DEPARTMENT OF HEALTH & HUMAN SERVICES

Food & Drug Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: October 9, 2009

To: STN 125297

From: Rajesh K. Gupta, HFM-407

Through: William McCormick, HFM-407

CC: Anissa Cheung, HFM-445
Bernard McWatters, HFM- 478
William McCormick, HFM-407

Subject: STN 125297: Influenza Virus Vaccine, Agrippal®, Novartis – Review of Drug Substance and Drug Product Analytical Procedures

Reference: Original BLA 125297/0 (submitted 7/11/2008) sections 3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2 and 3.2.P.5.3
Amendment 0.2 (submitted 11/10/2008) section 3.2.S.4 and 3.2.P.5 Analytical Procedure for -b(4)-
Amendment 0.4 (submitted 2/2/2009) section 1.11.4 Response to FDA Comments and 3.2.S.4.3 Validation of Analytical Procedures
Amendment 0.10 (submitted 3/31/2009) Updated response to FDA comments 125297/0.12 (submitted 4/10/2009), 125297/0.16 (submitted 05/29/2009, response to CR letter) and 125297.18 (submitted 08/19/2009).

Reviews of the analytical procedures and the associated validation protocols and reports were performed by the staff of Division of Product Quality. This memo includes description of the method taken from the submission and DPQ's comments (in regular font) on the original submission and additional information submitted in various amendments listed above. Novartis's responses to CBER's comments taken from various amendments are in bold font. DPQ reviewed Novartis's responses and provided final evaluation of the method, which is given in the bold font at the end of each method.

Methods were reviewed by Dr Alfred Del-Grosso with assistance from Nora Etz, Joe Progar and Brandon Duong, and by Drs Rajesh Gupta, James Kenney, Manju Joshi, Muhammad Shahabuddin, and Ramakrishna Velicheti.

Methods Reviewed

In-process
---b(4)---------

---b(4)----------
---b(4)----------
-----b(4)-- ----------
--b(4)----------
---b(4)----------
---b(4)----------
--b(4)----------
--b(4)----------
---b(4)----------
--b(4)----
--b(4)-----
--b(4)-----

Drug Product
Total Proteins --b(4)--------
Formaldehyde (---b(4)----------)
---b(4)----------
Sterility
---b(4)-------
---b(4)---------
Viral Inactivation
General Safety

RECOMMENDED ACTION

The data submitted to support the analytical methods used for testing of drug substance and drug product of Influenza Vaccine, inactivated (Agriflu®) were reviewed and found to ensure the quality of this product. Based on this review, I recommend approval of this product.

1. **Total Proteins (---------b(4)----------**

The Total Proteins determination is performed by the --b(4)----------. The method is
-----b(4)---- ----------

CBER's Evaluation: The method is suitable for intended purpose.

2. **Formaldehyde ---b(4)---** ----------

----b(4)----- ----------

CBER's Comment, Communicated as Comment 5a on 12/8/08 to Novartis

In validation report number b(4) 07.l28 VR.20 Rev 0, parts III 1a and 1b, repeatability and intermediate precision of the assay method are only evaluated at a concentration of approximately -b(4)---. The specification limit for the drug product is stated as --b(4) ----------. As recommended by the validation guidance ICH Q2(R1), precision should be at either a minimum of 9 determinations covering the specified range of the procedure (e.g., 3 concentration/3 replicate each); or a minimum of 6 determinations at 100% of the test concentration. Please commit to an evaluation of precision at, or bracketing the regulatory specification level for the drug product.

Company Response to Comment 003-5a-Q from amendment 0.4

We confirm that we use ----------b(4)- of the test concentration of the usual results of the drug product. The Company has performed an evaluation of the precision at the regulatory specification limit for the drug product using the linearity data generated during the assay validation. The Company takes the commitment to amend the validation report with precision study at the specification limit. Regarding linearity please refer to 003-5c-Q.

Updated Company Response to Comment 003-5a-Q from amendment 125297/0.10

The Formaldehyde analytical method and validation reports for ----b(4)---------- ----------have been amended to include the precision study at the specification limit.
The following Attachments in Sections 3.2.S.4.3 and 3.2.P.5.3 (Validation of Analytical Procedures) are being replaced:
-------b(4)------
3.2.S.4.3 [Formaldehyde]-1 – Protocol b(4) 07.28 VP 20 Rev.2 (Italian)
3.2.S.4.3 [Formaldehyde]-2 – Protocol b(4) 07.28 VP 20 Rev.2 (English)
3.2.S.4.3 [Formaldehyde]-3 – Validation Report b(4) 07.028 VR 20 Rev.2
-------b(4)-------
3.2.P.5.3 [Formaldehyde]-1 – Protocol b(4) 07.28 VP 20 Rev.2 (Italian)

3.2.P.5.3 [Formaldehyde]-2 – Protocol b(4) 07.28 VP 20 Rev.2 (English)
3.2.P.5.3 [Formaldehyde]-3 – Validation Report b(4) 07.028 VR 20 Rev.2

CBER's Evaluation: The response is adequate.

