Novartis Vaccines and Diagnostics, Inc. (NVD)
Product: Influenza Vaccine, Adjuvanted (FLUAD 65)
Meeting Chair: Brenda Baldwin, Ph.D.

1.0 CBER/FDA INVITEES

<u>Review Assignments</u>	<u>Committee Members</u>	<u>Attendance</u>	<u>Supervisors</u>	<u>Attendance</u>
Chair	Brenda Baldwin, PhD	✓	Elizabeth Sutkowski	✓
RPM	Theodore Garnett, PhD	✓	Elizabeth Sutkowski	✓
RPM	Kirk Prutzman, PhD	✓	Elizabeth Sutkowski	✓
RPM	Pin Zhang, Ph.D.	✓	Elizabeth Sutkowski	✓
Clinical	Sarah Browne, MD	✓	Jeff Roberts	✓
Toxicology	Nabil Al-Humadi, PhD	✓	David Green	
Assays Stats	Zhong Gao, PhD	✓	Tsai-Lien Lin/Dale Horne	
Clinical Stats	Gideon Solomon, PhD	✓	Dale Horne	
CMC - Antigens	Hang Xie, PhD	✓	Zhiping Ye	✓
CMC - Adjuvant	Marina Zaitseva, PhD	✓	Hana Golding	
DS and DP release assays	Manju Joshi, PhD	✓	William McCormick	
DS and DP release assays	Lokesh Bhattacharyya, PhD	✓	William McCormick	
DS and DP release assays	Alfred Del Grosso, PhD		Lokesh Bhattacharyya	✓
DS and DP release assays	Simleen Kaur, PhD	✓	James Kenney	
LRP and Testing Plan Development	Josephine Resnick, PhD		William McCormick	
Lot Release Protocol	Jacqueline Glen		Joseph Quander III	
CMC, CCIT, Facilities reviewer and inspector	Peter Amin	✓	Marion Michaelis	✓
BIMO	Anthony Hawkins	✓	Patricia Holobaugh	✓
Advertising/Promotional Labeling	Sonny Saini	✓	Lisa Stockbridge	
Pharmacovigilance	Yandong Qiang, MD, PhD	✓	Wei Hua	✓
OBE Regulatory Coordinator	Lori Austin-Hansberry, MSA, BSN		Steve Anderson	
Labeling	Daphne Stewart		Laraine Henchal	
Electronic Integrity	David Schwab, MSIS		Laraine Henchal	

Other Attendees:

Phil Krause
 Wellington Sun
 Roshan Ramanathan

Douglas Pratt
 Anissa Cheung
 Loris McVittie

Melisse Baylor
 Karen Campbell

2.0 PURPOSE

1. discuss the progress of the review,
2. identify and present substantive issues and plans to address substantive issues,
3. plan the remainder of the review including dates for further deliverables and interactions,
4. obtain supervisory feedback, and,
5. agree upon the material to be communicated in the Mid-Cycle Communication.

3.0 BACKGROUND

US development of Influenza Vaccine, Adjuvanted (FLUAD 65) was conducted under IND 14368, with an initial submission to CBER on May 14, 2010. The BLA was submitted on November 25, 2014 for licensure under the Accelerated Approval pathway.

The BLA is intended to support the following indication and use: active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.

4.0 MEETING AGENDA

4.1 Opening remarks from the RPM

The RPM updated the review committee and management of upcoming review milestones. Late-Cycle meeting invitations and VRBPAC preparatory meeting invitations will be sent in the coming weeks. The review team was also reminded to indicate any Information Requests sent to the sponsor and any Amendments reviewed in their reviews.

4.2 Status update (including any major concerns that have been identified so far) from each member of the review committee

4.2.1 Chair

The Chair confirmed that the proper name for the vaccine will be Influenza Vaccine, Adjuvanted. The chair discussed that the sponsor had responded to all of the information requests to date and that she did not expect any of the amendments to be classified as a major amendment. The original milestone dates for this BLA are expected to be met. The chair discussed that she had received several information requests from the review committee that would be sent to the sponsor after the mid-cycle meeting. She asked all of the reviewers to send her any other, new information requests if they had not already done so. They will be included with the other information requests and sent to the sponsor in one document.

