DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File BL STN 125297/0

From: Rebecca Olin, OCBQ/DMPQ/MRB2

Through: Chiang Syin, PhD, Chief, CBER/OCBQ/DMPQ/MRB2

Subject: Review of Novartis' response to the Complete Response letter dated April 27, 2009.

Action Due: November 28, 2009

Action Recommended

Additional questions were sent to the firm and responses were received on October 13, 2009. Reviews of the original and final responses were acceptable, and I recommend that this file be approved.

Summary

On April 27, 2009 a Complete Response Letter was issued to Novartis covering a range of product and facility issues. The original submission contained few complete summaries, poor translations, incomplete narratives and data summaries and misplaced documents which made review of the submission difficult. On May 29, 2009, Novartis responded to the Complete Response letter. Review of the firm's response generated additional questions which were conveyed to the firm on August 18, 2009. The firm responded to these questions on October 13, 2009 under Amendment 22. This Response Review memo covers the initial response to the CR letter as well as the response to the additional information request. Review of the firm's final responses was found to be acceptable and I recommend that this file be approved.

Additional Information Request

1. In CR Question #9, you were asked to provide your assessment used to determine equivalence between the filters; however you did not include filter characteristics and processing parameters. Please provide a comparison of filters including these criteria.

2. Regarding CR Question #9: Your assessment that the filters are equivalent to the --b(4)----- filter cannot be supported because your vaccine product was not used during the extractable testing for the ----b(4)---------- filters. A Model --b(4)---- approach was used by -b(4)- manufacturers based on the assumption that --b(4)--

----------b(4)----------; however there is no information that the product was tested to evaluate the presence of interfering substances in the bulk product. You have adequate data to support the use of the --b(4)----; however, you need to perform additional extractables testing in the presence of product for the -----b(4)---------- filters or provide scientific justification for why the Model --b(4)-- approach was acceptable. The additional extractable data can be submitted as a CBE-30. Please note that these filters should not be used until such testing is completed.

3. Regarding CR Question #7: Please note that in this question you were asked to provide information on -b(4)- testing and data in support of the extractables studies. You state at the bottom of Table 7-1 that the filters have been tested according to -b(4)- requirements. Please provide these reports and data.

Review

The following review covers the firm's responses to the CR letter dated April 27, 2009. Additional questions were generated and conveyed to the firm. For ease of review the CR questions appear below in bolded type followed by and evaluation and discussion of the firm's responses.

1. **According to the Quality Risk Analysis of Antigen Filtration for Flu in Building b(4), there are ---b(4)------- filters available for use at the -----b(4)--- filtration step; the ----b(4)---------- filters. This document states that the -b(4)--filters are identical but no information is provided in support of this claim. Please provide your evaluation of the filters and the data used to conclude that the filters are identical.**

Firm's Response: Acceptable

Novartis provided the same documents that were included in the BLA and did not provide their own assessment of equivalence among the filters. In their report for Process Validation of the for ----b(4)-- Filters which they presented as proof of the equivalence of the filters, the filters listed in Table 2 are listed only by the manufacturing name; no model names are identified. Each filter is also identified with a code number but the codes are not explained in this report. Additionally, as written in my review memo, the -b(4)--- filter is used for b(4) of the -b(4)- conformance lots; the -b(4)- filter is used in two lots and the-b(4)-is used in only one lot. There is no narrative defining the validation approach with regards to filter equivalence and it's not clear how the use of the filters proves the equivalence of the filters.

Novartis provided the same Quality Risk Analysis that was included in the original BLA. This Risk Analysis was conducted to identify, evaluate and document the critical process parameters for the for -----b(4)-- filtration of flu antigen. This report states that the filters are equivalent based upon the validation with product that was conducted and tested for -----b(4)----------. There is no mention of the extractables test, however, and since two of the -b(4)- filters were

not tested with product, it is unlikely the filters can be considered equivalent based on the incomplete extractables testing. Additionally, the factors used to determine equivalence do not include filter characteristics and processing parameters. **See IR #1**

To support the assertion that the filters are equivalent, vendor reports were included in the submission and to the CR response; however the vendor reports for the ---b(4)---------- filters used -b(4)- as the -b(4)- according to their Model --b(4)-- approach. There was no data or narrative provided that indicated that the product was assessed against b(4) to support -b(4)-as a suitable model -b(4)-. It appears that the --b(4)-- filter is used most often during processing and data exists that supports the use of this filter. **See IR #2.**

Response to IR#1: Novartis responded to the additional information request on October 13, 2009 in which they committed to provide a post-approval submission to support the use of the ------b(4)------ filters. The submission will contain a comparison of the -----b(4)---------- ---------- filters including filter characteristics and process parameters.