CBER's Comment, Communicated as Comment 5b on 12/8/08 to Novartis

The SOP for the determination of b(4) formaldehyde in vaccines, 202550-14 (b(4) 07.028) does not specify the lowest level of formaldehyde that may be reported by the procedure. Please submit a revision to the procedure to indicate that formaldehyde content should not be reported to a concentration lower than that of the lowest standard.

Company Response to Comment 003-5b-Q in amendment 0.4:

Procedure b(4) 07.028 is under revision to clearly specify as requested, the lowest level of formaldehyde that may be reported by the procedure.

The Chapter 4 paragraph 4.5 is going to report the following sentence:

----b(4)-------- ----------

--b(4)--- ----------

Updated Company Response to Comment 003-5b-Q from amendment 0.10:
The Formaldehyde Procedure b(4) 07.028 has been amended to clearly specify the lowest level of Formaldehyde that may be reported by the procedure. The revised documents are provided in Section 3.2.S.4.2 (Analytical Procedures).
The following Attachments are being replaced:
3.2.S.4.2 [Formaldehyde]-1 – b(4) 07.028; SOP 202550-17 (Italian)
3.2.S.4.2 [Formaldehyde]-2 – b(4) 07.028; SOP 202550-17 (English)

CBER's Evaluation: The response is adequate.

CBER's Comment, Communicated as Comment 5c on 12/8/08 to Novartis

In Validation Report b(4) 07.28 VR. 20 Rev. 0 for formaldehyde, Part III – 3 Linearity, linearity is evaluated ----------b(4)----------. Linearity of the procedure should be evaluated with respect to actual or simulated samples and should be established to a concentration in excess of the specification limit. While some data consistent with this requirement were obtained with the determination of Accuracy, Part III -2, this data should be expanded to include a concentration exceeding the limit specification of -b(4)---. We ask that you commit to an expanded study of the Linearity of this procedure using representative sample matrix.

Company Response to Comment 003-5c-Q from amendment 0.4:

We recognize that the accuracy data, that supports the requirement for linearity, partially covers the linearity range. Therefore we commit to expand the accuracy study with respect to actual or simulated samples exceeding the limit specification of --b(4)----.

Updated Company Response to Comment 003-5b-Q from amendment 0.10:

Please refer to the updated response to Comment 5a-Q.

CBER's Evaluation: The response is adequate.
The method for determination of formaldehyde in ----------
------b(4)-----is suitable for intended purpose.

3. <u>Polysorbate 80</u>

This method is based on --b(4)--of polysorbate 80 (Tween 80) from samples using -b(4)---. The amount of polysorbate 80 is then determined by ---b(4)----------

CBER's Evaluation: The method is suitable for intended purpose based on original submission and additional information received in amendment 0.18.

4. <u>Determination of ---b(4)----------</u>

---b(4)--- ----------

---b(4)----------

--b(4)--- ----------

--b(4)--- ----------

----b(4)--- ----------

2 Pages determined to be not releasable:
b(4)

6. <u>Determination of Cetyltrimethylammonium bromide (CTAB) by --b(4)----------</u>

CTAB (Cetyl-Trimethyl-Ammonium bromide) content in a solution is determined by the ---b(4)---- ----------

CBER's Comment, Communicated as Comment 8 on 12/8/08 to Novartis

In Validation Reportb(4) 07.06 VR. 2 Rev. 0, Part 4.4, Linearity is evaluated -b(4)----- reference to the "value(s) obtained from the elaboration of the ---b(4)---------- ---------- Linearity of the procedure should be evaluated with respect to actual samples or a representative product matrix. Please commit to an evaluation of Linearity based on a representative product matrix.

Company Response to Comment 003-8-Q from amendment 0.4:

Accuracy data support the requirement that linearity should be evaluated with respect to actual samples or a representative product matrix.

We recognize that the accuracy data partially covers the full range of linearity and therefore we commit to expand the linearity study, with respect to actual or simulated samples.

Updated Company Response to Comment 003-8-Q from amendment 0.10:

The analytical method for CTAB has been revised to -b(4)----- the number of samples and the number of matrices used in order to provide a more representative product matrix on which to evaluate linearity.
The following Attachments are being replaced:
3.2.S.4.3 [CTAB]-1 – b(4) 07.006 VP 2 Rev.1 (Italian)
3.2.S.4.3 [CTAB]-2 – b(4) 07.006 VP 2 Rev.1 (English) Agrippal - Novartis Vaccines and Diagnostics, Inc. 1.11.1 Information Amendment BLA 125297 Amendment 0010 March 09 Confidential Page 10 of 13

3.2.S.4.3 [CTAB]-3 – b(4) 07.006 VR 2 Rev.1

CBER's Evaluation: The response is adequate. The method is suitable for intended purpose based on evaluation of Company's responses to CBER's comments and additional information received in amendment 0.18.

