DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food & Drug Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: March 6, 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

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Reviews of the analytical procedures and the associated validation protocols and reports were performed by the staff of Division of Product Quality. Comments on the original submission were communicated to the BLA review team on December 1, 2008. These comments were sent to Novartis on December 8, 2009 by Bernard McWatters. Novartis's response (in bold font) was sent as an amendment, dated 30 January 2009. This memo covers DPQ's comments on original submission (in regular font) and review of Novartis's response (in italics font).

I. Analytical Chemistry Methods

(By Dr Alfred Del-Grosso with assistance from Nora Etz, Joe Progar and Brandon Duong)

Drug Substance

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

Drug Product

Total Proteins --b(4)-------
Formaldehyde (----------b(4)----------)

The Analytical Chemistry methods, as listed in the general methods, are adequately described and validation studies support the intended use of the procedures. The following issues should be addressed by the manufacturer before licensure.

DPQ's Original Comment

1. Formaldehyde (--b(4)---------- ----------), Communicated as Comment 5 to Novartis

   a) 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:

   We confirm that we use a ----------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.

   DPQ's Comments on Novartis's Response

   Please provide a copy of the amended validation report with precision study at the specification limit.

DPQ's Original Comment

   b) 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:

   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)**----------

DPQ's Comments on Novartis's Response

Please provide a copy of the revised procedure CQS 07.028.

DPQ's Original Comment

c) 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:

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)---**.**

DPQ's Comments on Novartis's Response

Please provide date of completion of additional studies you intend to perform and provide a copy of the revised validation report including data and discussion from additional studies.

DPQ's Original Comment

2. Determination of -- b(4) ---- (Drug Substance), Communicated as Comment 6 to Novartis

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

1 Page determined not to be releasable.

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

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Company Response to Comment 003-7-Q:

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

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

DPQ's Original Comment

3. Determination of Cetyltrimethylammonium bromide (CTAB) by -----b(4)----------, Communicated as Comment 8 to Novartis

   In Validation Report b(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:

   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.

   DPQ's Comments on Novartis's Response

   Please provide date of completion of additional studies you intend to perform and provide a copy of the revised validation report including data and discussion from additional studies.

II. Other Analytical Methods

(By Drs R. Gupta, J. Kenney, M. Joshi, M. Shahabuddin, and R. Velicheti)

Methods Reviewed

- b(4) - (Identity and Potency)
Sterility
Endotoxin
--b(4)-------
Viral Inactivation
Purity (-b(4)-----)
Mycoplasma
General Safety

DPQ's Original Comment

1. ----------b(4)---------- Communicated as Comments 4a and 4b to Novartis

   a) Although SOP 207057 is cited for determination of HA content, it is not clear how the HA content is calculated. Please provide English version of this SOP.

Company Response to Comment 003-4a-Q:

----------b(4)----------
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----------b(4)----------
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----------b(4)----------
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DPQ's Comments on Novartis's Response

----------b(4)----------
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4 Pages determined not to be releasable.

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

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

----------*b(4)*----------.

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

b. ----------
----------b(4)----------
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----------**b(4)**----------**:**

----------**b(4)**----------
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----------**b(4)**----------
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DPQ's Comments on Novartis's Response

Please provide date of completion of additional studies you intend to perform and provide a copy of the revised validation report including data and discussion from additional studies.

DPQ's Original Comment

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

Company Response to Comment 003-9c-Q:

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

DPQ's Comments on Novartis's Response

Range of the method should be between lower and upper levels of amounts that could be quantitated with acceptable accuracy and precision. Range should not be taken from the first and last point of the standard curve. Please comment.

DPQ's Original Comment

3. Viral Inactivation Test, Communicated as Comment 10 to Novartis

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

   Company Response to Comment 003-10-Q:

   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).

   DPQ's Comments on Novartis's Response

   Novartis has provided qualification reports for determining the inactivation of influenza virus strains (3.2.S.4.3 [Viral Inactiv]-4 and 3.2.S.4.3 [Viral Inactiv]-4a (Addendum)). Both reports are identical except the cover page and line 14 on page 2. Differences in these reports should be distinctly described with a justification -- b(4)*----------. Please explain in these reports the differences between ----------* b(4)*----------.*

   The - b(4)*- values for spikes in* b(4) *are* b(4) *times for H1N1 and H3N2 strains --* b(4) *---- times for B strain as compared to spikes in influenza vaccine matrices. That indicates either influenza vaccine matrix ----------* b(4) *---------- -----or presence of live virus in the influenza vaccines used as matrices in the qualification study. Though appropriate controls of influenza vaccines used as matrices have been included using* b(4) *eggs only, please confirm that the vaccine formulations used as matrices have been tested negative for the residual influenza virus in a test performed according to ---* b(4) *---------- eggs for each passage.*

   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* b(4) *temperatures for trivalent bulk preparations, ---------* b(4) *---------- ---------- incubation of inoculated eggs between -* b(4)*------. Please revise the SOP with regard of 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.*