

RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125510/0.0
Review Office	OVRR
Applicant	Novartis Vaccines and Diagnostics, Inc. / Lic. # 1751
Product	Influenza Vaccine, Adjuvanted
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	02-OCT-2015 02:58 PM
Author	GARNETT, THEODORE
Outside Phone Number	N/A – sent to applicant by e-mail
FDA Originated?	Yes
Communication Categories	OT - Late-Cycle Communication
Related STNs	None
Related PMCs	None
Telecon Summary	Late-Cycle Communication
FDA Participants	LCDR Theodore Garnett
Applicant Participants	Mayuresh Gadre

Telecon Body:

From: Garnett, Theodore

Sent: Friday, October 02, 2015 2:58 PM

To: 'GADRE, MAYURESH'

Subject: STN 125510/0 (FLUAD): Late-Cycle Communication Summary

Dear Mayuresh,

Please find attached a summary of the Late-Cycle Communication, held on September 3, 2015.

Regards,

RECORD OF TELEPHONE CONVERSATION

Ted

Theodore Garnett, Ph.D.

LCDR, U.S. Public Health Service

Microbiologist (Regulatory)

U.S. Food and Drug Administration

CBER|OVRR|DVRPA|CMC3

10903 New Hampshire Avenue

Building 71, Room 3023

Silver Spring, MD 20993-0002

O 240.402.0218 | BB (b) (6) | theodore.garnett@fda.hhs.gov

U.S. Public Health Service Rapid Deployment Force PHS-2 ("*Second to None*") Admin/Finance
Section, Home Support Branch Director

"THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone."



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Date: October 2, 2015

Number of Pages: 13 (including cover sheet)

Contact: Mayuresh Gadre, Ph.D.
Senior Regulatory Affairs Specialist

Company Name: Novartis Vaccines and Diagnostics, Inc.
Address: 350 Massachusetts Avenue
Cambridge, MA 02139
Telephone: 617-871-7000
Fax: 267-305-6407

From: Kirk Prutzman, Ph.D.
Microbiologist (Regulatory)
FDA/CBER/OVRR/DVRPA
10903 New Hampshire Avenue
WO71,
Silver Spring, MD 20993-0002
Telephone: 301-796-2640
Fax: 301-595-1244

STN #: 125510/0

Application Type: BLA (Original Application)

Subject: Summary of Late Cycle Communication, held September 3, 2015

Dear Dr. Gadre:

Please find attached a summary of our Late Cycle Communication meeting for STN 125510, held September 3, 2015. If you have any questions, please contact Theodore Garnett, Ph.D. or Brenda Baldwin, Ph.D. at (301) 796-2640.

THIS DOCUMENT IS INTENDED ONLY FOR THE PARTY TO WHOM IT IS ADDRESSED. THE DOCUMENT MAY CONTAIN INFORMATION PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, we now notify you that any review, disclosure, distribution, copying or other action based on the contents of this communication are not authorized. If this document is received in error, please immediately notify us by telephone and return it to us at the above address by mail.

LATE-CYCLE COMMUNICATION SUMMARY

STN #	125510/0
Submission Type	BLA (Original Application)
Product:	Influenza Vaccine, Adjuvanted (Fluad)
Proposed Indication:	Fluad is indicated for use in persons 65 years of age and older for active immunization against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.
Applicant:	Novartis Vaccines and Diagnostics, Inc. (NVD)
Meeting Date:	September 3, 2015
Meeting Time:	2:30 – 4:00 pm
Meeting Format:	Teleconference
Committee Chair:	Brenda Baldwin, Ph.D.
RPMs:	Theodore Garnett, Ph.D. and Kirk Prutzman, Ph.D.

