STATISTICAL REVIEW AND EVALUATION

BLA Number:	125297, Amendment 4
Product Name:	Influenza Virus Trivalent Subunit (A/A/B hemagglutinin and neuraminidase; embryonated hen's eggs) Vaccine, Inactivated (Agrippal®)
Applicant:	Novartis Vaccines and Diagnostics, Inc.
Date Submitted:	January 30, 2009
Statistical Reviewer:	Tsai-Lien Lin Mathematical Statistician
Through:	Lev Sirota Acting Team Leader, VBT A. Dale Horne Branch Chief, VEB
To:	Anissa Cheung Ira Berkower Rajesh Gupta
CC:	Henry Hsu, Christopher Egelebo, chron

1. EXECUTIVE SUMMARY

In response to CBER comments on the original submission and Amendment 2 conveyed to Novartis on December 8, 2008, the applicant submitted Amendment 4 to provide details on the ---b(4)---------- Assay method and to provide answers to CBER questions.

Based on the information provided in the original submission and Amendments 2 and 4, Novartis' --b(4)---------- Assay model is considered not valid under the similarity condition required for --b(4)-----assay methodology. Regarding the

assay validation, the results based on the values calculated using an invalid analysis method should be interpreted with caution. It is recommended that the data for the validation experiments be re-calculated using a -b(4)- model with ----b(4)---------- and the validation parameters be re-evaluated using the re-calculated data.

2. BACKGROUND

Sections 3.2.S.4.2 and 3.2.S.4.3 of the original BLA submission contain information on the -b(4)- assay, which was used to determine the HA content in the influenza vaccine. The potency determinations for all non-clinical, clinical, and stability batches have been calculated using the ---b(4)----- assay method. However, for commercial US distribution, -----b(4)- ---------- will be released according to -b(4)- determinations calculated from the -----b(4)- ---------- assay method and using CBER reagents. On November 7, 2008, Novartis submitted in Amendment 2 a new -b(4)- method validation report, using -b(4)- assay methodology and reagents. Statistical comments on the original submission and Amendment 2 were discussed with the CMC and DPQ reviewers on December 1, 2008 and were conveyed to Novartis on December 8, 2008.

Amendment 4 was submitted on January 30, 2009. Included in this BLA amendment are Novartis' responses to CBER comments, a validation report for -b(4)- USA method, and a technical report which provides justification for the statistical model used in the ----b(4)- ---- method. This statistical assay review is based on the information available in the original submission and Amendments 2 and 4.

3. STATISTICAL EVALUATION

3.1 ASSAY CALCULATION

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

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

- --b(4)-------- Method: ----------b(4)----------
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  ------b(4)----------
  ----------b(4)----------

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

Reviewer's Comments:

In the review of the original submission, it was noted that Novartis' --b(4)---------- model with separate intercepts was not a valid model and the description of the ----b(4)---------- method lacked sufficient details. Since Novartis has agreed to use the b(4) method for US commercial distribution, CBER only requested clarification of the b(4) method in the IR letter sent to Novartis on December 8, 2009. With the details provided in Amendment 4, it appears that Novartis performed both b(4) and b(4) methods incorrectly. See comments to Q4bS1 below for further discussions on Novartis' b(4) method.

3.2 NOVARTIS' RESPONSES TO CBER COMMENTS

Below are the statistical evaluations of Novartis' responses to those CMC comments that are statistical or involve statistical considerations.

CMC Comment 4bi:

b. In reviewing the Validation Report No.b(4)07.007 VR 5 Rev. 1, we have the following comments:

i) Results reported for Section 3.1 ----------b(4)----------.

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

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2 Pages determined to be not releasable:

b(4)

Company Response to Comment 4bS2:

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

Reviewer's Comments:

---b(4)---
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CMC Statistical Comment 4bS3:

1. ---b(4)---
   ---.

Company Response to Comment 4bS3:

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

Strain	-- b(4)--	95% CI
- b(4)-----	b(4)	-- b(4)-----
- b(4)-----	b(4)	-- b(4)-----
- b(4)-----	b(4)	-- b(4)-----

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

Reviewer's Comments:

A -- b(4)---------- means that as the dose increases, the assay will tend to underestimate the dose. Novartis' discussion focused on the 95% CIs' not including b(4). It is not the right hypothesis to test though. What we want to see is whether the 95%CIs are contained in an acceptable range. Without a pre-specified acceptable range of the b(4), however, it is difficult to determine whether the

assay demonstrated satisfactory linearity. The lowest lower confidence limit is ---b(4). It will be the DPQ and CMC assay reviewers' judgment as to whether this is good enough. It should be noted that given the invalid analysis model used, the results of the validation of an invalid method may not be as meaningful as we thought.

4. CONCLUSIONS / RECOMMENDATIONS

Based on the information provided in the original submission and Amendments 2 and 4, Novartis' -- b(4)------ Assay model is considered not valid under the similarity condition required for -- b(4)------ assay methodology. Regarding the assay validation, the results based on the values calculated using an invalid analysis method should be interpreted with caution. It is recommended that the data for the validation experiments be re-calculated using a b(4) model with dilution on the logarithmic scale and the validation parameters be re-evaluated using the re-calculated data.