REVIEW MEMORANDUM

To:	Brenda Baldwin, Ph.D., DVRPA, OVRR, CBER, FDA
From:	Marina Zaitseva, Ph.D., DVP, OVRR, CBER, FDA
Through:	Hana Golding, Ph.D. Supervisor, DVP, OVRR, CBER, FDA
Through:	Jerry Weir, Ph.D., DVP, OVRR, CBER, FDA Anissa Cheung, Regulatory Coordinator, DVP, OVRR, CBER, FDA
Subject:	STN125692/0
Product Name	Audenz/Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
Applicant	Seqirus
Proposed Indication	For active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Influenza A (H5N1) Monovalent Vaccine, Adjuvanted is approved for use in persons 6 months of age and older.
Cross-reference(s)	DMF (b) (4) Vials) DMF (b) (4) (13 mm stoppers) DMF (b) (4) (MF59C.1)

Review of the Chemistry, Manufacturing, and Control Information relevant to MF59C.1 Drug Substance and aH5N1c Pandemic Influenza Vaccine (b) (4) Prefilled Syringes (PFS) Drug Products submitted as part of the Initial Biologics License Application

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY, REVIEW HIGHLIGHTS, AND RECOMMENDATIONS

1.1 INTRODUCTION

The pandemic adjuvanted aH5N1c vaccine consisting of the purified viral surface proteins, hemagglutinin (HA) (b) (4) derived from an H5N1 influenza pre-pandemic virus and a MF59C.1 adjuvant (MF59), a squalene-based oil-in-water emulsion.

The vaccine antigens (HA (b) (4) are obtained from the reverse genetics virus, NIBRG-23, containing (b) (4) (b) (4) HA genes from A/turkey/Turkey/1/2005 (H5N1) and (b) (4) from A/Puerto Rico/8/1934 (H1N1) (b) (4)

The H5N1 influenza virus used to generate vaccine antigens is propagated in a suspension of culture-adapted Madin Darby Canine Kidney (MDCK) cell line using the manufacturing process established for the licensed seasonal influenza vaccine, Flucelvax®. The MF59 adjuvant is contained in the licensed seasonal vaccine, Fluad®. The proposed pandemic vaccine includes MF59 (b) (4) Fluad.

The vaccine antigen and MF59 adjuvant are manufactured by Seqirus at the manufacturing facility located at Holly Springs, NC, USA.

(b) (4) final drug product presentations were initially included in the file, (b) (4) single dose pre-filled syringe (PFS). (b) (4) presentations contain a combination of (b) (4) antigen for the H5N1c virus strain, MF59C.1 adjuvant, (b) (4) . However, due to problems associated with stability studies of (b) (4), the applicant decided to withdraw the (b) (4) drug product from the BLA (Amendment 32 Received at FDA 11/22/2019 DATS #842598). Therefore, review of information related to the manufacturing of the (b) (4) drug product is not provided in this memo.

PFS are formulated and filled/finished at Seqirus, Holly Springs, NC.

The potency of the vaccine is assessed by measuring concentration of the HA protein in the final formulation using the (b) (4) assay.

A series of two 0.5 mL doses will be given by intramuscular injection approximately 21 days apart. The dosing regimen is the same for all persons, starting from 6 months of age and older.

This vaccine is intended for distribution only in the case of an influenza pandemic declared by governmental authorities. Distribution is likely to be undertaken by CDC and state and local health departments. In the event of a pandemic, other distribution channels may be used. Vaccinations may be given at mass vaccination clinics. Additionally, vaccinations could be given in hospitals or by retail pharmacies or doctor's offices.

The applicant seeks approval under 21 CFR 601.2 (traditional approval) based on clinical immunogenicity and safety studies, as described in FDA's May 2007 Guidance for Industry "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" where the manufacture of the pandemic vaccine is the same as for a licensed seasonal vaccine.

This review covers the MF59C.1 adjuvant Drug Substance and parts of aH5N1c PFS Drug Product relevant to MF59 adjuvant including stability of the (b) (4) Finished (Filled) vials.

1.2 MF59C.1 ADJUVANT (b) (4)

GENERAL DESCRIPTION AND COMPOSITION

MF59C.1 adjuvant is an oil-in-water emulsion with a squalene internal oil phase and a citric acid/sodium citrate buffer external aqueous phase. The emulsion is stabilized by two non-ionic surfactants included in the formulation: Polysorbate 80 (b) (4) and Sorbitan Trioleate (b) (4) that are used at a ratio of Squalene : Polysorbate : Sorbitan Trioleate of (b) (4)

The use of a blend of lipophilic (Sorbitan Trioleate) and hydrophilic (Polysorbate 80) surfactants creates a stable emulsion that can be (b) (4)

Table 1 Composition of MF59C.1 (b) (4) Adjuvant

Name of Ingredients	Target Quantity/L*	Function
Squalene	(b) (4)	oil phase
Polysorbate 80		surfactant
Sorbitan Trioleate		surfactant
Sodium Citrate, dihydrate		buffer
Citric Acid, monohydrate		buffer
Water for Injection (WFI)		aqueous phase
(b) (4)		(b) (4)

* A range of ± 10% is permissible

COMPONENTS OF THE MF59C.1 DRUG SUBSTANCE

Squalene

The primary ingredient of MF59C.1 adjuvant is squalene, a well characterized highly unsaturated hydrocarbon. Squalene used in the production of MF59C.1 is derived from shark liver oil.

Squalene is the only substance of animal origin used in the (b) (4). Squalene is a well characterized biological substance with known chemical structure (2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene).

(b) (4)

Other ingredients

Polysorbate 80, Sorbitan trioleate, Sodium citrate dehydrate, and Citric acid monohydrate are all (b) (4) .

- *Polysorbate 80* (b) (4)
- *Sorbitan trioleate* (b) (4)
- Polysorbate 80 and Sorbitan Trioleate are two non-ionic surfactants. Blending of lipophilic (Sorbitan Trioleate) and hydrophilic (Polysorbate 80) surfactants creates a stable emulsion.
- *Citric Acid Monohydrate* and Sodium Citrate Dihydrate (b) (4)
- *Water* (Water for Injections) is produced by Seqirus (b) (4)

MANUFACTURING OF MF59C.1 DRUG SUBSTANCE

MF59C.1 Adjuvant (b) (4) is manufactured and released at Seqirus manufacturing facility in Holly Springs, NC, USA. Manufacturing process consists of (b) (4)

(b) (4) .

SPECIFICATIONS FOR RELEASE OF MF59C.1 ADJUVANT (b) (4) AND FOR STABILITY STUDIES

1 Page has been determined to be not releasable: (b)(4)

(b) (4)

.

The MF59C.1 (b) (4) adjuvant process validation at Holly Springs has been successfully completed in 2012 using (b) (4) . The process validation parameters were within the respective normal operating ranges and they met all acceptance criteria. The data confirms that the process is reproducible and produces product that meets specifications. Therefore, the MF59C.1 (b) (4) adjuvant production process at Holly Springs facility has been successfully validated.

1.3 aH5N1c – PFS DRUG PRODUCT

Influenza A (H5N1) Virus Vaccine, cell-derived and adjuvanted with MF59C.1 (aH5N1c) in Pre-Filled Syringes (PFS) is an inactivated influenza vaccine containing predominantly hemagglutinin HA surface antigens from A/turkey/Turkey/1/2005 NIBRG-23 (H5N1) influenza strain and MF59C.1 adjuvant. The H5N1 influenza virus used to generate vaccine antigens is propagated in a suspension of culture-adapted Madin Darby Canine Kidney (MDCK) cell line using the manufacturing process established for the licensed seasonal influenza vaccine, Flucelvax®. The vaccine contains 7.5 µg per dose of HA antigen formulated with MF59C.1 adjuvant in the presence of (b) (4) (Table 3). The vaccine is presented as a liquid for injection, in a (b) (4) glass pre-filled syringe ready for use containing 0.5 mL of antigen solution. Each syringe is intended for a single use. The vaccine is milky-white homogeneous fluid in appearance and is preservative-free.