I. ATTENDEES

A. CBER

Brenda Baldwin, Ph.D.	OVRR/ DVRPA
Theodore Garnett, Ph.D.	OVRR/ DVRPA
Kirk Prutzman, Ph.D.	OVRR/ DVRPA
Pin Zhang, Ph.D.	OVRR/ DVRPA
Elizabeth Sutkowski, Ph.D.	OVRR/ DVRPA
Sarah Browne, M.D.	OVRR/ DVRPA
Jeff Roberts, M.D.	OVRR/ DVRPA
Loris McVittie, Ph.D.	OVRR/ DVRPA
Robin Levis, Ph.D., Division Deputy Director	OVRR/ DVRPA
Lokesh Bhattacharyya, Ph.D.	OCBQ/ DBSQC
Josephine Resnick, Ph.D.	OCBQ/ DBSQC
Karen Campbell, M.S.	OCBQ/ DBSQC
William McCormick, Ph.D., Division Director	OCBQ/ DBSQC
Lori Austin-Hansberry	OBE
Alfred Del-Grosso, Ph.D.	OCBQ/ DBSQC
Karen Farizo, M.D.	OVRR
Marion Gruber, Ph.D., Office Director	OVRR
Lisa Stockbridge, PharmD.	OCBQ/ DCM
Laurie Norwood, Ph.D., Division Deputy Director	OCBQ/ DMPQ
Maria Said, M.D.	OBE/ DE
Craig Zinderman, M.D.	OBE/ DE
David Martin, M.D.	OBE/ DE
Dale Horne, Dr.P.H.	OBE/ DB
Wei Hua, M.D.	OBE

B. CDER

Azada Hafiz

CDER/OSP

C. Eastern Research Group (ERG)

Christopher Sese, Independent Assessor

Marc Goldstein, Independent Assessor

D. Novartis Vaccines and Diagnostics, Inc.

Kelly Lindert – Head, Development

Neil Johnson – Group Leader, Regulatory Affairs - CMC and Compliance

Sylvie Tomczyk – Head, Global Pharmacovigilance

Brett Leav – Senior Cluster Physician

Esther Heijnen – Head of Clinical Development Programs, Adjuvanted Influenza Vaccines

Ethan Settembre – ad interim Head of Research

Mayuresh Gadre – Senior Specialist, Regulatory Affairs

II. BACKGROUND

On August 13, 2015, CBER and NVD agreed to hold the late-cycle meeting for STN 125510/0 on September 3, 2015. On August 21, 2015, CBER sent the Late Cycle Memo (see Appendix A) to NVD. The memo provided an overview of significant review issues identified to date. On September 2, 2015, CBER provided a Late Cycle Meeting agenda (see Appendix B) to NVD. The agenda also included items provided by NVD on September 1, 2015.

III. DISCUSSION SUMMARY

Discussion was limited to status updates of items provided in the agenda, and to topics requiring discussion to work toward resolution.

A. Nonclinical Studies

CBER discussed that they are currently reviewing the reproductive and developmental reproductive toxicity study (AB09779) submitted to the BLA on August 24, 2015 (125510/0/19). Questions may be forthcoming once the review is complete.

B. Facilities

CBER discussed that they are currently reviewing the information regarding the change of the bulk, fill and finished drug products release site from (b) (4) submitted to the BLA in the amendment dated September 2, 2015 (125510/0/20). CBER will notify NVD if any questions or concerns arise.

C. Product

CBER discussed that they expect NVD to update the BLA to include the Agriflu manufacturing changes submitted to STN 125197, when they are approved.

D. Sample testing

CBER indicated that the sample lots for testing were received, but that the labels were handwritten and difficult to read. CBER asked NVD to submit a detailed list of the sample lots and their respective batch records. NVD indicated that they would be able to submit the documents for the trivalent lots containing MF59 to the BLA by the end of September. The batch records for the monovalent lots and the detailed list of the samples provided could be sent in the next few days.

Regarding the changes in the manufacturing of the antigen as approved under STN 125297, NVD indicated that the Fluad lots received by CBER on September 3, 2015 were manufactured with some of the changes. NVD stated that they would provide CBER information on the process used for the lots provided for in-support testing.

E. Analytical procedures and validations

- i. NVD indicated that they will be able to submit SOP 278841 and SOP 102843 to the BLA by October.
- ii. CBER asked NVD to submit their tech transfer and their bridging data including the master transfer plan for the change of the release testing location from (b) (4) [REDACTED]. NVD indicated that they will submit this information to the BLA. CBER indicated that they may have additional comments after the information is submitted.
- iii. NVD confirmed that they can submit their repeated SRID study report by September 22.

F. Current assessment of the need for risk management actions

- i. NVD agreed to conduct the routine passive surveillance indicated by CBER.
- ii. NVD agreed to conduct the enhanced surveillance indicated by CBER.

