



DEPARTMENT OF HEALTH AND HUMAN SERVICES **Public Health Service**
Food and Drug Administration

Memorandum

DATE: Nov. 9, 2012

FROM: Xianghong Jing, Ph.D., OVR, DVP, HFM-460

SUBJECT: STN 125408/0: Biologics License Application Original Submission, FLUCELVAX, Influenza vaccine (MDCK cells)

SPONSOR: Novartis Vaccines and Diagnostics GmbH Immune Vaccines Inc.

TO: STN 125408 file
Brenda Baldwin, OVR, DVRPA, HFM-475

THROUGH: Zhiping Ye, Ph.D., DVP
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Cross ref: IND 11580-Human Influenza Virus Type A and B (H1N1;H3N2; MDCK cells) Hemagglutinin Vaccine, Purified, Inactivated

BB-MF ----(b)(4)----- Description and Characterization of MDCK master cell bank

Executive Summary and Recommendation

Novartis Vaccines and Diagnostics, Inc. (Novartis) submitted a Biologics License Application (BLA) for human Influenza virus type A (H1N1; H3N2) and B hemagglutinin Vaccine, which is purified from virus propagated in Madin Darby Canine Kidney (MDCK) continuous cells. The inactivated vaccine, Flucelvax, is formulated to contain 45 micrograms (μg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 μg HA each of Influenza Type A (H1N1), Influenza Type A (H3N2) and Influenza Type B, to be administered intramuscularly. The Flucelvax is intended for active immunization of persons 18 years of age and older against influenza disease caused by influenza virus subtypes A and B contained in the vaccine. US development of this vaccine was conducted under BB-IND 11580.

In this submission, Novartis provided data to support the manufacturing process 1.1 for production of Flucelvax. Process 1.1 the “second generation” was established from the process 1.0 “first generation process” and was validated on manufacturing ---(b)(4)---, which are dedicated for production of influenza cell culture monovalent bulks in Marburg, Germany. Monovalent bulks are mixed and formulated with -----(b)(4)----- at the Marburg, Germany facility. The formulated trivalent bulk is transported to -----(b)(4)-----.

I have reviewed the CMC section of the submission and have focused on Module 3-Drug Substance, Drug Product and Batch Records, which include the manufacturing processes-validation, processes-control, the quality of the drug substance and product, and stability protocols. I have also reviewed Package Insert and Lot Release Protocol. During review of data provided in the original submission, the manufacturer was contacted for additional information and clarifications. The additional information related to the CMC issues are provided under amendments 125408/10, 12, 16, 17, 21, 22, 24, 26, 28, 29, 32, 34, 37, and 38, which were reviewed and found to be acceptable.

Below are some of the key issues in the memo from the CMC product reviewer’s perspective view:

1) *The comparability between process 1.0 and process 1.1:* The manufacturing process 1.0 was the “first generation process” and was validated on manufacturing (b)(4)-- during the 2004-2005 influenza season. Process 1.1 is an optimized process with several process improvements to enhance the robustness of the manufacturing platform. Since the Phase II and III clinical trials were conducted by using products from process 1.0, this review also focused on the comparability between process 1.0 and process 1.1. Among the strains used for process comparability study, A/Brisbane/59/2007 IVR148 (H1N1) was processed with both process 1.0 and 1.1 configurations. The results of validation runs with three lots from each process concluded that the products produced from both processes were comparable.

2) *Consistency of Manufacturing:* Among the (b)(4) monovalent lots analyzed for quality control,(b)(4)from process 1.0 (preclinical and clinical lots) and(b)(4)from process 1.1, a total of(b)(4) batches including (b)(4) from process 1.0 and (b)(4) batches from process 1.1 covering H1N1, H3N2, and B viruses, are used for process and stability consistency study. All the test parameters are within the acceptance criteria for monovalent bulk.

In addition, a total of(b)(4)trivalent lots from process 1.0 are put on trivalent batch analysis. Among which, three trivalent lots which are used in clinical study, lot# 522009010, 522008010, and 522011010 with strains A/New Caledonia (H1N1), A/New York (H3N2), and B/Jiangsu, are subjected to trivalent lot process and stability consistency study. As a parallel, three trivalent lots from process 1.1 (b)(4), lot# ----(b)(4)----, ----(b)(4)----, and ----(b)(4)---- with strains A/Victoria (H3N2), A/Brisbane (H1N1), and B/Brisbane have been put on stability and process consistency study. All the tested parameters meet the trivalent bulk specification.

For the final product used in the clinical phase III study, three consistency batches each in the presentation with needle or without needle were stability tested successfully.

