



MEMORANDUM

Date: October 1, 2015

To: STN 125510/0

From: Manju Joshi,
Division of Biological Standards and Quality Control (DBSQC),
Office of Compliance and Biologics Quality (OCBQ)

Through: William McCormick,
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Subject: STN 125510: Biologics License Application (BLA) for FLUAD, Adjuvanted, Formaldehyde Inactivated, Trivalent Seasonal Subunit Influenza Vaccine Novartis Vaccines and Diagnostics, Inc. (Novartis Vaccines): Review of Analytical Methods (for Haemagglutinin Content (b) (4) and Ovalbumin Content)

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Novartis Vaccines and Diagnostics, Inc. (Novartis Vaccines/NVD) submitted a BLA (STN 125510/0) on 25 November 2014 requesting approval of the FLUAD, an adjuvanted inactivated subunit influenza vaccine for use in persons 65 years of age and older. FLUAD is manufactured at Novartis Vaccines and Diagnostics (b) (4), located in (b) (4)

FLUAD is an Influenza Vaccine (Surface Antigen, Inactivated) which contains predominantly haemagglutinin (HA) and neuraminidase (NA) antigens from the three Seasonal influenza strains (recommended annually by regional health authorities) and MF59C.1 adjuvant (an oil-in-water emulsion, composed of squalene as the oil phase, stabilized with the surfactants polysorbate 80 and sorbitan trioleate, in a citrate buffer). Individual influenza strains are propagated in the allantoic fluid of embryonated chicken eggs, are inactivated; split; and purified to produce the monovalent bulk (Drug Substance, DS). The three monovalent bulks are then combined along with MF59C.1 adjuvant to produce the trivalent final Drug Product (DP). The antigens are suspended in a sterile, buffered aqueous solution for injection. The potency of the vaccine is expressed as the concentration of the HA proteins from each virus strain. The vaccine is formulated to

contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA each of Influenza Type A (H1N1), Influenza Type A (H3N2) and Influenza Type B, to be administered intramuscularly. The vaccine is presented as a 0.5 ml single dose sterile suspension for injection in a milky-white emulsion, contained in a glass pre-filled syringe.

The basic manufacturing platform for FLUAD is very similar to that of Agriflu approved in the US on the 27 Nov 2009 (BLA#125297). The FLUAD drug substances (DS) process is shared in its entirety with that of Agriflu which provides the antigens for FLUAD drug product (DP) formulation process. The DS for FLUAD to be supplied to US, is manufactured in (b) (4) while the formulation is performed at Novartis Vaccines and Diagnostics in (b) (4)

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test methods. These review activities support DBSQC's lot-release mission, which includes confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed/approved test methods and product specifications. This review memo covers the reviews of the analytical procedures and the associated validation reports for i) Single radial Immuno-diffusion assay (SRID) for determination of Haemagglutinin Content (b) (4) and ii) (b) (4) for determination of Ovalbumin content in (b) (4) Drug Product (DP)

SUBMISSIONS REVIEWED:

sBLA STN 103914/5733.0 Sections reviewed:

Section 2.3 - Quality Overall Summary

Section 2.3.S.4 - Control of Drug Substance (NVD (b) (4))

Section 3.2.S- MPH NVD (b) (4) and MPH NVD (b) (4)

Section 3.2.S.4.2 - Analytical Procedures-

- HA (SRID)
- Ovalbumin

Section 3.2.S.4.3 - Validation of Analytical Procedures

- Haemagglutinin Content (b) (4) [SRID]
- Ovalbumin

Section 3.2.P.1 - Description and Composition of the Drug Product

Section 3.2.P.5 - Control of Drug Product

Section 3.2.P.5.2 - Analytical Procedures

- Hemagglutinin (b) (4) Content (SRID)
- Ovalbumin

Section 3.2.P.5.3 - Validation of Analytical Procedures

- Introduction
- SRID
- Ovalbumin

RECOMMENDED ACTION:

Based on the review of analytical methods (SRID and Ovalbumin (b) (4) covered in this review memo, DBSQC reviewer recommends approval of this supplement. The sponsor should be advised to communicate with CBER at the start of each flu season for selecting reagents for potency (b) (4) testing of the product.

