

DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Review and Research
Division of Viral Products



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From: Hang Xie, Ph.D., DVP/OVRR

Subject: **STN BLA125510, CMC (Antigen only) Review of Fluad (Adjuvanted, Formaldehyde Inactivated, Trivalent Seasonal Subunit (A/A/B hemagglutinin and neuraminidase; embryonated hen's eggs) Influenza Vaccine)**

Sponsor: Novartis Vaccines & Diagnostics, Inc.

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To: STN BLA125510 file
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Cross-ref: BLA125297 AGRIFLU® (Influenza Virus Vaccine)
(b) (4) (Syringes)
(b) (4) (Tip cones)
(b) (4) (Plunger stopper)

Executive Summary and Recommendation

Novartis Vaccines and Diagnostics, Inc. (Novartis) has submitted a Biologics License Application (BLA) for Fluad, a human influenza virus type A (H1N1; H3N2) and B hemagglutinin (HA) and neuraminidase (NA) vaccine, inactivated (embryonated hen's eggs) and adjuvanted with MF59C.1 (an oil-in-water emulsion). The vaccine has been formulated to contain 45 micrograms (µg) 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, in the presence of MF59C.1 in a pre-filled syringe to be administered intramuscularly. Fluad is intended for active immunization of persons 65 years and older against influenza disease caused by influenza virus subtypes A (both H3N2 and H1N1) and B contained in the vaccine. US development of this vaccine was conducted under BB-IND 14368. The BLA is being submitted for review under the Accelerated Approval procedure as agreed by CBER/FDA.

The CMC review on adjuvant MF59C.1 of this original submission has been covered separately by Dr. Marina Zaitseva, DVP/OVRR.

The current review memo is focused on CMC of Antigen (Ag) only in Module 3 including the sections outlined below:

BLA125510/0

3.2.S DRUG SUBSTANCE (DS)-Agriflu MPH

3.2.S.2 Manufacture

3.2.S.3 Characterization

3.2.S.4 Control of Drug Substance

3.2.S.5 Reference Standards and Materials

3.2.S.6 Container Closure System

3.2.S.7 Stability

3.2.P FLUAD DRUG PPRODUCT (DP)

3.2.P.1 Description and Composition of Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.3 Manufacture

3.2.P.4 Control of Excipient

3.2.P.5 Control of Drug Product

3.2.P.6 Reference Standards or Materials

3.2.P.8 Stability

The DS (Ag) sections of the current Fludad BLA are identical to those contained in approved BLA125297 for AGRIFLU® licensed in the US market. Subsequent changes to the Agriflu DS submitted to BLA125297 have been reviewed and approved separately. Those changes were reiterated in this review memo of Fludad BLA125510.

During the review process, additional information requests and further clarifications related to CMC (Ag) development were relayed to the sponsor, resulting in several amendments outlined below:

Amend 3 HAI

Amend 4 HAI & SRID

Amend 5 Formaldehyde

Amend 6 Ovalbumin

Amend 7 Bioburden & Endotoxin

Amend 8 HAI

Amend 10 SRID & Endotoxin (b) (4)

Amend 13 Bioburden

Amend 14 Labeling

Amend 15 LRP, CCIT& Viral Inactivation

Amend 16 Total protein & GST

Amend 18 LRP

Amend 20 Latex in PI

Amend 22 SRID

Amend 23 LRP remove formaldehyde testing

Amend 24 Agriflu DS change & Bioburden

Amend 25 (b) (4) preparation & updated DS section

Amend 26 Updated DS section

These amendments have been reviewed and CMC (Ag) related changes and final decisions/actions are summarized below:

1. The following changes were made to the approved manufacturing process of Agriflu since the submission of BLA125510.
 - a. BLA125297_s68 (CBE30): approved on 9/3/2015
 - 1) Introducing a (b) (4) step in the clarification of the (b) (4) virus pool in the (b) (4) Agriflu manufacturing process;
 - 2) Introducing (b) (4) in the (b) (4) Agriflu manufacturing process.
 - b. BLA125297_s69 (CBE0): approved on 9/3/2015
 - 1) Replacing (b) (4) facility in (b) (4) with (b) (4) as the preparation site for Kanamycin/Neomycin Antibiotics (b) (4) solutions used in the manufacturing process of Agriflu drug substance;
 - 2) The manufacturing process of Antibiotics and (b) (4) solutions in (b) (4) remains the same as that currently employed in (b) (4), except the followings:
 - a) The dispensing system for aliquoting/filling of the antibiotics and (b) (4) has been changed from an (b) (4)
 - b) The bioburden specification for the (b) (4)
 - c) The release testing for Kanamycin/Neomycin Antibiotics has been revised to include (b) (4) in addition to sterility;
 - d) The release testing for (b) (4) solution has been revised to include (b) (4) in addition to sterility;
 - e) The bioburden for the (b) (4) has been added as In Process Control Test for (b) (4)
 - 3) The storage of Kanamycin/Neomycin Antibiotics (b) (4) (b) (4) because the new facility does not have the equipment for the storage at (b) (4)

These approved changes have been updated in Flud BLA125510 Module 2.3.S Drug Substance- (b) (4) and Module 3.2.S. Drug Substance (b) (4) (BLA125510/0.25, 0.26).

2. As required by CBER/FDA, the HA inhibition (HAI) titers of the pivotal clinical trial V70_27 performed by (b) (4) in 2011 were recalculated because an incorrect dilution factor was used for calculation and revised HAI titers were provided (BLA125510/0.3, 0.4 and 0.8).
3. The formaldehyde testing was removed from the (b) (4) Release test panel because Novartis states MF59C.1 interferes with formaldehyde test results (BLA125510/0.23).
4. The general safety test (GST) was exempted for the Final Bulk Release test panel (BLA125510/0.14).
5. The final vaccine release site was changed from (b) (4) (BLA125510/0.20).

All CMC (Ag) related outstanding issues have been resolved. This BLA is recommended for approval.