Response to IR#2: Novartis responded to the additional information request on October 13, 2009 in which they committed to provide a post-approval submission to support the use of the ---b(4)---------- filters. The submission will contain either additional extractable testing in the presence of product or a scientific justification as to the suitability of the use of the Model --b(4)-- approach.

These responses are acceptable.

2. **In the Quality Risk Assessment, the Batch Record, and the Validation Report for the** -----b(4)-- **Filtration Process the specific type of filter is not identified; however the vendor validation of the** -----b(4)-- **filters provided in your submission related to specific filters such as the ----------b(4)---------- ---------- Please provide the specific models of** -----b(4)---------- **filters that you are using for** -----b(4)---------- **filtration and indicate if the filters are being used** -----b(4)-- **among strains. If so, please provide your justification in light of the vendors' use of specific strains in their validation reports.**

Firm's Response: Acceptable

The filters and code numbers were identified as the -----b(4)---------- ----------. The similarity in the monovalents' characteristics was provided in support of how the filters were used during process validation.

Novartis states that influenza viruses A and B are very similar in overall structure. The virus particle is -b(4)- nanometers in diameter and either roughly spherical or less commonly filamentous. Monovalent Pooled Harvest ----b(4)---------- ---------- The chemical difference between HA

and NA from different virus types is not considered to be significant, therefore, the presence of HA and NA from different virus types (A/H1N1, A/H3N2 and B) is not considered to influence the performance of the -----b(4)--- filtration.

The similarity between monovalent strains does support how the filters were used during process validation and also supports --b(4)-------- use of the filters during processing; however, the equivalence of the filters has not been fully supported because the extractable studies for the ---b(4)-------- filters did not use the product in their testing. See IR #1.

3. There is no data in the submission regarding -b(4)- testing for extractables and leachables for the -----b(4)---------**filters. Please provide data for these studies.**

Firm's Response: Acceptable

Validation of the -----b(4)-- filters used at the -b(4)- facility was conducted per SOP #247319-01, Guidelines for the validation of a ---b(4)---------- filter to be used for the final production process." Study reports were provided for the following filters:

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

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

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

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

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

Novartis concludes this response by stating that -b(4)-- also used the Model -b(4)----- approach because in their available analytical methods to detect extractable substances, -b(4)-- in Novartis drug product could cause interference. However, there is no data to support that the product produces interference to detection of extractable substances. --b(4)-- did use product in their testing but used -----b(4)---------- to detect extractables. Additional information regarding the use of Model ---b(4)--- was asked of Novartis. Their response, dated October 13, 2009, was acceptable. See response to Question #1.

-b(4)-testing for extractables and leachables included ---------b(4)---------- ---

--- **See IR #3.**

Response to IR#3: Novartis responded to the IR letter on October 13, 2009 in which a summary of tests were presented. They included General Chapters ---b(4)---------- Reference was made to the ---b(4)---------- Validation Guide and Biocompatibility Certificate which contained references to Current -----b(4)---------- -----b(4)----------

4. **The vendor reports for the --------b(4)------- filters are not consistent as to the types of tests or in some cases the depth of testing conducted (see the --b(4)------ extractables testing compared to that of --b(4)-----). Please provide your testing protocol including information as to what specific validation tests were required, what worst case testing was required, the acceptance criteria and your evaluation of the study results.**

Firm's Response: Acceptable

Novartis provided SOP 247319-01, "Guidelines for the validation of a --b(4)---------- ---------- filter to be used for the final production processes," as their approach to filter validation. Tests required include ----------b(4)---------- ----------

5. **According to Validation Report for the Syringe Filling Process for Filling Machine --------b(4)----------, reference is made to a dosage verification study conducted on samples taken every --b(4)----. There was no information regarding the purpose of the study and no data was presented to indicate the outcome of the study. Please provide information regarding the study, the test results and study conclusions.**

Firm's Response: Acceptable

The dosage verification study referred to in the submission is synonymous with the target fill volume check that is routinely performed during filling operations. Data was provided for three lots. Results showed no syringes were outside of Control Limits (---b(4)-------) or Reject Limits (---b(4)---------).