5 Pages determined to be not releasable:

b(4)

CBER's Evaluation: Additional studies performed by the company are adequate assess accuracy of the method over the entire range of the method.

CBER's Comment, Communicated as Comment 9c on 12/8/08 to Novartis

c. Range of the method is not clearly defined. Please comment.

Company Response to Comment 003-9c-Q in amendment 0.4

The report is under revision to better explain that the range is ----------b(4)-------.

Updated Company Response to Comment 003-9c-Q in amendment 0.10

Please refer to the updated response to Comment 9b-Q.

CBER's Evaluation: The response is adequate. The method is suitable for intended purpose.

9. Sterility (Drug Substance and Drug Product)

The method is performed in agreement with --b(4)----------

CBER's Evaluation: The method is suitable for intended purpose.

10. Endotoxin --b(4)----------

---------b(4)--- ----------

CBER's Evaluation: The method is suitable for intended purpose.

11. Viral Inactivation Test

---b(4)--- ----------

--b(4)----------

CBER's Comment, Communicated as Comment 10 on 12/8/08 to Novartis

Qualification Report for the viral inactivated test for --b(4)---------- has not yet been provided.

Company Response to Comment 003-10-Q in amendment 0.4

The qualification report for determining the inactivation of influenza virus strains is provided. See 3.2.S.4.3 [Viral Inactiv]-4 and 3.2.S.4.3 [Viral Inactiv]-4a (Addendum).

CBER's Comment, Communicated as Comment 5a in the CR letter (27-Apr-09)

We have the following concerns regarding your viral inactivation test:

You have provided qualification reports for determining the inactivation of influenza virus strains (3.2.S.4.3 [Virus Inactiv]-4 and 3.2.S.4.3 [Virus Inactiv]-4a (Addendum). Both reports are identical except for the cover page and line 14 on page 2. Differences in these reports should be distinctly described with a justification for not using all b(4). Please explain in these reports the differences between -b(4)---------

Company Response to Comment 5a from amendment 0.16

--b(4)--- ----------

CBER's Evaluation: The response is adequate.

CBER's Comment, Communicated as Comment 5b in the CR letter (27-Apr-09)

Though appropriate controls of influenza vaccines used as matrices have included using only b(4) eggs, please provide evidence that the vaccine formulations used as

matrices have tested negative for residual influenza virus in a test performed according to ---b(4)---------- eggs for each passage.

Company Response to Comment 5b from amendment 0.16

---b(4)---- ----------

----b(4)----- ----------

[**b(4)**]

The test result was negative (absence of live virus); for this reason, it was not considered necessary to test on b(4)more eggs to demonstrate the validity of the results. Inoculation of justb(4)eggs with these samples instead demonstrated that the samples did not interfere with the good outcome of qualification and that they behaved like the --b(4)----------, not interfering with hemaagglutination.

CBER's Evaluation: The response is adequate.

CBER's Comment, Communicated as Comment 5c in the CR letter (27-Apr-09)

Experiments described in the qualification report have been performed at -b(4)- However the SOP FLU 07.003 (SOP 203564-07) describes incubation of inoculated eggs atb(4) temperatures for trivalent bulk preparations, ---b(4)----------

--b(4)---------- requires incubation of inoculated eggs between --b(4)----------
Please revise the SOP with regard to the incubation temperature that it should not be lower than b(4) to ensure compliance with the --b(4)---------- and also to be consistent with the qualification study.

Company Response to Comment 5c from amendment 0.16

The qualification tests described were conducted only at --b(4)------ because the incubation temperature prescribed by Influenza Production for the propagation production conditions on the strains used for preparation of the Trivalent vaccine for the 2007/2008 influenza season was --b(4)---------
The tests conducted at QC have always been carried out at the temperature found to be the optimum for virus propagation by the Influenza Production department for production of influenza vaccine; thus, in some cases tests were conducted at --b(4)---------- since this was the optimal incubation temperature indicated and used by the Influenza Production department for propagation of certain strains of viruses.
Notwithstanding this, the Company takes the commitment to revise the SOP FLU 07.003 in order to be in compliance with -b(4)--- requirements by replacing the --b(4)---- temperature value with a value of --b(4)-----------
The SOP is currently under revision and will be implemented upon approval for the testing of remaining ----------b(4)----------produced in the 2009-2010 influenza season.

CBER's Evaluation: The response is adequate. The viral inactivation test is suitable for intended purpose.

12. <u>General Safety (Drug Product)</u>

The method for the General Safety is carried out according to -b(4)---- CFR 610.11 and -b(4)--- requirements using 2 guinea pigs and 5 mice.

CBER's Evaluation: The test for General Safety is suitable for intended purpose.

13. <u>--b(4)----------</u>

-----b(4)---- ----------

----b(4)----- ----------

-----b(4)----- ----------

------b(4)- ----------