Review Structure

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2.1.3 Changes in the manufacturing process of DS

2.2 Drug Product (Fluad)

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2.2.5 Control of Drug Product

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2.2.8 Stability

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2.2.8.2 Post-approval Stability Protocol and Stability Commitment

2.2.9 HA Inhibition Test for Pivotal Clinical Study

2.2.10 CMC- related preclinical studies

3. Draft Lot Release Protocol (LRP) Template and Product Information (PI)

1. Introduction

The current BLA is submitted by Novartis to support market approval of Fluad for active immunization of persons 65 years and older against influenza disease caused by influenza virus subtypes A (both H3N2 and H1N1) and B contained in the vaccine. Fluad is an Influenza Vaccine (Surface Antigen, Inactivated) which contains predominantly HA and NA antigens from the three seasonal influenza strains (recommended annually by regional health authorities) and MF59C.1 adjuvant (an oil-in-water emulsion). The DS of Fluad is from a U.S licensed vaccine- AGRIFLU® (cross-ref. BLA125297), in which individual influenza strains are propagated in the allantoic fluid of embryonated chicken eggs, then inactivated, split and purified to produce the monovalent bulk. The three monovalent bulks are then combined along with MF59C.1 adjuvant to produce the trivalent final DP. The antigens are suspended in a sterile, buffered aqueous solution for intramuscular injection. The potency of the vaccine is expressed as the concentration of the HA proteins from each virus strain. Approval of Fluad would be based on non-inferior immune response relative to Agriflu.

2. Chemistry, Manufacturing and Controls

2.1. Drug Substance (DS) (AGRIFLU®, cross-ref. BLA125297)

2.1.1 Description and general properties of DS (Ag only)

Novartis states that the Fluad DS (MPH) process is shared in its entirety with that of US licensed AGRIFLU® (cross-ref BLA125297), which provides the antigens for Fluad DP formulation process. As agreed by CBER (Type C Meeting on September 20, 2013), an identical copy of the Agriflu DS sections has been included in the current Fluad BLA filing (3.2.S) for both MPH produced in (b) (4) and MPH produced in (b) (4). The (b) (4) site is no longer intended for MPH production, but is included in the current Fluad BLA as part of the development history of Agriflu BLA described in the (b) (4) DS section. Agriflu related DS sections in facilities and equipment (3.2.A.1) and regional (3.2.R) information are also included in the Fluad BLA filing. Novartis states that the Fluad DS sections are updated with all the changes approved in Agriflu BLA upon the approval of the Fluad BLA.


(b) (4)

(b) (4)


(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)



(b) (4)



2.2 Drug Product (DP) (Fluad)

2.2.1 Description and Composition of DP

The Fluad vaccine is an inactivated subunit influenza vaccine composed of three viral surface antigens (H1/H3/B) and the adjuvant MF59C.1 in prepared buffer solutions. The Fluad contains no preservative. The potency of the vaccine is assessed on the concentration of the HA protein in the final formulation using the SRID assay. The vaccine is presented as a 0.5 ml single dose sterile suspension for injection in a milky-white emulsion contained in a glass pre-filled syringe with the following composition:

Table 2.2.1 Composition of Flud^a 0.5 mL Syringe Presentation

Names of Ingredients	Quantity per dose	Function	Reference to Standards
<u>Active Ingredients</u>			
Haemagglutinin (HA) and Neuraminidase (NA) antigens from the influenza virus strains recommended by the WHO and endorsed by CBER for the manufacture of influenza vaccine for the current season	15 µg HA ^b (per strain)	influenza vaccine	(b) (4)
<u>Other Ingredients</u>			
(b) (4)			
squalene	9.75 mg	adjuvant	In-house specification
polysorbate 80	1.175 mg	adjuvant	(b) (4)
sorbitan trioleate	1.175 mg	adjuvant	(b) (4)
sodium citrate	0.66 mg	adjuvant	(b) (4)
citric acid	0.04 mg	adjuvant	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

^a Each single dose pre-filled syringe of Flud contains an overfill of up to (b) (4) to permit withdrawal of a nominal volume of 0.50 mL.

^b An overage of up to (b) (4) of the HA concentration is included for each virus strain to assure the potency specification can be met for the 12-month shelf-life.

No reconstitution diluents or dosage devices are required for injection.

Flud in single dose pre-filled syringe may contain trace amounts of neomycin ($\leq 0.02 \mu\text{g}$ by calculation), kanamycin ($\leq 0.03 \mu\text{g}$ by calculation), barium ($< 0.5 \mu\text{g}$ by calculation), formaldehyde ($\leq 10 \mu\text{g}$) and CTAB ($\leq 12 \mu\text{g}$) which are used in the process of (b) (4) as well as residual amounts of egg protein-ovalbumin ($< 0.4 \mu\text{g}$) (BLA125510/0.23).

Comments: Due to the presence of the emulsion adjuvant MF59C.1, which confounds the formaldehyde test result, the amount of formaldehyde could not be tested at the (b) (4) stage. Internal discussion at October Monthly Meeting of BLA125510 agreed that the residual formaldehyde should be estimated based on the release specification of residual formaldehyde at (b) (4) level and the detection limit of formaldehyde in (b) (4).

2.2.2 Manufacturers of DP

The facilities associated with the Flud DP manufacturing process and testing are summarized in the table below.

Table 2.2.2 Facilities associated with Fludad Manufacturing Activities

Site	Responsibility
Novartis Vaccines and Diagnostics (b) (4)	<ul style="list-style-type: none"> (b) (4)
Novartis Vaccines and Diagnostics (b) (4)	<ul style="list-style-type: none"> (b) (4)
Novartis Vaccines and Diagnostics Ltd (b) (4)	<ul style="list-style-type: none"> (b) (4) (b) (4)
Novartis Vaccines and Diagnostics (b) (4)	<ul style="list-style-type: none"> (b) (4)

Comments: In the email dated on 7/30/2015, Novartis proposed to change the final vaccine release site from (b) (4). Novartis states that there are no changes proposed to the release testing assays but only a transfer of release activity such as the review of batch production records from (b) (4), and all the tests and the manufacturing activities remain the same. In the email dated on 8/6/2015, Novartis clarified that implementation of this change is for business purposes as a result of the business transaction between GSK and Novartis, which included the transfer of (b) (4) manufacturing and quality operations from Novartis to GSK in March 2015. Novartis also confirms that an adequate quality unit and related procedures are already in place at the (b) (4) site to conduct product release activities. Section 3.2.P.3.1 Manufacturer(s) has been updated to reflect this change in BLA125510/0.20. In the same amendment, Novartis confirms that there are no modifications to any manufacturing process, equipment, facilities or utilities as part of this batch releasing site change from (b) (4).

