

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: 20-February-2015 11:52 AM Initiated by FDA? Yes

Telephone Number: N/A – E-mail communication

Communication Category(ies):
1. Information Request

Author: Theodore Garnett

Telecon Summary:
Questions on CTAB, (b) (4), formaldehyde, extractable
volume and (b) (4)

FDA Participants: Theodore Garnett
Non-FDA Participants: Matthew Gollwitzer

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

From: Garnett, Theodore
Sent: Friday, February 27, 2015 1:16 PM
To: 'Gollwitzer, Matthew'
Cc: Baldwin, Brenda
Subject: RE: STN 125510/0 (FLUAD 65) - New Information Request

Hi Matt,

The CBER has revised the previous IR to address to your CMC review team's concerns (see attached). Please disregard the first IR and consider this the official request; however, you may still use 20-Feb-2015 as the request date.

Below is a synopsis of the changes. Please contact me by phone for additional details.

1a – 1c: CBER requests that Novartis either provide the explanation requested in these IRs or give us references (STN and Amendment number) for where the information can be obtained.
1d: Table 5 is new data. If validation data in the approved Agriflu BLA has been modified, a response should be provided to this question.
1e, 1f: These questions have been withdrawn.
1g: This is new information/data. The LOQ was not reported in the previous validation report.
1h: This is new information/data. Robustness was not reported in the previous validation report.
1i, 1j: The CBE-30 submitted on November 12th it is not approved yet. So, a response to these questions should be provided.

Regards,
Ted

From: Gollwitzer, Matthew [<mailto:matthew.gollwitzer@novartis.com>]
Sent: Tuesday, February 24, 2015 11:58 AM
To: Garnett, Theodore
Subject: RE: STN 125510/0 (FLUAD 65) - New Information Request

Hi Ted,

Our CMC review team has a question regarding the attached IR dated 20Feb2015. It seems that question 1, subpart “a” through “h” (CTAB Assay for (b) (4) is a method validation that resides in the Agriflu BLA (and copied over to the Fluad BLA) and was already previously approved. So the team is a little confused why the Reviewer is asking questions on an already approved method. Further, question 1, subpart “i” and “j” seem to relate to a recent CBE-30 that was submitted to the Agriflu BLA in Sequence 0101 on November 12th where we are submitting already approved methods from our (b) (4) facility to our (b) (4) facility. So I guess the team is just asking for clarity whether we should provide responses to assays that are already approved in the Agriflu BLA (and were then copied over to the Fluad BLA (b) (4) section).

Let me know if you would like to discuss by phone or if you need any further clarity.

Kind Regards,

Matt

From: Garnett, Theodore [<mailto:Theodore.Garnett@fda.hhs.gov>]
Sent: Friday, February 20, 2015 11:52 AM
To: Gollwitzer, Matthew
Subject: STN 125510/0 (FLUAD 65) - New Information Request

Matt,

Attached is a new request for information that didn't make it into the last IR (i.e., the one I sent to you on Wednesday, February 18). The reviewer is requesting a 2-week turn around for this one. Let me know if you have any questions.

Thanks,

Ted



Our STN: BL 125510/0

Novartis Vaccines and Diagnostics, Inc.
Attention: Mr. Matthew Gollwitzer
350 Massachusetts Ave.
Cambridge, MA 02139

Dear Mr. Gollwitzer:

We are reviewing the quality control test methods and their method validations for your biologics license application (BLA) dated November 25, 2014 for Influenza Vaccine, Adjuvanted and have determined that the following information is necessary to continue evaluating your BLA.

1. CTAB Assay for (b) (4)

- a. It is not clear in your SOP (Translation of SOP 202705 – 08), if you are conducting (b) (4) measurements of standard, control and samples at each dilution. Please revise your SOP to clarify. This being a (b) (4) method, we feel that you should have (b) (4) measurements at each dilution, as you are doing for the CTAB assay method for the (b) (4). Also, please include an appropriate RSD of (b) (4) measurements at each dilution of standard, control and samples as a Test Validity Criterion (section 4.6 in your SOP). If this information has been provided before in relation to Agriflu, please provide the reference.
- b. As per your title of the method validation report (b) (4) No. 294157-02), you have validated your method for (b) (4). However, you have conducted your method validation using (b) (4). Please explain with the details of composition of the samples how using these two samples could validate the method for the determination of all the samples in your title. If this information has been provided before in relation to Agriflu, please provide the reference.
- c. We could not understand the information in Table No. 3 (Accuracy) of your validation report (b) (4) No. 294157-02). The data spread from (b) (4). It is not clear what that means. Please explain the data in this table and how you determine accuracy of your

method from this data. If this information has been provided before in relation to Agriflu, please provide the reference.

