

## RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125510/0 Office: OVRR

Product:

Influenza Vaccine, Adjuvanted

Applicant:

Novartis Vaccines and Diagnostics, Inc.

Telecon Date/Time: 15-May-2015 4:31 PM Initiated by FDA? Yes

Telephone Number: N/A – E-mail communication

Communication Category(ies):

1. Information Request

Author: Theodore Garnett

Telecon Summary:

CBER comments regarding facilities and equipment, lot release protocol template, CMC, pharmacovigilance and clinical issues

FDA Participants: Theodore Garnett

Non-FDA Participants: Mayuresh Gadre

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

**From:** Garnett, Theodore

**Sent:** Friday, May 15, 2015 4:31 PM

**To:** 'GADRE, MAYURESH'

**Subject:** STN 125510/0 (FLUAD 65): Request for information

**Importance:** High

Dear Mayuresh,

Please find attached a new request for information from CBER. Feel free to contact me if you have any questions or concerns.

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: May 15, 2015

TO: Mayuresh Gadre, M.S.

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

SUBJECT: BLA 125510/0

PRODUCT: FLUAD 65

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 determined that the following additional information is necessary. Please promptly submit your written response to the following items so that we may continue evaluating your BLA:

**Clinical:**

1. We note in table 14.3.1.2 (section 5.3.5.1 V70\_27 study report body) that 314 systemic adverse events (AEs) and 10 other AEs were experienced within 30 minutes of vaccination. Please provide a table with the absolute number and percentage of subjects within each category (e.g., nature and severity by grade) as was done for local AEs in table 14.3.1.2.16 of section 5.3.5.1 V70\_27 study report body.
2. In the tables submitted on May 5, 2015 (section 1.11.3) with the updated HAI titers, the percent seroconversion rate differences do not equal the difference between the values indicated for each cohort (Tables 14.2.1.2.4, 14.2.1.2.7, 14.2.1.3.7, 14.2.1.4.4, 14.2.1.4.5, 14.2.1.4.7). Please explain the cause of these discrepancies and/or send revised tables with corrected values. Additionally, please verify that all other tables contained in this submission do not contain similar discrepancies.

**Pharmacovigilance:**

3. In 2012, FLUAD and Agriflu were temporarily suspended in Italy, France, Switzerland and Canada due to (b) (4) observed in one batch produced in (b) (4). Please submit the investigation reports (in English) by Novartis and EMA, and the date the suspension was lifted from each country.
4. On November 27, 2014, Agenzia Italiana del Farmaco (AIFA) suspended the use of two FLUAD lots (lots 143301 and 142701) as a precautionary measure due to serious adverse

events and deaths observed in a short period of time. Please submit Novartis' investigation report and adverse event reports in English.

5. Regarding the Risk Management Plan (version 2.0) located in module 1.16:
  - a. On pages 63-64, section 10.1.1 "Additional routine pharmacovigilance activities," you proposed to work with the Public Health Agency/Canadian Institutes of Health Research Influenza Research Network (PCIRN) to generate a safety surveillance report specific to FLUAD for the 2014-15 season. You anticipated issuing the report in early to mid-November 2014. You also stated that "Novartis has a multiyear tender in place for FLUAD in Canada, including the 2014-15 season."
    - i. Please submit PCIRN's 2014-15 season report(s) specific to FLUAD.
    - ii. Please provide a detailed description of the PCIRN surveillance system, if not already included in the report, including, but not limited to design, data collection, applied methods, and analysis.
    - iii. Please provide an update on the plan of using PCIRN surveillance system for FLUAD enhanced surveillance in the post 2014-15 seasons.
  - b. On page 65, you proposed to implement an active surveillance in the Lazio region in Italy during the 2014-15 season. The study would prospectively follow-up vaccine recipients for adverse events following vaccination. Please submit the study protocol and provide an update on the status of the study.