2.2.3 Manufacture of Drug Product

2.2.3.1 Description of manufacturing process and process controls

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2.2.5 Control of Drug Product

2.2.5.1 Specifications, Impurities and Justifications

2.2.5.1.1 Release Specifications

Proposed release specifications for the Final Bulk, the Finished Product and Packed Product including the requirements of the (b) (4) for Influenza Vaccine (Surface Antigen, Inactivated) are summarized below.

(b) (4)

Table 2.2.5.1.1-2 Final Filled Vaccine Release Specifications

Test	Method	Reference	Specifications
<u>Identify</u>			
HA identity	(b) (4)	Internal	Positive
A (H1N1)			Positive
A (H3N2)			Positive
B	(b) (4)	Internal	Positive
Squalene Identity			Positive
<u>Potency/Strength</u>			
HA content	SRID (potency)	Internal	(b) (4)
A (H1N1)			(b) (4)
A (H3N2)			(b) (4)
B			(b) (4)
Squalene Strength	(b) (4)	Internal	(b) (4)
(b) (4)	(b) (4)	Internal	(b) (4)
(b) (4)			
(b) (4)	(b) (4)	Internal	(b) (4)
(b) (4)			
(b) (4)			
<u>Quality</u>			
Sterility	(b) (4)	(b) (4)	Sterile
Endotoxin	(b) (4)	(b) (4)	(b) (4)
Appearance	Visual	Internal	Conforms
Visible particles	Visual	(b) (4)	Conforms
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)			(b) (4)
(b) (4)			(b) (4)
pH	(b) (4)	(b) (4)	6.9 -7. 7
Extractable Volume	(b) (4)	(b) (4)	(b) 0.50 ml

(b) (4)

(b) (4)

(b) (4)

2.2.5.1.2 Process Impurities

The process impurities in Fludad Final Product carrying over from the

manufacturing process of (b) (4) include (1) ovalbumin; (2) endotoxin; (3) bacterial contamination; (4) viral inactivation; (5) residual formaldehyde; (6) residual CTAB; (7) polysorbate 80; (8) barium (b) (4) and (9) sodium citrate. These impurities are controlled at the (b) (4) level. Ovalbumin, endotoxin, viral inactivation and residual CTAB are tested (b) (4) at DP stage. Bacterial contamination is controlled by validated aseptic processes and sterility test at (b) (4) DP stages.

Comments: Polysorbate 80 and sodium citrate are also the components of MF59C.1. Please see Marina Zaitseva's review memo for impurities related to MF59C.1.

2.2.5.1.3 Justifications of Specifications

Testing for ovalbumin and total protein will be performed on the adjuvanted final DP (b) (4) per CBER recommendations. Testing for residual infectious virus, CTAB and HA will also be performed on the adjuvanted final DP per CBER recommendations.

2.2.5.1.3.1 HA Identify and Content

The release of Flud for the US market is based on the (b) (4) analysis of the (b) (4) data. Flud is formulated at $\geq 15 \mu\text{g}$ of HA per dose for each of three antigens. The theoretical HA content with a (b) (4) overage per antigen is (b) (4). For the potency testing of final formulated vaccine, the reportable result is the (b) (4) valid tests. If the (b) (4) valid test results are not within the specifications of (b) (4) valid results are generated and the (b) (4) valid tests is reported. The specification for the (b) (4) valid tests is (b) (4). The specifications are determined based on an assay variability of (b) (4) from the expected theoretical content of (b) (4). For the identity test, a single test is performed for each of the 3 influenza strains present in the vaccine.

2.2.5.1.3.2 pH

The target pH of Flud final product is 6.9-7.7, which provides an optimal environment for HA antigen in solution and for emulsion stability.

2.2.5.1.3.3 Appearance

Flud is an adjuvanted vaccine in the presence of MF59C.1 adjuvant, an oil-in-water emulsion, which gives the final DP the appearance of a milky-white emulsion.

2.2.5.1.3.4 Extractable Volume

The specification for extractable volume is (b) (4) 0.50 ml to ensure the delivered volume is accurate.

2.2.5.1.3.5 Endotoxin

For the Flud 0.5 ml presentation, the limit (b) (4) ml has been set per US requirements.

Comments: Novartis confirms that the endotoxin release specifications for (b) (4) DP destined for the US market are set at (b) (4) respectively based on the process capability data, and are not based on CBER's reference lot (b) (4) (BLA125510/0.7). The endotoxin specification of (b) (4) HA for

(b) (4) has been approved in Agriflu BLA125297/50 on January 27th, 2014. Novartis also accepted CBER's suggestion and established the endotoxin alert limit of (b) (4) for DP and (b) (4) (ratio Endotoxin/ HA), respectively (BLA125510/0.10).

2.2.5.1.3.6 Total Protein (other than HA)

The specification for Total Proteins other than HA is determined by (b) (4) results of HA from the Total Proteins amount. The limit is set at (b) (4) to meet the (b) (4) requirement for the protein content in the Final (b) (4). (i.e. (b) (4) per virus strain per human dose and (b) (4) a total of (b) (4)

(b) (4)

2.2.5.1.3.8 Ovalbumin

The Ovalbumin limit is set at (b) (4) 0.4 µg/0.5 ml according to process capability, which also meets the (b) (4) requirement for the ovalbumin content in the (b) (4) (i.e. Not more than (b) (4) per Human dose).

2.2.5.1.3.9 Viral Inactivation

Viral Inactivation is performed in compliance with the specification outlined in the (b) (4) for the influenza vaccine (surface antigen inactivated).

2.2.5.1.3.10 CTAB, Formaldehyde and Barium/Citrate

Barium (b) (4), sodium citrate, CTAB and formaldehyde are the components used in the process of (b) (4). The residual concentrations of barium (b) (4) and sodium citrate carrying over from (b) (4) process are controlled for release of (b) (4). The residual concentration of CTAB from (b) (4) process is evaluated in (b) (4) DP. The testing of residual formaldehyde is removed from the (b) (4) Release test panel because Novartis states MF59C.1 may interfere with formaldehyde test results (BLA125510/0.5 & 0.23). Thus the residual concentration of formaldehyde is only controlled at the (b) (4) level.