- d. Most of the recovery data in Table 5 (Accuracy) of your validation report are significantly below 100% and none above 100%. This indicates a significant negative bias of your assay results and that your CTAB results are under-reported by this assay. Please evaluate your historical data to come up with a correction factor that you can apply to your result to address this under-reporting issue and submit for review. Since the results seem to be highly variable (accuracy acceptance criteria (b) (4), which is extremely wide for a (b) (4) method), you should evaluate a large number of historical data to come up with the correction factor.
- e. You concluded that the Limit of Quantitation (LOQ) of the assay is (b) (4), based on the standard curve only. However, the limit of quantitation of an analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. Please provide accuracy, precision and linearity data from your samples to support LOQ of your method.
- f. Please provide robustness data for your method by evaluating the effect of variations of concentrations of the reagents around the concentrations specified in your SOP.
- g. In Table 2.3 of your Analytical Method Transfer Report (Doc. Ref. No. R/0130/03/14 Rev. 01), you have only indicated Pass/Fail but did not provide the actual data. Please provide the actual data.
- h. In your comparability study (Doc. Ref. No. R/0130/03/14 Rev. 01), you have evaluated only (b) (4). This is too little. Please provide comparability data for sufficiently large number of lots from both sites to permit adequate statistical evaluation of comparability together with statistical evaluation of the data. We recommend that you submit data from at least (b) (4) lots, the same lots being analyzed at both sites. Also, you did not provide descriptions of these (b) (4) samples. Please provide full description of samples used in the comparability study.

2. CTAB Assay for (b) (4)

- a. Please include an appropriate RSD of (b) (4) measurements at each dilution of standard, control and samples as a Test Validity Criterion in your SOP and submit for review.
- b. In your validation report (b) (4) No. 294160-01), you concluded method specificity based on the accuracy results only. We do not agree that you have demonstrated method specificity adequately because the accuracy is determined by (b) (4) method.

Please provide data from the analysis of a representative (b) (4) for the (b) (4) to demonstrate no or negligible (b) (4) by the method, to demonstrate method specificity.

- c. You have demonstrated linearity of your assay by data from the standard only. We do not agree that you have demonstrated linearity of your assay adequately. Please provide linearity data using representative sample matrix of the (b) (4) and demonstrate parallelism between the standard and the samples within a reasonable confidence interval.
- d. It is not clear what the lines mean in Figure 1 of your validation report (b) (4) No. 294160-01). Clearly, they are not linear-regression fit lines. Please explain the significance of the lines in the figure.
- e. You concluded that the Limit of Quantitation (LOQ) of the assay is (b) (4) based on the standard curve only. Please provide accuracy, precision and linearity data from your samples to support LOQ of your method.
- f. Please provide robustness data for your method by evaluating the effect of variations of (b) (4) around the parameters specified in your SOP.
- g. In Table 2.3 of your Analytical Method Transfer Report (Doc. Ref. No. R/00401/09/13 Rev. 01), you included (b) (4). It seems that you have applied (b) (4) and you need to use this (b) (4). But use of such (b) (4) is not indicated in the description of Analytical Procedure that you have submitted. Please explain your (b) (4), why you need to use it (background information) and why the (b) (4) is not indicated in the description of the Analytical Procedure, and provide details of data showing how you came up with the (b) (4).
- h. You have only evaluated reproducibility between the (b) (4) sites but no comparability data in your Analytical Method Transfer Report. Please provide comparability data for sufficiently large number of lots from both sites to permit adequate statistical evaluation of comparability together with statistical evaluation of the data. We recommend that you submit data from at least (b) (4) lots, the same lots being analyzed at both sites.