3) The suitability of using egg-based reference virus for Flucelvax production in MDCK cells: The HA and NA identities of the reference viruses are confirmed by WHO collaborating center. Currently all reference viruses provided by the WHO collaborating center are derived from embryonated eggs. The working seed viruses used in the production of Flucelvax are passaged ---(b)(4)---- times on MDCK cells for further adaptation. The optimal growth condition and quality attributes for each strain on MDCK cell is characterized by a panel of analytical methods during the growth kinetics study.

4) The suitability of ----(b)(4)----- red blood cells in detection of mammalian cell adapted influenza virus: Since -(b)(4)- RBC may not be suitable for some vaccine candidate viruses, such as those directly isolated from cell, the applicant submitted the validation reports of ---(b)(4)--- red blood cell based HA titer testing for all three vaccine components, H1N1, H3N2 and B viruses. The data is satisfactory.

5) Evaluation of Manufacture production lines: This submission includes the manufacturing lines, ---(b)(4)-----, which are dedicated for production of influenza cell culture monovalent bulks. The validation master plan of (b)(4) is also included in the submission and reviewed for its suitability to evaluate (b)(4) as an additional line to produce Flucelvax. The product reviewers conclude that ---(b)(4)----- are adequate for production of Flucelvax, but Comparability Protocol submitted to support manufacturing -(b)(4) does not provide sufficient detail in order to make an adequate assessment. CBER recommended removing -(b)(4) from the BLA and requesting a meeting at a later time to discuss the licensing plans for -(b)(4).

6) Validation of ---(b)(4)----- columns and column life time study: -----
------(b)(4)-----
----- columns are critical for concentration and purification of Flucelvax vaccine. In additional to evaluate the quality of the vaccine product, this review also focused on the process validation of the effective life span of the packed ----
---(b)(4)----- columns under production conditions.

There is a concern on the accumulation of viral contaminants in the ----(b)(4)----- columns especially between manufacturing campaigns when there is a strain change involved. Together with DMPQ, we communicated with Novartis regarding the column life time ((b)(4) runs) studies and cleaning and regeneration procedures. Accordingly, Novartis developed a procedure for regenerating the ---(b)(4)----- columns between product loads for each production run and between influenza strain changes. A continuous routine monitoring program has been implemented to monitor the cleanliness of ----(b)(4)----- columns. Column life time study report will be submitted to the agency by Dec. 2014 when the proposed (b)(4) runs are completed.

7) Beta-propiolactone (BPL) inactivation kinetics and removal validation: BPL inactivation validation is required per season for each novel influenza strain in order to

demonstrate the validity of the inactivation process. The inactivation kinetics as characterized by ----(b)(4)----- reveals a time dependent decrease of the infectious virus titers during the course of the inactivation.

Removal of BPL for process 1.0 has been adequately validated, showing the residual BPL level in the ----(b)(4)----- is less than (b)(4). Validation report for the process 1.1 was incomplete in the original BLA. With additional information request, we noticed that Novartis altered the testing method to (b)(4) based limit test. Novartis has been advised that the altered (b)(4) test is only suitable for limit test of BPL level in ---(b)(4)-----, but is not acceptable for BPL ----(b)(4)----- validation. For the 2012-2013 influenza vaccine production season, Novartis committed to test the residual BPL level in all the ---(b)(4)-----, with specification less than (b)(4), until BPL -----(b)(4)----- is successfully validated.

8) Strain change for 2012-2013 Influenza vaccine campaign: In order to market Flucelvax in US for the current influenza season, the strain change information for the 2012-2013 influenza vaccine composition was submitted as an amendment 125408/33. It contains the data of WHO and VRBPAC recommended strains, package insert, and cartoon/syringe labels. The vaccine is formulated to contain 15 µg HA of each of the following three influenza strains recommended for the 2012/2013 influenza season in a pre-filled syringe: A/Brisbane/10/2010 (Wild Type) (H1N1); A/Victoria/361/2011 IVR-165 (H3N2); and B/Wisconsin/1/2010 (Wild Type) (B). The data and information in this amendment are adequate.

All outstanding issues related to CMC have been resolved; this BLA is recommended for approval.