Comments: Sodium citrate is also a component of MF59C.1. Please see Marina Zaitseva's review memo for residual concentration of sodium citrate in adjuvanted final product. Novartis' justification on removing formaldehyde testing from Flud (b) (4) release is that "this test is not required in other licensed markets due to the presence of the emulsion adjuvant MF59C.1 which presents the possibility to confound the formaldehyde test result at the (b) (4) stage, since formaldehyde is also a degradation by-product (trace levels) of MF59C.1" (BLA125510/0.5). During the internal discussion, Marina Zaitseva (Adjuvant Reviewer) clarified that formaldehyde cannot be the degradation by-product of the adjuvant. DBSQC reviewers also explained that the method used to determine formaldehyde is semi-quantitative and the presence of MF59C.1 makes the determination of formaldehyde impossible. Since formaldehyde is controlled adequately at (b) (4) level and no formaldehyde is added in DP formulation, CBER agrees removing formaldehyde testing from Flud (b) (4) release. The residual concentration of formaldehyde in DP is estimated based on (b) (4) stage.

2.2.5.3 Analytical Procedures and Validation

Analytical methods used for (b) (4) Final Vaccine release and stability testing are listed in the table below.

Table 2.2.5.3 Analytical Methods

Test	Method	Reference	Method No & Performing Site
Appearance	Visual Inspection	Internal	207269 (b) (4)
CTAB	(b) (4)	Internal	315799 (b) (4)
Endotoxin	(b) (4)	(b) (4)	07.149 (b) (4)
Extractable volume	(b) (4)	(b) (4)	294900 (b) (4)
Formaldehyde	(b) (4)	(b) (4)	306259 (b) (4)
Haemagglutinin (HA) Content and Identity	(b) (4)	Internal	267633 (b) (4)
(b) (4)	(b) (4)	Internal	102846 (b) (4)
(b) (4)	(b) (4)	Internal	264896 (b) (4)
(b) (4)	(b) (4)	(b) (4)	306647 (b) (4)
Ovalbumin	(b) (4)	Internal	276833 (b) (4)
pH	(b) (4)	(b) (4)	278840 (b) (4)
Squalene Identity and Content	(b) (4)	Internal	306198 (b) (4)
Sterility	(b) (4)	(b) (4)	07.001 (b) (4)
Total Protein	(b) (4)	Internal	306039 (b) (4)
Viral Inactivation	Haemagglutination	(b) (4)	271322 (b) (4)
Visible Particles	Visual Inspection	Internal	207269 (b) (4)
(b) (4)	(b) (4)	(b) (4)	308240 (b) (4)

Comments: Novartis states that the microbial detection assays, sterility and bioburden and endotoxin are performed close to the site of production in (b) (4) to avoid transport of samples back to (b) (4) for analysis which may increase the risk for samples to be compromised. Novartis also asked for a waiver for general safety test (GST) on Final Product. Since GST is no longer required on vaccine final product effective on August 3, 2015, the request for a waiver is also no longer needed.

2.2.5.3.1 Endotoxin

Endotoxin testing on DP (b) (4) uses the same quantitative (b) (4) assay which has been validated for precision, repeatability and intermediate precision using lots of Fluad vaccine (b) (4) (Section 3.2.P.5.3 Attachment 47).

Comments: Please see DBSQC reviewers' review memo for details.

2.2.5.3.2 Formaldehyde

The method to detect formaldehyde in DP is based on the same principals as that used in (b) (4) except the formaldehyde detection in (b) (4) is quantitative while its detection in DP is semi-quantitative due to the interference of MF59C.1. In BLA125510/0.5, Novartis proposed to remove this test from the release of Fluad (b) (4) because of the interference of MF59C.1 in formaldehyde detection. CBER accepted their proposal.

2.2.5.3.3 Total Protein

Total protein content in DP is determined by the (b) (4) method by comparing the absorbance of the sample to a standard curve. The assay was initially

validated in (b) (4) for Precision, accuracy, specificity, linearity and range (Section 3.2.P.5.3 Attachment 28/29/30). Now this assay has been transferred to (b) (4) and has been reevaluated for dual site precision studies demonstrating equivalence, linearity, precision (intermediate precision) and limit of quantitation (Section 3.2.P.5.3 Attachment 31).

Comments: All results were within the acceptance criteria. Please see DBSQC reviewers' review memo for details. Novartis clarified that Total Protein (other than HA) (b) (4) validation report for (b) (4) was part of Agriflu (b) (4) manufacturing transfer from (b) (4) which has been approved in Agriflu BLA125297/s46 on 10/26/2011 (BLA125510/0.16). In the same amendment 16, Novartis further clarifies that they have no intention to use (b) (4) QC laboratories to test (b) (4) DP post Fluad approval.

2.2.5.3.4 Ovalbumin

Ovalbumin determinations for (b) (4) DP use the same (b) (4) kits, equipment and reagents. The method was originally validated a (b) (4) for precision, accuracy, specificity, linearity, limit of quantification, range and robustness (Section 3.2.P.5.3 Attachment 16/17/18). The test has been transferred to (b) (4) and has been reevaluated for dual site precision studies demonstrating equivalence, linearity, precision (intermediate precision) and limit of quantitation (Section 3.2.P.5.3 Attachment 19).

Comments: In Amendment 6, Novartis provided a copy of the (b) (4) SOP 276833 for determination of Ovalbumin Content by (b) (4) Fluad (b) (4). The Ovalbumin method transfer protocol P-0392-09-13 for adjuvanted product was also provided in Attachment 19.1 (BLA1254510/0.6). Novartis also provided the associated (b) (4) lot data used to calculate the ovalbumin results in the excel spreadsheet (BLA1254510/0.6). Please see DBSQC reviewers' review memo for details.

2.2.5.3.5 Sterility

Sterility is determined using (b) (4) method according to (b) (4). The (b) (4) method was validated at (b) (4) for elimination of inhibition or anti-microbial effects of the sample without impairing the recovery of viable microorganisms (Section 3.2.P.5.3 Attachment 15).

Comments: The method was validated and the final report attached has typographic errors corrected. Please see DBSQC reviewers' review memos for details.

2.2.5.3.6 CCIT

Updated CCIT method, SOP and validation are provided in Section 3.2.P.2.5, Microbiological Attributes and Attachment 3/4/5/6 (BLA125510/0.15).

Comments: The review of CCIT has been covered in 2.3.2.4.2 Validation of Fluad Filling Process. Please also see Pete Amin's review memo for details.

2.2.5.3.7 SRID

The SRID testing on Final Lots released for the European Union is performed using WHO reagents and the analysis is done using the (b) (4). For Final Lots destined for the US market, the SRID testing is performed using CBER reagents and evaluated using the (b) (4) method in accordance with US release specifications for HA content (b) (4).

