



**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:** BLA STN 125408/0, Influenza Virus Vaccine (MDCK Cells)  
**From:** Pankaj Amin, CSO, OCBQ/DMPQ/MRB II, HFM-676  
Ellen Huang, CSO, OCBQ/DMPQ/MRB II, HFM-676  
**Through:** Marion Michaelis, Acting Branch Chief, OCBQ/DMPQ/MRB II, HFM-676  
**cc:** Timothy Nelle, Ph.D., Chair, OVRR/DVRPA, HFM-478  
**Subject:** Review of the BLA submitted by Novartis Vaccines and Diagnostics, Inc., (Lic. # 1751), with an indication for active immunization of persons 18 years of age and older for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine.  
**Due Date:** December 21, 2012

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**REVIEW RECOMMENDATIONS**

We recommend approval of this BLA based on the review of this BLA and related amendments.

**REVIEW SUMMARY**

Novartis Vaccines and Diagnostic, Inc. (Novartis) submitted a BLA under STN 125408/0 for the licensure of Flucelvax, the influenza virus vaccine (MDCK Cells). Novartis Vaccines and Diagnostics, Inc., a US entity headquartered in Cambridge, Massachusetts will be the license holder of this BLA. The BLA was received by CBER on November 1, 2011.

The proposed indication is for active immunization of persons 18 years of age and older for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine.

Novartis Vaccines and Diagnostics GmbH, which is located in Marburg, Germany, manufactures the monovalent bulks and formulates the trivalent bulk. Novartis Vaccines and Diagnostics GmbH is a contractor for Novartis Vaccines and Diagnostics, Inc. Filling and packaging is performed by Novartis Vaccines and Diagnostics ---(b)(4)-----.

The manufacturing process (process 1.0) for clinical trial material was summarized as “first generation process” and was validated on manufacturing -(b)(4)- during the 2004/2005 influenza season (see Section 3.2.S.2.5.2). Since the manufacturing of phase III clinical lots, several process improvements were implemented to enhance the robustness of the manufacturing platform. During this “second generation” development phase, an optimized process scenario for the new --- (b)(4) --- process was established as process 1.1 and validated on both manufacturing lines, ---- (b)(4) ----- . The following table provides comparison between two process.

[(b)(4)]

**[(b)(4)]**

-(b)(4)

The BLA submission includes the bulk manufacturing lines ----(b)(4)----- in Marburg, Germany that are dedicated to production of influenza cell culture monovalent bulks from seasonal and pandemic (H1N1, H3N2, H5N1 and B) strains. The drug substance is manufactured at Marburg, Germany site either on ----(b)(4)----- for which comparability has been demonstrated.

## Product Information

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

Location	Processing Steps
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**[(b)(4)]**

-(b)(4).

In the submission, Novartis provided a HVAC system overview of the cell bank, seed virus, ----(b)(4)-----, Formulation area, cleaning/pre-treatment area, and media/buffer preparation area. Additionally, the firm provided the environmental parameters, room classifications, and limits for environmental monitoring. Room humidity and temperature and differential pressure are continuously monitored electronically by an installed alarm and monitoring system, which operates independently from the controller unit of the HVAC system. The performance of the air handling system is checked as an operative unit together with the clean room area supplied by the system. Novartis provided summary of the manufacturing operations as follow:

-(b)(4).

**[(b)(4)]**

1 Page Determined to be Not Releasable: (b)(4)

[(b)(4)]

Containment features are in place for areas with different clean room classifications and/or for areas that are utilized for different functions. These features include higher-pressure differentials from more controlled (higher classified) areas to less controlled (less classified) areas. The different pressure levels of the rooms are adjusted by constant volume regulators in the supply and outlet air stream of every room.

The clean room validation consists of an IQ, OQ, PQ, and, a demonstration of the airflow direction by a smoke study where there are Class (b)(4) zones within the clean room area. The duration of the clean room PQ was (b)(4) consecutive days where the clean rooms are monitored for viable/non-viable particles, airborne particles, and surface microbial contaminants.