Table 3 Composition of Adjuvanted H5N1c Influenza Vaccine (PFS)

Ingredient	Quantity per Adult Dose (0.5 mL/dose)	Function
Active Ingredient		
H5N1 monovalent (b) (4)	7.5 µg	HA antigen
Adjuvant		
Squalene	9.75 mg	Oil phase
Polysorbate 80	1.175 mg	Surfactant
Sorbitan triolate	1.175 mg	Surfactant
Sodium citrate	0.66 mg	Buffer
Citric acid	0.04 mg	Buffer
(b) (4)		

Ingredient	Quantity per Adult Dose (0.5 mL/dose)	Function
(b) (4)		
Water for injection	(b) (4)	Diluent

The primary packaging consists of a (b) (4) 1 mL syringe with a (b) (4) of rubber formulation (b) (4) that is closed with a (b) (4) bromobutyl plunger stopper.

The MF59C.1 (b) (4) Adjuvant is manufactured as (b) (4) material at Holly Springs. (b) (4)

The release specifications for aH5N1c – PFS is shown in Table 4 below.

Table 4 Release specifications for the Filled aH5N1c Product – PFS

Test	Method	Requirements
Sterility	(b) (4)	No evidence of microbial growth
Endotoxin	(b) (4)	(b) (4)
Appearance	Visual inspection	White homogeneous suspension
Extractable volume	(b) (4)	(b) (4) 0.50 mL
Visible Particulates[1]	Tested according to (b) (4)	Essentially free of visible particulates
Sub-Visible Particulates[1]	Tested according to (b) (4)	(b) (4)
Hemagglutinin antigen (HA; potency)	(b) (4)	
pH	(b) (4)	6.5 – 7.7
Squalene (b) (4)	(b) (4)	(b) (4)
Squalene (b) (4)	(b) (4)	(b) (4)
Number of Large Particles (b) (4)	(b) (4)	(b) (4)
Mean Particle Size	(b) (4)	(b) (4)

Test	Method	Requirements
		(b) (4)

[1]Update: The specification for aH5N1c PFS at the time of BLA submission did not include testing for Visible Particulates and Sub-Visible Particulates. In response to IR sent by CBER on December 6, 2019, analytical testing for Visible Particulates and Sub-Visible Particulates in aH5N1c PFS as shown in Table 4 above was added to the list of release testing in Amendment 39 (Table 2, section 3.2.P.5.1 in the Amendment) received at FDA on 12/16/2019 – DATS 855840.

[2]Update: The specification for aH5N1c PFS at the time of BLA submission did not include testing for (b) (4) as described in section 2.2.4.6 of this memo. However, the firm re-introduced testing for (b) (4) in the filled product as was described in Amendment 8, received at FDA on 5/17/2019 (DATS 809513). In Amendment 8, the applicant provided a revised release specification for aH5N1c Filled Product that included testing for (b) (4) with acceptance criteria.

The updated release specifications and acceptance criteria for aH5N1c PFS shown in Table 4 above are based on updated release specifications as shown in Table 2, section 3.2.P.1 in Amendment 39 (12/16/2019).

USAGE OF aH5N1c PFS IN PHASE III CLINICAL TRIAL AND TO SUPPORT LICENSURE

Influenza vaccine cell culture-based production in Madin-Darby Canine Kidney (MDCK) cells was initiated in (b) (4) . Over the period of development, the production facility operated under (b) (4) followed by Chiron Behring GmbH & Co. KG (Chiron Vaccines), and then Novartis Vaccines and Diagnostics (NVD). The drug product was filled and packaged in (b) (4) . The flu cell culture (FCC) process and drug product manufacturing processes were subsequently (b) (4) NVD Holly Springs, NC (now Seqirus).

The manufacturing process for seasonal and pandemic influenza vaccines in MDCK cell line was optimized during development to increase yield and robustness of the process. Three major processes were developed and were used to obtain material for clinical trials: the initial Process 1.0 followed by Process 2.0, Process 1.1, and Process 3.0. Process 3.0 was approved on July 27, 2018 in a Supplement to the Flucelvax BLA 125408. Future pandemic lots will be manufactured under Process 3.0 (commercial production).

To support the Phase III clinical trial of the aH5N1c pandemic influenza vaccine, three consecutive lots 181053 (b) (4) 181054 (b) (4) and 181675 ((b) (4) were manufactured under Process 1.1 (for vaccine antigen), were formulated with MF59C.1 adjuvant, and were filled in PFS at a Holly Springs site on (b) (4) .

To align Process 1.1 used to manufacture Phase III clinical lots and Process 3.0 proposed for licensed product, CBER recommended to demonstrate comparability between aH5N1c products manufactured using Process 1.1 vs Process 3.0 (CRMTS 9354).

Following this recommendation and to support proposed (b) (4) months shelf-life of the finished product in syringes, Seqirus manufactured (b) (4) stability drug product (b) (4)) in (b) (4) using a Process 3.0 PPQ (b) (4)

The long-term stability results for three clinical lots (181053, 181054, and 181675, Process 1.1) met all specifications through (b) (4) months, when stored at 2°C to 8°C except for HA content at 9-month time-point that showed an OOS value that was investigated and resolved by the applicant.

The long-term (2°C to 8°C) and accelerated (b) (4)) stability results of the stability lot (b) (4) (Process 3.0) met all specifications through the 9- and 6-month time-points, respectively. The stability study is on-going.

1.4 LIST OF INFORMATION REQUESTS (IR) SUBMITTED TO SEQIRUS RELATED TO MF59C.1 AND AUDENZ MANUFACTURING PROCESSES AND STABILITY STUDIES

1. **In IR1 (July 1, 2019), the applicant was asked to provide the Certificate of Analysis (CoA) for the (b) (4) used for manufacture of MF59C.1 adjuvant at Holly Springs facility.**

Company's response (Question 4, Amendment 19, July 11, 2019). The firm added the most recent Certificate of Analysis of the (b) (4) used for manufacture of MF59C.1 adjuvant as attachment Att_(b) (4) _CoA (in Section 3.2.S.2.3 Control of Materials – MF59C.1).

Reviewer: I reviewed the Certificate of Analysis for the (b) (4) from (b) (4) . that confirms (b) (4) (Lot (b) (4)). The CoA is acceptable.

2. **In IR2 (July 1, 2019), the firm was requested to provide information on the content of (b) (4) used for (b) (4) MF59.C1 (b) (4) .**

Company's response (Question 5, Amendment 19, July 11, 2019). Seqirus provided the results of the study of (b) (4) performed by (b) (4) manufacturer in the document (b) (4) (b) (4) - (b) (4) in the attachment att_(b) (4) (b) (4) .

Reviewer: I reviewed the results of the (b) (4) and concur with the firm that the level of (b) (4) obtained from (b) (4) is negligible and does not pose any safety concern.

