



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

April 11, 2012 MEETING Summary

Date and Time:	April 11, 2012 – 11:00-12:30
Location:	WOCII – room 3101
STN #:	125408/0
Supplement Type:	Original BLA submission
Sponsor:	Novartis Vaccines and Diagnostics Inc.
Product:	Optaflu, Influenza Vaccine (MDCK cells)

CBER/FDA Invitees

COMMITTEE MEMBERS:

<u>Name</u>	<u>Role</u>	<u>Division</u>	<u>Present</u>
Timothy Nelle, Ph.D.	Chair	DVRPA/OVRR	yes
Melisse Baylor, M.D.	Clinical Reviewer	DVRPA/OVRR	yes
Nabil Al-Humadi, Ph.D.	Toxicology Reviewer	DVRPA/OVRR	yes
Tammy Massie, Ph.D.	Statistical Reviewer, Clinical	DB/VEB/OBE	no
Alan Ou, M.D., MPH	Epidemiology Reviewer	DE/OBE	yes
Lihan Yan, Ph.D.	Statistical Reviewer, Bioassay	DB/VEB/OBE	yes
Rajesh Gupta, Ph.D.	CMC Reviewer, Analytical Methods	DPQ/OCBQ	yes
Karen Campbell	Lot Release	DPQ/OCBQ	yes
Zhiping Ye, Ph.D.	Product Reviewer	DVP/OVRR	yes
Haruhiko Murata	Product Reviewer	DVP/OVRR	yes
Xianghong Jing	Product Reviewer	DVP/OVRR	yes
Pankaj Amin	Facility Reviewer	DMPQ/OCBQ	yes
Ellen Huang	Facility Reviewer	DMPQ/OCBQ	yes
Anthony Hawkins	Bioresearch Monitoring Reviewer	DIS/BMB/OCBQ	yes
Maryann Gallagher	Labeling Reviewer	DCM/APLB/OCBQ	yes
LT David Schwab	Electronic Integrity Reviewer	DVRPA/OVRR	yes
Brenda Baldwin, Ph.D.	Regulatory Project Manager	DVRPA/OVRR	yes
Timothy Fritz, Ph.D.	Regulatory Project Manager	DVRPA/OVRR	yes
Anissa Cheung, Ph.D.	Product Specialist, Inspection	DVP/OVRR	yes

CBER/FDA Invitees:

Elizabeth Sutkowski, Ph.D.	Branch Chief	DVRPA/OVRR	yes
Douglas Pratt, M.D.	Associate Director Medical Affairs	DVRPA/OVRR	no
Martin Green, Ph.D.	Supervisory Toxicologist	DVRPA/OVRR	no
Rakesh Pandey, Ph.D.	Branch Chief	DVRPA/OVRR	yes
Amelia Horne, Ph.D.	Supervisory Mathematician	DB/VEB/OBE	no
Tsai-Lien Lin, Ph.D.	Lead Mathematician Statistician	DB/VEB/OBE	no
William McCormick, Ph.D.	Division Director	DPQ/OCBQ	yes
Jerry Weir, Ph.D.	Division Director	DVP/OVRR	no

Chiang Syin, Ph.D.	Supervisory Chemist	DMPQ/OCBQ	no
Lori Austin-Hansbury	Senior Supervisory Regulator	DE/OBE	no
Lisa Stockbridge	Supervisory Consumer Safety Officer	DCM/APLB/OCBQ	yes
Patricia Holobaugh	Supervisory Consumer Safety Officer	DIS/OCBQ	no
Keith Peden, Ph.D.	Supervisory Microbiologist	DVP/OVRR	yes
Prakash Rath, Ph.D.	Commissioner Fellow	OCS/OSAI	yes
Catherine Poole	Biologist	DPQ/OCBQ	no
Lucia Lee	Medical Officer, Team Leader	DVRPA/OVRR	no
Wellington Sun, M.D.	Division Director	DVRPA/OVRR	yes
Loris McVittie, Ph.D.	Division Deputy Director	DVRPA/OVRR	yes
Maureen Hess	Health Science Advisor	OD/OVRR	no
Phil Krause, M.D.	Office Acting Deputy Director	OD/OVRR	yes

Other attendees:

Anuradha Poonepali, MD.	Visitor	Singapore HSA	yes
Zhang Wei, Ph.D.	Visitor	Singapore HAS	yes

1.0 Background and Purpose of Meeting

BLA STN #125408/0, Sequence #0 was submitted by Novartis Vaccines and Diagnostics GmbH on October 31, 2011 and received by CBER on November 1, 2011. Payment was not received until November 22, 2011 and thus the review clock was reset to begin November 22, 2011 with an action due date of September 21, 2012.

The proposed indication is for active immunization of persons 18 years of age and older for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine.

The purpose of this meeting is to convey any issues, comment on the need for post marketing commitments and to update management and others on the review team the progress that has been made.

2.0 Outstanding Issues:

2.1 CBER Requests for Information- response from Novartis still pending:

- IR/advice e-mail regarding CMC sent on 3-13-12.

2.2 CBER Requests – Novartis response:

- Additional facilities information requested on 1-19-12 – submitted as amendment 2 on 2-13-12.
- Information on the columns used in the manufacturing process requested on 2-15-12 – submitted as amendment 3 on 2-28-12.
- Proprietary name review (PNR) document for “Optaflu” requested on 12-15-11 – submitted as amendment 5 on 3-16-12. Review of the name will be performed this week.
- SRID validation and reagent qualification demonstrating suitability of egg-based reagents for testing cell-based product requested 12-23-11 – interim scientific

report submitted in e-mail on 3-23-12 and 3-30-12 (updated) and by amendment 8 on 4-6-12. A/Brisbane monobulk, B/Brisbane monobulk and ----(b)(4)----- SRD reports submitted as amendment 8 on 4-6-12. Although not requested, Novartis additionally submitted an ----(b)(4)----- validation report in this amendment.