Summary reports on the qualification and validation for the HVAC system were provided for each of the areas and reviewed. Excursions were reported and the deviation was resolved appropriately.

Novartis reported that the smoke study was performed for the Formulation facility, in order to demonstrate the laminar flow and the airflow direction for the applicable clean room area ----(b)(4)----- . For execution of this study, the area and equipment were prepared in the manner required for routine production. The smoke study was performed under static



and dynamic conditions and recorded by video. The recorded airflows met all of the requirements for laminar flow, as well as those for the required flow direction.

#### Environmental Monitoring (EM) Program

Novartis also provided a description about their environmental monitoring (EM) program, which is comprised of viable active air monitoring, viable passive air monitoring, non-viable air monitoring, surface monitoring, and personnel monitoring. Monitoring frequencies depend on the environmental classification of the area (grade/class) and criticality of the process and include in-process monitoring as well as daily, weekly, monthly, and quarterly monitoring. All sampling is performed under dynamic conditions.

Additionally, in order to ensure the quality of EM, all microbiological samples are evaluated in the microbiological lab of the QC department. Excursions from limits in class --- (b)(4) --- area are genetically identified according to validated procedures and the QC EM group evaluates all particle samples. If an action limit or (b)(4) successive alert limits are exceeded, a deviation report and immediate corrective actions will be initiated according to defined procedures.

Room classification submitted in the BLA for the various areas:

[(b)(4)]

[(b)(4)]

Clean Utilities

*Water Systems*

For the firm's manufacturing process, they use Water for Injection (WFI), Purified Water (PUW), and Clean Steam (CS). -----

----- (b)(4) -----  
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An IQ and OQ were completed for all water systems (WFI, PW, and CS). Validation of the water systems is conducted during the PQ for (b)(4) consecutive working days. For PUW, -- (b)(4) -- tested for ----- (b)(4) -----

----- during the PQ. For WFI and CS, -- (b)(4) -- was tested for ----- (b)(4) -----

----- during the PQ. The frequency of monitoring during the PQ is -- (b)(4) --.

A summary report, that includes water systems, was provided by the firm, reviewed, and found acceptable.

*Process Gases*

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

## Containment and Cross-Contamination Control

Containment is controlled through facility cleaning, equipment cleaning, EM, engineering controls, training, and procedures.

Novartis has a program in place for cleaning all classified clean rooms. Cleaning and disinfection requirements and practices (frequency and cleaning agents) and behavior in clean rooms are described in SOPs. The effectiveness of the cleaning regime used for rooms and surfaces in the manufacturing areas has been validated as part of the room qualification. The summary report for the room qualification was reviewed and found adequate. The EM program is in place to provide an indication of the ongoing effectiveness of cleaning/sanitization of the equipment and the facility. The data is reviewed on a routine basis.

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#### Fluvaxcel Final Product

Flucelvax is presented as a liquid for injection, in a --(b)(4)- glass pre-filled syringe (intended for a single use), containing 0.5 mL of antigen suspension. The drug product is a sterile parenteral suspension and is tested for sterility prior to release. No preservatives are used in the drug product. The container closure system of the syringes are in common use for vaccines. The aseptic filling process has been validated.

#### Flucelvax Container Closure

The vaccine is presented in 1 mL --(b)(4)- colorless glass syringes with plastic rigid tip cap (PRTC) and with a grey stopper, 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.

#### Syringe materials of construction

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

The syringe is closed with a grey, ---(b)(4)--- plunger stopper ----(b)(4)----- . The material does not contain any animal origin components. The luer lock syringe barrels with PRTC are supplied -----(b)(4)----- . The plunger stoppers are purchased -----(b)(4)----- .

Novartis provided a components dimensions and diagrams for the syringes barrels, tip cap, plunger rod and plunger stopper. The lure lock syringe and plunger rod inside diameters showing same inside diameters that will provide positive seal and prevent any leaks.