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2.3 Drug Product (Trivalent Inactivated Influenza Cell Culture Vaccine)

2.3.1 Description and Composition of the Drug Product

2.3.2 Manufacture of Drug Product

2.3.2.1 Description of manufacturing process and process controls

2.3.2.2 Batch Formula

2.3.2.3 Control of critical steps and intermediates

2.3.2.4 Process validation and/or evaluation

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2.3.4 Control of Drug Product

2.3.4.1 Specification

2.3.4.2 Analytical Procedures

2.3.4.3 Validation of Analytical Procedures

2.3.4.4 Batch Analyses

2.3.5 Reference Standards or Materials

2.3.6 Container Closure System

2.3.7 Stability

2.3.7.1 Stability Data Summary and Conclusions

2.3.7.2 Post-approval Stability Protocol and Stability
Commitment

2.3.8 Validation of Hemagglutination inhibition test for clinical study

2.4 Strain change for 2012-2013 influenza vaccine composition

1. Introduction

Flucelvax is a seasonal influenza virus vaccine predominantly containing the purified outer membrane proteins, haemagglutinin (HA) and neuraminidase (NA), from each of the three influenza virus strains recommended annually by the World Health Organization (WHO) for the Northern Hemisphere and FDA-Vaccine and Related Biological Products Advisory Committee (VRBPAC) for the US.

The documentation and information in this BLA submission is to support market approval for active immunization of persons 18 years and older against influenza disease caused by influenza virus subtypes A (both H3N2 and H1N1) and B contained in the vaccine.

The Drug Substance (monovalent bulk) from each of these three selected virus strains is produced in Madin-Darby Canine Kidney (MDCK) cell culture. Each of the three monovalent bulks is prepared by inactivation, detergent disruption, and purification before combined to produce the trivalent final drug product, containing 15 µg per dose of hemagglutinin antigen from each of the three virus strains. The final product is preservative-free and non-adjuvanted. Flucelvax is presented as a liquid for injection, in a (b)(4) glass pre-filled syringe, containing 0.5 mL of antigen suspension. The antigens are suspended in a clear, sterile, buffered aqueous solution for injection. The potency of the vaccine is expressed as the concentration of the HA protein.

Protection against influenza can be conferred by serum antibodies, and the immune responses to injectable influenza vaccines are routinely assessed using serological haemagglutinin inhibition (HI) antibody measurements. All post vaccination sera for immunogenicity analyses in the Flucelvax clinical studies were collected at 3 weeks after vaccination. Effectiveness of Flucelvax was confirmed in an international (U.S. Finland and Poland) randomized, placebo-controlled, clinical study for prevention of culture-confirmed influenza in adults 18 through 49 years of age. The effectiveness of Flucelvax in adults older than 49 years of age, including in the elderly, was supported by immunogenicity data in adults in which the antibody responses in Flucelvax recipients were comparable to antibody responses to those who received Agriflu (an egg-derived US-licensed) vaccine.

Alternate names and designations for Flucelvax vaccine that are used in the documentation provided with this BLA include: 1) Trivalent, inactivated subunit-influenza vaccine, consisting primarily of haemagglutinin and neuraminidase (US compendial name); 2) Influenza vaccine, surface antigen, inactivated, prepared in cell cultures (EU compendial name); 3) Cell-culture derived influenza vaccine (CCI); 4) Influenza cell culture vaccine (FCC); 5) cTIV (cell-culture derived trivalent influenza vaccine); 6) FLUCELVAX (proposed trade name). The trade name FLUCELVAX was used in the draft Package Insert that is included with this BLA.

2. Chemistry, Manufacturing and Controls

2.1. Manufacturing Facilities

The manufacture of Flucelvax is carried out at Novartis locations in three countries:

Marburg, Germany manufacturing facility is for 1) manufacture and testing of the monovalent bulk drug substance, 2) trivalent bulk formulation and QC testing, 3) supporting areas and materials management. The manufacture consists of the production of monovalent bulk concentrates by fermentation, purification, inactivation, and splitting, followed by the formulation of a trivalent final bulk. The formulated bulk is then ----(b)(4)----- for aseptic filling into single-use syringes. The shared/dedicated use of each manufacturing area is described.

---(b)(4)--- manufacturing facility is for 1) Syringe filling, 2) QC testing and 3) materials management. Flucelvax syringe filling and inspection operations are performed in -----(b)(4)----- and final packaging and labeling operations performed in ----(b)(4)-----.

Facilities information including filling lines, warehouse, cleaning and pretreatment area, media and buffer preparation, and Quality Control areas are provided.

In amendment 26 and 28, Novartis provided plan for Holly Springs site through year (b)(4). Based on the timing of licensure for the 2012-13 flu season, the role of Holly Springs warehouse for Flucelvax for the 2012-13 flu season is limited to quality control test and final product storage. The Quality Control department is responsible for SRID testing on ---(b)(4)----. Novartis plans to submit a PAS in (b)(4) to support primary manufacturing out of Holly Springs after approval of this BLA. This will enable Holly Springs to conduct ----(b)(4)----- manufacturing as well as package -----(b)(4)-----

All three sites (Marburg, (b)(4), and Holly Springs) have Quality Control laboratories.