(b) (4) The new data are consistent with previous accuracy data generated under SOP R/0400/09/13, confirming that the presence of MF59 has no impact on the accuracy of SRID testing. Novartis thus states that all future SRID validation/verification studies will be performed according to SOP R/0400/09/13, specifically (b) (4)

This is acceptable for CMC (Ag) reviewer. Please see DBSQC reviewers' review memo for details on SRID method and validation.

2.2.5.3.8 Viral Inactivation

Detection of residual virus after viral inactivation is based on (b) (4), and is performed on both MPH and Final (b) (4). Samples are passaged (b) (4) in SPF embryonated eggs before HA determination. For MPH, detection of residual virus is performed at (b) (4) for each MPH strain. For Flud DP which is composed of both A and B type influenza strains, (b) (4)

The original method validation was conducted in (b) (4) (Section 3.2.P.5.3 Attachment 43/44/45). The testing has been transferred to (b) (4) and has been reevaluated for dual site pass/fail studies and limit of detection (Section 3.2.P.5.3 Attachment 46). The SOP is provided in BLA125510/0.15 Attachment 04.

Comments: Residual virus detection has been validated based on the detection limit- the lowest concentration of virus that can be detected in a sample. In the validation study performed in (b) (4)

The method has been successfully validated for Flud (b) (4). In the viral inactivation transfer study performed in (b) (4) batch of (b) (4) destined for the US clinical study was used. This is acceptable since the (b) (4) shares the same formulation process and facilities as that of Flud, and (b) (4) represents the "worst case" matrix due to the presence of a (b) (4). Both studies confirm that the (b) (4) matrix does not interfere with the sensitivity of residual virus detection after viral inactivation.

2.2.5.4 Batch Analyses

Multiple batches of Final Bulk and Final Filled Product are submitted for batch analysis and are summarized below:

1. Commercial Batches (produced using (b) (4) MPH) from NH 2010/2011
 - (b) (4) batches of Final Bulk (b) (4):

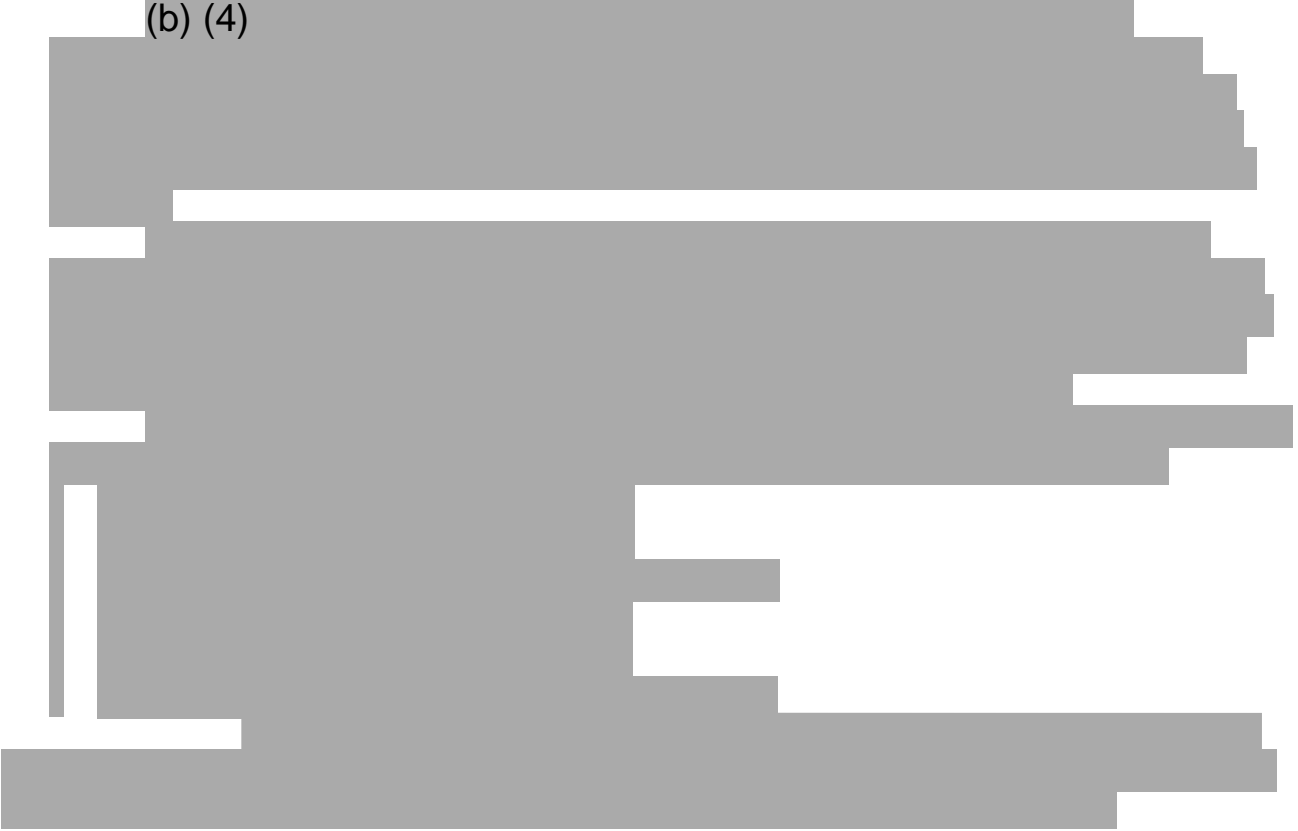
- (b) (4)
- for commercial use and stability
- (b) (4) Final Lots (b) (4) syringes for commercial use and stability
2. Commercial Batches (produced using (b) (4) MPH) from NH 2011/2012
- (b) (4) batches of Final Bulk (b) (4) for commercial use;
 - (b) (4) Final Lots (b) (4) syringes for consistency study
3. Commercial Batches (produced using (b) (4) MPH) from NH 2012/2013
- (b) (4) batches of Final Bulk (b) (4) for commercial use;
 - (b) (4) Final Lots (b) (4) syringes for consistency
4. Canadian Commercial Batches in Luer-lock Syringes (produced using (b) (4) MPH) from NH 2011/2012
- (b) (4) batches of Final Bulk (b) (4) for commercial use
 - (b) (4) Final Lots (b) (4) syringes for commercial use;
 - Lot (b) (4) also on stability study
5. Canadian Commercial Batches in Luer-lock Syringes (produced using (b) (4) MPH) from NH 2012/2013
- (b) (4) batch of Final Bulk (b) (4) for consistency study;
 - (b) (4) Final Lots (b) (4) syringes for consistency study
6. (b) (4) Filling Line Validation Batches (produced using (b) (4) MPH)
- (b) (4) batches of Final Bulk (b) (4) for validation;
 - (b) (4) Final Lots, lots (b) (4) syringes for validation and stability studies
7. Consistency Batches (produced using (b) (4) MPH)
- (b) (4) batches of Final Bulk (b) (4) for consistency and stability studies;
 - (b) (4) Final Lots (b) (4) syringes for consistency and stability studies
8. US Clinical Batches in Luer-lock Syringes (produced using (b) (4) MPH)
- (b) (4) batches of Final Bulk (b) (4) each for pivotal clinical trial V70_27;
 - (b) (4) Final Lots (b) (4) A52P14H1, A52P14H1, A52P16H1, at (b) (4) syringes for pivotal clinical trial V70_27 and stability study