G. New information requests to be communicated

- i. NVD's response to the IR from CBER dated August 5, 2015, was submitted in the Amendment dated September 2, 2015 (STN 125510/0.20). CBER noted that in NVD's response to the latex statement language comment, NVD indicated that they would not change the language as requested. CBER stated that to be consistent with what all other manufacturers are being required to state in their PIs if rubber latex is present, NVD will need to state "The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals."
- ii. NVD's response to the IR from CBER dated August 7, 2015, was submitted in the Amendment dated September 2, 2015 (STN 125510/0.20).
- iii. CBER indicated that they are still waiting for NVD to submit their responses to the clinical IR dated August 19, 2015. NVD stated that the response will be submitted the following week.

H. NVD Agenda Items

- i. CBER indicated that they would provide a list of AESIs; however, the MedDRA terminology for each of the AESIs will need to be handled by NVD as it is an internal business process.
- ii. CBER indicated that NVD will need to request a waiver for electronic submissions of ICSRs of adverse events for Fluad to the BLA.
- iii. NVD indicated that because methods have evolved an updated enhanced passive surveillance plan was included in the Amendment dated September 2, 2015 (STN

125510/0.20). This new plan may differ from what was included in the VRBPAC briefing documents.

I. General VRBPAC discussion

- i. NVD asked CBER if they had prepared their questions for the VRBPAC committee. CBER indicated that the questions were “standard” questions concerning the adequacy of the safety and immunogenicity data.
- ii. CBER advised NVD that they should be prepared to discuss the added benefit of including the MF59C.1 adjuvant in Fluad at the September 15, 2015, VRBPAC meeting. NVD should also be prepared to discuss their confirmatory trial design.

Meeting ended.

IV. ACTION ITEMS

- A. As indicated in the information request dated October 1, 2015, please submit the tech transfer and bridging data including the master transfer plan for the change of the release testing location from (b) (4) as an amendment to STN 125510.
- B. As indicated in the information request dated October 1, 2015, please submit the Agriflu manufacturing changes submitted to and approved under STN 125197 as an amendment to STN 125510. Please also indicate if the Fluad lots received by CBER on September 3, 2015, for in-support testing were manufactured with these changes.

V. APPENDICES

- A. Late Cycle Memo, sent to NVD on August 21, 2015 (begins page 6)
- B. Late Cycle Meeting Agenda, sent to NVD on September 2, 2015 (begins page 10)

APPENDIX 1 - Late Cycle Memo, sent to NVD on August 21, 2015



125510/0: Late Cycle Memo

To:	The File
Date:	August 21, 2015
Re:	Status of Review of STN 125510/0
Late Cycle Meeting Date:	September 3, 2015
Late Cycle Meeting Time:	2:30 pm – 4:00 pm (Eastern)
Call-in Details:	local# (b) (4) toll-free# (b) (4) ; Meeting ID (b) (4)
STN #:	125510/0
Submission Type:	BLA (Original Application)
Product:	Influenza Vaccine, Adjuvanted (Fluad)
Indication:	Fluad is indicated for use in persons 65 years of age and older for active immunization against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.
Applicant:	Novartis Vaccines and Diagnostics, Inc.
Meeting Chair:	Brenda Baldwin, Ph.D.

1. Current status of pending issues that will require resolution prior to Action Date:

A. Nonclinical Studies

Based on prior communications, CBER anticipates:

- a. Novartis to submit the reproductive and developmental reproductive toxicity study AB09779 to the BLA by August 28, 2015.

B. Facilities

Based on prior communications, CBER is expecting:

- a. An amendment to be submitted to the BLA regarding the change of the bulk, fill and finished drug products release site from (b) (4). CBER understands that all tests and manufacturing activities will remain the same.

C. Sample Testing and Lot Release

Based on prior communications, CBER expects:

- a. Novartis to send all samples for in-support testing to CBER by September 2, 2015. Please contact CBER prior to shipping the samples.

D. Analytical Procedures and Validations

- a. In amendment 16 (received on July 17, 2015) Novartis committed to update the following SOPs: SOP 278841 (Sodium Citrate (b) (4) – incorporation of an additional standard concentration); and SOP 102843 (Squalene ID and Content in Adjuvant (b) (4) incorporation of System Suitability criteria). These updated SOPs will need to be submitted to the BLA as soon as possible.
- b. To ensure that the SRID assay can accurately measure HA content in the presence of the adjuvant in the final drug product, Novartis has agreed in amendment 15 (received on July 13, 2015) to perform the study using the correct Drug Product matrix data and in amendment 18 (received August 18, 2015) to submit the report to the BLA by the end of September. CBER

requests that the repeated SRID study report be provided to the BLA no later than September 22, 2015.