**CMC:**

6. We have the following questions/comments regarding the MF59C.1 adjuvant:
  - a. Reference Standards and Materials: (b) (4) content (3.2.S.5): You state that "New batches of MF59C.1 reference standard are prepared per SOP 102845. The (b) (4) (b) (4) must be in the average working range of the method. If a batch with these characteristics is not available, the control batch can be (b) (4) by adding certified and approved (b) (4) standard to achieve the appropriate average working range. If required, (b) (4) standards can be (b) (4)" Please provide an example of data where the control batch of MF59C.1 was (b) (4) standard to achieve MF59C.1 reference standard with desired concentration of (b) (4) .
  - b. Master Formula for (b) (4) FLUAD (Table 3.2.P.3.2-1) needs revision as it has inaccurate information on the content of (b) (4) and MF59C.1 bulk adjuvant. Please correct.
  - c. Justification of Specifications (3.2.P.5.6): You make a statement that "The amount of squalene, MF59C.1, added to the DP formulation varies depending on the number of factors described in Batch Formula calculation (3.2.P.3.2). Due to this variation in the amount of MF59C.1 added in the formulation process, the squalene content varies from lot to lot." According to the description of Batch Formula in 3.2.P.3.2, MF59C.1 is added at (b) (4) of the final volume of the DP batch with constant quantity of squalene per liter (b) (4) . Please clarify what factors during Batch Formula calculation affect the squalene content and how the specification for squalene strength of (b) (4) (Table 3.2.P.5.1-2) was derived.
  - d. Reference Standards or Materials (3.2.P.6): Please provide information on the source and the methods to determine expiration date of the squalene standard used for analytical

testing for squalene identity and content in Formulated Vaccine (b) (4) Filled Vaccine Product.

7. Please clarify if there are differences in the procedure for influenza viral inactivation between the Drug Substance and Drug Product, and provide the SOP for each.
8. We have the following questions in reference to validation of the SRID method as applied to the FLUAD drug product:
  - a. Regarding Validation Report No. ISU 07.007 VR 15 Rev. 2 (Attachment 39 (b) (4) Val Report): The data for each parameter are summarized in Tables 4-11. Each data point in these tables is designated as Test 1, 2 and 3. Please clarify if each data point is generated from a (b) (4)   
Please confirm if the various validation parameters have been evaluated for “reportable results (i.e., a reportable result for Trivalent is (b) (4) independent tests).
  - b. In reference to accuracy results described in a) Validation Report No. ISU 07.007 VR 15 Rev. 2 (Attachment 39 (b) (4) Val Report) and b) the Interim Analytical Method Transfer Report (attachment (b) (4) Transfer report) we have the following question: To evaluate accuracy of the method, (b) (4)   
  
This implies that (b) (4) recovery was evaluated in presence of half the concentration of adjuvant. Please comment.
9. We have the following questions/comments regarding the Total Protein (other than HA) (b) (4) Validation Report for the (b) (4), Document CQS 07.71 QR 6 Rev.0:
  - a. You have not studied linearity for this assay. Please provide data to show linearity based on the analysis of representative (b) (4) samples (b) (4). To demonstrate linearity, we require that you provide at least (b) (4) data points between the intended lower range and the highest concentration relevant to the specification limit of (b) (4).
  - b. As per the data presented in Table 4.0, you have studied the accuracy of (b) (4) samples at one concentration level (b) (4) of the nominal value). Please provide the results of accuracy of the method using (b) (4) samples over the intended range of the assay.
  - c. Please establish the range of the assay based on the linearity/accuracy (as requested above) and precision data obtained from your (b) (4) samples.
10. Please address the following questions regarding your determination of (b) (4) in the MPH Drug Substance by (b) (4) analytical procedure:
  - a. Section 4.3 of your SOP 202706-05 (ISU 07.009) instructs to dilute the samples. However, in your validation report, you have reported that the concentration of (b) (4) in samples is below the specified range of the standard curve. Please revise your SOP to include appropriate sample preparation method so that the (b) (4) concentrations in samples are within the range of the standard curve and data reporting of vaccine samples.