Comments: All batches of Final Bulk and Final Lots complied with EU specifications for batch release. SRID was performed using WHO reagents and the (b) (4) for the release of Final Lots in EU. For the Final Lots destined for the US market, SRID was performed using CBER reagents and the (b) (4) method.

The MPH production process was transferred from (b) (4) in 2010/2011 and was successfully validated. It is concluded that the primary manufacturing process, facilities and equipment employed at (b) (4) and the resulting MPH are comparable with those produced at (b) (4). These changes have been approved under Agriflu BLA125297 before the submission of Fluad BLA125510. Thus, stability data from Final Formulated DP using (b) (4) MPH can be used to support the current Fluad filing which will be manufactured using (b) (4) MPH in the future.

2.2.6 Reference Standards or Materials

(b) (4)



2.2.7 Container Closure System

The primary container closure for Fluad is a (b) (4) 1mL syringe with Plastic Rigid Tip Cap (PRTC) - referred as a Luer-lok syringe with no needle attached. The Luer-lok adaptor is present at the level of the tip of the syringe to ensure a better and stronger connection of the disposable needle to the syringe.

The cone of the syringe is sealed by an (b) (4) tip cap (Formulation (b) (4) (b) (4)). The tip cap may contain natural rubber latex. The tip cap itself is lodged in a rigid plastic shell which is screwed into the Luer-lok adaptor. The plastic shell protects the tip cap from damage.

The syringe is closed with a grey, (b) (4) (b) (4). The plunger is made of a (b) (4) rubber formulation that meets (b) (4) requirements for Type (b) (4) Closures with no natural rubber latex contained.

Evaluation of extractables and leachables has been performed on Agriflu and Fluad vaccine prefilled syringes to determine the safety and compatibility of the plunger stopper for use in the packaging of human biologics. (b) (4) was selected as the

worst-case marker as it is more soluble in water than the rest of potential extractables identified in the plunger stopper. The maximum (b) (4) value in a Fluad pre-filled syringe was determined to be (b) (4) times less than the maximum yearly allowable (oral) intake of (b) (4) for an infant with a body weight of 10 kg. The stability of Fluad pre-filled syringes showed no significant variation or trend in any parameters potentially affected by leachables. The summary of extractable and leachable evaluation on (b) (4) of the syringe stopper is provided (Section 3.2.P.2.4 attachment 1). Although Fluad is not in direct contact with the (b) (4) tip cap, leachable studies were also conducted to determine additional volatile organic compounds in Fluad that might be found in long term presence (up to 12-month) with the (b) (4) rubber tip cap. A compound below the Safety Concern Threshold (SCT) of (b) (4) possesses negligible safety concerns for carcinogenic and non-carcinogenic toxic effects and is exempted from compound-specific risk assessment, and a non-carcinogenic compound is not required for toxicity studies unless it is above the Qualification Threshold (QT) of (b) (4). Out of (b) (4) volatile organic compounds identified in Fluad prefilled glass syringes with the (b) (4) rubber tip caps during the leachable study, (b) (4) were below both SCT and QT. (b) (4) were slight above SCT but below QT.

Further analysis determines that these (b) (4) compounds individually and cumulatively in a vaccine dose are hundreds to thousands of folds below the safe human exposure thresholds reported for the inhalation route (Section 3.2.P.2.4 attachment 2). Thus, Fluad pre-filled syringes with (b) (4) Rubber Tip Caps stored up to 12 months possess no safety concerns for human usage.

The syringe was also evaluated for extractable volume to ensure the syringe delivered volume is accurate according to (b) (4)

(b) (4). The specification for extractable volume is (b) (4) 0.50 ml/syringe based on the mean extractable volume calculated from (b) (4) syringes containing expelled vaccine for each lot (BLA125510/0 Section 3.2.P.5.2).

The pre-filled syringes with the inserted plungers are packed into the plastic blister strips with the peelable paper sealed around the edges. The blisters are then packed in a double layer of 2x5 syringes along with the package insert into each cardboard box with the batch number and expiry date of the batch printed. The packed cardboard boxes are then assembled into “cartoners”.

Two blister packs (2X5 syringes) are packed in a double layer into a cardboard box along with the package insert. The (b) (4) line will also package syringes in a (b) (4) pack consisting of 10 syringes. The cardboard boxes are assembled by a “Cartoner” with the batch number and expiry date of the batch printed. For Line (b) (4), labeled syringes are packed into a cardboard box that has been assembled by a “Cartoner”. The assembly of the syringes into the package is monitored by an imaging system.

Comments: *The extractable and leachable studies on Fluad pre-filled syringes are adequate to CMC (Ag) reviewer. Please also see Marina Zaitseva’s review memo for comments.*

2.2.8 Stability

2.2.8.1 Stability Data Summary and Conclusions

Novartis plans to market Fluad in pre-filled LL syringes containing 0.5 mL of vaccine. The proposed shelf life for Fluad vaccine is 12 months from the date of formulation when stored at 2-8°C, protected from light. Thus Novartis proposes to place three lots of Final Product from each flu season into the ongoing stability program at $5 \pm 3^\circ\text{C}$ for up to (b) (4) months with the sampling time points at 0, 3, 6, 9, 12, (b) (4) months. Syringes are stored (b) (4) to permit contact between the vaccine and all

components of the container/closure system. Additionally, samples of at least (b) (4) lot are held under accelerated and stressed conditions of (b) (4) for up to (b) (4). Sampling time points are (b) (4). The stability of Final Product is assessed for the parameters and specifications outline in Table 2.2.8.1. All the methods remain the same as those used to release the Final Product. There are no analytical methods that are unique to the stability program.