REVIEW:

SINGLE RADIAL IMMUNODIFFUSION (SRID) METHOD (POTENCY ASSAY)

Background:

The Single Radial Immunodiffusion (SRID) method is used to determine the haemagglutinin (HA) content in the inactivated influenza vaccines using specific anti-HA antibodies and reference HA antigens authorized by the regulatory agencies. The SRID assay is based on a precipitation reaction between HA antigens and anti-HA specific antibodies. Both sample and reference antigen are treated with a zwitterionic detergent (to disrupt the virus); are appropriately diluted and loaded into the wells in an agarose gel containing HA specific antibodies. The gels are incubated in a moist chamber at room temperature to facilitate diffusion of the antigen. Reaction of the antigen with the antibody results in formation of immuno-precipitation zone (*i.e.* precipitin ring). Following incubation, washing, drying, and staining the gels, the precipitin ring is visualized and can be measured. The size of the immuno-precipitin zone (ring diameter) is proportional to the amount of HA applied in the well. By using a reference antigen of known concentration, a standard curve is generated from SRID ring sizes against concentration of HA antigen in the reference antigen. The HA quantitation is performed by comparing the ring diameters of samples with the diameters of known concentrations of the reference antigen.

As per the information provided by Sponsor the SRID related documents that are new to FLUAD BLA (*i.e.* were not provided to the agency as a part of approved BLA for Agriflu, STN 125297) are reviewed in this memo.

Validation Related Documents Reviewed:

1) Doc. No. 267633 Ver .3: SOP-Single Radial Immunodiffusion (SRID) Assay for Agrippal Platform Production Samples

- 2) Doc. No. 278991 Ver .5: Procedure for the Use of the SRID Reader System for Agrippal Platform Samples
- 3) Doc. No. ISU 07.007 VR 15 Rev.2: Validation Report of the SRID method, applied to FLUAD product, phases of (b) (4), Filled Product and Packaged Product with MF59 and (b) (4), for the US market.
- 4) Doc. No. ISU 07.007 VP 15 Rev. 0 (Translated): Validation Protocol of SRID method, applied to the phases: trivalent (b) (4) and anti-influenza vaccine filled product with MF59, (b) (4), for US.
- 5) Doc. No. R/0400/09/13 Rev. 01: Interim Analytical Method Transfer Report-Interim report for the Analytical Method Transfer of SRID testing for (b) (4) and filled samples, from the (b) (4) Site to the (b) (4) Site, Novartis Vaccine and Diagnostics.
- 6) Translation of Reagents and Standards Flu Tables for SRID test (SOP 201727 - ISU 07.007)
- 7) Doc. No. ISU 07.07 VR 2 Rev. 0: Validation Report for the determination of the Haemagglutinin content in the Influenza (b) (4), whole influenza virus product (b) (4) and final influenza vaccine Agrippal S1 and FLUAD (b) (4) with (b) (4) traces by (b) (4) test.
- 8) Doc. No. AVR/0023/15 Rev. 01: Assay Validation Report to provide additional Accuracy data for Single Radial Immunodiffusion test (SRID) for US products at the (b) (4) site, Novartis Vaccines.

SRID Review Summary:

Novartis uses a SRID assay as a release test to determine (b) (4) HA content in for the (b) (4) and the Drug Product (DP). In addition SRID assay is also used as an in process control test to determine HA content (b) (4) at (b) (4) step of manufacturing.

Validation of SRID Method Using (b) (4)

Hemagglutinin content (b) (4) is determined by SRID method. The method was originally validated in (b) (4) according to a pre-approved protocol (Doc. No. ISU 07.007 VP 15 Rev. 0) for the following parameters:

- Precision (Repeatability and Intermediate Precision);
- Accuracy;
- Linearity;
- Specificity (Identity);
- Range

The results of this validation study are described in the validation report (Doc. No. ISU 07.007 VR 15 Rev.2). With the exception of repeatability and linearity where only (b) (4) batch was used, for evaluation of other validation parameters (b) (4) batches of trivalent (b) (4) with MF59 containing following strains: A/California/7/2009 (X-181) (H1N1); A/Victoria/210/2009 (NYMC X-187) (H3N2) and B/Brisbane/60/2008 were used. All the validation parameters met the pre-defined acceptance criteria. The linearity was demonstrated by performing (b) (4) standard curves at (b) (4) different concentrations of sample, for each of three strains. The range for the SRID method was found to be between (b) (4) HA/mL for all the three strains evaluated and was established based on the concentrations that fall on the linear portion of the curve and meet acceptance criteria for accuracy, precision, and linearity and was. The specificity of antiserum to form precipitin rings with corresponding homologous antigen was used to establish the suitability of SRID assay as an HA (b) (4) test. Considering that the matrix of the trivalent (b) (4) sample with MF59 is equivalent to the matrix of the correspondent filled product sponsor has concluded that validation can be also extended to the filled product.