- b. In the Method validation report, Document ISU 07.009 VR 3 Rev.2: Please provide robustness study data obtained using representative drug substance samples, which address the effect of deliberate variations of critical method parameters.
  - c. In the Method transfer/ Comparability Report, Document AVR/0023/10: Section 2.3 states the assay results as (b) (4). However, the LOQ value in your validation report is (b) (4). Please provide an explanation or change your reported results to make it consistent with your validation report.
11. We have the following questions/comments regarding your Adjuvant (b) (4) Squalene Identity and Content by (b) (4) analytical procedure:
- a. In SOP 102843, the squalene calibration standards are prepared in the range of (b) (4). Please provide the details of analysis procedure and calculations used to obtain the squalene concentrations of (b) (4) as presented in the calibration curves in this submission (attachments 1.01, 1.03, 1.07 and 1.09).
  - b. Your SOP 102843 does not include system suitability criteria for (b) (4). Please revise this procedure to include specifications for (b) (4) system suitability.
  - c. Your SOP 102843 includes retention time as an assessed parameter (under Measurement and Evaluation). Please specify the calibration standard evaluated to establish the identity of squalene peak in adjuvant samples.
  - d. We could not understand the Accuracy data presented in section 4.2 and attachment 1.08 of your Method validation report, Document 268445-01. Please explain (1) the initial squalene concentration of MF59C.1 adjuvant samples and provide the units for squalene amount/level, (2) how much squalene is added to the (b) (4) samples to obtain fortified samples, (3) the measured squalene concentration and recovery at each concentration level, (4) the range covered in the accuracy studies.
  - e. In your Method validation report, Document 268445-01 you have demonstrated linearity of squalene standards in the range of (b) (4) and MF59C.1 adjuvant samples in the range of approx. (b) (4). Please provide the details of the preparation of adjuvant samples to show that the dilutions are within the calibrated range. Please re-evaluate your assay range for MF59C.1 samples based on the accuracy data as requested above, and accordingly modify your validation report.
  - f. According to your assay procedure in your Method validation report, Document 268445-01, the MF59C.1 adjuvant samples and control are prepared at a concentration of approx. (b) (4). Please explain how you have evaluated the (b) (4) squalene concentration of approx. (b) (4) in adjuvant samples in section 4.3 (precision) of your validation report.
12. Regarding your Final Filled Drug Product, Squalene Identity and Content by (b) (4)
- a. Please submit SOP 306198 “Squalene Identity and Content by (b) (4)” Please ensure that this includes the specific make of the (b) (4)
  - b. In the Method validation report, Document 2933539-02 (ISU 07.014 VR 3 Rev. 7): Please provide details of preparation of final container FLUAD samples for Accuracy and Linearity studies to show that these validation characteristics were appropriately assessed in the drug product matrix.

13. Please provide information on the 2015-2016 strain change to support the adjuvanted trivalent final bulk samples of FLUAD that represent lots for release of which you will be providing in the near future.

**Lot Release Protocol template (Section 3.2.P.5.1)**

14. Regarding the Lot Release Protocol template:
- Page 1: Please make sure that the template summary (and all other portions of the lot release protocol) is provided in English.
  - Pages 7, 11 and 15: the specification for the (b) (4) endotoxin test is shown as (b) (4), but should be (b) (4) HA. Please correct.
  - Pages 6, 10 and 14 (Potency test of (b) (4), 'Acceptance Criteria': P value (b) (4): Per SOP document 278991 (V5) and the (b) (4) method specification, this acceptance criteria should be "t-value (b) (4) Please correct.
  - Page 18: Under 'Acceptance Criteria': P value (b) (4) should read t-value (b) (4). Please correct.
  - Please include at the top of each page a header showing the strain and lot details. For example, pages 5 to 8 show the results for A(H1N1) Monovalent Pooled Harvest, but the header is only shown on page 5. Pages 17-22 show results for trivalent bulk, but the 'trivalent bulk lot' header is only provided on page 17.

**Facilities and Equipment (3.2.A):**

15. Novartis (b) (4) Drug Substance facility
- Please list any changes (changes that are not already approved or still currently under review) made to the facility, equipment, cleaning, disinfection, sanitization or sterilization process for introduction of the FLUAD vaccine (US market) into the already approved (b) (4) facility for seasonal and pandemic flu vaccine.
  - Regarding Shipping Validation:
    - Please provide the shipping validation protocol and summary report for the Seed virus shipped (b) (4) between NVD (b) (4) and NVD (b) (4)
    - Please provide the shipping validation protocol and report for the shipping of (b) (4) [136] from NVD (b) (4) to NVD (b) (4)
  - Regarding equipment cleaning validation (product contact equipment):
    - Please provide the rationale for your acceptance criteria used during the cleaning validation.
    - Please describe the worst-case sampling locations tested during validation. Also provide the frequency/acceptance of routine monitoring after cleaning.
    - Please explain the adequacy of your current cleaning procedure to remove FLUAD product residue.
  - Please provide summary data for the environmental monitoring performed during manufacturing of conformance lot(s).
16. Novartis (b) (4) Drug Product facility
- Regarding your visual inspection process (automated visual inspection using (b) (4) please address the following:

- i. The BLA states that Inspection Machine (b) (4) has the capability to check the following parameters: (b) (4).  
However, the following exceptions for the FLUAD product are noted in the BLA:
- Presence of particle into the product (not for FLUAD)
  - Presence and correct positioning of the plunger (not for FLUAD)
  - (b) (4) check (not for FLUAD)
- In addition, we noted the following statement in your BLA: FLUAD product falls into the category of opalescent product. The (b) (4) check (b) (4) is not used for the product FLUAD, as the product's physical composition is a white dispersion and does not allow the analytical ray of light to pass through it. For the same reason, the examination and verification of particles within the product cannot be carried out for the product FLUAD. Please describe how you plan to detect particulates using a visual inspection process (need supporting validation data for detection of particulate in FLUAD and routine procedure used during conformation lots).
- ii. The Validation Results of your last activities (42/059/(b) (4) /RPQR/03) does not include any test for particulate defect. Please justify.
- iii. Regarding the concurrent validation (42/059/(b) (4) /PQR/02), the BLA states that the FLUAD product falls into the category of opalescent product, so the PQ concurrent Report reference is the one executed using the product opalescent Anatetall. Please provide justification for using the (b) (4) product PQ data and how these data are applicable for the FLUAD product.
- iv. Please provide the validation protocol and summary report for the following qualification studies performed using the (b) (4) for opalescent product.
- | Re-PQ Reports          | Qualification Description              |
|------------------------|--|
| 42/059/(b) (4) /PQR/00 | 1 <sup>st</sup> Prospective Validation |
| 42/059/(b) (4) /PQR/02 | 1 <sup>st</sup> Concurrent Validation  |
- v. We have the following additional questions regarding visual inspection revalidation (42/059/(b) (4) /RPQR/03) :
- 1) Please provide a description of the method used to compare the manual to the automated process.
  - 2) How does the automated inspection system performance compare to manual inspection when inspecting particle.
  - 3) Please provide a list of all FLUAD lots inspected on the automated inspection machine and their summary results.
  - 4) Please provide verification that the challenge sets are evaluated post run.
  - 5) Were any deviations reported during qualification? If so, please submit a summary of the reports including a brief event description, resolution, and evaluation of impact to qualification.
  - 6) During validation, what was the sampling scheme (AQL) used for the statistical sampling performed post inspection of accepted material of the production lots?
  - 7) Have you established an upper control limit for reject rate for each defect?



- b. Regarding the container closure integrity test for final container:
    - i. Please specify the (b) (4) test method sensitivity to demonstrate container closure integrity.
    - ii. The BLA states that a study has been completed to evaluate the feasibility of introducing holes less than (b) (4). In these studies it (b) (4). Please provide the study protocol and results.
    - iii. Furthermore, the BLA states that Novartis intends to investigate a nondestructive (b) (4) test in house. A new improved method will be selected, validated and implemented when sufficient data has been accumulated. Please provide the study protocol and current status on the method validation.
  - c. Regarding equipment cleaning validation: Please provide the cleaning validation protocol and summary reports for the equipment cleaning validation described in the BLA (e.g., information not provided for sampling locations, study date, worst case location, worst case soil tests, list of deviations and resolutions....)
  - d. Regarding the media simulation study: Please provide the most recent (routine (b) (4) media fill protocol and reports for the MF59C.1 (b) (4)
  - e. Please provide the environmental data summary including lists of all deviations and resolutions for the environmental monitoring conducted during conformance lots.
17. Novartis (b) (4) adjuvant facility
- a. Regarding (b) (4) – EM program: Please provide a written procedure that addresses frequency of sampling, sampling locations, alert and action limit, specific equipment and techniques, and response to deviations from alert and action level.
  - b. Regarding Equipment (product contact /shared) cleaning validation – (b) (4) Please provide the cleaning and sanitization validation protocol and reports (most recent) including acceptance criteria, summary report and list of all deviations and corrective actions.
  - c. Please provide a (b) (4) performance qualification protocol and summary report.

### **Labels and Promotional Materials:**

#### **18. Container Label:**

- a. The detachable portion of the label will need to have NDC, Proprietary Name, Lot and Expiry.
- b. The complete NDC will need to be placed under the linear barcode.
- c. Rx Only will need to be placed on the label.

#### **19. Carton Labels:**

- a. The labels will need the correct and complete seasonal strains.
- b. The complete NDC will need to be placed under the linear barcode.
- c. The 65+ appears too prominent. It should not be more prominent than both the proper name and trade name.
- d. It appears to be 2D barcodes on two different flaps on the carton labels however, you did not mention placing 2D barcodes on the flaps of the carton labels in the cover letter nor

have you submitted any documentation for the (b) (4) of these 2D barcodes on the label.

20. Please provide any draft promotional material you intend to distribute to consumers if this product is licensed. Please also submit the references to support your claims.

Please submit your response in a timely manner or submit a partial response, so we may continue the review of your application. If we determine that your response to this information request constitutes a major amendment which will extend the review period an additional three months, we will notify you in writing.

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