2. Current assessment of the need for risk management actions:

The following actions are recommended for post-licensure safety surveillance activities:

A. Routine passive surveillance:

In order to support risk management strategies and to ensure compliance with regulatory reporting requirements, routine (standard) pharmacovigilance activities will need to be performed for Flud. We require that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). Some aspects of the routine pharmacovigilance activities include: 1) routine data collection on all adverse event reports and asymptomatic maladministration spontaneously reported or actively captured in post-marketing studies; 2) global literature review, timely reports (daily, PSURs, summary for licenses renewal); 3) production and distribution reports; 4) production of IND Safety Reports, signal detection, evaluation, and management; and 5) close monitoring of the following AEs: Bell's palsy, convulsion, demyelinating disorders, encephalitis, GBS, neuritis, vasculitis, vaccination failure, ITP, haemolytic anaemia, anaphylactic reactions, extensive limb swelling, death due to all causes, medication errors, and off-label use. These pharmacovigilance activities shall be conducted at different Novartis sites and countries where Flud is licensed.

B. Enhanced surveillance to provide reporting of all serious and non-serious autoimmune-mediated conditions as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS).

C. Active surveillance:

Novartis is proposing to conduct prospective active surveillance in both Canada and Italy, or different active surveillance approach(es) pending Novartis' response to CBER's IR dated August 7, 2015. We request that you work with CBER to develop pharmacovigilance activities tailored to the regulations and guidelines of the FDA.

3. Information requests sent and not received:

- A. IR dated August 5, 2015, regarding the request to update latex statement language in the labels
- B. IR dated August 7, 2015, regarding the request for a description of the alternative plans for safety surveillance
- C. IR dated August 19, 2015, regarding the imbalance seen in the number of deaths associated with Flud versus the non-adjuvanted influenza vaccines, and MF59 container questions

4. New information requests to be communicated:

No new information requests are pending as of August 21, 2015. However, additional information requests may be forthcoming as review continues.

5. Projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates:

- | | |
|---|--------------------|
| A. PerRC Meeting to discuss PSP: | September 30, 2015 |
| B. First Labeling Comments to Applicant: | October 26, 2015 |
| C. Identify any need for PMC/PMR (target date): | October 26, 2015 |

6. Status Update

We acknowledge your request for an exemption from the General Safety Test (GST) submitted November 25, 2014. However, the final rule for revocation of the GST became effective on August 3, 2015, therefore, you are not required to conduct the GST and it is not necessary to request an exemption.

7. Novartis Agenda Items

CBER asked Novartis to inform CBER by September 1, 2015, regarding items that Novartis would like to include in the agenda for the Late Cycle Meeting. This will ensure that CBER has the appropriate reviewers and supervisors in attendance at the meeting. A meeting agenda will be sent to Novartis on September 2, 2015. There will be an opportunity for discussion during the meeting if further topics for discussion arise.

APPENDIX 2 - Late Cycle Meeting Agenda, sent to NVD on September 2, 2015



125510/0: Late-Cycle Communication Agenda

Agenda Date:	September 2, 2015
Late Cycle Meeting Date:	September 3, 2015
Late Cycle Meeting Time:	2:30 pm – 4:00 pm
Call-in Details:	local# (b) (4) ; US toll-free# (b) (4) ; Netherland (b) (4) ; UK (b) (4) ; Meeting ID (b) (4)
STN #:	125510/0
Submission Type:	BLA (Original Application)
Product:	Influenza Vaccine, Adjuvanted (Fluad)
Indication:	Fluad is indicated for use in persons 65 years of age and older for active immunization against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.
Applicant:	Novartis Vaccines and Diagnostics, Inc.
Meeting Chair:	Brenda Baldwin, Ph.D.

I. Introduce Attendees from Novartis Vaccines and Diagnostics, Inc., CBER, and ERG Contractor

II. Issues requiring resolution prior to Action Date:

A. Nonclinical Studies

Novartis submitted the reproductive and developmental reproductive toxicity study AB09779 to the BLA on August 24, 2015 (125510/0/19). CBER is currently reviewing.

