



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

July 9, 2012 MEETING Summary

Date and Time:	July 9, 2012 from 1-2 pm
Location:	WOC2 room 2330
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	No
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
Scott Winiecki, M.D.	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	No
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	No
Pankaj Amin	Facility Reviewer	DMPQ/OCBQ	Yes
Ellen Huang	Facility Reviewer	DMPQ/OCBQ	Yes
Anthony Hawkins	Bioresearch Monitoring Reviewer	DIS/BMB/OCBQ	No
Maryann Gallagher	Labeling Reviewer	DCM/APLB/OCBQ	No
LT David Schwab	Electronic Integrity Reviewer	DVRPA/OVRR	No
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	No

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	No
Amelia Horne, Ph.D.	Supervisory Mathematician	DB/VEB/OBE	No
Tsai-Lien Lin, Ph.D.	Lead Mathematician Statistician	DB/VEB/OBE	Yes
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-Hansberry	Senior Supervisory Regulator	DE/OBE	No
Lisa Stockbridge	Supervisory Consumer Safety Officer	DCM/APLB/OCBQ	No
Patricia Holobaugh	Supervisory Consumer Safety Officer	DIS/OCBQ	No
Keith Peden, Ph.D.	Supervisory Microbiologist	DVP/OVRR	No
Prakash Rath, Ph.D.	Commissioner Fellow	OCS/OSAI	No
Catherine Poole	Biologist	DPQ/OCBQ	No
Lucia Lee, M.D.	Medical Officer, Team Leader	DVRPA/OVRR	Yes
Jeff Roberts, M.D.	Clinical Branch Chief	DVRPA/OVRR	Yes
Wellington Sun, M.D.	Division Director	DVRPA/OVRR	Yes
Manju Joshi	Lead Biologist	DPQ/OCBQ	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 and to update management and others on the review team of the progress that has been made.

2.0 Outstanding Issues:

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

- IR e-mail regarding further CMC and facilities questions ---(b)(4)----- columns, equipment cleaning, aseptic filling report, environmental monitoring report, optical character verification report, HAI with ---(b)(4)----- RBC, etc.) sent on 6-22-12
- Draft review of label has begun. Initial comments sent to Novartis on 6-28-12

2.2 Additional points:

- Consistency Trial V58P9 – issues
 - Lithuanian site report (site 1) and NVD audits (site 1 and 2) – found sites suboptimal due to investigator conduct (information submitted by Novartis on 3-8-12 (amendment 4), 4-13-12 (amendment 9), and 5-23-12 (amendment 11)).
 - Sensitivity analysis they have provided may not be adequate.
 - A new Clinical Lot Consistency Trial using product from Holly Springs may be necessary.
- Proprietary name review (PNR) document for “Optaflu” submitted as amendment 5 on 3-16-12 – name is unacceptable. Letter for unacceptable

name sent to Novartis on 5-24-12. Amendment 14 received 6-28-12 contains two alternative names for review – Flucelvax or --(b)(4)----.

- Monovalent Bulk/Trivalent Bulk sample lots for CBER testing requested on 1-30-12 – 15 monovalent lots shipped to CBER on 3-21-12 (5 from each strain). Testing is complete – results will be sent to Novartis. Still awaiting the trivalent bulk samples for CBER testing.
- Novartis may also be sending in the monovalent and trivalent bulks for the 2012-2013 season flu vaccine soon.
- CMC IR/advice request sent on 3-13-12 – submitted as amendment 10 on 4-26-12. Response is adequate.
- The re-validation data for the removal of residual BPL by the modified FCC process 1.1 will not be ready until August 31, 2012.
- IR e-mail regarding additional CMC (polysorbate assay, CTAB assay, total protein assay, mycoplasma test, residual infectious virus, BPL inactivation results and validation, HA and -----(b)(4)----- comparability between FCC process 1.0 to 1.1) sent on 5-4-12. Response received as amendment 12 on 6-20-12. Further clarification is still needed from Novartis.
- Novartis intends to distribute --(b)(4)--- doses of Optaflu in the US for the 2012-2013 season. UNII codes were requested on May 7, 2012. UNII codes will be provided to Novartis after 2012-2013 strain information is submitted as an amendment to the BLA.
- Question regarding difference in SRID results between CBER and Novartis sent on 6-6-12 – response received on 6-21-12 as amendment 13.
- IR e-mail regarding 483 observations for the Marburg, Germany facility and non-483-related issues at ---(b)(4)---, sent on 6-22-12 – response received on 7-6-12 as amendment 15. DMPQ needs further clarification and will set up a teleconference.

3.0 Review Updates: Final reviews due July 14th from all reviewers.

3.1 Clinical	Melisse Baylor (50%)
3.2 Statistical	
3.2.1 Clinical	Tammy Massie (?)
3.2.2 Bioassay	Lihan Yan (100%)
3.3 Product	
3.3.1 CMC – MDCK cell substrate	Haru Murata (75%)
3.3.2 CMC – Flu vaccine	Xianghong Jing, Zhiping Ye (75%)
3.3.3 CMC – Analytical Methods	Rajesh Gupta (75%)
3.4 Toxicology	Nabil Al-Humadi (100%)
3.5 Epidemiology	Scott Winiecki (75%)
3.6 Facilities	Pete Amin, Ellen Huang (70%)

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)

Final Reviews Due: July 14, 2012

PeRC forms submitted: August 8, 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: August 22, 2012 (this date was moved from the original June 27th meeting)

VRBPAC Planning: No longer needed

Safety Working Group (SWG): Not needed

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

1. Regarding the sterility test for the trivalent bulk – DPQ has decided to waive the requirement for a sterility test for this year due to changes in the CFR 610.12 (requires sterility test only on the final filled product). DPQ also noted that the sterility test will not be included in the trivalent bulk lot release protocol.
2. The team agreed that a PMC may be necessary for a lot consistency trial to be performed using product from Holly Springs facility.
3. Product reviewers indicated they still needed clarification on several CMC issues.
4. As part of a response to CMC questions, Novartis has submitted the extractable/leachable study for the -(b)(4)- syringe combined with the -(b)(4)- rubber plunger stopper. The report identified “(b)(4)” as one of the leachables from the plastic syringe ---(b)(4)-----
----- . The same syringe is also used in the EU.