3. **In IR3 sent on July 1, 2019, the applicant was requested to provide relevant Process Validation report 299968 and Process Validation Report Protocol 298215 performed during manufacturing process validation of MF59C.1 Drug Substance.**

Company's response (Question 6, Amendment 19, July 11, 2019). Seqirus clarified that their Electronic Document Management System was updated from a legacy system (b) (4) , which utilized a six-digit numbering system to (b) (4) which utilizes a prefix followed by a nine-digit number. Documents

migrated from the legacy system received a new (b) (4) number but retain the (b) (4) document number within the document itself if it has not been revised. Seqirus confirms that process validation protocol 298215 is VAL-000072737 in the submission and process validation report 299968 is VAL-000071676 in the submission, which both refer to the process validation for MF59C.1 that occurred in 2012.

Reviewer: the company's response is acceptable. I reviewed both, process validation protocol (298215) VAL-000072737 and process validation report (299968) VAL-000071676 and concur with the company's conclusion that the manufacturing process for MF59C.1 at Holly Springs facility was validated.

4. **In IR4 sent on July 1, 2019, the firm was requested to provide the** (b) (4)

Company's response (Question 7, Amendment 19, July 11, 2019): (b) (4)

Reviewer: the provided information on the levels of (b) (4) **is acceptable. It can be concluded that the** (b) (4) **is suitable for use.**

5. **In IR5 (July 1, 2019), the firm was requested to provide the stability data to support the (b) (4) months shelf life of the (b) (4) MF59C.1 (b) (4) adjuvant.**

Company's response (Question 8, Amendment 19, July 11, 2019). Seqirus provided the results of the stability up-date through (b) (4) months (Batch (b) (4) and through (b) (4) months (Batch (b) (4) and Batch (b) (4)) in Section 2.5 of 3.2.P.3.5 (Process Validation and (or) Evaluation).

Reviewer: I reviewed the provided stability data for (b) (4) MF59C.1 adjuvant and confirm that all results met the acceptance criteria.

6. **In IR6 (July 1, 2019), the firm was requested to provide the data to support the maximum shelf life of the in-house MF59C.1 reference standard and to provide qualification information of the in-house reference standard used for assessment of (b) (4) squalene (b) (4).**

Company's response (Question 9, Amendment 19, July 7, 2019). Seqirus clarifies that the squalene (b) (4)

. There is no additional qualification performed. (b) (4)

Reviewer: I reviewed the qualification information of MF59C.1 standards (b) (4) routinely used for characterization of the lots of MF59C.1 adjuvant and I find it acceptable.

1.5 HIGHLIGHTS OF THE REVIEW OF MF59C.1 ADJUVANT DRUG SUBSTANCE AND AH5N1C - PFS DRUG PRODUCT AND RECOMMENDATION

1. **The manufacturing of pandemic adjuvanted aH5N1 vaccine, Audenz, incorporated processes previously developed for production of two licensed vaccines, Flucelvax and FLUAD. Specifically, propagation of the virus in a suspension of culture-adapted Madin Darby Canine Kidney (MDCK) cell line was used in the manufacturing of Flucelvax; manufacturing of squalene-based MF59C.1 adjuvant and formulation of adjuvant with Haemagglutinin (HA) antigen was utilized in FLUAD. The previous significant manufacturing experience allowed the applicant to develop a straight forward process where all major hurdles were resolved during pharmaceutical development of Flucelvax and FLUAD.**

2. **The aH5N1 vaccine Drug Product is produced by (b) (4) of a cell culture-derived Haemagglutinin (HA) antigen from A/turkey/Turkey/1/2005 NIBRG-23 (H5N1) (b) (4) MF59C.1 adjuvant (b) (4) followed by filling into a single dose Pre-filled Syringe (PFS). Vaccine is administered at volumes of 0.5 mL per dose that contains 7.5 μg of HA and (b) (4) of MF59C.1 adjuvant. PFS is preservative-free.**
3. **The firm pursues licensure based on completed Phase III clinical trial with aH5N1c vaccine presented in PFS.**
4. **Historically, MF59C.1 development started in 1990 by Chiron, which was later acquired by Novartis Vaccines and Diagnostics (now Seqirus). Since the beginning of the pilot production, the chemical composition of MF59 (Squalene, Polysorbate 80, and Sorbitan Trioleate) (b) (4) The MF59.C1 adjuvant for formulation with HA antigen from H5N1c virus is manufactured at Holly Springs facility in North Carolina as a (b) (4) with a shelf-life of (b) (4) months. (b) (4), MF59C.1 adjuvant (b) (4). The stability data for (b) (4) MF59C.1 confirms (b) (4)-month stability when stored at (b) (4) The stability data provided in this BLA confirms that the (b) (4) MF59C.1 adjuvant (b) (4) does not negatively affect the stability of the emulsion as monitored by measuring (b) (4)**
5. **The applicant provided several sets of data to support the shelf-life of aH5N1c in PFS for (b) (4) months when stored at 2°C to 8°C protected from light. For aH5N1c - PFS, stability study for three Phase III clinical lots manufactured under Process 1.1 is completed for (b) (4) months and the data is available. (b) (4) PFS stability (b) (4) was produced under Process 3.0 and stability data for long-term storage for this (b) (4) was available for 3-month time-point at the time of the BLA submission. All stability results provided met all specifications. The results confirm that the material is stable up to (b) (4) months supporting a shelf life of (b) (4) months, when stored at 2°C to 8°C. No changes in squalene (b) (4) or the number of large particles was noted. Thus, available data showed that the presence of MF59C.1 does not negatively affect the potency of the antigen when stored in PFS. The applicant expressed commitment to continue monitoring the stability of the Audenz vaccine post-approval.**

CONCLUSION AND RECOMMENDATION

In summary, the CMC information and data relevant to the MF59C.1 adjuvant in aH5N1c vaccine presented in this BLA is complete and adequate to demonstrate that the MF59C.1 adjuvant is manufactured under GMP by a validated process and the MF59C.1 adjuvant meets generally accepted standards of purity and quality as required for an adjuvant or constituent material as per 21 CFR 610.15. Overall, the MF59C.1-relevant CMC information presented in the Quality Module of the BLA supports the approval of the BLA for manufacture of aH5N1 vaccine

I recommend approval of the BLA for Audenz.

2.0 FULL REVIEW OF MF59C.1 ADJUVANT DRUG SUBSTANCE AND aH5N1c PFS DRUG PRODUCT

The following sections were assigned to and reviewed by this product reviewer

3.2.S MF59 DRUG SUBSTANCE
- 3.2.S.1 General Information
- 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 aH5N1c - PFS DRUG PPODUCT
- 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

2.1 MF59C.1 ADJUVANT DRUG SUBSTANCE

2.1.1 General Information, Nomenclature, Structure, and Properties

Nomenclature

The notation 'MF59' is used to describe a family of Novartis Squalene-in-water emulsions. In the past, a number of terms (laboratory codes) have been used to describe these emulsions at Seqirus (previously Novartis and Chiron).

The term MF59C.1 refers to the current formulation which includes a sodium citrate/citric acid (b) (4) aqueous phase. There is no chemical name, Chemical Abstracts Service (CAS) name or International Union of Pure and Applied Chemistry (IUPAC) name that describes MF59C.1.

The following nomenclature is used for squalene, the primary component of MF59C.1 in the BLA:
Chemical name: 2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene
Chemical Abstracts Service (CAS): 111-02-4
International Union of Pure and Applied Chemistry (IUPAC): (6Z,10E,14E,18E)-2,6,10,15,19,23 hexamethyltetracosa-2,6,10,14,18,22-hexaene
Company names or laboratory codes: Squalene (b) (4)

Structure and General Properties

MF59C.1 adjuvant is a stable oil-in-water emulsion in which oil droplets are dispersed within a citrate buffer continuous phase. The emulsion is stabilized by inclusion of two non-ionic surfactants (Polysorbate 80 and Sorbitan Trioleate) in the formulation at a ratio of squalene: Polysorbate (b) (4) : Sorbitan Trioleate (b) (4) as shown in the figure below.