3. Determination (b) (4) (for Drug Product)

- a. The description of analytical procedure for the determination of (b) (4) of the adjuvant, which you submitted does not provide sufficient details of the method to permit review. Please provide a representative version of your SOP # 102847. Please provide the refractive index values used to calculate the (b) (4) of your standards and samples, if they are not indicated in the SOP.
- b. The method is validated for (b) (4) DP (Fluad) in the same report (Document No. 294442-01), which specifies that it is done according to SOP 102847 in the title. However, as indicated in the DP analytical procedure the determination of (b) (4) for Fluad uses SOP 308163. Please describe the differences between SOP 102847 and SOP 308163 or provide a representative version of your SOP # 308163.
- c. You have not evaluated accuracy of your method in your validation report (Document No. 294442-01) citing that oil-in-water emulsion standards are not available. Please provide results from an appropriate orthogonal method to demonstrate accuracy of your method for the (b) (4) the drug product.

4. Determination of (b) (4)

- a. In the Principle of the Method Summary (3.2.S.4.2) it is stated that “The (b) (4)

 ” Please explain how you identified and counted (b) (4)s from the adjuvants separated from (b) (4) present in the drug product (for example, leachetts, environmental).
- b. Please explain why an evaluation of accuracy was not performed as part of the method validation.
- c. Please provide the frequency in which the instrument is qualified and the historical accuracy data for at least three years for this assay as obtained during the instrument qualifications.
- d. Please provide the operational range of your instrument (b) (4) and the qualification report of the instrument related to the operational range.

5. Formaldehyde Assay—(b) (4)

- a. In the Validation Protocol CQS 07.028 27 VP Rev. 0, Section 1: Introduction and Scope it is stated that “... the sample is prepared following the procedure of the samples of type I. The method of type II is followed for the preparation of the curve and the white, the procedure and the expression of the result”. You have used such terminologies as

“samples of type I” and “type II, also in Section 1 of the Validation Report (CQS 07.028 VR Rev. 1). Please define the terms “samples of type I” and “type II” as these are not defined or used in the method summary or other submitted materials.

- b. Batch Results: 3.2.P.5.4 - Results for formaldehyde are not included in the data submitted for (b) (4) testing. Please submit this information.

6. Extractable Volume—Final Container Vaccine

- a. In your analytical procedure, you indicated that the weight is divided by (b) (4) while in the qualification report (Report No. 293538-01) you used (b) (4). Please revise the SOP to replace (b) (4) by (b) (4) because you have qualified your method using (b) (4).
- b. Please provide the data on the determination of (b) (4) that you used in method qualification, analytical transfer, and will continue to use in lot release testing at (b) (4) sites.
- c. In section 3.1 of your qualification report (Report No. 293538-01) you indicated that operator 2 calculated the (b) (4). Please explain how and provide a comparison of the (b) (4) calculated data and the data obtained by a (b) (4).
- d. In your Analytical Method Transfer Report (Doc. Ref. No. R/0003/13 Rev. 01), you did not provide any comparability data between the two sites. Please provide comparability data between (b) (4) sites.
- e. For the precision data you presented in the Analytical Method Transfer Report, the syringes were filled (b) (4), not by using the actual manufacturing process. Thus, the data is not representative. Please provide precision data from (b) (4) sites using syringes that are filled by actual manufacturing process.

7. (b) (4) —Final Container Vaccine

- a. In Table 2.3.1 of your Analytical Method Transfer Report (Doc. Ref. No. R/0447/10/13 Rev. 01), you have only indicated Pass/Fail but did not provide the actual data. Please provide the actual data.
- b. In your comparability study (Doc. Ref. No. R/0130/03/14 Rev. 01), you have evaluated only (b) (4) between two laboratories. This is too little. Please provide comparability data for sufficiently large number of lots from both sites to permit adequate statistical evaluation of comparability together with statistical evaluation of the data. We

recommend that you submit data from at least (b) (4), the same lots being analyzed at (b) (4)

If possible, please submit your response in 2 weeks so we may continue the review of your application. If you are unable to provide a complete response in 2 weeks, please indicate when we should expect to receive your response. 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, Theodore Garnett, Ph.D., at (301) 796-2640.