Transfer of SRID Method from (b) (4) site and Validation of Method:
SRID assay was transferred from (b) (4) site following a pre-approved protocol. (b) (4) site studies were performed and statistical analysis by the Two One Sided t-Test (TOST) was used to demonstrate that the method when performed in (b) (4) was equivalent to the method performed in (b) (4), using reagents, equipment and analysts from the relative sites. In addition to assess if the performance of the method in (b) (4) in line with the validation performed in (b) (4), method verification was performed using a (b) (4) filled product. The parameters of Accuracy, Linearity and Precision (Intermediate Precision) were evaluated. Samples containing (b) (4) strains were used in these studies. The results of this transfer study are provided in an analytical method transfer report (Doc. No. R/0400/09/13 Rev. 01)

As explained in the report, during TOST analysis the combined results from the (b) (4) (b) (4) did not meet the requirements of TOST analysis for the (b) (4) strain (i.e. the two sample populations were not shown to be practically equivalent). For the other (b) (4) strains the required criteria were met and the testing in (b) (4) was shown to be practically equivalent. An investigation was performed to rule out potential root cause for this discrepancy and 4 potential root causes were identified. These included: Difference in zone analysis; Zwittergent contact time; Sample Potency/Stability and Sample shipment affecting potency/stability. Since with the available data a root cause of this difference could not be determined, an investigative testing was performed to determine if the results observed with H1N1 strain represent a true difference in method when performed at two sites. A retest plan was designed to examine if any of the four potential root causes identified could be attributed as the main cause for these differences. The aim of this retesting was to determine if the initial results were in fact a true representation of an issue with the performance of the method. The testing involved each site testing one batch of H1N1, a total of (b) (4) times

using (b) (4) analysts over (b) (4) days. Where possible all critical time parameters were aligned. Testing was performed on neat sample to avoid any additional analyst manipulations. The results of this testing showed that there is no significant difference in the test results obtained by two sites.

The results of method verification studies showed that the parameters of Linearity, accuracy and precision met the pre-defined acceptance criteria. Based on the results of this method transfer study Sponsor had concluded that the SRID method for testing adjuvanted (b) (4) and filled samples for release to the US market (by the (b) (4) association method) has been successfully transferred to the (b) (4) site.

After review of SRID validation reports it was concluded that the study design for evaluation of the accuracy of the method was not appropriate. The samples prepared to demonstrate the accuracy of the method contained only (b) (4) the concentration of adjuvant and were not true representation of adjuvanted drug product. An information request (see SRID IR#4 below for details) was sent. In response to CBER information Novartis has performed a repeat study for the accuracy parameter of the SRID assay validation using the adjuvant at the concentration found in the final product. The results of this additional study are summarized in an assay validation report (Doc. No. AVR/0023/15). The accuracy of the assay was evaluated using a trivalent formulation containing the three strains for 2014-2015 Influenza season (*i.e.* A/California/07/2009 X-181 (H1N1); A/Texas/50/2012 X223 and B/Massachusetts/02/2012). The spike recoveries for all the 3 strains were evaluated at (b) (4) different concentrations and were found to be within the range of (b) (4), and met the pre-defined acceptance criteria. The data generated in this repeat study were also consistent with accuracy data previously generated and reported in method transfer report (Doc No. R/0400/09/13). Results of this study demonstrated that presence of MF59 adjuvant has no effect on the accuracy of SRID method to determine the HA content in the formulated product.

Information Requests regarding SRID assay:

During the review of SRID assay, additional documents and clarification about submitted data was needed. Following Information requests (IR) were sent:

For each IR, CBER's questions to sponsor (in bold), Sponsor's response (italicized) and CBER comment to these responses (in bold italicized) are listed below:

SRID IR #1

SRID assay related IR was sent on Feb 18, 2015 and responses to these questions were received in an amendment (STN 125510/0.4)

FDA Comment # 9: We have following questions regarding the Haemagglutinin Content Determination by Single Radial Immuno-diffusion (SRID) assay:

a. Section 3.2.P.5.2 Analytical Procedures-Hemagglutinin (b) (4) Content SRID: In reference to testing of formulated drug product on page 2 you have

mentioned that the “same basic methodology is applied to (b) (4) samples as to (b) (4) Final Filled Product with slight differences. DP is tested using (b) (4) per strain for (b) (4) samples or (b) (4) per strain for Filled samples.” In the SRID assay, (b) (4) samples are appropriately (b) (4). Since the samples of (b) (4) filled product contain the MF59C.1 adjuvant, please clarify whether any modifications to the SRID assay are necessary for HA content determination.