Table 2.2.8.1 Stability Plan for Fludad

Test	Dose/test	Specification	Test Interval (months) 5± 3°C					Test Interval	
			0	3	6	9	12	(b) (4)	(b) (4)
appearance	(b) (4)	Milky white liquid	X	X	X	X	X	(b) (4)	
pH		6.9 – 7.7	X	X	X	X	X		
HA content		Identity: Positive	X	X	X	X	X		
		(b) (4)							
Endotoxin		(b) (4)	X				X		
Sterility		sterile	X				X		
Squalene		(b) (4)	X				X		
(b) (4)		(b) (4)	X		X		X		
(b) (4)		(b) (4)	X		X		X		
Visible		conform	X		X		X		
(b) (4)		(b) (4)	X		X		X		
(b) (4)									
CCIT		conform	Verified by T0 sterility test					X	

Comments: An additional test for (b) (4) is included in the post-approval stability program, which is captured in the above Table.

(b) (4)

2.2.8.1.2 Assessment of (b) (4) Filling Line Validation Batches

The validation of (b) (4) filling line in Building (b) (4) was performed using (b) (4) manufactured during the 2007/2008 NH (Table 2.2.8.1.2). These lots were subsequently placed on stability as part of the routine stability program for the 2007/2008 NH Campaign. The final stability report is provided in Section 3.2.P.8.3 Attachment 7. This final report also contains the stability data for validation lots (b) (4) manufactured in Building (b) (4) and validation lots (b) (4) manufactured in Building (b) (4) during the 2007/2008 campaign.

Table 2.2.8.1.2 (b) (4) Filling Line Validation Batches

Lot Number	Syringe	Date of Filling	Size (syringes)	Storage Condition	Storage Period
(b) (4)				5 ± 3°C	0, 3, 6, 9, 12, (b) (4) months
(b) (4)				5 ± 3°C	0, 3, 6, 9, 12, (b) (4) months
				(b) (4)	(b) (4)
				(b) (4)	(b) (4)

Comments: Stability data up through the 12-month shelf life has met all acceptance criteria at the intended storage temperature of 5 ± 3°C. Accelerated data was performed for information only. There are 3 deviations related to HA content at 12-month, which had a slightly decrease but was still within the EU specification. These batches were formulated according to EU requirement and had a lower starting HA content than US requirement. CMC (Ag) reviewer has no concerns on the HA stability, since the batches destined for the US market are formulated at higher HA values according to CBER's requirements.

2.2.8.1.3 Assessment of (b) (4) Agrippal Process Technical Transfer Consistency Batches

As part of the transfer of MPH process from (b) (4), MPH consistency batches manufactured at the (b) (4) site using the 2010/2011 seasonal strains were subsequently used to produce Final Formulated and Filled Product. (b) (4) Filled batches have been placed on stability under the same conditions and criteria as used for the seasonal stability (Table 2.2.8.1.3). The testing was performed for pH, appearance, HA, endotoxin, and sterility. Filled batches were also tested for (b) (4) squalene. Stability data for (b) (4) Filled batches are provided in Section 3.2.P.8.3 Attachment 8 and Attachment 09, respectively.

Table 2.2.8.1.3 2010/2011 (b) (4) Consistency Batches (b) (4) Filled)

Lot Number	Container	Mfg. date	Size	Storage Condition	Storage Period
(b) (4)				5 ± 3°C	0, 1, 2, and 3 months
(b) (4)				5 ± 3°C	0, 3, 6, 9, 12, (b) (4)
				(b) (4)	
				(b) (4)	

Comments: The stability data for the three consistency batches of (b) (4) manufactured at (b) (4) met all the acceptance criteria for a hold time up to (b) (4)

HA content in all three filled lots was (b) (4) up to 12 months at $5 \pm 3^\circ\text{C}$. H1N1 HA content in batch (b) (4) was low at (b) (4) at T0. At (b) (4), all HA contents fell below the specification limit of (b) (4). These lots were filled according to EU requirement. The 12-month stability met EU specifications. The OOSs of HA content were due to the low starting HA content. CMC (Ag) reviewer has no concerns on the HA stability, once the batches destined for the US market are formulated at higher HA values based on CBER's requirements.

2.2.8.1.4 US Clinical Batches (V70_27) for Lot-to-Lot Consistency

Three batches of US trial V70_27 in LL syringes used to show lot-to-lot consistency were placed on stability under the same conditions and criteria as used for the seasonal stability (Table 2.2.8.1.3). The testing was performed for pH, appearance, HA, endotoxin, sterility, (b) (4) and squalene. Accelerated data is for information only. Stability data are provided in Section 3.2.P.8.3 Attachment 10.

Table 2.2.8.1.4 V70_27 US Clinical Batches for Lot-to-Lot Consistency

Lot Number	Container	Mfg. date	Size (syringe)	Storage Condition	Storage Period
A52P15H1	LL	(b) (4)	(b) (4)	$5 \pm 3^\circ\text{C}$	0, 3, 6, 9, 12, (b) (4) months
A52P16H1		(b) (4)	(b) (4)		
A52P14H1		(b) (4)	(b) (4)	$5 \pm 3^\circ\text{C}$	0, 3, 6, 9, 12, (b) (4) months
				(b) (4)	(b) (4)
				(b) (4)	(b) (4)

Comments: These batches were filled according to US requirement. Stability data met all acceptance criteria including HA content (b) (4)/dose up to 12 months confirming the proposed 12 months shelf life at $5 \pm 3^\circ\text{C}$. No concerns from CMC (Ag) reviewer are raised on the HA stability.

2.2.8.1.5 Seasonal Stability on the Batches Supplied to the Canadian Market

Per CBER's request, Novartis also submitted stability data for Fludac LL lots supplied to the Canadian market (pre BLA Follow-up response February 24, 2012 telecom IND14368 CRMTS#8235). The testing was performed for pH, appearance, HA, endotoxin, sterility, (b) (4) and squalene. Accelerated data is for information only. The 2011/2012 seasonal report with (b) (4) months data and the 2012/2013 interim report with 12 months data are provided in Section 3.2.P.8.3 Attachment 4 and Attachment 5, respectively (Table 2.2.8.1.5).