Comments: CBER performed pre-licensure inspection at the Marburg facility in March 2012. Total 11 observations were documented (see EIR report). The responses from Novartis were reviewed in separate review memos from inspection team.

2.2. Drug Substance (Influenza Cell Culture Monovalent Bulk)

2.2.1 Description and general properties of the Drug Substance

35 pages redacted due to (b)(4)

2.3 Drug Product (Trivalent Inactivated Influenza Cell Culture Vaccine)

2.3.1 Description and Composition of the Drug Product

The vaccine is prepared by inactivation, detergent disruption, and purification to contain 15 µg per dose of hemagglutinin antigen from each of the three virus strains. The final product is preservative-free and non-adjuvanted. Flucelvax is presented as a liquid for injection, in a (b)(4)-- glass pre-filled syringe, containing 0.5 mL of antigen suspension. The antigens are suspended in a clear, sterile, buffered aqueous solution for injection. The composition of the final product is listed in the table below:

Names of Ingredients	Quantity per dose (0.5 mL/dose)	Function
<u>Active Ingredients</u> hemagglutinin (HA) and neuraminidase (NA) antigens from the influenza virus strains	≥15 µg HA (per strain)	Influenza vaccine antigen
<u>Excipients</u> ---(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)-----	(b)(4)----- (b)(4)----- (b)(4)---- (b)(4)- (b)(4)- (b)(4)-

2.3.2 Manufacture of Drug Product

2.3.2.1 Manufacturers and facility sites

Manufacturer / Site	Responsibility
<u>Novartis Vaccines and Diagnostics GmbH</u> Emil-von-Behring-Str. 76 35041 Marburg - Germany	Production of final bulk (formulation) Quality control tests
----- <u>(b)(4)</u> ----- ---(b)(4)--- -----(b)(4)-----	Filling and Packaging ----- <u>(b)(4)</u> -----
<u>Novartis Vaccines and Diagnostics</u> 475 Green Oaks Parkway Holly Springs, NC 27540	Quality control tests (SRD test).

2.3.2.2 Description of manufacturing process and process controls

5 pages redacted due to (b)(4)

Redacted due to [(b)(4)]

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

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

Table 2.3.4.1-1: Finished Product (Release Specifications)

Test	Method	Requirements
Sterility	----- (b)(4) -----	Complies
Endotoxin	----- (b)(4) -----	---- (b)(4) -----
General safety	General safety in mice and guinea pigs	Pass
Appearance	Visual inspection	Clear to slightly opalescent liquid
Extractable volume	---- (b)(4) -----	--- (b)(4) ----
Hemagglutinin antigen (potency)	Single-radial diffusion (SRD) method	----- (b)(4) ----- ----- (b)(4) -----

* if calculated as arithmetic mean of 3 replicates
** if calculated as arithmetic mean of 6 replicates

Comment: CBER agreed to waive the sterility release test for final trivalent bulk based on the current testing scheme. Endotoxin --(b)(4)---- is included as a releasing test for

---(b)(4)----- . Regarding final container potency testing, we recommended that the sponsor add a potency test to final container release tests. The test was included in the final Lot Release Protocol (please see LRP), and reviewed by DBSPQ.

Regarding test of residual infectious virus in the --(b)(4)---- lots, CBER requested to use both ----(b)(4)----- assay for the first three --(b)(4)---- batches. Novartis provided the (b)(4) safety report in amendment 38 with --(b)(4)----- . The (b)(4) based test is adapted from Fluvirin, an egg based inactivated flu vaccine manufactured by Novartis. The validation report is included in amendment 38.

----- . All three Flucelvax ----(b)(4)---- batches, -----(b)(4)-----, were shown to be successfully inactivated. In addition, the sample matrix of the --(b)(4)--- is not inhibitory to the growth of the three seed viruses of 2012-2013 season.

For the 2013-14 influenza season, Novartis has committed to testing the first three lots of --(b)(4)-- of each strain using ----(b)(4)----- and testing all --(b)(4)---- lots with --- (b)(4)----- . If all the -----(b)(4)----- pass the (b)(4) test, then can drop (b)(4) testing for the rest of the season. All subsequent lots during the same season will be released for residual virus using only --(b)(4)--.

Review of --(b)(4)-- based residual infectious virus assay is covered by DBSPQ.

2.3.4.2 Analytical Procedures

The analytical methods used to release the ----(b)(4)-----, the finished product, and the packaged products are compiled in the following Table.

