



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

June 11, 2012 MEETING Minutes

Date and Time:	June 11, 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	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	Yes
Scott Winiecki, M.D.	Epidemiology Reviewer	DE/OBE	No
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	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	No
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	Yes
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	No
William McCormick, Ph.D.	Division Director	DPQ/OCBQ	No
Jerry Weir, Ph.D.	Division Director	DVP/OVRR	Yes

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	Yes
Prakash Rath, Ph.D.	Commissioner Fellow	OCS/OSAI	No
Catherine Poole	Biologist	DPQ/OCBQ	No
Lucia Lee	Medical Officer, Team Leader	DVRPA/OVRR	No
Wellington Sun	Director	DVRPA/OVRR	Yes
Loris McVittie	Deputy Director	DVRPA/OVRR	Yes
Theresa Finn	Assoc Director, Regulatory Policy	OVRR	Yes
Karen Farizo	Act Assoc Dir Med Policy Vaccine Safety	DVRPA/OVRR	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 the monthly meetings is to convey any issues and to update management and others on the review team of the progress that has been made. For the June 2012 meeting, GCP issues surrounding the lot consistency study, Novartis' ability to produce cell-culture derived vaccine, and whether we should require a new lot consistency study will be discussed.

2.0 Outstanding Issues:

2.1 Discussion points for the June 11, 2012 Monthly Meeting

- Consistency Trial V58P9 – issues (discussed further internally June 7, 2012)
 - Lithuanian site report (site 1) and NVD audits (site 1 and 2) – found sites suboptimal for several reasons including: investigators of the study sites were later charged with fraud and/or forgery in connection with a later clinical study (Aflunov), questions as to whether some data was fabricated, 173 subjects did not have an ICF signed by the investigator, and questionable enrollment practices.
 - EMA was contacted regarding their knowledge of the GCP violations that occurred during Novartis' Aflunov clinical studies. In an e-mail of May 14, 2012, they informed us that no GCP issues arose for Optaflu during or after the initial assessment. Furthermore, according to EMA guidance, influenza vaccine lot-to-lot consistency does not require a clinical study component; only CMC consistency must be demonstrated.

- The sponsor's sensitivity analysis supporting exclusion of data from study site 2 was discussed and found unacceptable by the CBER statistician. She explained that there were other ways to conduct such analyses, but most would result in the lot consistency study failing.
- 2005 lots used in the lot consistency study (manufactured using CMC Process 1.0) are similar to 2012 lots (CMC Process 1.1) from a manufacturing perspective. Proprietary name review (PNR) document for "Optaflu" submitted as amendment 5 on 3-16-12 – name is unacceptable to APLB and several other team members. Letter for unacceptable name sent to Novartis on 5-24-12.

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

- 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.
- New set of OCBQ/DVP comments in draft preparation.

2.3 Additional points:

- 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.
- Lot release protocol submitted by e-mail on 3-30-12 – DBSQC will provide a response on its acceptability once the response to the IR request of May 4, 2012 is received. Novartis also has question regarding sterility that will need a response.
- CMC IR/advice request sent on 3-13-12 – submitted as amendment 10 on 4-26-12. Any further comments from CBER to Novartis' response?
- 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.
- Draft review of label has begun.
- Novartis intends on distributing --(b)(4)--- doses of Optaflu for the 2012-2013 season. UNII code was requested on May 7, 2012.

3.0 Review Updates: Still need first draft review from Melissa Baylor and Tammy Massie. Second draft review due from all reviewers.

3.1 Clinical Melissa Baylor (?)

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 (70%)

3.3.2 CMC – Flu vaccine

Xianghong Jing, Zhiping Ye (70%)

3.3.3 CMC – Analytical Methods

Rajesh Gupta (70%)

3.4 Toxicology

Nabil Al-Humadi (100%)

3.5 Epidemiology

Alan Ou (100%)

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 Inspections | 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

The Clinical and Clinical Statistics Reviewers presented summaries of the clinical lot consistency study V58P9. Several concerns were raised regarding the acceptability of this study including:

- Use of Principal Investigators accused of fraud or forgery in association with another clinical trial (Aflunov)
- The study had no pre-defined success criteria (study was not conducted under IND)
- Uncertainty in Novartis' sensitivity analysis results due to possible alternate, failed outcomes assuming a worst-case scenario
- High enrollment rate (500 subjects in 6 days) by a single nurse where enrollment required a blood draw on the same day

Based upon their reviews, the Clinical and Clinical Biostatistics Reviewers recommended a Complete Response (CR) letter be issued to Novartis requiring a new clinical lot consistency study prior to licensure.

The question of whether a BIMO inspection could alleviate the concerns was raised. Though the data should still be available, it was not clear that inspection of the sites could resolve the problems with study V58P9. The BIMO Reviewer noted that, though BIMO does not generally override another country's inspection results, the information presented by the Clinical Reviewer raised compliance concerns about study V58P9.

No issues were raised regarding manufacturing consistency or comparability between Novartis' manufacturing previous process 1.0 and the current, 1.1 process. It was noted that the clinical studies were conducted using manufacturing process 1.0.

There was a general consensus among the review team and others in attendance that a CR letter was appropriate and that Novartis should repeat the clinical lot consistency study prior to licensure. This recommendation would require additional discussion within OVR and CBER management.