(b) (4)

The use of a blend of lipophilic (Sorbitan Trioleate) and hydrophilic (Polysorbate 80) surfactants creates a stable emulsion that can be (b) (4)

The primary ingredient of MF59C.1 is squalene. Squalene is an unsaturated trans isopreneoid hydrocarbon containing six isoprene units. It has a molecular weight of 410.70 g/mol and the following chemical formula: *2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene*

In humans, squalene is biosynthesized in the liver and is an intermediate in the biosynthetic pathways producing human steroid hormones including cholesterol (for which squalene is a direct synthetic precursor). Squalene is also the principal hydrocarbon of human surface lipids.
Squalene used in the production of MF59C.1 is derived from shark liver oil.

2.1.2 Manufacture

2.1.2.1 Manufacturer and Overview of the Manufacturing for MF59 Drug Substance

MF59C.1 (b) (4) adjuvant is manufactured by Seqirus Inc

475 Green Oaks Parkway
Holly Springs, North Carolina 27540
United States

MF59C.1 (b) (4) Adjuvant lots are utilized at Holly Springs or shipped to third party facilities for final vaccine formulation and/or final container filling.

Overview of the MF59C.1 Drug Substance Manufacturing process

(b) (4)

(b) (4)

The composition of MF59C.1 adjuvant is described in Table 5

Table 5 MF59C.1 adjuvant (b) (4) Composition

Name of Ingredients	Target Quantity/L*	Function
Squalene	(b) (4)	oil phase
Polysorbate 80		surfactant
Sorbitan Trioleate		surfactant
Sodium Citrate, dihydrate		buffer
Citric Acid, monohydrate		buffer
Water for Injection (WFI)		aqueous phase
(b) (4)		(b) (4)

(b) (4)

Sodium citrate/Citric acid buffer, Polysorbate 80 (b) (4) Water for Injection, Squalene (b) (4) Sorbitan Trioleate (b) (4) .

2.1.2.2 Detailed manufacturing process

(b) (4)

3 Pages have been determined to be not releasable: (b)(4)

(b) (4)

.

Squalene

Squalene is the only substance of animal origin used (b) (4) . Squalene is a well characterized biological substance with known chemical structure (2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene).

Table 13 (b) (4) squalene testing requirements

(b) (4)

(b) (4)

(b) (4)

.

(b) (4)

Other ingredients

Polysorbate 80, Sorbitan Trioleate, Sodium citrate dehydrate, and Citric acid monohydrate are (b) (4) Certificates of Analysis are included in the BLA.

- Polysorbate 80 (b) (4))
- Sorbitan trioleate (b) (4)
- Polysorbate 80 and Sorbitan Trioleate are two non-ionic surfactants.

Reviewer: The CoA for Citric acid monohydrate, Sodium Citrate dehydrate (b) (4) Sorbitan Trioleate, Polysorbate 80, and for Squalene are all provided in attachments in 3.2.S.2.3; the CoAs are acceptable

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

9 Pages have been determined to be not releasable: (b)(4)

(b) (4)

The detailed review of the manufacturing processes of MF59C.1 (b) (4) Adjuvant confirmed that the manufacturing of MF59C.1 in Audenz is well-aligned with the current manufacturing process for MF59C.1 in Fluad (post supplement 48). Some minor differences in the manufacturing of MF59C.1 in Fluad and in Audenz (or description of manufacturing) are specified in the body of the review memo.

2.1.2.7 Characterization

Elucidation of Structure and Other Characteristics

Squalene

The primary ingredient of MF59C.1 adjuvant is Squalene, a well characterized highly unsaturated hydrocarbon. Squalene is biosynthesized in many animals and some plants. In humans, Squalene is biosynthesized in the liver and is an intermediate during the production of human steroid hormones and cholesterol.

Squalene used in the production of MF59C.1 is derived from shark liver oil. It is purchased as a purified raw material from the vendor and is formulated (unmodified) into an emulsion. Squalene (b) (4) is confirmed as part of the release testing for MF59C.1 (b) (4) Adjuvant.

MF59C.1 Emulsion

MF59C.1 (b) (4) Adjuvant is a stable oil-in-water emulsion in which (b) (4)

Polysorbate 80 (b) (4) and Sorbitan Trioleate (b) (4) ratio. The MF59C.1 (b) (4) Adjuvant emulsion is (b) (4) .

(b) (4)

11 Pages have been determined to be not releasable: (b)(4)

2.2 INFLUENZA A (H5N1) MONOVALENT VACCINE ADJUVANTED DRUG PRODUCT - PRE-FILLED SYRINGES (PFS)

2.2.1 Description and composition of the influenza A (H5N1) Monovalent Vaccine, Adjuvanted Drug Product – PFS

- Influenza A (H5N1) Virus Vaccine, cell-derived and adjuvanted with MF59C.1 (aH5N1c) is an inactivated influenza vaccine containing predominantly hemagglutinin (HA) (b) (4) surface antigens from a Madin Darby Canine Kidney (MDCK) cell-derived H5N1 virus subtype.
- The manufacturing platform of this pandemic monovalent (b) (4) antigen (b) (4) is the same as the (b) (4) for the licensed Flucelvax® cell-based influenza vaccine (STN 125408, approved November 20, 2012). Flucelvax® contains monovalent pooled harvests from four strains: A/H1N1, A/H3N2 and B (Victoria and Yamagata lineages). Both vaccines are prepared by inactivation, detergent disruption, and purification prior to formulation.
- The final product is adjuvanted with MF59C.1, an oil-in water emulsion containing squalene oil as the dispersed phase and low ionic strength citrate buffer as the continuous phase. The emulsion is stabilized by the inclusion of two non-ionic surfactants (Polysorbate 80 and Sorbitan Trioleate). The composition of MF59C.1 is described in section 2.1.2.1 of this review.
- The potency of the vaccine is expressed as the concentration of the HA protein; it is formulated to contain (b) (4) 7.5 µg per dose of HA antigen. The vaccine is presented as a liquid for injection, in a (b) (4) glass pre-filled syringe ready for use containing 0.5 mL of antigen solution. Each syringe is intended for a single use. The vaccine is milky-white homogeneous fluid in appearance and is preservative-free.

Table 23 Composition of Adjuvanted H5N1c Influenza Vaccine (PFS)

Ingredient	Quantity per Adult Dose (0.5 mL/dose)	Function
Active Ingredient		
H5N1 monovalent (b) (4)	7.5 µg	HA antigen
Adjuvant		
Squalene	9.75 mg	Oil phase
Polysorbate 80	1.175 mg	Surfactant
Sorbitan triolate	1.175 mg	Surfactant
Sodium citrate	0.66 mg	Buffer
Citric acid	0.04 mg	Buffer
(b) (4)		

Ingredient	Quantity per Adult Dose (0.5 mL/dose)	Function
Water for injection	(b) (4)	Diluent

Type of Container Closure used

- The primary packaging consists of a (b) (4) 1 mL syringe with a (b) (4) of rubber formulation (b) (4) that is closed with a (b) (4) bromobutyl plunger stopper.
- The syringe and (b) (4) are manufactured as a luer lock syringe. No needle is present on the syringe. The end of the syringe is sealed by an elastomeric tip cap with rubber formulation (b) (4) (free of natural rubber). The tip cap is lodged in a (b) (4) and screwed into the luer lock adaptor; the plastic shell protects the tip cap from damage. The material does not contain any materials of animal origin.
- The syringe barrel is composed of (b) (4) borosilicate glass; the syringe plunger stopper is composed of bromobutyl rubber (b) (4) The (b) (4) tip cap rubber and the bromobutyl rubber used for the syringe plunger stopper, both comply with the requirements of the (b) (4) for (b) (4) and the (b) (4) (b) (4)

2.2.2 Pharmaceutical Development

2.2.2.1 Components of the drug product

(b) (4) : aH5N1c is an inactivated influenza vaccine containing predominantly hemagglutinin (HA) (b) (4) surface antigens from a Madin Darby Canine Kidney (MDCK) cell-derived H5N1 virus subtype. The potency of the vaccine is expressed as the concentration of the HA protein. The final product is a preservative-free adjuvanted vaccine.