Table: Analytical procedures overview

Assay	Method
---(b)(4)----	----- (b)(4)-----
(b)(4)	----- (b)(4)-----
---(b)(4)----	----- (b)(4)-----
Total DNA content ---(b)(4)-----	----- (b)(4)-----
hemagglutinin antigen	single radial diffusion (SRD) method
sterility	----- (b)(4)-----

Assay	Method
endotoxin	----- (b)(4) -----
general safety	in vivo test in guinea pigs and mice
appearance	visual inspection
extractable volume	----- (b)(4) -----
hemagglutinin antigen	----- (b)(4) -----

2.3.4.3 Validation of Analytical Procedures

The analytical procedures for the release of the ----(b)(4)----, the finished product, and the packaged product areas described above have been validated according to the relevant guidance from ----(b)(4)----- . The validation results are satisfactory.

Validation of Single Radial Immunodiffusion (SRD) assay:

SRD is the potency assay of monovalent ----(b)(4)----- . The Haemagglutinin (HA) molecule is the active ingredient in the Influenza vaccine and HA content is determined by single radial immuno-diffusion (SRD) using polyclonal antisera specific for each strain in the monovalent bulk, ----(b)(4)--- and final vaccine. In addition, the test results of the SRD assay are also used for the stability evaluations of the Flucelvax monovalent bulks and final product.

Novartis provided sufficient data to validate the SRD assay. For Flucelvax production in US, the SRD method for determining HA potency will follow the US standard, using CBER reagents and the parallel line model to release all monovalent ----(b)(4)----- .

Comment: *The US SRD method validation (parallel line method) was performed with one monovalent lot from each of A/Brisbane(H1, -----(b)(4)-----, A/Victoria/210/2009 X-187(H3, lot# ----(b)(4)----, and B/Brisbane/60/2008 -----(b)(4)----- . The antisera used are CBER Influenza antibody reagents to A/Brisbane/59/2007-like, A/perth/16/2009-like, and B/Briabane/60/2008 for H1, H3 and B monovalent bulk samples respectively.----- (b)(4)----- . The assay validation reports provide the details of testing parameters, including specificity, repeatability, intermediate precision, accuracy, linearity, limit of quantification range, and robustness. Validation study results for both 3 monovalent lots and ----(b)(4)---- met the acceptance criteria. Therefore, the assay validation is successfully achieved. The validation for SRD assay was reviewed by the reviewers from OCBQ/DBSPQ in a separate review memo.*

Qualification for suitability of CBER egg-based influenza reference reagents

Flucelvax is produced in MDCK cell culture. Studies have shown that the physicochemical properties of the HA derived from infected MDCK cells and eggs are

very similar. Only the ----(b)(4)----- determined in ----(b)(4)----- is slightly higher in the MDCK derived protein, which could be explained by a different carbohydrate composition. Usually the analysis of the HA antigen, produced in MDCK cells, works properly with the egg-based NIBSC reference substances. Novartis provided qualification report for suitability of CBER egg-based Influenza reference reagents for use with the flu cell culture generated material for testing of HA potency.

The SRD method is used to determine the relative potency of a test sample by comparison of Test to Standard assay response. EP method uses a slope ratio model to calculate the SRD results, whereas parallel line model is used in US. The calculation of HA potency using the parallel line method is based on the assumption that reference and test samples contain the same functional proteins in the similar proportion. A consequence of biological similarity implies statistical similarity manifested by standard and test curves in the SRD assay have equal slope - are parallel.

Amendments 6 and 8 provide the summary of the testing performed to assess suitability of CBER egg based influenza reference material for SRD HA potency determination of monovalent bulk samples produced in cell culture.

Comments: *Three lots of monovalent bulk for each strain, A/Brisbane/59/07 (H1N1), A/Victoria/210/09(H3), and B/Brisbane/60/2008 are included in the qualification study. The testing results of influenza vaccine from MDCK cells with egg based reagents met the predefined criteria. However, the percentage of Recovery of the HA content measurement by SRD to the one determined through -----(b)(4)----- is only (b)(4). It appears that the calculation of HA potency by SRD test for cell culture product using egg-based reagent may underestimate the HA content. Novartis explained this underestimation was due to the loss of SRD activity in these samples. Overall, Novartis provided sufficient data to support the use of egg-based reagents in testing HA potency by SRD for the influenza vaccine made in MDCK cells. This reagent qualification needs be done for each new strain. We have concurrence with DBSPQ reviewer in this regard.*

Since suitability of egg based reagents in determining the HA content by SRD needs be evaluated for each new strain, DBSPQ/CBER sent recommendation on the usage of SRD reagents for Flucelvax 2012-2013 season to Novartis, depending on the availability of homologous cell based reagents for each stain. Confirmation testing of the HA content is carried out by DBSPQ. The review details are covered in the DBSPQ memo.