Sponsor’s Response:

The Company would like to clarify that the test method for SRID analysis of (b) (4) drug product is the same and is comparable to the methodology described in the (b) (4). There is no modification required for the preparation of assay reagents or samples within the SRID assay to account for the presence of MF59C.1 adjuvant.

The number of individual plates used within the test method is dependent upon the stage of product manufacture in line with (b) (4) requirements i.e. (b) (4) drug product.

The Company wishes to clarify in future that it is intended to follow the (b) (4) requirements for (b) (4) filled drug product by testing (b) (4) per strain, with the option to test (b) (4) per strain in the event of an out of specification / out of trend result.

CBER Comment: Sponsors response is acceptable.

b. Please provide a copy of the current SOP for the determination of Hemagglutinin (b) (4) Content by SRID in the FLUAD vaccine covering testing of (b) (4) final container DP.

Sponsor’s Response:

Section 3.2.P.5.2 Analytical Procedures –Hemagglutinin (b) (4) Content (SRID) has been updated with a copy of the SOP for the SRID assay and the reader system in Attachment 1 and Attachment 2 respectively.

CBER Comment: The submitted documents are reviewed and sponsors response is acceptable.

c. In reference to SRID Validation: For the SRID assay the reference standard is prepared in an aqueous buffer while the final formulated FLUAD vaccine contains adjuvant. No data has been provided in the SRID validation reports that describes the effect or the lack of effect of the presence of adjuvant upon the performance or accuracy of the SRID assay for measurement of HA content. Please clarify.

Sponsor's Response:

The presence of MF59C.1 and its effect on performance or accuracy of the SRID assay for measurement of HA content was previously determined in a separate SRID method validation report, ISU 07.07 VR2 Rev.0, submitted with the Agriflu BLA (STN#125297). The report is being provided again in this submission for your review in Section 3.2.P.5.3 in Attachment 42.2 and the data can be found in Section 3 of the report on pages 6 and 7. (b) (4) studies were performed on (b) (4) batches of Agrippal (Agriflu) and on (b) (4) batches of FLUAD using the same reference standard antigen strains. The results obtained show similar (b) (4) levels for both Agrippal (Agriflu) and FLUAD products thereby demonstrating that there are neither inhibitory or enhancement effects due to the presence of MF59C.1.

CBER Comment: The referenced sections (section 3 Pg 6 and 7) of method validation report (ISU 07.07 VR2 Rev. 0) were reviewed. Additional IR was sent in regards to evaluation of accuracy of the SRID assay for measuring HA content in adjuvanted product.

d. Section 3.2.P.5.3: An “Interim Analytical Method Transfer Report” (attachment 42 LVP transfer report) describing the transfer of method for determination of hemagglutinin content (b) (4) from (b) (4) has been included. For method transfer, (b) (4) final product was used. In reference to this report please clarify the following:

a) Why was a (b) (4) trivalent) product used in this evaluation?

Sponsor's response:

The determination of HA content by SRID is performed on multiple products/stages. In order to transfer the method across multiple products/stages, a product grouping strategy was used. The production of (b) (4) and filled material uses the same production facilities and manufacturing process as is used in the production of FLUAD. The two products therefore have very similar sample matrices. The only difference between the two sample matrices occurs during formulation activities for (b) (4)

(b) (4) use in the transfer of SRID US adjuvanted Agrippal platform products and so represents all adjuvanted products for the US markets.