Table 2.2.8.1.5 Batches Supplied to the Canadian Market

Lot Number	Container	Mfg. date	Size (syringe)	Storage Condition	Storage Period
117701	LL	(b) (4)	(b) (4)	$5 \pm 3^\circ\text{C}$	0, 3, 6, 9, 12, (b) (4) months
117903		(b) (4)	(b) (4)	(b) (4)	(b) (4)
118301		(b) (4)	(b) (4)	(b) (4)	
129001		(b) (4)	(b) (4)		
129004		(b) (4)	(b) (4)		
129002A		(b) (4)	(b) (4)	9	

Comments: The Canadian batches for both 2011/2012 and 2012/2013 seasons, again formulated according to EU requirement, showed an expected decreasing trend for three strains but all met EU acceptance specifications up to 12-months (HA content (b) (4)). No concerns from CMC (Ag) reviewer are raised on the HA stability.

2.2.8.1.6 Routine Seasonal Stability

Routine seasonal stability data of Final Lots from 2010/2011, 2011/2012 and 2012/2013 NH seasons are provided in Section 3.2.P.8.3 Attachment 1/2/3. The testing was performed for pH, appearance, HA, endotoxin, sterility, (b) (4) and squalene. Accelerated data is for information only (Table 2.2.8.1.6).

Table 2.2.8.1.6 Batches for Routine Seasonal Stability

Lot Number	Container	Mfg. date	Size (syringe)	Storage Condition	Storage Period
(b) (4)	LL	(b) (4)	(b) (4)	5 ± 3°C	0, 3, 6, 9, 12, (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)	(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)	(b) (4)

Comments: EU specification limit of (b) (4)/dose was used for these batches. The stability data suggest that Fluad vaccine filled in LL syringes for 2010/2011 season was stable up to 12 months, and Fluad vaccine filled for 2011/2012 and 2012/2013 seasons were stable up to (b) (4) months when stored at recommended temperature of 2°-8°C, protected from light. These stability reports confirm the current shelf life of 12 months for Fluad.

2.2.8.2 Post-approval Stability Protocol and Stability Commitment

All stability testing presented in this BLA submission were performed in the (b) (4). Future stability testing for Fluad destined for the US market will be transferred to (b) (4) which has been approved under the Agriflu BLA125297 on 11/27 2009. MPH manufactured at (b) (4) will be used to formulate Fluad Final Product release for the US market. Each batches of Final Product from each season will be placed on real-time stability program at 5 ± 3°C, protected from light. At least (b) (4) lot from each season will be tested under accelerated stability program at (b) (4).

The stability protocol has been updated to include the additional test for (b) (4) (see Table 2.2.8.1 Stability Plan for Fluad).

Comments: Novartis has shared with CBER at Mid Cycle Review meeting (5/20/2015) and again on 6/8/2015 that they have no plan to launch Fluad in the 2015/16 season even if approval is received by November, 2015. The company has noted that CBER agrees this strategy in an email received on 5/5/2015. The Company agrees with CBER's recommendation to submit the strain change for the 2016/17 season instead of the requested 2015/16 season as a supplement to STN125510, if approval is received for the BLA before the 2016/17 season. The company's plan is to provide 3 commercial lots for BLA testing at the start of the 2016/17 campaign (BLA125510/0.15).

Novartis has assigned (b) (4) of each of the three batches (b) (4) from the Fluad NH 2014/15 campaign for CBER to use for assay optimization (BLA125510/0.4). These lots were not formulated per US specifications. Novartis acknowledges that the testing of these lots will not fulfil the requirements of sample testing for the BLA. Novartis intends to provide CBER both (b) (4) lots and the first three lots of 2015/16 NH Final Formulated Product using US specifications. This will be confirmed following the 2015/16 strain announcement and upon availability of US specific reagents (BLA125510/0.4). This plan is acceptable to CMC (Ag) reviewer.

2.2.9 HA Inhibition Test for Pivotal Clinical Study

The SOP TSOP.119.057 and SOP TSOP.119.00510 were developed by (b) (4) and were used for HAI testing for clinical studies in support of the current Fluad BLA filing. The differences between these two SOPs are listed below:

- SOP TSOP.119.057
 - Starting serum dilution of (b) (4);
 - Neutralization condition: (b) (4);
 - Used between 2006-2012;
 - Used for pivotal trial V70_27
- SOP TSOP.119.00510
 - Starting serum dilution of (b) (4)
 - Neutralization condition: (b) (4)
 - Used since 2012.

Both SOPs were validated. A comparison study (REPT.119.00092-FDX) was conducted to bridge two SOPs showing that HAI titers determined by two SOPs were comparable with acceptance criteria based on confidence intervals for the slope within (b) (4)

However, the HAI titers of pivotal trial V70_27 were determined and calculated based on SOP TSOP.119.057, in which final HAI titer was calculated by (b) (4). CBER requires that HAI titers are determined by the (b) (4). Thus Novartis was asked to recalculate and reanalyze the HAI titer values as measured in pivotal trial V70_27 and submit the results for CBER to review.

Comments: Novartis agreed to recalculate the HAI titer values as measured in study V70_27 by dividing the original value by (b) (4). The results after recalculation and reanalysis have been submitted to CBER for review by clinical reviewer (Sarah Browne) and clinical statistician (Gideon Solomon) (BLA125510/0.8). Please also see Zhong Gao's review memo for HAI assay validation and statistics.

2.2.10 CMC-related preclinical studies

Novartis has performed nonclinical studies with Fluad include immunogenicity (mice and rabbits) and challenge studies (mice), repeat dose toxicity (rabbits), reproductive and developmental toxicity (rabbits) and sensitization (Guinea pigs). These data are submitted in Section 2.4 and 2.6.

Comments: The nonclinical data regarding immunogenicity, efficacy, toxicity, and tolerability of Fluad in conjunction with clinical data support the clinical use of Fluad in adults 65 years of age and older. Please also see the review memos of Marina Zaitseva and Toxicology reviewer (Nabil Al-Humadi) for additional comments including nonclinical studies performed to characterize MF59 adjuvant.

2.2.11 Draft Lot Release Protocol (LRP) Template and Product Information (PI)

Comments: *Novartis' request of removing formaldehyde from LRP is justified (BLA125510/0.23). Residual formaldehyde listed in PI will be based on the release specification of (b) (4). In Amendment 26, bioburden (b) (4) test at (b) (4) manufacturing stage (b) (4) is included in the LRP template per CBER's requirement (BLA125510/0.26). Reviews on LRP and PI are still ongoing. Comments including latex statement in PI have been shared at internal discussions and will be reflected in the final PI.*