Adjuvant: MF59C.1 adjuvant is an oil-in-water emulsion containing squalene oil as the dispersed phase and low ionic strength citrate buffer as the continuous phase. The emulsion is stabilized by the inclusion of two non-ionic surfactants (Polysorbate 80 and Sorbitan trioleate). The manufacturing of MF59C.1adjuvant is described in section 2.1.1 of this memo.

- Polysorbate (e.g., Tween) and Sorbitan esters (e.g., span) are commonly used surfactants with hydrophile: lipophile (HLB) values in the 9 - 16 and 2 - 9 range, respectively. (b) (4)
- The Citrate buffer acts as a chelator of transition metals removing the catalyst required for (b) (4)

(b) (4)

- (b) (4)
- Water for Injection (WFI) (b) (4)

2.2.2.2 Formulation development

- The vaccine is produced in Madin Darby Canine Kidney (MDCK) cells adapted to grow in suspension culture under protein-free conditions. The formulation for the pandemic vaccine, Influenza A (H5N1) Monovalent Vaccine, Adjuvanted and cell derived (aH5N1c) has been adapted from the seasonal influenza vaccines Flucelvax (STN 125408) and Fluad (STN 125510) and contains only one influenza virus strain for H5N1.
- (b) (4) . The concentration per dose is (b) (4) 7.5 µg HA for the aH5N1c (b) (4) .
- (b) (4)

2.2.2.3 Manufacturing process development

- Influenza vaccine cell culture-based production in Madin-Darby Canine Kidney (MDCK) cells was initiated in (b) (4) . Over the period of development, the production facility operated under (b) (4) Chiron Behring GmbH & Co. KG (Chiron Vaccines), and then Novartis Vaccines and Diagnostics (NVD). The drug product was filled and packaged in (b) (4) . The flu cell culture (FCC) process and drug product manufacturing processes were subsequently (b) (4) NVD Holly Springs, NC (now Seqirus).
- The (b) (4) processes used to manufacture the batches supporting the Phase I, Phase II, and Phase III clinical trials for the pandemic H5N1 vaccine is described in detail in Sections 3.2.S.2.2, Description of Manufacturing Process and Process Controls, and 3.2.S.2.2, Description of Manufacturing Process and Process Controls – Process 1.1, and is reviewed in detail by the antigen reviewer, Dr. Xing Li
- In brief, the manufacturing process for seasonal and pandemic influenza vaccines in MDCK cell line was optimized during the years to increase yield and robustness of the process. Three major processes were developed and were used to obtain material for testing in clinical trials: the initial Process 1.0 followed by Process 2.0, Process 1.1, and Process 3.0.
- A comparability assessment was performed between Process 1.1 and Process 3.0 with respect to the process, equipment, and facility. Process 3.0 was filed as a Prior Approval Supplement to the Flucelvax BLA 125408 on March 28, 2018 (STN 125408/271) and was approved on July 27, 2018. Future pandemic lots will be manufactured under Process 3.0.
- Comparability of the Phase 3 drug substance lots manufactured under Process 1.1 to drug substance lots manufactured under Process 3.0 and comparability of Process 2.0 and Process 3.0

drug substance lots are provided in Section 3.2.S.2.6, Manufacturing Process Development of the submission (reviewed by antigen reviewer, Dr. Xing Li).

- For Phase II trials, three consecutive lots (C53D28N1, C53D29N1, and C53D30N1) were formulated and filled in syringes at the (b) (4) site. A summary of the release and stability results (long-term stability for (b) (4) months and accelerated stability for 6 months) including squalene (b) (4) for the finished (filled) product is provided in Tables 8, 9, 10 and 11 in section 3.2.P.2.3, Manufacturing Process Development – PFS, in the submission. Significant trends were observed for (b) (4) and the number of large particles at accelerated conditions. There was no impact to the study since the lots were not stored at the recommended storage temperature. All other test results complied with the product specifications.
- The Phase III clinical trial, material was formulated and filled at the Holly Springs site using a (b) (4) formulation and filling process. The differences in the formulation and filling processes from Phase II ((b) (4)) to Phase III (Holly Springs) are outlined in Table 12 in section 3.2.P.2.3, Manufacturing Process Development – PFS, in the submission.
- Impact assessments were performed to demonstrate that the changes to the formulation and filling of Phase III clinical trial materials did not adversely impact the safety, integrity, strength, purity, and quality of the drug product. In the assessment, the Phase III drug product vaccine produced in Holly Springs was assessed against Phase II clinical trial material formulated and filled at the (b) (4) .
- The assessments were performed to evaluate facilities and equipment; process (including in-process checks, in-process controls and hold times); analytical methods and specifications; stability; and validation (b) (4) .
- For facilities and equipment, operational parameters, raw materials and consumables, in-process checks, controls, and hold times, it was concluded that the sites of production (b) (4) Holly Springs) are comparable: comparison is shown in Tables 13, 14, and 15 in section 3.2.P.2.3, Manufacturing Process Development – PFS, in the submission and conclusion is acceptable.
- Some analytical methods and specifications for the formulated/ adjuvanted Phase III material (b) (4) filled product) were added or modified per Table 16 to reflect harmonization with other licensed FCC influenza drug products and the progression from Phase II to Phase III clinical trials.

Reviewer: I reviewed Table 16 in the submission showing comparison of In-Process Checks, Controls, and Hold Times between Phase II and Phase III material and found it acceptable.

- *Stability, Phase III PPQ clinical lots:* All three Phase III PPQ clinical lots were placed on long-term stability protocols at 2°C to 8°C and accelerated conditions (b) (4) through (b) (4) 6 months, respectively, as reported in Section 3.2.P.8.3 of the submission (Stability Data – PFS).
- *Validation, Phase III PPQ clinical lots* Validation was performed on the three PPQ Phase III clinical lots. The results are reported in Sections 3.2.P.3.5 (Process Validation and/or Evaluation – Formulation – PFS) and 3.2.P.3.5 (Process Validation and/or Evaluation – Filling – PFS) in the submission.

- The formulation of adjuvanted monovalent vaccine for Phase III (b) (4) Holly Springs site, is achieved by (b) (4) .
- The results of the (b) (4) study for adjuvanted monovalent FCC drug product formulation process is discussed in Section 3.2.P.3.5 (Process Validation and/or Evaluation – Formulation – PFS) in the submission.
- A (b) (4) assessment was performed on all equipment with product-contact materials of construction; the results are summarized in Section 3.2.P.3.5 (Process Validation and/or Evaluation – Formulation – PFS) in the submission.