The glass syringe made of ----(b)(4)----- glass that complies to the requirements of the -----(b)(4)----- . The tip cap made of elastomeric --(b)(4)--, the rubber formulation complies with the requirements of the -----(b)(4)----- closures for injections -----(b)(4)----- for "-----  
----- (b)(4)-----". The plunger stopper made of --(b)(4)----- and the rubber formulation complies with the requirements of the ----(b)(4)----- ----- closures for injections (b)(4) and the -----(b)(4)----- for "-----  
----- (b)(4)-----". Novartis uses --- (b)(4)--- to covers the barrel and the stopper to provide easy and smooth plunger stopper motion. Novartis stated that the -(b)(4)- used for stopper is a ----(b)(4)----- and conformed to -----(b)(4)----- .

#### Secondary Packaging

Novartis stated that Prefilled labeled syringes are placed into a pre-formed plastic blister sealed with peelable paper. The blister package is then placed for storage and shipping into a cardboard box composed of fully coated folding box board ----- (b)(4)----- .



Novartis successfully completed three consecutive runs of syringe integrity test after media fill. The Closure Integrity Test (CCIT) was performed after 6 months, ----(b)(4)----- as part of stability. A microbiological challenge test was performed as part of container closure integrity. -----

---(b)(4)--- conducted extractable study on ---(b)(4)--- syringe combined with the ---(b)(4)---  
 ----- rubber plunger stopper and rubber tip cap -----  
 -----(b)(4)-----

Novartis performed -----(b)(4)----- method for the sterility test according to harmonized -----(b)(4)-----, Novartis has completed sterility test validation according to the current -----(b)(4)-----, A volume of -----(b)(4)-----

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### Endotoxin Assay

Novartis performed the ---(b)(4)---- test for the detection of endotoxin according to (b)(4). Novartis completed the (b)(4) test validation. The test method validation included the verification of absence of interfering factors. In addition, method precision, repeatability, intermediate precision were evaluated. All results were within the acceptance criteria and the firm concluded that the test is performed consistently and results are reliable. Novartis run negative control, spike control, product spike, and verification of coefficient of the repeat determination during each routine test.

### Release testing sites

Process Step	Analytical Procedure for Release	Marburg
---(b)(4)----- -----	total protein	yes
	(b)(4)	yes
	(b)(4)----	yes
	total DNA content	yes
	hemagglutinin antigen	yes
Finished product, filled syringe	sterility	yes
	endotoxin	yes
	general safety	yes
	appearance	yes
	extractable volume	yes
packaged product	Identity / ---(b)(4)----	yes

### (b)(4) Bulk (Release Specifications)

Test	Method	Requirements
total protein	----- (b)(4) -----	----- (b)(4) -----
(b)(4)	----- (b)(4) -----	---(b)(4)-----
---(b)(4)---	----- (b)(4) -----	----- (b)(4) -----
total DNA content	----- ----- (b)(4) -----	----- (b)(4) ----
hemagglutinin antigen	----- (b)(4) ----- -----	----- (b)(4) -----

### 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) ---

**Packed Product (Release Specifications)**

Test	Method	Requirements
Hemagglutinin antigen (identity)	----- (b)(4) -----	pass

**Process Validation**

The ----(b)(4)---- formulation operation is performed in Building (b)(4) on the Marburg site, Germany. The filling operation is performed in --- (b)(4) --- filling area of Building (b)(4)-----  
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[(b)(4)]

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**Additional Information Request were made based on our CMC review.**

February 15, 2012 (email request by Ellen Huang)

- *Please provide a description of the columns used in your manufacturing process including the size, dimension, vendor, model number, how the columns are packed and stored, and where each of these columns are used in the process.*

**Novartis Response**

Per Amendment 3, the ---(b)(4)----- manufacturing process for the monovalent strain consists of (b)(4) distinct steps where columns are employed.

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**CBER Response:** Response is acceptable.

- Please provide your plan to detect and prevent column fouling. Please describe how you will demonstrate that impurities do not leach from columns during subsequent production runs.

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[(b)(4)]

**CBER Response:** In a telecon dated August 15, 2012 the cleaning validation reports were requested. Additionally, the limit for ----(b)(4)----- column appeared much higher than the actual run results. The firm was asked what (b)(4) limit was actually selected for routine monitoring and to consider selecting at least an alert limit closer to the process capability. Refer to the August 15, 2012 IR Questions below.