4.2.2 Clinical

The Clinical reviewer reported that her review was ongoing and that she was reviewing the revised HAI titer data that was received on May 5, 2015. There were no major safety issues identified however, an IR was forthcoming to have NVD explain 10 AEs indicated as “other” in the datasets.

The Clinical reviewer reported that she had completed a preliminary review of the revised HAI data. The data indicate that the sponsor met their endpoints for lot-to-lot consistency and for non-inferiority. The sponsor did not meet their endpoints for

superiority for 2 of 3 strains at day 22. They were able to show superiority against one strain (H3N2). The vaccine did not meet any of the secondary endpoints.

4.2.3 Clinical Stats

The Clinical Stats reviewer discussed that his review was ongoing and that he had not finished reviewing the revised HAI titer data received on May 5, 2015. There were no issues identified that would preclude approval.

4.2.4 Assay Stats

The Assay Stats reviewer discussed that his review was ongoing and that he had not finished reviewing the revised HAI titer data received on May 5, 2015. He indicated that the sponsor had adequately revised the HAI titer data and that his review should be able to be completed with the current data.

4.2.5 CMC-Antigen

The CMC-Antigen reviewer reported that her review was ongoing and that there were no major issues identified. The CMC-Antigen reviewer indicated that manufacturing changes submitted in supplements to the Agriflu BLA were currently being reviewed and appear to be acceptable. If approved, these changes will also be incorporated into the FLUAD file. The CMC-Antigen reviewer indicated that some antigen strains may have stability issues because they may be unable to meet the potency specification during their shelf life, and although this would not affect approval of the BLA, it may have implications for future strain changes. The CMC-Antigen reviewer also indicated that an IR may be forthcoming requesting the SOPs for viral inactivation.

4.2.6 CMC-Adjuvant

The CMC-Adjuvant reviewer reported that her first draft review of the drug substance was complete and her review of the drug product was partially complete. All information requests that were sent to the sponsor were adequately addressed. Some additional IRs need to be sent to NVD. There were no issues thus far that would preclude approval.

4.2.7 Toxicology

The Toxicology reviewer reported that his review is complete and awaiting supervisory approval. His review indicates that there are no significant safety issues to preclude approval of this BLA.

4.2.8 Facilities

The Facilities reviewer reported that the review of all of the antigen and adjuvant manufacturing facility information has been completed and that there are no major issues that would preclude approval; however, an IR will need to be sent to NVD to resolve review issues.

4.2.9 BiMO

The BiMO reviewer reported that inspections were pending for the clinical trial sites in Bogota, Colombia, Raleigh, North Carolina, and Winston Salem, North Carolina. There were no review issues to report.

4.2.10 DS and DP Release Assays

4.2.10.1 DP/DS Coordinator

The DP/DS Coordinator reported that an updated lot release protocol (LRP) was received on April 20, 2015, and was under review. An IR regarding the LRP was forthcoming. A draft product testing plan had been created and was to be circulated to reviewers in the weeks following the Mid-Cycle Meeting. In-support testing of samples was to be carried out for all the tests agreed to in the DBSQC-CMC meeting. Samples for this testing had not been received, as the submission will be for lots formulated with the 2015-16 recommended strains. These lots were expected to be received by early summer.

4.2.10.2 Potency Testing

The Potency Testing reviewer reported that the sponsor's responses to her IR regarding the validation of the SRID Assay (b) (4) DP) and the Ovalbumin Assay (b) (4) DP) were being reviewed. An additional IR to clarify the SRID validation report was forthcoming.

Regarding Samples for Assay Set Up, the Potency Testing reviewer reported that the sponsor has provided 3 (b) (4) lots of final container product from the EU 2014/15 season for testing, but that they had not submitted their testing results.

Regarding Samples for in support testing, the sponsor communicated in 125510/0.4 that they intend to provide CBER both monovalent lots and the first three 2015/16 NH influenza drug product bulk lots formulated using US specifications. This was to be confirmed following the 2015/16 strain announcement and upon availability of US specific reagents.