- Monovalent Bulk/Trivalent Bulk sample lots for CBER testing requested on 1-30-12 – Fifteen lots of monovalent bulk were shipped to CBER on 3-21-12. DPQ is analyzing the total protein and potency (by SRID) for each lot. They have noticed that their SRID results using the egg-based reagents are less than the results obtained with the cell-based reagents, and believe that Novartis may be over-formulating by as much as 50%. DPQ also noted that 80-90% of the total protein is HA. A question was raised as to how Novartis determined their clinical lot concentrations.
- Lot release protocol submitted by e-mail on 3-30-12 – Novartis has question regarding sterility
- IR/advice e-mail regarding Toxicology Study 191-44 sent on 3-6-12 – submitted as amendment 7 on 4-4-12. Nabil noted that their response would not affect the approval of the BLA.

2.3 Additional points discussed:

- Sensitivity Analysis for Trial V58P9 – Panevezys site (amendment 4 submitted 3-8-12). Melisse discussed the issues with the trial in her slide presentation (see attachment). There are concerns with how both site 1 and 2 performed the trial. It was determined that more information would be needed from a Lithuanian Competent Authority audit document and also from the EMA before a decision can be made on the adequacy of this trial. A possible request for a lot-to-lot consistency clinical trial using the Holly Springs manufactured product was discussed.
- No PMCs or PMRs have been identified thus far; however, Novartis will need to monitor the stability of the product for possibly more than ---(b)(4)----.
- OBE has determined that REMS is not needed.
- SWG presentation probably will not be necessary since a PMR has not been identified.
- Marburg Germany facility inspection performed week of March 19th. Overall, the inspection went well. A few of the issues that were noted: cleaning validation, BPL removal, stability data not provided, and the working virus did not have -----(b)(4)----- testing.
- Holly Springs facility inspection to be performed week of April 16th. Inspection team noted that there will only be 1 quality control test so the inspection will be fairly quick.

3.0 Review Updates: Still need draft review from Melisse Baylor and Tammy Massie.

3.1 Clinical Melisse Baylor – had PowerPoint presentation on the pivotal and supportive clinical trials submitted in the BLA (see attachment). Melisse noted that AE reports were still needed from some of the subjects in V58P13.

3.2 Statistical

3.2.1 Clinical Tammy Massie

3.2.2 Bioassay Lihan Yan – in review had questioned the HA validation approach for the cell-derived antigens. Zhiping Ye agreed that the assay should be optimized for future clinical trials, but would not be necessary for the past clinical trials.

3.3 Product

3.3.1 CMC – MDCK cell substrate Haru Murata

3.3.2 CMC – Flu vaccine Xianghong Jing, Zhiping Ye

3.3.3 CMC – Analytical Methods Rajesh Gupta

3.4 Toxicology Nabil Al-Humadi

3.5 Epidemiology Alan Ou

3.6 Facilities Pete Amin, Ellen Huang

4.0 Schedule

4.1 Milestones (Updated, milestones in gray have been completed)

Submitted: October 31, 2011

BLA Received: November 1, 2011; Fee Received November 22, 2011

Committee Assignment: November 15, 2011

First Committee Meeting: November 21, 2011

Filing Meeting: December 12, 2011

Filing Action: January 21, 2012 (sent January 12, 2012)

VRBPAC Determination: January 21, 2012

PeRC Determination: January 21, 2012

Deficiencies Identified: February 4, 2012

First Draft Reviews Due: February 20, 2012 (March 21 for Stats and PhV)

SWG Determination: April 20, 2012

FDAAA Postmarketing determination: April 20, 2012

Second Draft Reviews Due: May 15, 2012 (May 30 for Stats and PhV)

PeRC forms submitted: June 13, 2012

Final Reviews Due: July 14, 2012

Action Due: September 21, 2012

Action Package for Posting Due: September 21, 2012

4.2 Meetings (meetings in gray have been completed)

First Committee Meeting (via e-mail): November 16, 2011

Filing Meeting: December 12, 2011

Monthly Team Meetings: January 18, 2012 February 29, 2012

May 7, 2012 June 11, 2012

July 9, 2012 August 6, 2012

Mid-Cycle Review Meeting: April 11, 2012

PeRC: June 27, 2012

VRBPAC Planning: No longer needed

Safety Working Group (SWG): TBD

Labeling Meetings: TBD

4.3 Summary of Additional Action Items

- Prelicensure Facility Inspection (or waiver) December 13, 2011
- Schedule Facility Inspection (Marburg, Holly Springs?) January 22, 2012
- Determine Consistency/Launch Lots February 20, 2012
- **Facility Inspection Complete April 22, 2012**
- BIMO Inspections Complete Not needed
- PMC to FDAAA SWG August 4, 2012
- Labeling Target September 3, 2012

5.0 CONCLUSION

- **Regarding the lot-to-lot consistency trial, we need to (1) request from Novartis the Lithuanian audit document (translated into English) concerning the Site 2 issues, and (2) set up a meeting with the EMA to discuss their reviews for Optaflu. Following the review of this information a decision will be needed on whether the V58P9 trial will be adequate for licensure.**
- **Ask Novartis on their marketing plans for Optaflu if approved for licensure in the US.**
- **Need to look further into the pipetting issues which could impact the reliability of the immunogenicity data.**