Commercial manufacturing (Process 3.0): comparability with Phase III (Process 1.1)

- There were no differences between the PFS formulation and filling manufacturing processes that were utilized for the Phase III clinical trial material (b) (4) Process 1.1) and those proposed for the licensed aH5N1c pandemic vaccine (b) (4) Process 3.0).
- Two differences were noted for inspection and packaging. Inspection of Phase III material was performed (b) (4) . The inspection of commercially produced aH5N1c pre-filled syringes will be performed by a (b) (4) , previously qualified for the inspection of Flucelvax, Fluad, and aQIV pre-filled syringes.
- Packaging of commercially produced aH5N1c pre-filled syringes will be performed at Seqirus instead of a 3rd party CMO that was used during Phase III. Packaging unit operations are the same for aH5N1c as for Flucelvax and are considered qualified.

Reviewer: I concur with the conclusion that the changes made from Phase III to commercial manufacturing for inspection and packaging are considered comparable.

- As Process 1.1 and Process 3.0 (b) (4) materials have been demonstrated to be equivalent (reference Section 3.2.P.2.6 Manufacturing Process Development in the submission and the recently approved PAS for Flucelvax (approved by CBER on July 27, 2018 STN 125408/274), Seqirus does not plan to perform any additional process validation studies for the PFS formulation and filling processes. (b) (4) PFS drug product (b) (4) has been manufactured with Process 3.0 H5N1c (b) (4) material and has been placed on stability (referred to as the stability (b) (4) .
- (b) (4) PFS (b) (4) was manufactured under Process 3.0 and was used to assess comparability to the drug product manufactured with Process 1.1 (b) (4) used forthe Phase III clinical trial material.

2.2.2.4 Container Closure system

Container Closure system is reviewed by antigen reviewer

2.2.2.5 Microbiological attributes

- The aH5N1c drug product is a sterile parenteral solution. No preservatives are used in the drug product.
- Formulation is performed as a closed aseptic process using sterilized equipment and sterile disposable components. The monovalent drug substance is (b) (4) to release of the drug product.
- The container closure system for the syringes is commonly used for vaccines. Its integrity is supported by the stability studies for the product which include sterility tests.
- The (b) (4) meet their respective (b) (4) standards. The components of the adjuvant also meet the required (b) (4) standards, except for squalene which meets internal standards.
- The aseptic filling process has been validated. A detailed microbiological/test scheme for formulation and filling is outlined in Table 1 section 3.2.P.2.5, Microbiological attributes – PFS, in the submission.

Reviewer: I reviewed Table 1 (section 3.2.P.2.5, Microbiological attributes – PFS, in the submission) showing the schema for microbiological monitoring during formulation and filling of the PFS and I found the monitoring plan acceptable.

2.2.3 Manufacture

2.2.3.1 Manufacturers

- Manufacture of MF59C.1, production of (b) (4) filling, inspection and packaging, and quality control testing are all performed at Seqirus manufacturing facility: 475 Green Oaks Parkway, Holly Springs, NC 27540, USA

2.2.3.2 Batch size and batch formula

- The final formulation batch size is (b) (4) The target strength is 7.5 µg of HA antigen per 0.5 mL dose.
- (b) (4)

(b) (4)

(b) (4)

Table 25 Composition of MF59C.1 adjuvant

Component	Amount per Liter
Squalene	(b) (4)
Polysorbate 80	
Sorbitan triolate	
Sodium citrate	
Citric acid	
Water for injection	

(b) (4)

(b) (4)

2.2.3.3 Description of manufacturing process and process controls, formulation

- Formulation of the monovalent aH5N1c drug product consists of (b) (4)

8 Pages have been determined to be not releasable: (b)(4)

(b) (4)

2.2.4 Control of drug product

2.2.4.1 Specification(s)

Table 31 Release specifications for the (b) (4) (as presented in the original submission of the BLA)

(b) (4)

(b) (4)

.

(b) (4)

(b) (4)

Table 33 Release Specifications for Filled aH5N1c Product (as presented in the original submission of the BLAs)

Test	Method	Requirements
Sterility	(b) (4)	No evidence of microbial growth
Endotoxin	(b) (4)	(b) (4)
Appearance	Visual inspection	White homogeneous suspension
Extractable volume	(b) (4)	(b) (4) 0.50 mL
Hemagglutinin antigen (HA; potency)	(b) (4)	(b) (4)

Test	Method	Requirements
pH	(b) (4)	6.5 – 7.7
Squalene (b) (4)	(b) (4)	(b) (4)
Squalene (b) (4)	(b) (4)	(b) (4)
Number of Large Particles (b) (4)	(b) (4)	(b) (4)
Mean Particle Size	(b) (4)	(b) (4)

Update: In Amendment 8, received at FDA on 5/17/2019 (DATS# 809513), the applicant provided a revised release specification for aH5N1c Filled Product that included testing for (b) (4)

Update: In Amendment 39 (received at FDA on 12/16/2019 DATS# 855840), the applicant provided the revised release specifications for aH5N1c Filled Drug Product. Testing for Visible Particulates and Sub-Visible Particulates were added. The revised specifications that include changes provided in Amendment 8 and 39 are shown in Table 34.

Table 34 Release Specifications for Filled aH5N1c Product (revised, as of 12/16/2019)

Test	Method	Requirements
Sterility	(b) (4)	No evidence of microbial growth
Endotoxin	(b) (4)	(b) (4)
Appearance	Visual inspection	White homogeneous suspension
Extractable volume	(b) (4)	(b) (4) 0.50 mL
Visible Particulates	Tested according to (b) (4)	Essentially free of visible particulates
Sub-Visible Particulates	Tested according to (b) (4)	(b) (4)
Hemagglutinin antigen (HA; potency)	(b) (4)	
pH	(b) (4)	6.5 – 7.7
Squalene (b) (4)	(b) (4)	
Squalene (b) (4)	(b) (4)	(b) (4)
Number of Large Particles	(b) (4)	
Mean Particle Size	(b) (4)	

Reviewer: the inclusion of (b) (4) **testing as well as testing for visible particulates and sub-visible particulates in the release specifications for aH5N1c Filled Product is acceptable.**

Table 35 Release specifications for packaged aH5N1c product

Test	Method	Requirements
Identification	(b) (4)	Identity Confirmed

(b) (4)

2.2.4.2 Analytical procedures

The analytical procedures that are related to MF59C.1 adjuvant and that were reviewed in detail by the reviewer are as follows: (b) (4)

- (b) (4)

1 Page has been determined to be not releasable: (b)(4)

(b) (4)

Reviewer: I reviewed analytical methods developed by the applicant to assess MF59C.1 adjuvant within the adjuvanted aH5N1c drug product and I agree that the developed methods adequately control the quality (b) (4) **and quantity (squalene) of adjuvant in the vaccine**

2.2.4.3 Validation of analytical procedures

Review of the validation of analytical procedures is performed by DBSQC reviewer

2.2.4.4 Batch analysis

For batch analysis, (b) (4) sets of clinical lots were used: three clinical lots (lots 181053, 181054, and 181675) manufactured using antigen produced under Process 1.1 and a (b) (4) produced using antigen manufactured under Process 3.0.

- Batch analysis for clinical lots 181053, 181054, and 181675

Three consecutive lots 181053 (b) (4) 181054 (b) (4) and 181675 (b) (4) manufactured under Process 1.1 (for vaccine antigen), were formulated with MF59C.1 adjuvant, filled in the single use syringes at Holly Springs site on (b) (4), and were used during the Phase III clinical trial of the aH5N1c pandemic influenza vaccine. These three clinical lots also served as the process PPQ lots for the vaccine. Review of the batch analysis data for the three Phase III clinical lots is provided by the reviewer in this section.
Release Results for clinical lots 181053, 181054, and 181675 for (b) (4) and for filled lots are shown in Table 2 and Table 3, respectively, in the submission (section 3.2.P.5.4 – PFS) and the information for one out of three lots, lot 181053, is shown in Table 36 (for (b) (4)) and Table 37

(for filled product) of this memo. Analytical attributes for other two lots were very close and were all within specifications.