4.2.10.3 Chemistry Testing

The Chemistry Testing reviewer indicated that he had identified deficiencies in the validation of the CTAB assay for the drug product, the Total Protein assay for the (b) (4) (b) (4), the Sodium Citrate Content assay for the (b) (4) (b) (4), and the Squalene (b) (4) assay for the (b) (4) drug product. An IR regarding these deficiencies was forthcoming. The Chemistry Testing reviewer also discussed that there was no plan to conduct adjuvant specific testing. The required equipment (i.e., for (b) (4) was not available, but efforts were underway to try and obtain the necessary equipment for future testing.

4.2.10.4 Endotoxin/Bioburden/Sterility Testing

The Endotoxin/Bioburden/Sterility Testing reviewer reported that her review was complete. There were no major issues that would preclude approval.

4.2.11 Pharmacovigilance

The Pharmacovigilance reviewer reported that her review was ongoing. Except injection site pain and tenderness, no important safety issues were identified in the pivotal trial, the ISS reports, and the postmarketing studies. Subjects with clinically severe underlying medical conditions, and immunocompromised individuals were excluded from the pre-licensure clinical trials and the Italian observational study. Safety data among individuals with underlying medical conditions and immunocompromised was not systematically

summarized in the PSURs. Therefore, a safety profile on these populations is not available. Concerning the risk management plan and previous suspension of FLUAD, the reviewer noted that additional questions would need to be sent to NVD regarding the routine surveillance and active surveillance activities investigation reports for the suspensions.

4.2.12 APLB

The APLB reviewer reported that he was waiting to consult the clinical review before providing comments on the Package Insert and Carton/Container labels.

5.0 INFORMATION REQUESTS

1. IR from BiMO (12-9-14): For each of the clinical studies listed in section 5.2 of the BLA, please furnish a list showing the name and address of each participating clinical investigator along with their telephone number and corresponding study site number.
2. IR from clinical (12-17-14): For pivotal trial V70_27, provide for each site, the number of subjects enrolled, the % of subjects with major protocol violation, the % of subjects with any protocol violation and the % of subjects meeting primary endpoints for superiority and noninferiority.
3. IR from DBSQC (1-9-15 and follow-up on 1-23-15): sample availability for CBER testing
4. IR from CMC (1-16-15): Request for (b) (4) SOP on the HAI assay and illustration of sera dilution and calculations; request for additional information on the 3 PAS's to be submitted to the Agriflu file.
5. IR from DMPQ (1-30-15): Request to determine need for facilities inspection.
6. IR (2-18-15): comments/questions on CDISC, clinical, DBSQC and CMC
7. IR from DBSQC (2-20-15): questions on CTAB, (b) (4)
[REDACTED]
8. IR from DBSQC (3-17-15): questions regarding the Ovalbumin assay
9. IR from DBSQC (3-31-15): questions regarding bioburden and endotoxin testing
10. IR from CMC and clinical (4-1-15): request to again correct HAI titers and report for pivotal trial V70_27
11. IR from DBSQC (4-16-15): request for SRID-related documents/reports and clarification on the sites to be used for SRID testing
12. IR from CMC-adjuvant reviewer (4-17-15): request for English translation of COAs and confirmation of post-licensure production parameters
13. IR from DBSQC (4-24-15): request regarding endotoxin testing

6.0 AMENDMENTS

125510/0.1 – XML formatted PI Labeling

125510/0.2 – Partial response to IR dated 1-16-15

125510/0.3 – Response to IR dated 12-9-14, 12-17-14 and 1-16-15

125510/0.4 – Response to IRs dated 1/9/15, 1/23/15 and 1/30/15. Partial response to IR dated 2/18/15

125510/0.5 – Response to IRs dated 2/18/2015 and 2/20/2015

125510/0.6 – Response to IRs dated 3/17/2015

125510/0.7 – Response to IR dated 3/31/15 and update to IR dated 2/18/15 (#7 and #8)

125510/0.8 – Partial response to IR dated 4/1/15

125510/0.9 – Resubmission of revised SDTM datasets originally submitted in the partial response to IR dated 4/1/15 due to an error in the version of the datasets provided

125510/0.10 – Response to IRs dated 4/16/2015, 4/17/2015 and 4/24/2015