An assessment of the SRID assay, specification and validation performed in (b) (4) on (b) (4) and FLUAD determined that the two different product types are tested using identical methodology, have the same product specification and were validated to the same acceptance criteria in (b) (4). Local verification studies performed in (b) (4) with (b) (4) adopted these same acceptance criteria and demonstrated (b) (4) was able to perform the method with comparable accuracy and precision to (b) (4) As discussed in the response to question 9b below, (b) (4)

(b) (4) (b) (4)
does not alter the method applied for the transfer of FLUAD. The use of (b) (4) trivalent product is therefore deemed an acceptable approach by Novartis for evaluation of the transfer of the SRID method from (b) (4) as the two products can be deemed equivalent. Samples for equivalence testing were prepared in an identical manner using the (b) (4) material. The premise of the transfer testing was to demonstrate equivalency of the FLUAD US SRID methodology, which is independent of the sample matrix used, and this has been achieved.

CBER Comment: Sponsors response is acceptable.

b) The cross reactivity of the B-strain antibodies may impact the measurement of HA content for B-strains in a (b) (4) SRID assay. Please clarify the approach used to measure the amount of HA for B-strains in the (b) (4) sample.

Sponsor's Response:

The SRID method transfer was performed on a 'like for like' basis using the current approved US method that has been validated in (b) (4) for Trivalent products, i.e. (b) (4). The dual site testing performed during the transfer was therefore identical to the test that will be used for FLUAD, with the exception that the test was performed for (b) (4) strains. The sample preparation was identical at both sites resulting in the ability to compare assay methodology independent of the sample matrix used.

In line with CBRE's recommendations to account for the lack of a specific B antisera, and to minimize the effect of cross-reactivity on HA measurement due to the presence of a (b) (4) B-strain, the HA content assay for (b) (4) will be performed using a (b) (4).

CBER Comment: Sponsors response is acceptable.

c) On page 9 of the report you have mentioned that "Reagents were all qualified in (b) (4), reagent usage details used as detailed in (b) (4) document 257612." Please provide a copy of document 257612

Sponsor's Response to 9 d. part (c)

Section 3.2.P.5.3, Validation of Analytical Procedures – Hemagglutinin Content (b) (4) (SRID) has been updated with a copy of the document 257612 Table of reagents and standards and is provided in Attachment 42.1

CBER Comment: The submitted documents are reviewed and sponsors response is acceptable.

SRID IR #2

SRID assay related IR was sent on April 16, 2015 and responses to these questions were received in an amendment (STN 125510/0.10)

Comment #1) Please provide a list of all the SRID related documents/reports present in the BLA and indicate: if they are new to the FLUAD 65 BLA or were submitted with the Agriflu submission (STN 125297).

Sponsor's Response:

Please find attached the spreadsheet detailing all the SRID related documents submitted in Agriflu BLA and in the FLUAD BLA. The Agriflu BLA had SRID documents for (b) (4) submitted under (b) (4). FLUAD DP (as it relates to SRID) is the only new section that is being provided in this BLA for FDA review. Additional notes are provided in the spreadsheet indicating whether the document was submitted in the original FLUAD BLA or in a subsequent informational response and if it is new to the FLUAD BLA. Note: The SRID validations are specific for the FLUAD sample matrix. Therefore these reports would not have been submitted previously in the Agriflu BLA and are specific and new to the FLUAD DP section of this BLA.

CBER Comment: The sponsor has identified the SRID related documents that are new to the FLUAD BLA and these were reviewed for this memo.

Comment#2: Please clarify the sites that would be used for SRID testing of (b) (4) final product.

Sponsor's response:

FLUAD for the US market will have (b) (4) manufactured in (b) (4). The DP will be manufactured in (b) (4). SRID testing for (b) (4) final product will be performed in (b) (4).

CBER Comment: Sponsor has provided clarification and the response is acceptable.

SRID IR #3

During the review of submitted reports clarification/explanation was needed in reference to validation of the SRID method as applied to the FLUAD drug product. An IR was sent on May 15, 2015 and response to these questions were received in an amendment (STN 125510/0.15)

Comment #8a.: 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)

(b) (4) as required for trivalent (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).

Sponsor’s Response:

The company confirms that all data points reported in Tables 4 to 11 in the (b) (4) validation report ISU 07.007 VR 15 Rev. 2 were generated from the (b) (4) performed on samples. For filled product (b) (4) were used for each strain. For (b) (4) (b) (4) were used for each strain. The company can confirm that all validation parameters (Repeatability, Linearity, Intermediate Precision and Accuracy) have been calculated and evaluated for “reportable results”, using the (b) (4)

CBER Comment: Sponsor response is acceptable.

Comment #8b: 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 42 LVP Transfer report) we have the following question: To evaluate accuracy of the method, (b) (4)

. This implies that (b) (4) was evaluated in presence of (b) (4) the concentration of adjuvant. Please comment.