2.3.4.4 Batch Analyses

Batch analysis data for all relevant trivalent and final product lots (preclinical, clinical, And consistency studies) are provided. The genealogy of these lots is provided in Table below.

Results of these batches and Quality Control summaries are presented for lots used in the clinical studies and manufacturing consistency batches.

Fill/Finish Product Lot	Trivalent Bulk Lot	Monovalent Bulk Lots	Batch Use(s)
Process 1.0			
---(b)(4)---	---(b)(4)---	----(b)(4)---- ----(b)(4)---- ----(b)(4)----	Pre-Clinical tox
---(b)(4)--- (w/o needle)	---(b)(4)---	----(b)(4)---- ----(b)(4)---- ----(b)(4)----	Pre-Clinical study
522 002 011 (w/o needle)	---(b)(4)---	----(b)(4)----- ----(b)(4)----- ----(b)(4)-----	Phase 1/2 (V58P1)
522 003 011 (w/needle)	---(b)(4)---	----(b)(4)----- ----(b)(4)----- ----(b)(4)-----	Phase 2 (V58P2)
522 007 011 (w/needle)	---(b)(4)---	----- (b)(4)----- ----- (b)(4)----- ----- (b)(4)-----	Phase 3 (V58P4)
522 008 011 (w/o needle)	---(b)(4)---	----- (b)(4)----- ----- (b)(4)----- ----- (b)(4)-----	Phase 1/2 (V58P5) Consistency batch

Finish Product Lot	Trivalent Bulk Lot	Monovalent Bulk Lots	Batch Use(s)
522 008 012 (w/needle)	---(b)(4)---	----- (b)(4)----- ----- (b)(4)----- ----- (b)(4)-----	Phase 3 (V58P4E1) Phase 3 (V58P9)
522 009 011	---(b)(4)---	----- (b)(4)-----	Phase 3 (V58P9)

(w/needle)		----- (b)(4) ----- ----- (b)(4) -----	
--- (b)(4) ---(w/o needle)	--- (b)(4) ---	----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) -----	Consistency batch
522 011 011 (w/needle)	--- (b)(4) ---	----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) -----	Phase 3 (V58P9)
--- (b)(4) ---(w/o needle)	--- (b)(4) ---	----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) -----	Consistency batch
522 017 011	--- (b)(4) ---	---- (b)(4) ----- ---- (b)(4) ----- ---- (b)(4) -----	US Efficacy trial Phase 3 (V58P13)
Process 1.1			
--- (b)(4) ---(w/o needle)	---- (b)(4) -----	-- (b)(4) -- -- (b)(4) -- -- (b)(4) --	Stability and process consistency
--- (b)(4) ---(w/o needle)	---- (b)(4) -----	-- (b)(4) -- -- (b)(4) -- ---- (b)(4) -----	Stability and process consistency
--- (b)(4) ---(w/o needle)	---- (b)(4) -----	---- (b)(4) ----- ---- (b)(4) ----- --- (b)(4) -----	Stability and process consistency

Comment:

Batch analysis data of total ~~(b)(4)~~ trivalent lots manufactured from process 1.0 are provided. This includes three consistency lots, -----~~(b)(4)~~----- with strains A/New Caledonia, A/New York, and B/Jiangsu.

Batch analysis data of three trivalent lots from process 1.1 -----~~(b)(4)~~----- with strains A/Victoria, A/Brisbane, and B/Brisbane have been provided. These 3 lots are used for stability and process consistency study.

The testing parameters in the trivalent batch analysis include-----
-----~~(b)(4)~~-----

------(b)(4)-----, All the batch analyses data meet the trivalent bulk specification. All the batch analyses data provided are within the acceptance criteria.

2.3.5 Reference Standards or Materials

This section is reviewed by OCBQ/DBSPQ.

2.3.6 Container Closure System

Primary packaging of the drug product consists of a 1ml syringe with Plastic Rigid Tip Cap (PRTC) referred to as luer lock syringe. No needle is present on the syringe. The cone of the syringe is sealed by an elastomeric tip cap. The tip cap itself is lodged in a rigid plastic shell which is screwed in the --(b)(4)-- adaptor. The plastic shell protects the tip cap from damage.

Component	Product Contact	Materials of Construction
glass barrel	yes	----- ----- ------(b)(4)----- -----
plunger stopper	yes	------(b)(4)----- ----- ----- ----- -----.
lubricant	yes	-----(b)(4)----- ----- ----- ----- -----
tip cap (PRTC)	yes	------(b)(4)----- ----- -----.
plunger rod	no	plastic
rigid shell*	no	plastic
--(b)(4)---- adaptor	no	plastic

Extractables and leachables of the 1.25 mL ------(b)(4)----- syringe containing the ----(b)(4)---- stopper were evaluated for ------(b)(4)----- . This syringe is considered

representative for the syringes proposed for licensure since the primary product contact materials (plunger stopper) and syringe barrel are the same.