Table 36 Release results for aH5N1c Phase III clinical (b) (4) Lot 181053

(b) (4)

Table 37 Release results for aH5N1c phase III clinical trial finished (filled) lot 181053

Test	Method	Specification	Lot Number 181053
Sterility	(b) (4)	Conforms	Conforms
pH	(b) (4)	6.5 – 7.7	(b) (4)
Endotoxin	(b) (4)		
Appearance	Visual inspection	White homogeneous suspension	Conforms
HA Antigen	(b) (4)		
Visible Particles	(b) (4) analysis	Essentially free of visible particulates	Free of visible particulates
Sub-visible Particles	(b) (4) analysis	(b) (4) (b) (4)	
Extractable Volume	(b) (4) analysis	(b) (4) 0.50 mL	(b) (4) 0.50 mL
Squalene (b) (4)			
Squalene (b) (4)			
Number of Large Particles	(b) (4)		
Mean Particle Size	(b) (4)		
(b) (4)			

Test	Method	Specification	Lot Number 181053
		(b) (4)	

(b) (4) testing was performed on Lot 251069; however, it was removed from release specification at a time of the BLA submission (see Section 2.2.4.6 of this memo), and then was later re-introduced in release specification for the filled product in Amendment 8 received at FDA on 5/17/2019 DATS #809513 (see page 71).

Batch analysis for lot (b) (4)

To support aH5N1c (b) (4) manufactured under Process 3.0 at the Holly Springs site and the proposed minimum shelf life of (b) (4) months for the finished product in the syringe presentation, (b) (4) stability drug product lot (b) (4) was produced on May 31, 2018 using a Process 3.0 PPQ (b) (4) formulated and filled in 1.0 mL (b) (4) syringes ((b) (4) syringes total) with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal.

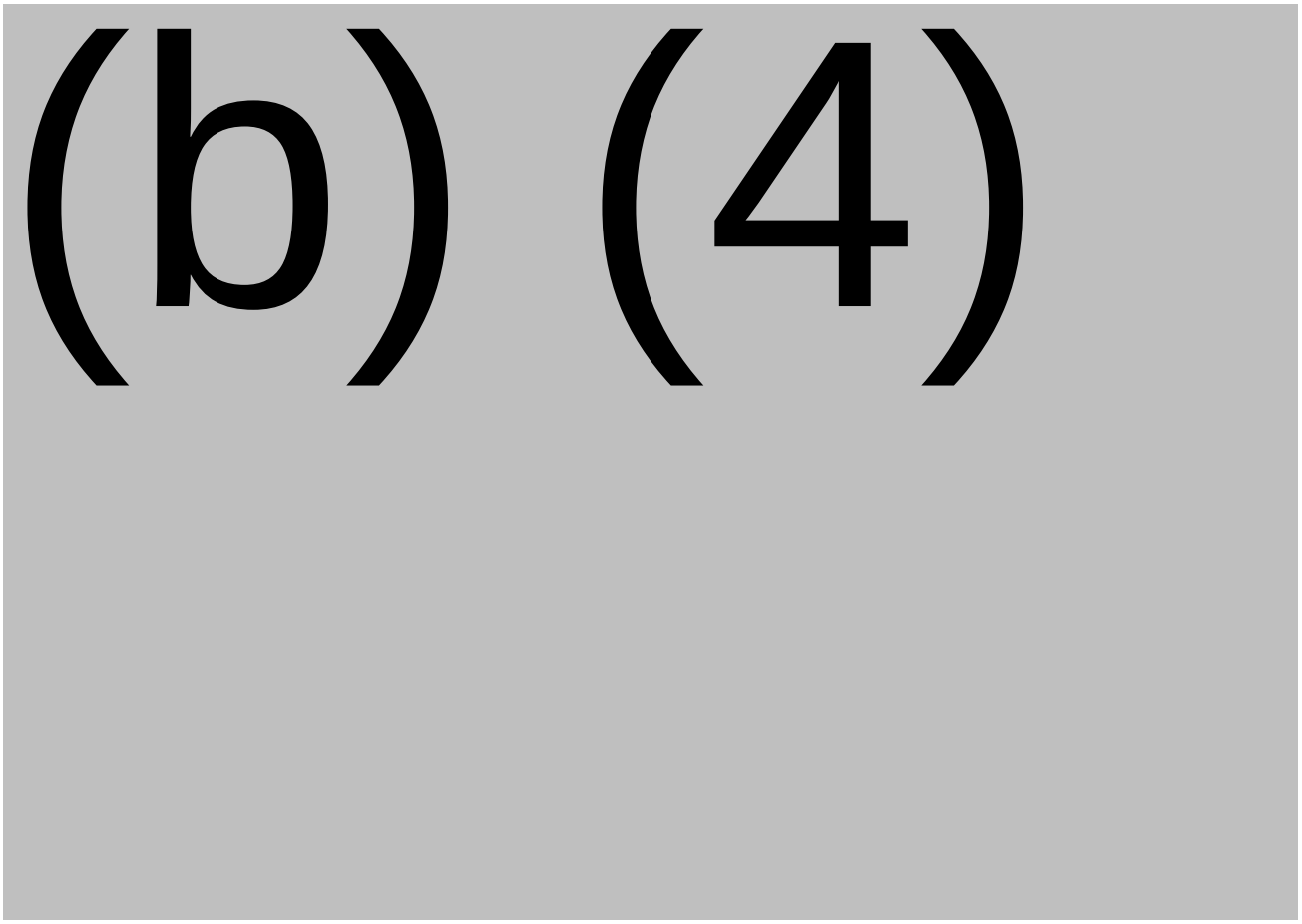
Release results are shown for aH5N1c (b) (4) finished filled product in Table 5 and Table 6, respectively, section 3.2.P.5.4, Batch Analysis in the submission, and are summarized below (for filled product only) in Table 38.

Table 38 Release Results for aH5N1c Process 3.0 Finished (Filled) Lot (b) (4)

Test	Method	Specification	Lot Number 251069
Sterility	(b) (4)	Conforms	Conforms
pH	(b) (4)	6.5 – 7.7	(b) (4)
Endotoxin	(b) (4)		
Appearance	Visual inspection	White homogeneous suspension	Conforms
HA Antigen	(b) (4)		
Extractable Volume	(b) (4)	(b) (4) 0.50 mL	(b) (4) 0.50 mL
Squalene (b) (4)		(b) (4)	
Squalene (b) (4)			
Number of Large Particles	(b) (4)		
Mean Particle Size	(b) (4)		
(b) (4)			

(b) (4) testing was performed on Lot (b) (4); however, it was removed from the release specification at a time of the BLA submission (see Section 2.2.4.6 of this memo), and was later re-introduced in Amendment 8 received at FDA on 5/17/2019 DATS #809513 (see page 71).
[2]Specification at the time of the release

2 Pages have been determined to be not releasable: (b)(4)



- Stability studies performed on the lots manufactured for Phase I clinical studies (Table 5, 6, 7 section 3.2.P.2.3 Manufacturing Process Development – PFS in the submission), Phase II clinical study (Table 8, Table 9, Table 10, Table 11 section 3.2.P.2.3 Manufacturing Process Development – PFS in the submission) demonstrated that (b) (4) remained well within the initially established specifications for the duration of the study (b) (4) The levels of (b) (4) in the final vaccine observed in stability studies were below the reported threshold for a degradation product for a daily dose by an order of magnitude or more (calculated values are shown in Table 3 in section 3.2.P.5.6 in the submission)
- In addition, Release results from three aH5N1c Phase III Clinical Finished (Filled) lots 181053, 181054, 181675, and for the stability (b) (4) showed that all (b) (4) were well below established specifications (Table 3 and Table 6, respectively, in 3.2.P.5.4 Batch Analysis – PFS in the submission)
- (b) (4) .