Sponsor’s Response:

The company confirms the agency’s interpretation of the accuracy study that has been performed. It had been adopted directly from the current approved methodology for determination of accuracy for non-adjuvanted vaccines.

Virus reference standard supplied by CBER is (b) (4)

for assessment within an accuracy study. This study will be undertaken for all strains in 2015.

CBER Comment: In response to Sponsor’s comment above, additional IR (i.e. IR #4 below) was sent.

SRID IR #4:

Response to CBER question related to SRID accuracy study (see IR3# above) a response was submitted in an amendment (125510/0.15). Following review of this response more

clarification was needed. Additional IR was sent on July 29, 2015 and response to the questions was received in an amendment (STN 125510/0.18).

Comment #3: Please provide the timeline when the results of the planned repeat accuracy study will be submitted. We recommend that these results be submitted as soon as possible so that review of potency assay can be completed.

Sponsor's Response:

The Company will provide results of the planned repeat accuracy study by end September 2015.

CBER Comment: In response to Sponsor's comment above, additional request was sent (i.e. IR #5 below).

SRID IR #5:

In response to Novartis' comment about submission of the repeat accuracy study, a request was made in the Late Cycle Memo dated August 21, 2015. The response to this request was received in an amendment (STN 125510/0.22)

Comment: 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.

Sponsor's Response:

A commitment was made by Novartis in Amendment 15 (submitted on July 13, 2015) to perform a repeat study for the accuracy parameter of the SRID assay validation for the measurement of HA content using the adjuvant at the drug product matrix concentration found in the final product. The SRID assay validation report is provided herein as Attachment 1.

CBER Comment: The submitted report was reviewed and is acceptable (see the SRID Review Summary section of the memo).

**(b) (4)) for determination of
Ovalbumin content**

Background:

The Ovalbumin content in (b) (4) DP is determined using commercially available, (b) (4). The (b) (4)

(b) (4)

Validation Related Documents Reviewed:

1) Translation of SOP 201731-03 (ISU 07.017): Determining the Ovalbumin Content in the Anti-influenza Vaccine using the (b) (4) Method Commercial Kit.

2) Doc. No. 276833: Determining the Ovalbumin Content in Agrippal Platform Production Samples Using the (b) (4) Commercial Kit

3) Doc. No. ISU 07.017 VR 1 Rev. 1: Validation Report of the Ovalbumin determination in Flu vaccine (b) (4)

method

4) Doc. No. ISU 07.017 VP 3 Rev. 0: Validation Protocol for the determination of ovalbumin in the (b) (4) with (b) (4) method. (DP (b) (4))

5) Doc. No. ISU 07.017 VR 3 Rev. 2: Validation Report for the determination of Ovalbumin in Flu vaccine phase (b) (4) by using an (b) (4) method)

6) Doc. No. AVR/0025/10: Assay Validation Report- Report for the Validation and Transfer of the Ovalbumin (b) (4) Assay from (b) (4) for the (b) (4) Project

7) Doc. No. P/0392/09/13: Protocol for the Analytical Method Transfer of Ovalbumin Testing for adjuvanted (MF59 containing), (b) (4) samples from the (b) (4) Site to the (b) (4) Site, Novartis Vaccines and Diagnostics.

8) Doc. No. R/0392/09/13: Report for the Analytical Method Transfer of Ovalbumin Testing for adjuvanted (MF59 containing), (b) (4) samples from the (b) (4) Site to the (b) (4) Site Novartis Vaccines and Diagnostics.

Ovalbumin (b) (4) Review Summary:

Validation of Ovalbumin (b) (4) :

The validation of ovalbumin (b) (4) was performed using (b) (4) of following drug product and (b) (4) samples:

- (b) (4)

Validation parameters of Precision, Repeatability, Intermediate Precision, Accuracy, Specificity, Linearity and Range were evaluated. The results of this validation study are described in the validation report (Doc. No. ISU 07.017 VR 1 Rev.1). This report was submitted and reviewed during the licensure of in the Agriflu BLA (STN 125297) and was approved by agency. All the validation parameters met the pre-defined acceptance criteria. The obtained results confirmed that the (b) (4) method using the commercially available kit is suitable for the Ovalbumin concentration determination in samples of (b) (4)