6. **In your submission there was no information or data submitted for the --b(4)---------- ------used to -b(4)-- the stopper bags or the -b(4)----- machine used to unpack syringes. Please provide the validation protocol and final reports for these pieces of equipment.**

Firm's Response: Acceptable

The --b(4)---------- of materials that are to be introduced into the Class b(4) area. Materials not suitable for -b(4)----------by means of the --b(4)-- system. The machine consists of a --b(4)---------- and a -b(4)- compartment. The ----------b(4)---------- ----------. The non-sterile side is equipped with a ----------b(4)---------- that controls the machine.

Validation included maximum and minimum loads for each standard load. Biological indicators containing at least -b(4)- concentration of ----*b(4)*---------- with a D value of -b(4)-; at least -b(4)- pieces were placed within maximum loads and at least b(4) were placed within minimum loads.

The b(4) cycle consists of the following steps:

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

All BIs were negative for growth. Data shows that bioburden is reduced by b(4) lots within b(4) ------

7. The new filling machine referred to in the submission and that has been subsequently withdrawn includes an -b(4)- syringe --b(4)----------. There is no reference to a --b(4)-- step for the syringe -b(4)- for filling line --b(4)---. Are the syringe -b(4)- for this line--b(4)--before they enter the Class b(4) filling room? If so, please provide the validation of this step. If not, please explain how you control potential contamination from syringe -b(4)- from entering the filling room.

Firm's Response: Acceptable

The unpacking (debagging) of the -b(4)- is carried out under Grade b(4) conditions. b(4) are sterilized by b(4) and the external surface of the b(4) is sterile.

8. Regarding Inspection Machine -b(4)--: The validation information provided was insufficient to conduct a complete review. Please provide your validation protocol and final report which should include:

a. A complete description of the inspection machine;
b. A description of what --b(4)---------- results mean;
c. A description of how the validation tests were conducted including a description of test sets, number of runs, acceptance criteria and a discussion of the results and conclusion;
d. Please provide data to support how the False Reject Rate was calculated and provide data for the False Accept Rate.
e. Provide your procedure for the performance test runs conducted before and after each batch is inspected including.

Firm's Response: Acceptable

a. A complete description of the inspection machine;

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

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

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

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- ----b(4)----------
- ----b(4)----------
- ----b(4)----------
- ----b(4)----------
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----------b(4)----------
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b. **A description of what ----------b(4)----------results mean;**

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

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c. A description of how the validation tests were conducted including a description of test sets, number of runs, acceptance criteria and a discussion of the results and conclusion;

---------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)--------

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

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d. Please provide data to support how the False Reject Rate was calculated and provide data for the False Accept Rate.

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

---------b(4)-------- ---
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e. Provide your procedure for the performance test runs conducted before and after each batch is inspected including a description of the test sets.

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

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

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9. Please provide media fill data to support the assurance of sterility after ---------- b(4)---------- through formulation, storage and aseptic filling of the final product.

Firm's Response: Acceptable

Novartis provided data from three media fills conducted in 2006 to support the aseptic processing in ---b(4)----------. For the purposes of this file, I reviewed only --b(4)----- data as that is the formulation and filling line that is included in this submission. All three media simulations were carried out under worst case conditions including the greatest number of aseptic connection, the maximum number of people (b(4)) was present during formulation; materials and equipment used were out of date for sterile hold times; and cleaning of the area exceeded the hold time. Formulation was conducted in a --b(4)--- -------
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10. The documents referred to as containing extractable and leachable data (3.2.P.2.3) for the container closure qualification did not contain this information. Please submit all extractable and leachable studies and data including those conducted according to -b(4)- requirements.

Firm's Response: Acceptable

This question was asked because the section/link noted above did not contain E&L information for the rubber plunger stopper for the staked needle closure. Novartis provided additional information to that in the original submission and included the correct location of additional E&L information. The syringe stopper formulation complies with the requirements of the ----------b(4)---------- and the --b(4)----------

The plunger stopper for the new --b(4)---- syringe is the same as that used for the staked needle and, thus, also complies with --b(4)--------- Additionally, a leachable study is underway focusing on the tip cap (--b(4)----------). Although the possible contact area of the tip cap and the product is very small and considered to be an unlikely source of leachable components, the leachable study was limited to ----b(4)---------- months of data are available and were included in the response. The technical report conclusion at the -b(4)- month time point was there were no ----b(4)---------- found above the reporting limit. The study will be continued to b(4) months and Novartis commits to informing the Agency of any anomalous result during the study.