A Container Closure Integrity Test (CCIT) was performed and is provided as Attachment 3.2.P.7.1.3-1. The CCIT after ----(b)(4)----- years was proven successfully.

Comment: *The 1ml syringe with Plastic Rigid Tip Cap (PRTC) is also used for other similar influenza vaccine. Novartis has submitted the extractable/leachable study for the (b)(4) syringe combined with the (b)(4) rubber plunger stopper. In the report, (b)(4) -----(b)(4)----- was identified as one of the leachable from the plastic syringe. Novartis submitted the health and hazard risk assessment from -(b)(4)--- to justify the (b)(4)level as safe and part of syringe manufacturing process. The risk assessment of (b)(4) in animal study at ----(b)(4)----- by injection is well justified and the data is acceptable.*

Extractable and leachable studies have been also reviewed by DMPQ reviewers.

2.3.7 Drug Product Stability

2.3.7.1 Stability Data Summary and Conclusions

Stability evaluation of drug product packaged in proposed commercial presentation has been completed for ----(b)(4)----- + 2 °C to + 8°C for normal storage conditions and -----(b)(4)----- for accelerated stability conditions. In addition, supportive data from 1.25 ml PRTC syringes , Phase III study syringes, stake needle syringes for (b)(4) months at --(b)(4)- normal storage conditions and (b)(4) months accelerated stability at ----(b)(4)----- are provided.

For the clinical phase III, three consistency batches each in the presentation with needle and without needle were stability tested. The tests were performed with these batches at 5 ±3 °C -----(b)(4)----- months, respectively. The stability of two batches (batch no -----(b)(4)-----, which were manufactured as clinical phase III backup material for the Northern Hemisphere, was determined at 2-8°C and at ----(b)(4)----- months. This clinical backup material is presented in syringes with needle.

A phase 4 clinical study was conducted in Germany during the influenza season to evaluate the safety and immunogenicity of the product. To confirm the stability of the commercial material, samples of three filled production batches were evaluated for up to ---(b)(4)----- . The batches represent the influenza vaccine strain composition of the 2007/2008 campaign. The batches -----(b)(4)----- are included in the stability evaluation. All the test parameter are within the acceptance criteria.

From process 1.1, three consistency trivalent lots -----(b)(4)----- were evaluated for the proposed (b)(4) month shelf-life of the final product. The final product was packaged in proposed commercial presentation of ---(b)(4)----, 1 ml luer lock syringe with a plastic rigid tip cap and plunger stopper. The stability study was performed as indicated in the tables below.

Table 2.3.7.1- The stability testing plan for annual commercial batches are as below:

Storage conditions	Storage time (months)				
	0	3	6	9	(b)(4)
5 °C ± 3 °C	X ¹	X	X	X	X

[(b)(4)]

X¹: result from release testing; Based on amendment 17, Novartis will change the shelf life start definition for Flucelvax US to the date of final filtration.

X: planned testing time points

Table 2.3.7.2- Stability Indicating Parameters

Category / Purpose (ICH)	Parameter	Method	Acceptance Criteria
Potency (equivalent)	Hemagglutinin antigen	single radial diffusion (SRD)	----- (b)(4) -----
Purity	Homogeneity of hemagglutinin ---- ----- (b)(4) ----- -----	--- (b)(4) ---	----- ----- ----- (b)(4) ----- ----- -----
Other product characteristics	Sterility	----- (b)(4) ----- -----	Pass
Other product characteristics	-- (b)(4) --	---- (b)(4) -----	--- (b)(4) ---
Other product characteristics	(b)(4)	General safety (-(b)(4)-.) in mice and guinea pigs	Pass

Category / Purpose (ICH)	Parameter	Method	Acceptance Criteria
Other product characteristics	Total protein	-----(b)(4)-----	----(b)(4)-----
Other product characteristics	Appearance	Visual inspection	Pass (clear to slightly opalescent fluid; not more opalescent than reference)

Comments: In the original submission, only --(b)(4)-- months of stability data for the consistency lots -----(b)(4)----- were provided. Upon CBER's requests, Novartis updated the stability data at Stability Report (SRQ522-013-05) in amendment 17. Hemagglutinin antigen in SRID assay was determined according to the -----(b)(4)-----, but not according to the US specification of ----(b)(4)----- . At some of the time points, the HA contents were below -(b)(4)---. During reviewing the stability data, we noticed that, to fulfill (b)(4) requirement, the initial HA contents in these lots were formulated close to ----(b)(4)-----/strain. After internal discussion, we decided to accept the HA content of ----(b)(4)----- in the current stability study, but requested Novartis to revise their stability protocol to use CBER reagents and follow the (b)(4) specification ----(b)(4)----- in the future stability study. In amendment 9, Novartis stated that they will conduct all future stability studies for Flucelvax US following CBER SRID specification for the finished product of not less than --- (b)(4)----.