- *Please provide the number of purification runs that were ----(b)(4)----- prior to your cleaning validations of the ----(b)(4)----- columns. Was the number of these purification runs evaluated as part of your risk assessment before executing your cleaning validation for these columns? If so, please provide your risk assessment. If not, please provide your rationale for selecting the number of purification runs processed prior to your cleaning validation.*

Novartis Response

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- *We strongly recommend that you perform -----(b)(4)----- testing or another suitable test method during routine production----(b)(4)----- columns and during periodic monitoring. You may want to consider testing samples for -----(b)(4)----- run when you are testing the performance of the column. Please also provide what acceptance criteria you would be using. Please note that in your cleaning validation your acceptance limit for the(b)(4) column was ---(b)(4)---. This acceptance limit would not be appropriate for your periodic monitoring.*

## Novartis Response

Per Amendment 16, the established monitoring programs (Document# 290306 and Document# 290308) will be revised to implement acceptance limits which reflect current process capability. This was committed until 9/30/2012. Currently the concept for the revision of the acceptance limits is under evaluation. Therefore, the real acceptance limits are not yet available. However, the revised ---(b)(4)---- for the ---(b)(4)---- will be ---(b)(4)--- whereas the --(b)(4)---- for the (b)(4) column will not be changed because the limit reflects the current process capability. Within the revision of the monitoring program also the frequency will be adapted from -(b)(4)--- -----.

**CBER Response:** Response is acceptable.

- *Please provide your facility cleaning procedure to be implemented between pandemic and seasonal influenza vaccine manufacture. Additionally, please clarify if you monitor for potential residual pandemic viruses in your facility as part of the change over process after a pandemic vaccine campaign.*

## Novartis Response

Per Amendment 16, the facility cleaning procedure has the following activities per the change from pandemic to seasonal influenza vaccine manufacturing:

-(b)(4)

**CBER Response:** The main concern is live virus and the firm performs -----(b)(4)----- categorized pandemic virus, which is acceptable. However, the firm also discussed using the ---(b)(4)---- assay and the sensitivity and specificity of the assay are unknown. Refer to August 1, 2012 Information Request below for a response from the firm.



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**[(b)(4)]**

-(b)(4)

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(b)(4)

- *Please describe your plan for the Holly Springs, North Carolina manufacturing site.*

Per Amendment 28, based on the timing of licensure for the 2012-13 flu season, NVD intends to store and distribute final product from the ----(b)(4)----- warehouse. The scope of Holly Springs warehouse for Flucelvax for the 2012-13 flu season is limited and will serve as a backup on a need basis. Reference is made to Sequence 0026 where Novartis outlined the plan to submit a PAS to obtain licensure to manufacture monovalent bulk at the Holly Springs facility. Subsequently, Novartis will submit a PAS to license secondary manufacture out of Holly Springs. This will enable Holly Springs to conduct primary and secondary manufacturing as well as package and fill for the ----(b)(4)---- influenza season. Please refer to the table below summarizing plans for the Holly Springs facility through ---(b)(4)----- flu season.

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[(b)(4)]

Question

*The container closure integrity test (CCIT) for the monovalent bulk was performed in 2005 and on a ---(b)(4)---. You indicated that you started a new for the (b)(4) monovalent bulk container in January 2012. Please provide a summary interim report of the new CCIT study.*

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#### CBER questions

*Regarding samples that are shipped from Marburg to Holly Springs for the SRID test, please describe how you maintain the sample integrity during the sample shipping and storage. Please provide data to demonstrate that there is no significant difference in the potency of the monovalent bulk during shipping. We suggest that you compare the SRID results using the same sample tested at both the Marburg and Holly Springs locations.*

#### Novartis Response

Novartis stated that in order to ensure sample integrity, the sample are shipped using --- (b)(4)--- to verify the appropriate storage condition during shipment. Novartis will conduct shipping study using the same courier, flight path and containment/monitoring (---(b)(4)---,-- (b)(4) container). Novartis will ensure sample integrity during shipping process. Novartis will provide the shipping validation study data to the agency. Novartis response is acceptable for committing to conduct the sample-shipping validation. Regarding conducting comparable study between Marburg and Holly spring test laboratories, Novartis did not provided any comment. Dr. Gupta (CBER) also following the SRID sample integrity issue and I differ to his resolution for this issue.

