



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

May 7, 2012 MEETING Summary

Date and Time:	May 7, 2012
Location:	e-mail
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>Responded</u>
Timothy Nelle, Ph.D.	Chair	DVRPA/OVRR	yes
Melisse Baylor, M.D.	Clinical Reviewer	DVRPA/OVRR	no
Nabil Al-Humadi, Ph.D.	Toxicology Reviewer	DVRPA/OVRR	no
Tammy Massie, Ph.D.	Statistical Reviewer, Clinical	DB/VEB/OBE	no
Alan Ou, M.D., MPH	Epidemiology Reviewer	DE/OBE	no
Lihan Yan, Ph.D.	Statistical Reviewer, Bioassay	DB/VEB/OBE	no
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	no
Haruhiko Murata	Product Reviewer	DVP/OVRR	no
Xianghong Jing	Product Reviewer	DVP/OVRR	no
Pankaj Amin	Facility Reviewer	DMPQ/OCBQ	yes
Ellen Huang	Facility Reviewer	DMPQ/OCBQ	no
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	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	yes

CBER/FDA Invitees:

Elizabeth Sutkowski, Ph.D.	Branch Chief	DVRPA/OVRR	no
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	no
William McCormick, Ph.D.	Division Director	DPQ/OCBQ	no
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	yes
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	Medical Officer, Team Leader	DVRPA/OVRR	no

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 additional CMC (polysorbate assay, CTAB assay, total protein assay, mycoplasma test, residual infectious virus, BPL inactivation, HA and -----(b)(4)----- monovalent comparability between FCC process 1.0 to 1.1) sent on 5-4-12.

2.2 CBER Requests – Novartis response:

- 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. Will discuss name further in meeting on May 16, 2012 with DVRPA and OVRR IOD.
- SRD validation and reagent qualification demonstrating suitability of egg-based reagents for testing cell-based product requested 12-23-11 – report submitted by amendment 8 on 4-6-12. A/Brisbane monobulk, B/Brisbane monobulk and trivalent bulk SRD reports also submitted in amendment 8 on 4-6-12. DPQ noted that some of the lots that were received for testing were also used in the qualification study and that the SRID results for most of those lots reported in the qualification report are different that what were provided to us via email.

- 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.
- Lot release protocol submitted by e-mail on 3-30-12 – Novartis has question regarding sterility. DBSQC is still working on their review and hopes to have a meeting (by phone or e-mail) with the CMC reviewers this week or next.
- Lithuanian site inspection report requested 4-13-12 – submitted as amendment 9 on 4-13-12. See comments below.
- CMC IR/advice request sent on 3-13-12 – submitted as amendment 10 on 4-26-12.

2.3 Additional points for comment:

- Clinical Lot Consistency Trial V58P9 – issues (amendment 4 submitted 3-8-12) –
 - EMA meeting to discuss their inspections and reviews of Optaflu – date TBD
 - Lithuanian site report– identified ten GCP violations at the Panevezys Hospital study site during the inspection of study V87P4 (Aflunov). All violations were deemed either significant or dangerous and included (but not limited to): lack of oversight by the senior investigator, inadequate informed consent, uncontrolled patient flow (334 subjects enrolled in only 4 days), enrollment of involved vulnerable individuals, multiple violations of inclusion/exclusion criteria and lack of adequate resources. Following the Lithuanian inspection, the site was subsequently closed for enrollment for V87P4, with consent of NVD as sponsor, after enrollment at Visit# 1. Subsequently, both investigators for V87P4 (Dr. Rimantas Paksys and Dr. Ligita Balciuniene) were charged criminally by the Lithuanian authorities and are currently the subject of criminal court proceeding. The investigators who participated in V87P4 (2005-2006) were also the same investigators that participated in V58P9 (2007).
 - 2006 lots similar to 2012 lots?
- Pipetting issue from 2007 – HI validation acceptable at this time – will need to improve upon validation for future trials.
- Marburg Germany facility inspection performed week of March 19th – some issues observed – no validation for removal of BPL (new process 1.1), processes do not provide assurance against microbial contamination, cleaning validation and verification program is inadequate, insufficient data to support (b)(4) month shelf life. Novartis' response on the PLI 483 observations was received on April 19, 2012. All responses related to the product issues were adequate. For the residual BPL in the ---(b)(4)----- manufactured by the modified FCC process 1.1, the re-validation data for the removal of residual

BPL will not be ready until August 31, 2012. We asked them to provide results of the residual BPL for the most recently manufactured -----(b)(4)----- with the new process 1.1, as well as the validation of the assay used for this test through the latest IR sent on May 4, 2012.

- Holly Springs facility inspection performed on April 20th. No 483 was issued during this inspection. Novartis noted that they may not use Holly Spring facility to store the Optaflu finished product and will amend the BLA with new final product storage information. Regarding potency (SRID) testing at Holly Spring, Novartis will perform method validation for the current year flu strain with the co-ordination with CBER/DMPQ (Dr. Rajesh Gupta group). Last year, Novartis completed the method validation with available flu strain.

3.0 Review Updates: **Still need first draft review from Melissa Baylor and Tammy Massie.**

Second draft review due May 15th for most (May 30th for Tammy and Alan). **Please fill in % completed.**

3.1 Clinical	Melisse Baylor (no information)
3.2 Statistical	
3.2.1 Clinical	Tammy Massie (no information)
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)
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): 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

The principle outstanding issue is whether the clinical lot consistency study will need to be repeated. This will be the focus of the June monthly meeting.