Novartis provided a stability plan in amendment 17 which was designed to support stability of Flucelvax for (b)(4) months after filling into syringes and for the additional hold time of (b)(4) days to account for transportation prior to filling. However, due to an out of specification result on the hemagglutinin B content during the final time point, the data only supports stability at 2-8C for 11 months after filling.

2.3.7.2 Post-approval Stability Protocol and Stability Commitment

The stability protocol and acceptance criteria will be according to those listed in the above tables 2.3.7.1 and 2.3.7.2. The stability evaluation for 3 commercial batches will be performed for up to (b)(4) months at the regular storage condition (5 ± 3 °C) annually. Only (b)(4) batch will be placed on stability if it is the same strains as previous year and (b)(4) batches if the strains are new.

Comments: CBER recommend that three batches of commercial product should be placed on stability annually regardless of whether there are the same or new strains. In the amendment 16 in July 2012, Novartis responded to our request as following: “Novartis intends to implement the requirement to use three batches of Flucelvax (drug product) independent of the strain composition for annual stability each year. Once sufficient data over a period of time is collected to demonstrate stability of repeat strains Novartis proposes to submit a supplement to reduce testing to a single lot for repeat strains”. The responses are satisfactory.

2.4 Strain change for 2012-2013 influenza vaccine composition

Strain change information for the 2012-2013 influenza vaccine composition was submitted as an amendment 33 on Sept. 11, 2012. It contains the data of WHO recommended strains, package insert, and carton/syringe labels. The vaccine has been formulated to contain a total of 45 micrograms (mcg) hemagglutinin (HA) per 0.5 mL Flucelvax dose in the recommended ratio of 15 mcg HA of each of the following three influenza strains recommended for the 2012/2013 influenza season:

A/Brisbane/10/2010 (wild type) (A/California/7/2009-like virus) (H1N1);
A/Victoria/361/2011virus IVR-165 (reassortant) (H3N2);
B/Wisconsin/1/2010 (wild type) (B Yamagata lineage).

The strains to be used for the 2012-2013 season are consistent with VRBPAC and WHO recommendations for composition of influenza virus vaccines. All working virus seeds of the three vaccine component strains have been assessed by CBER, FDA and characterized as being antigenically similar to their reference antigens.

The passage histories have been provided for all three strains:

- For the A/Brisbane10/2010 (Wild Type) (H1N1) (working seed batch# ---(b)(4)----- obtained from WHO collaborating center at Australia, it underwent 2 passages in egg before they received it at Novartis. They then passaged it (b)(4) more times on MDCK (b)(4) -- cells for a total of (b)(4) passages.
- For the A/Victoria/361/2011virus IVR-165 reassortant (H3N2) (working seed batch# ---(b)(4)----- obtained from NIBSC, it underwent 6 passages post reassortment before they received it at Novartis. They then passaged it (b)(4) more times on MDCK ---(b)(4)--- cells for a total of (b)(4) passages. The identity of IVR-165 NA has been confirmed with specific anti-sera, and absence of helper virus, (b)(4), NA has been confirmed with (b)(4) specific anti-sera as well.
- For the wild type B/Wisconsin/1/2010 (working seed batch# ----(b)(4)----- obtained from NIBSC, it underwent 4 passages before they received it at Novartis. They then passaged it (b)(4) more times on MDCK ---(b)(4)----- for a total of (b)(4) passages.

Working seed viruses for all three vaccine component strains have been assessed by CBER and characterized as being HA antigenically similar to their strains of origin. Therefore, these seed viruses have been determined to be suitable for the 2012-2013 vaccine preparation.

Labeling: The container labels, cartons, and package inserts for 2012-13 Flucelvax influenza virus vaccine have been reviewed cross Divisions within CBER, and the revised labeling has already been incorporated into this submission.

Storage and handling: FLUCELVAX is supplied as a 0.5 mL dose in a pre-filled syringe in one package size: package of 10 pre-filled Luer Lock syringes without needles. Store this product refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze.

Comments: The data provided in this amendment are adequate to support the strain change for Flucelvax 2012-2013 season.