- After evaluation of the available body of data, at the time of BLA submission, the firm decided not to perform testing for (b) (4) during release of the aH5N1 final container.

Update (Amendment 8 received at FDA on 5/17/2019 DATS #809513): The firm added testing for (b) (4) to the release specifications for filled aH5N1c product by (b) (4) method. The following acceptance criteria for (b) (4) was established: (b) (4)

Reviewer, I concur with modified release specifications for Filled aH5N1c PFS and with established specifications as shown in Table 2 in section 3.2.P.1 in Amendment 8.

2.2.4.7 Reference standards or materials

The following reference standards are used in analytical testing of adjuvant component of the vaccine:

- (b) (4)
  - .

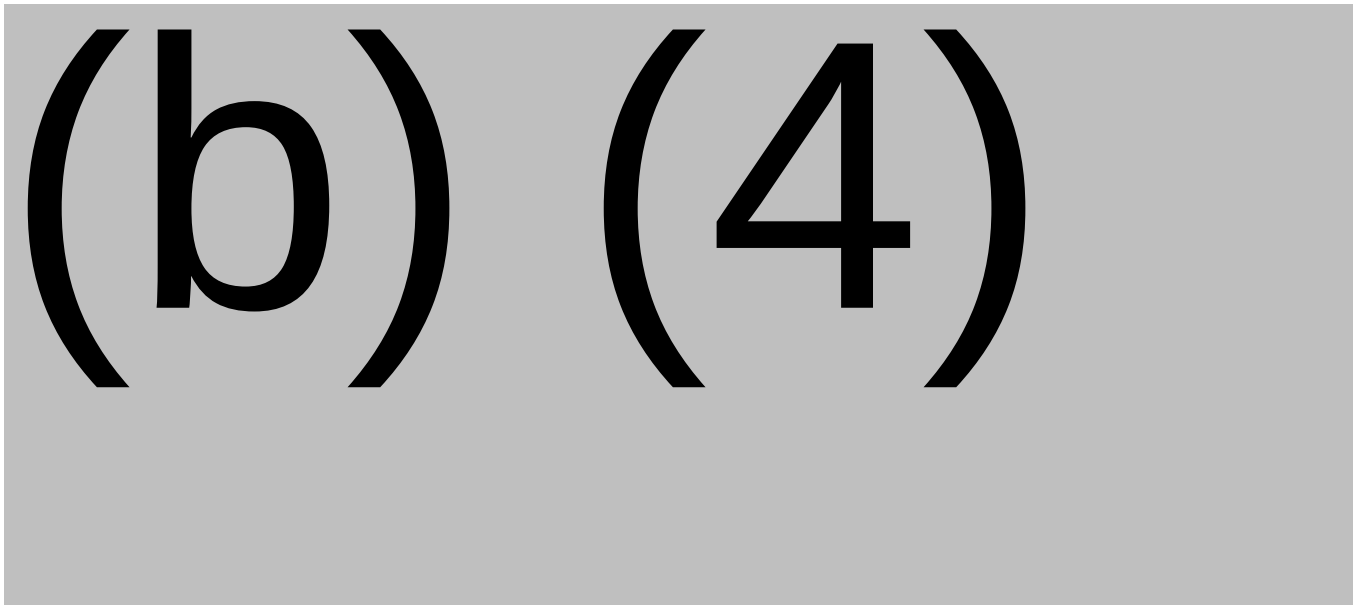
2.2.5 Stability

2.2.5.1 Description of the stability study

- Stability studies were performed on three aH5N1c Phase III clinical trial lots (181053, 18054, and 18165) and (b) (4) stability (b) (4)) containing (b) (4) manufactured under Processes 1.1 and 3.0, respectively, and filled in 1.0 mL (b) (4) syringes to support licensure of the aH5N1c pandemic influenza vaccine, and to confirm the (b) (4) -month shelf life when stored at 2°C to 8°C.
- Based on a CBER recommendation (CRMTS 9354), the stability lot was manufactured to demonstrate comparability between drug product batches manufactured utilizing Processes 1.1 and 3.0 (b) (4) material.
- Container for Phase III Clinical Lots: 1 mL (b) (4) syringe with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal.
- Container for Stability (b) (4) formulated with (b) (4) produced with Process 3.0: 1 mL (b) (4) syringe with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal.
- (b) (4)
  - .

- The analytical procedures used for the stability studies are the same procedures used for the release of the (b) (4) finished (filled) product.
- Stability indicating parameters: According to ICH Q5C, the stability indicating profile has been identified for the drug product. The current analytical procedures used to evaluate the quality of the vaccine are described in Table 40.

Table 40 Stability indicating parameters – PFS



STABILITY DATA PHASE III CLINICAL LOTS

Long-Term study Results

- The long-term stability results at 2°C to 8°C for the three Phase III clinical lots, formulated with Process 1.1 (b) (4) material are provided in Table 2, Table 4, and Table 6 (section 3.2.P.8.3 Stability data – PFS in the submission) for Lots 181053, 181054, and 181675, respectively. The long-term stability results for all three lots met all specifications through (b) (4) months, when stored at 2°C to 8°C with the following exceptions:
- (b) (4)

Accelerated Study Results

- The accelerated stability results at (b) (4) for the 3 Phase III clinical lots are provided for Lots 181053, 181054, and 181675, respectively (Table 3, Table 5, and Table 7, section 3.2.P.8.3 Stability data – PFS in the submission). The accelerated stability results for all three lots met all specifications through 6 months with the following exceptions: OOS were observed for all three lots at the (b) (4)-month time-points for HA (b) (4). These results were not unexpected since (b) (4) HA is typically observed over time. There was no impact on the assigned shelf life of the final product since the storage conditions for the accelerated study at (b) (4) is not the intended storage condition for the product (2°C to 8°C); the results are for information only.

Reviewer: The long-term and accelerated stability studies for Phase III Clinical lots have been completed. The results confirm that the material is stable up to (b) (4) months supporting a shelf life of (b) (4) months, when stored at 2°C to 8°C. No changes in squalene (b) (4), or the number of large particles was noted; statistically significant decrease in the mean particle size was observed but the mean particle size remained within specification confirming stability of MF59C.1 adjuvant in aH5N1c vaccine.

STABILITY DATA FOR STABILITY (b) (4) (b) (4)

- (b) (4)

Update: In Amendment 7 (5/8/2019), additional stability data for (b) (4) is provided for up to 9 months under long-term storage conditions and up to 6 months under accelerated storage conditions (Tables 9 and 10 in the submission). All analytical attributes are within specification.

2.2.5.2 Post-approval stability study and commitment

A minimum of (b) (4) aH5N1c commercial PFS batches will be placed on stability (b) (4) (if batches are manufactured) for a minimum of (b) (4) months at the recommended long-term storage condition of 2°C to 8°C. The stability testing plan is described in Table 41; stability samples will be tested at time 0, and at 3-, 6-, 9-, 12-, (b) (4)-month time-points.

Table 41 Stability Test Plan for (b) (4) Commercial Batches

(b) (4)

(b) (4)

Reviewer: post-approval stability plan is acceptable.