

# RECORD OF TELEPHONE CONVERSATION

## Submission Information

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

## Telecon Details

<b>Telecon Date/Time</b>	18-SEP-2015 03:02 PM
<b>Author</b>	GARNETT, THEODORE
<b>Outside Phone Number</b>	N/A – sent to the applicant by e-mail
<b>FDA Originated?</b>	Yes
<b>Communication Categories</b>	IR - Information Request
<b>Related STNs</b>	None
<b>Related PMCs</b>	None
<b>Telecon Summary</b>	Questions regarding the Risk Management Plan, PSUR, lot release protocol and squalene identity and content
<b>FDA Participants</b>	LCDR Theodore Garnett
<b>Applicant Participants</b>	Mayuresh Gadre

### Telecon Body:

**From:** Garnett, Theodore

**Sent:** Friday, September 18, 2015 3:02 PM

**To:** 'GADRE, MAYURESH'

**Subject:** STN 125510/0 (FLUAD): Request for information

Dear Mayuresh,

Please find attached a new request for information from CBER. Please respond by September 25th, if possible.

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Best regards,

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

Silver Spring, MD 20993

Office: 301-796-2640

Cell: (b) (6)

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993-0002

DATE: September 18, 2015

TO: Mayuresh Gadre, M.S.

FROM: LCDR Theodore Garnett, Ph.D.  
CBER/OVRR/DVRPA

SUBJECT: BLA 125510/0

PRODUCT: FLUAD

SPONSOR: Novartis Vaccines and Diagnostics

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We are reviewing your biologics license application (BLA) dated November 25, 2014, for Influenza Vaccine, Adjuvanted and have the following additional comments and requests:

1. Regarding Pharmacovigilance:

- a. The new Risk Management Plan (version 3.0) should function as a stand-alone document. The Risk Management Plan (version 3.0) contains a paragraph on page 69 of the document about the support of an “investigator initiated” active surveillance study in the Lazio region in Italy. There is more information about this study included in the previous Risk Management Plan (version 2.0). Please include in version 3.0 the information provided in version 2.0 concerning this active surveillance study so that version 3.0 can function as a stand-alone document.
- b. The Risk Management Plan (version 2.0) on pages 63-64 discusses active surveillance that would occur through the Public Health Agency/Canadian Institutes of Health Research Influenza Research Network (PCIRN). This activity is no longer included in the Risk Management Plan (version 3.0). Please clarify what has happened/will happen with this activity.
- c. In PSUR 37, section 9.1.1.2.6, you report on AEs of Special Interest and AEs Following Immunization. In subsequent PSURs, we would like to continue to receive data on these same AEs.

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- d. In PSUR 37, section 8, you write, “As additional routine pharmacovigilance activity in the EU RMP, for the purpose of fulfilling the requirements of the ‘Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU,’ a report was submitted from ongoing safety surveillance for influenza vaccines in Canada (PCIRN) during the reporting interval. In addition, Novartis also supported a third party active surveillance study in Italy (V70\_58OBTP). A summary of the results of V70\_58OBTP and the PCIRN report can be found in EU Regional Appendix 2 – ‘Proposed additional pharmacovigilance and risk minimization activities.’ Planned activities on Enhanced Passive Safety Surveillance for the next season to fulfill the requirements of the interim guidance are also described in EU Regional Appendix 2 - ‘Proposed additional pharmacovigilance and risk minimization activities’.”

We were able to find the “PCIRN Canadian National Vaccine Safety (CANVAS) Network 2014 Seasonal Influenza Safety Surveillance: Final Report”; “Project Svevaplus: Evaluation of the Events Found after the Seasonal Flu Vaccination in Italy, in the Year 2014/2015”; and the planned activities on Enhanced Passive Safety Surveillance as described in the Risk Management Plan (version 3.0). However, we could not locate “EU Regional Appendix 2- ‘Proposed additional pharmacovigilance and risk minimization activities’” and would like to make sure we are not missing any additional information. Please submit this information or indicate where in the PSUR it can be found.

2. Regarding the Lot Release Protocol (LRP) and specifications table: In amendment 5, section 1.1.11: Quality Information amendment – IR 10, page 21, you state that formaldehyde testing at the (b) (4) stage could be impacted by the presence of the adjuvant MF59C.1. As such, you proposed to remove formaldehyde testing from the Flud (b) (4) Release test panel. An updated specifications table and LRP template was received on August 18th (amendment 18, section 3.2.P.5.1); however, both of these documents still show formaldehyde testing as part of the (b) (4) test panel. Please confirm whether this test will be performed at this stage. If not, please remove this test from the specifications table and the LRP template.
3. Regarding Squalene Identity and Content by (b) (4)
  - a. For the Adjuvant (b) (4) we have the following questions/comments regarding the Method validation report, Document 268445-01 and response to CBER IR dated 17 July 2015:
    - i. In your response to FDA question #11d, you have demonstrated accuracy in the range of (b) (4) by the analysis of (b) (4) MF59C.1 samples. Please explain how this range translates to a range of (b) (4) neat adjuvant samples (1.11.1 Information Amendment Page 11).

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- ii. Please provide linear regression plots of analyte (squalene) concentration vs. response (peak area) for your final container samples and squalene standard used to obtain the data described in section 4.6 of your validation report. Please also submit data for linearity fit ( $R$  or  $R^2$ ), slope and distribution of residuals based on concentration vs. response.
- b. For the Final filled vaccine we have the following questions/comments regarding the Method validation report, Document 2933539-02 (ISU 07.014 VR 3 Rev. 7):
  - i. Please provide the linear regression plots of analyte (squalene) concentration vs. response (peak area) for the squalene standard and your final container FLUAD samples used to obtain the validation data described in Tables 9 and 10 of your validation report. Please also submit data for linearity fit ( $R$  or  $R^2$ ), slope and distribution of residuals based on concentration vs. response.
4. Regarding the concentrations of the buffers in the final drug product, it appears that the final concentrations of the components in (b) (4)

Please explain why you are using this calculation approach.

Please submit the requested information as an amendment to the BLA by September 25, 2015, if possible. We recommend that you restate each item and follow it with your response. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference.

If you have any questions, please contact the Regulatory Project Manager, LCDR Theodore Garnett, Ph.D., at (301) 796-2640.