To verify the applicability of the Ovalbumin (b) (4) to the samples of (b) (4), additional validation study was done using t^(o) (4) lots of Trivalent (b) (4), for US). Validation parameters of Precision, Accuracy, Specificity Linearity Limit of Quantitation (LOQ), Range and Robustness were evaluated. The results of this validation study are summarized in a report (Doc No. ISU 07.017 VR 3 Rev. 2). All the parameters met the pre-defined acceptance criteria. Based on these results Sponsor has concluded that the (b) (4) method is suitable to determine Ovalbumin concentration in samples of (b) (4) for US (at suggested working (b) (4))

Transfer of Ovalbumin (b) (4) Facility:

The validated Ovalbumin (b) (4) was transferred from Novartis Vaccines and Diagnostics (NVD) (b) (4) to NVD (b) (4). After transfer, the method was validated at (b) (4) according to a pre-approved protocol for the following parameters: Reproducibility (i.e. Repeatability and Intermediate Precision) and Comparability (between two NVD sites). (b) (4) were used to evaluate method reproducibility. (b) (4)

(b) (4) to compare the method at two sites. The results of this transfer study are described in a validation report (Doc. No. AVR/0025/10). All results were within the acceptance criteria and it was concluded that the test can be consistently performed at the (b) (4) site. This report was previously submitted in the BLA file for Agriflu (STN 125297/15) and was approved by agency.

In addition, an analytical method transfer study was performed to demonstrate the successful transfer of the Ovalbumin (b) (4) method for testing adjuvanted (b) (4) samples from (b) (4), site to (b) (4) site. This transfer study was performed as part of global change control under the Analytical Method Transfer Master Plan. The study design is outlined in a validation protocol (Doc. No. P/0392/09/13). As a part of transfer procedure, the performance of Ovalbumin (b) (4) assay was verified at (b) (4)

site. In addition an (b) (4) material) was tested at both the sites to evaluate equivalence in performance of the assay at (b) (4) site to (b) (4) sites.

The data for ovalbumin (b) (4) transfer study are summarized in a report (Doc. No. R/0392/09/13). The assay verification study at (b) (4) site involved evaluation of linearity, limit of quantitation (LOQ) and precision. The results of this study show that all the acceptance criteria for each of the parameters evaluated were met. As a part of assay transfer procedure, the data generated by the two sites (b) (4) was compared. Statistical evaluation using two one sided t-test (TOST) showed that the results generated by two sites were practically equivalent.

Information Requests regarding Ovalbumin (b) (4)

During the review of Ovalbumin (b) (4), additional documents and clarification about submitted data was needed. Following Information requests (IR) were sent:

For each IR, CBER's questions to sponsor (in bold), Sponsor's response (italicized) and CBER comment to these responses (in bold italicized) are listed below:

Ovalbumin Assay IR #1

Ovalbumin assay related IR was sent on March 17th 2015 and response to these questions were received in an amendment (STN 125510/0.6)

Comment # 1: Please provide the current SOP for the determination of Ovalbumin Content by (b) (4) in the FLUAD vaccine covering testing of (b) (4). In addition, please include the Excel spreadsheet (associated with this SOP) which is used to calculate the results.

Sponsor's Response:

As described in the BLA this method was recently transferred from (b) (4) to (b) (4). A copy of the (b) (4) SOP 276833 for determination of Ovalbumin Content by (b) (4) in (b) (4) for the FLUAD vaccine is provided in Section 3.2.P.5.2 Analytical Procedure – Ovalbumin in Attachment 3. The associated validated spreadsheet used to calculate the ovalbumin results along with a spread sheet with (b) (4) lot data was include in an email to CBER on 26 March, 2015. A PDF copy of the spreadsheets is provided in this response in Attachment 1 and 2 in Section 1.11. At this time the spread sheet has not been translated into English and the Italian version is being provided.

CBER Comment: The submitted SOP was reviewed. Sponsor response is acceptable

Comment # 2: Please provide a copy of the method transfer plan for transfer of the Ovalbumin assay from Novartis Vaccines and Diagnostics, (b) (4) site to the (b) (4) site.

Sponsor's Response:

The method transfer validation protocol P-0392-09-13 for the Ovalbumin assay for adjuvanted product is provided in Section 3.2.P.5.3, Validation of Analytical Procedure-Ovalbumin in Attachment 19.1.

CBER Comment: The submitted validation protocol was reviewed. Sponsor response is acceptable