B. Facilities

CBER is expecting an amendment to be submitted to the BLA regarding the change of the bulk, fill and finished drug products release site from (b) (4). CBER understands that all tests and manufacturing activities will remain the same. CBER will determine the acceptability of this change following review of the submission.

C. Product

Based on prior communications, CBER expects Section 3.2 of STN 125510/0 to be updated with the changes to the manufacture of the antigen as approved under STN 125297 (Agriflu).

D. Sample Testing

- Novartis has sent the samples for in-support testing to CBER. CBER will notify Novartis if there are any further questions or comments.
- Please indicate if the changes in the manufacture of the antigen as approved under STN 125297 were used in producing the Fluad lots to be analyzed for in-support testing.

FDA -- For Official Use Only

E. Analytical Procedures and Validations

- a. In amendment 16 (received on July 17, 2015) Novartis committed to update the following SOPs: SOP 278841 (Sodium Citrate (b) (4) – incorporation of an additional standard concentration); and SOP 102843 (Squalene ID and Content in Adjuvant (b) (4) incorporation of System Suitability criteria). These updated SOPs will need to be submitted to the BLA as soon as possible.
- b. To ensure that the SRID assay can accurately measure HA content in the presence of the adjuvant in the final drug product, Novartis has agreed in amendment 15 (received on July 13, 2015) to perform the study using the correct Drug Product matrix data and in amendment 18 (received August 18, 2015) to submit the report to the BLA by the end of September. CBER requests that the repeated SRID study report be provided to the BLA no later than September 22, 2015.

F. Current Assessment of the need for risk management actions

The following actions are recommended for post-licensure safety surveillance activities:

- a. Routine passive surveillance: In order to support risk management strategies and to ensure compliance with regulatory reporting requirements, routine (standard) pharmacovigilance activities will need to be performed for Fluad. We require that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). Some aspects of the routine pharmacovigilance activities include: 1) routine data collection on all adverse event reports and asymptomatic maladministration spontaneously reported or actively captured in post-marketing studies; 2) global literature review, timely reports (daily, PSURs, summary for licenses renewal); 3) production and distribution reports; 4) production of IND Safety Reports, signal detection, evaluation, and management; and 5) close monitoring of the following AEs: Bell's palsy, convulsion, demyelinating disorders, encephalitis, GBS, neuritis, vasculitis, vaccination failure, ITP, haemolytic anaemia, anaphylactic reactions, extensive limb swelling, death due to all causes, medication errors, and off-label use. These pharmacovigilance activities shall be conducted at different Novartis sites and countries where Fluad is licensed.
- b. Enhanced surveillance to provide reporting of all serious and non-serious autoimmune-mediated conditions as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS).

G. Information Requests sent and not received

- a. IR dated August 5, 2015, regarding the request to update latex statement language in the labels
- b. IR dated August 7, 2015, regarding the request for a description of the alternative plans for active safety surveillance
- c. IR dated August 19, 2015, regarding the imbalance seen in the number of deaths associated with Fluad versus the non-adjuvanted influenza vaccines, and MF59 container questions

H. New information requests to be communicated

No new information requests are pending as of September 3, 2015. However, additional information requests may be forthcoming as review continues.

FDA -- For Official Use Only

III. Novartis Vaccines and Diagnostics, Inc. Agenda Items provided September 1, 2015

- A. Regarding Pharmacovigilance, Novartis has the following questions and concerns:
 - a. Will CBER provide the list of MedDRA accepted AESIs intended for use?
 - b. Does CBER accept regular automated MedDRA updates for preferred terms for the AESI list?
 - c. Novartis currently has a waiver (ref STNs: BL 125297/70; 103837/5267; (b) (4) as of June 3, 2015) for electronic submission of ICSRs of adverse events until June 10, 2016 for Agriflu (125297), Fluvirin (BLA 103837) and Flucelvax (BLA 125408); will Novartis be allowed to extend this waiver to Fludac?
 - d. Alignment on Pharmacovigilance post-marketing commitments.
- B. Regarding VRBPAC, does CBER intend to discuss the study design of the confirmatory efficacy study with the advisory committee members?

IV. Action Items