MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: June 10, 2009

From: Anissa M. Cheung

Through: Jerry Weir

Subject: Investigator's comments on CMC Item# 2 of the Complete Response to FDA Action Letter dated April 27, 2009, STN 125297 Amendments 14 &16

Sponsor: Novartis Vaccines and Diagnostics, Inc.

Title: Complete Response to FDA Action Letter dated April 27, 2009

To: License Application File 125297/0
Bernard McWatters

Novartis has submitted these amendments to provide complete response to FDA Action Letter dated April 27, 2009, and I am responsible to review the response with regards to the Validations of the --b(4)---------- holding time for the -b(4)----------in the -b(4)--------- process, and the ---b(4)---------- holding time for the ---b(4)---------- between the ----------b(4)---------- (CMC Comment 2).

After the issuance of FDA Action Letter, Novartis submitted Amendment 14 on April 30, 2009 which includes the validation report of ----b(4)---------- holding time for the --b(4)---------- during the ---b(4)--------- steps and an interim validation report of -b(4)--- holding time of the ---b(4)---------- process. In the validation study of --b(4)--- holding time of the ----------b(4)---------- lots of A/H3N2 strain (A/Uraguay/716/2007, NYMC X-175 C) and b(4) lots of A/H1N1 (A/Brisbane/59/07, IVR 148) were executed in the validation process. The virus from each lot of inactivated allantoic fluid is concentrated and purified by --b(4)---------- centrifugation and --b(4)--------- to produce ------b(4)---------- Therefore, the maximum hold time ----------b(4)---------- The purpose of this validation study is to demonstrate that the bioburden will not significantly increased during this hold time period and the --b(4)---------- holding time ------b(4)---------- has no adverse effect on the quality of the product.

The validation was initially executed on b(4) full scale lots of A/H1N1 (A/Brisbane/59/07, IVR 148) with lot numbers ----b(4)---------- concurrent with the b(4) 2009 production campaign. However, because of the mistake made in the calculation of the holding time, data from these -b(4)- lots of A/H1N1 strain would only be used as supporting information. The validation study was repeated with b(4) lot -b(4)-- of A/H1N1 (A/Brisbane/59/07, IVR 148) and b(4) lots (----b(4)----------) of A/H3N2 (A/Uraguay/716/2007, NYMC X-175 C) as shown in Tables 1 and 2 below.

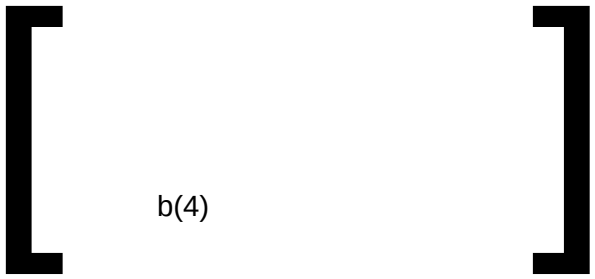
[b(4)]

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

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

[b(4)]

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



Based on the -b(4)- lots (--------b(4)----------) executed in the validation study, the bioburden of the --b(4)---------- collected after --b(4)--- holding time met the pre-defined acceptance criteria. All the validation lots met the specified critical control parameters and passed the routine in-process test specifications. The same types of micro organisms were identified in the samples --b(4)---------the -b(4)------ holding time in which there was an increase in bioburden. Therefore, I agreed that the --b(4)---------- holding time for the --b(4)---------- has no negative impact on the effectiveness of the production steps subsequent to the --b(4)---------- treatment.

An interim validation report of --b(4)---- holding time of the ----b(4)----------only includes data for -b(4)- lots of A/H3N2 strain and -b(4)- lots of A/H1N1 strain. The hold time validation data for the B strain was not provided in either amendment 14 or 16. ---------- -b(4)----- ----------. On July 13, 2009, OCBQ has received an update regarding Novartis' commitments in response to Pre-licensure inspection in February 5-13, 2009. In this submission, Novartis has included the complete validation report of -b(4)---- holding time of the -b(4)---------- This report contains data for b(4) lots of each seasonal influenza virus vaccine strain for the 2009-2010 season (A/H1N1/IVR-148, A/H3N2/X-175C, and B/Brisbane).

Instead of validating the -b(4)---------- holding time of the ----b(4)---------- between the ----------b(4)----------, Novartis decided to shorten the holding time to -b(4)--, and execute the validation with b(4)lots of A/H1N1 strain (A/Brisbane/59/07, IVR 148), b(4) lots of A/H3N2 strain (A/Uraguay/716/2007, NYMC X-175 C), and b(4)lots of B/Brisbane/60/2008 as shown in Table 1 below. The -b(4)---- holding time was chosen based on their standard manufacturing schedule.

[b(4)]

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

[b(4)]

Bioburden and endotoxin content of the ---------b(4)---------- holding time, were monitored during the validation study. The acceptance criterion for the bioburden at the end of the holding time was set at --b(4)---CCFU/ml, --b(4)--- than the action limit of the -------b(4)---------- The endotoxin acceptance criterion was set at --b(4)-------, which was the maximum value measured for --b(4)-------- in the last two years (2007-2008).

The reported data indicated that all validation lots (b(4) lots of A/H1N1 strain IVR-148:----b(4)---------- lots of A/H3N2 strain X-175 C:-b(4)----------lots of B/Brisbane/60/2008: --b(4)----------) met the specified critical control parameters and passed the routine in-process test specifications. The endotoxin levels of the ---------b(4)---------- storage at -b(4)- were very comparable, and they all passed the defined acceptable range. The bioburden content for each analyzed lot --b(4)---------- holding time showed an increase when

compared with the -b(4)---------- (---------- --b(4)----------); however, they are all within the defined acceptable range. Nevertheless, this increase in bioburden did not appear to have any impact in the --b(4)---------- process because the bioburden level dropped to ----------b(4)---------- -b(4)----------

[b(4)]

[b(4)]

[b(4)]

As shown in Tables 2, 3, and 4 above, the increased of bioburden after holding time is not constant for all lots, and the amount of bioburden increased seemed to be independent from the initial bioburden levels. However, the micro organisms identified at step -b(4)---------- after stored at ---b(4)---------- were the same species of micro organisms isolated in the previous phase of the process. I agreed that the --b(4)---- holding time for the -b(4)---------- between ----------b(4)---------- with -b(4)-has no negative impact on the effectiveness of the production steps subsequent to -b(4)------

Conclusion:

Based on the submitted data in these two amendments, I concur that Novartis has provided adequate information to support the --------b(4)---------- holding time for the --b(4)---------- during the --b(4)------ steps, and the --b(4)------- holding time for the -----b(4)----------. Intermediate products stored at these two hold time periods at -b(4)- have no negative impact on the quality of the --b(4)----------.