

**FILING MEETING SUMMARY**

To: The File
Date and Time: January 9, 2015, 10:00 AM – 11:00 AM
STN #: 125510/0
Submission Type: Original BLA
Applicant: Novartis Vaccines and Diagnostics, Inc.
Product: Influenza Vaccine, Adjuvanted (FLUAD 65)

Meeting Chair: Brenda Baldwin, Ph.D.

CBER ATTENDEES

<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	✓
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	Sang Ahnn, 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, Ph.D.	✓	William McCormick	✓
DS and DP release assays	Alfred Del Grosso, PhD	✓	William McCormick	✓
DS and DP release assays	Simleen Kaur, PhD	✓	William McCormick	✓
LRP and Testing Plan Development	Josephine Resnick, PhD	✓	William McCormick	✓
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

Loris McVittie
Carmen Collazo
Wellington Sun

Melisse Baylor
Jay Eltermann
Marion Gruber

Karen Campbell
Anissa Cheung

1.0 PURPOSE

To discuss the completeness of the BLA submission and ensure it is acceptable to file.

2.0 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.

3.0 REVIEW COMMITTEE STATUS UPDATES AND FILING RECOMMENDATIONS

3.1 Chair (Brenda Baldwin) and RPM (Theodore Garnett)

Opening remarks were provided by the RPM with additional remarks from the Chair. The review team was reminded that the Filing Action due date was January 24, 2015, and that they were expected to submit their filing checklists/recommendations via e-mail to the Chair and RPMs as soon as possible. The RPM stated that IRs from the BiMO and Clinical reviewers had already been sent to the firm, and the Chair indicated that future IRs would be compiled into one letter, when possible.

The following review timelines were highlighted by the RPM:

- Deficiencies identified (February 7, 2015)
- Draft reviews complete (May 7, 2015)
- Mid-cycle meeting (May 11, 2015)

Reviewers were informed that monthly meetings would occur as needed and that the first monthly meeting was scheduled for February 9, 2015.

3.2 Clinical (Sarah Browne)

Sarah discussed a potential filing issue regarding the use of SDTM preferred terms in the pivotal study (V70_27), noting that AEs were often inconsistently classified in the organ systems, which could make analysis very challenging. OVRR and DVRPA leaders and senior staff discussed whether this issue met the threshold for refusal to file and concluded that it didn't and could be dealt with by requesting a major amendment from the firm if needed.

3.3 Clinical Stats (Sang Ahnn)

The BLA was recommended for filing. No issues were identified that would prevent filing; however, Sang noted that Novartis combined the V70_27 pivotal trial immunogenicity data with all of the supportive trial immunogenicity data. This is not typical and will take more effort to review.

3.4 Assay Stats (Tsai-Lien Lin *on behalf of Zhong Gao*)

The BLA was recommended for filing. No issues were identified that would prevent filing.

3.5 CMC-Antigen (Hang Xie)

Hang noted a potential filing issue regarding the serum dilution used as a starting point for the HAI assay. A discussion of this issue ensued and the general consensus was that the firm would need to recalculate their immunogenicity data and update their tables as needed. However, OVRR and DVRPA leaders and senior staff did not believe that this issue met the threshold for refusal to file and suggested that a major amendment approach was reasonable.

3.6 CMC-Adjuvant (Marina Zaitseva)

The BLA was recommended for filing. No issues were identified that would prevent filing.

3.7 Toxicology (Nabil Al-Humadi)

The BLA was recommended for filing. No issues were identified that would prevent filing.

3.8 Facilities (Peter Amin)

Peter did not attend the meeting; however, he sent an email to the chair recommending that he BLA be filed.

3.9 BiMO (Anthony Hawkins)

The BLA was recommended for filing. No issues were identified that would prevent filing.

3.10 DS and DP Release Assays

The BLA was recommended for filing. No issues were identified that would prevent filing.

3.11 Pharmacovigilance (Yandong Qiang)

The BLA was recommended for filing. No issues were identified that would prevent filing; however, the impact of inconsistent classification of adverse events by organ systems on safety signal evaluation was noted.

3.12 APLB (Sonny Saini)

The BLA was recommended for filing. No issues were identified that would prevent filing.

4.0 ADDITIONAL DISCUSSION

- Anissa Cheung noted that the (b) (4) facility is no longer used in manufacturing Agriflu (the antigen platform that Fluad is based). It was requested that we determine if this is also the case for Fluad.
- Alfred Del Grosso noted that there may be issues with the (b) (4) assay as applied to the drug product. Due to the presence of the adjuvant, formaldehyde content is estimated by (b) (4). Assay validation is, as a limits test, at the specification limit of (b) (4) and is not considered adequate. These issues should be able to be addressed during the review and were not identified as preventing filing.