#### CBER Question

*Please confirm your plans for the Holly Springs location.*

#### Novartis response

Novartis stated that NVD intends to store and distribute final product from the -----(b)(4)--- ----- warehouse. The scope of Holly Springs warehouse for Flucelvax for the 2012-13 flu season is limited and will serve as a backup on a need basis. Novartis describe their plan to submit a prior approval supplement for secondary manufacturing at holly spring. Novartis plan to conduct primary and secondary manufacturing as well as package and fill for the --- (b)(4)----- influenza season. Novartis response is adequate however, I recommend that field office should inspect the ----(b)(4)----- warehouse facility for CGMP compliance.

CBER Question

*Please provide the filling and other product contact equipment sterilization protocol and validation summary including the thermal qualification and microbiological efficacy of the cycle. (Amendment 0015)*

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[(b)(4)]

All sterilization studies completed successfully. Novartis response is adequate.

CBER Question

*Please describe your acceptance criteria for the ---(b)(4)----- syringe and stopper used in the Optaflu filling process including a summary of vendor qualification. (Amendment 0015)*

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CBER Question

*Please provide the most recent aseptic filling (syringe filling on -----(b)(4)-----  
media fill protocol and summary report (for media fill conducted after May 2010).*

Novartis response

A summary report of the recent media fills performed during 2010 to 2012 on filling machine  
----- (b)(4) ----- attached to this amendment:

Novartis provided following media fill summary

[(b)(4)]

(b)(4)

*Please provide an environmental monitoring summary report for the last three months of environmental monitoring including all deviations and corrective actions for Building(b)(4).*

Novartis provided the environmental monitoring trend reports (Building -----(b)(4)-----  
----- for a time period of 1st March 2012 to end of May 2012. There was no EM  
excursion for a total of -----(b)(4)----- microbiological samples and (b)(4)  
non viable particulate samples during reported period. There was no negative trend identified  
in the class(b)(4) or class(b)(4) areas of the filling room. These data demonstrate control on a  
define clean room environment quality. Novartis response is adequate.

*Please provide the validation protocol and summary report for the automated inspection machine (fill syringe inspection machine) and qualification protocol and summary report for the -----(b)(4)----- system.*

[illegible]

----- During qualification the associated (b)(4) checks for accuracy and presence/absence of the printed data on the label were verified. In addition, the printed codes (lot number and data) on the carton

## CBER Questions

## Novartis response

Novartis stated that the CCIT reference study for the syringe type Luer Lock (SOP 241449) and plunger stopper -----(b)(4)----- is on going and currently results are available up to --(b)(4)--. The filling for Optaflu was executed on filling line --(b)(4)--- in building ----(b)(4)----- . The syringe container closure integrity assay was performed according to SOP 201635 (CST 07.011) in the (b)(4) facility.

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Novartis response appears adequate; However, CCIT ongoing test method sensitivity -----  
----- (b)(7)(e)(b)(5) -----.

*b) We need clarification regarding the syringe media fill, specifically - CC type and size used during media fill, type and volume of media used in each containers, list of simulation used during media fill, allowable contamination rate, detail on how all of the shift covered during the media fill, incubation parameters, number vials incubated/filled/positive, number of samples used in media fill, summary of growth*

*promotion test and results, and summary of recent media fill results.*

[(b)(4)]

[(b)(4)]

Review comment:

Novartis media fill response appears adequate, all three recent media fill successfully completed and it can be concluded that Novartis able maintain continuous aseptic process control.

CBER question

*Please provide the test method validation for the syringe leachable study.*

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Review comment:

It appear that the Novartis response is adequate based on the (b)(4) method validation report. Dr. Zhiping Ye (CBER) also review this method validation and will provide his comment if necessary.