CBER/DMPQ CMC Biologics License Application Review Memorandum

BLA STN 125692/0

Product Name:
Influenza A (H5N1) Monovalent Vaccine, Adjuvanted

Obinna Echeozo, Microbiologist, DMPQ
Facility/CMC Reviewer

1. BLA#: STN 125692/0

2. APPPLICANT NAME AND LICENSE NUMBER

Name: **Seqirus Inc**.
License #: **2049**

3. PRODUCT NAME/PRODUCT TYPE

Proper name: **Influenza A (H5N1) Monovalent Vaccine, Adjuvanted**
Proprietary name: **AUDENZ**

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Dosage form: **Suspension for injection [pre-filled syringes (PFS)]**
b. Strength/Potency [the concentration of drug product]: **7.5 mcg HA/0.5 mL**
c. Route of administration: **Intramuscular**
d. Indication(s): **Indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine.**

5. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Seqirus Inc. (Seqirus) submitted a Biologics License Application (BLA) under STN 125692/0 for the licensure of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted. The application was submitted as a rolling BLA with a CBER receipt date of February 1, 2019. Influenza A (H5N1) Monovalent Vaccine, Adjuvanted is intended to prevent illness from pandemic influenza caused by an A/H5N1 influenza strain. The vaccine antigen is manufactured following the same manufacturing process used for the licensed seasonal influenza vaccine, FLUCELVAX® (Flucelvax) and includes MF59C.1 adjuvant (MF59), a squalene-based oil-in-water emulsion. This adjuvant is also contained in the licensed seasonal vaccine, FLUAD® (Fluad).

Initially, BLA STN 125692/0 was submitted for approval of both PFS (b) (4) presentations of the vaccine. On October 22, 2019, Seqirus withdrew the (b) (4) presentation from the scope of this BLA. The PFS presentation of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted will be manufactured at Seqirus Holly Springs, North Carolina, where Flucelvax and Fluad are currently being manufactured. Pre-license inspection was waived for this submission since the most recent surveillance inspection for Seqirus Holly Spring was conducted in June 2018, covering areas, equipment and processes that are relevant to this BLA. Consequently, an Inspection Waiver Memo was prepared. Seqirus clarified that no facility changes were made at the Holly Springs facility as a result of this BLA.

With the exception of a (b) (4), all the equipment used in the manufacture of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted drug product (DP) has been approved for use in the manufacture of Flucelvax and Fluad. The same container closure used in manufacturing Flucelvax is implemented in the manufacture of

Influenza A (H5N1) Monovalent Vaccine, Adjuvanted DP and no changes were made to the container closure under this BLA.

The overall control strategy appears adequate and this BLA submission can be approved from a CMC/facility perspective.

B. RECOMMENDATION

I. APPROVAL

Based on the information submitted in this original BLA and the related amendments, I recommend approval of this BLA. The approval letter should acknowledge approval of the following manufacturing facility responsible for drug substance (DS) manufacturing, formulation and DP Fill/Finish manufacturing activities:

- Seqirus, Inc. 475 Green Oaks Parkway Holly Springs, NC 27540 United States

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Obinna Echeozo/Reviewer/ OCBQ/DMPQ/BII	Concur	
Qiao Bobo/Branch Chief OCBQ/DMPQ/BII		
John Eltermann/Division Director OCBQ/DMPQ		

Review of CTD
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Module 3

(b) (4)
Influenza A (H5N1) Monovalent Vaccine Adjuvanted vaccine is a monovalent, subunit, inactivated influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cell line, (b) (4) Influenza A viruses are divided into subtypes based on the hemagglutinin (HA) and neuraminidase (NA) glycoproteins on the surface of the virus. The(b) (4) is a suspension containing influenza A virus surface antigens derived from an H5N1 pre-pandemic virus. The resulting H5N1 strain (which is a strain that has been attenuated by reverse genetics) is designated as A/turkey/Turkey/1/2005 NIBRG-23. This designation represents: virus type (describing the antigenic specificity of the nucleoprotein antigen), host of origin (for viruses isolated from non-human hosts), location of isolation, isolate number, year of isolation, laboratory and reverse genetics strain number respectively.

3.2.S.2 Manufacture
3.2.S.2.1 Manufacturer(s)

Manufacturer / Site	Responsibility
Seqirus, Inc. (FEI: 3007867647) 475 Green Oaks Parkway Holly Springs, NC 27540 United States	(b) (4)
(b) (4)	(b) (4)
(b) (4)	
(b) (4)	

3.2.S.2.2 Description of Manufacturing Process
Following manufacturing process development (*refer to the manufacturing process development section below*), Process 3.0 was used in the manufacture of the Flu Cell Culture (FCC) influenza vaccine (b) (4). The manufacturing process is composed of: (b) (4)

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

(b) (4)

Reviewer's comment*: Review of Stability is deferred to the product office.*

3.2.P DRUG PRODUCT[1]

3.2.P.1 Description and Composition of the Drug Product

The H5N1 adjuvanted influenza vaccine final DP is presented as a liquid for injection, in a (b) (4) glass PFS ready for use (intended for a single use), containing 0.5 mL of antigen suspension. The vaccine potency is expressed as the concentration of the HA protein and is formulated to contain (b) (4) 7.5 µg per dose of hemagglutinin antigen. A summary of the DP composition is provided in Table 7 below

Table 7: Composition of Adjuvanted H5N1c Influenza Vaccine DP

Ingredients	Quantity per Adult Dose (0.5 mL/dose)	Function	Reference Standards
Active Ingredient			
H5N1 monovalent (b) (4)	7.5 µg	HA antigen (active ingredient)	NIBSC
Adjuvant			

Ingredients	Quantity per Adult Dose (0.5 mL/dose)	Function	Reference Standards
Squalene	9.75 mg	Oil phase	Seqirus (Internal)
Polysorbate 80	1.175 mg	Surfactant	(b) (4) .
Sorbitan triolate	1.175 mg	Surfactant	(b) (4)
Sodium citrate	0.66 mg	Buffer	(b) (4) .
Citric acid	0.04 mg	Buffer	(b) (4)
(b) (4)			

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Manufacturer / Site	Responsibility
Seqirus 475 Green Oaks Parkway Holly Springs, NC 27540, USA (FEI: 3007867647)	• Manufacture of MF59C.1 • Production of (b) (4) • Filling • Visual Inspection and Packaging • Quality control testing
(b) (4)	• Container Closure - (b) (4) syringe - Tip Cap - Plunger Stopper

3.2.P.3.3 Description of DP Manufacturing Process

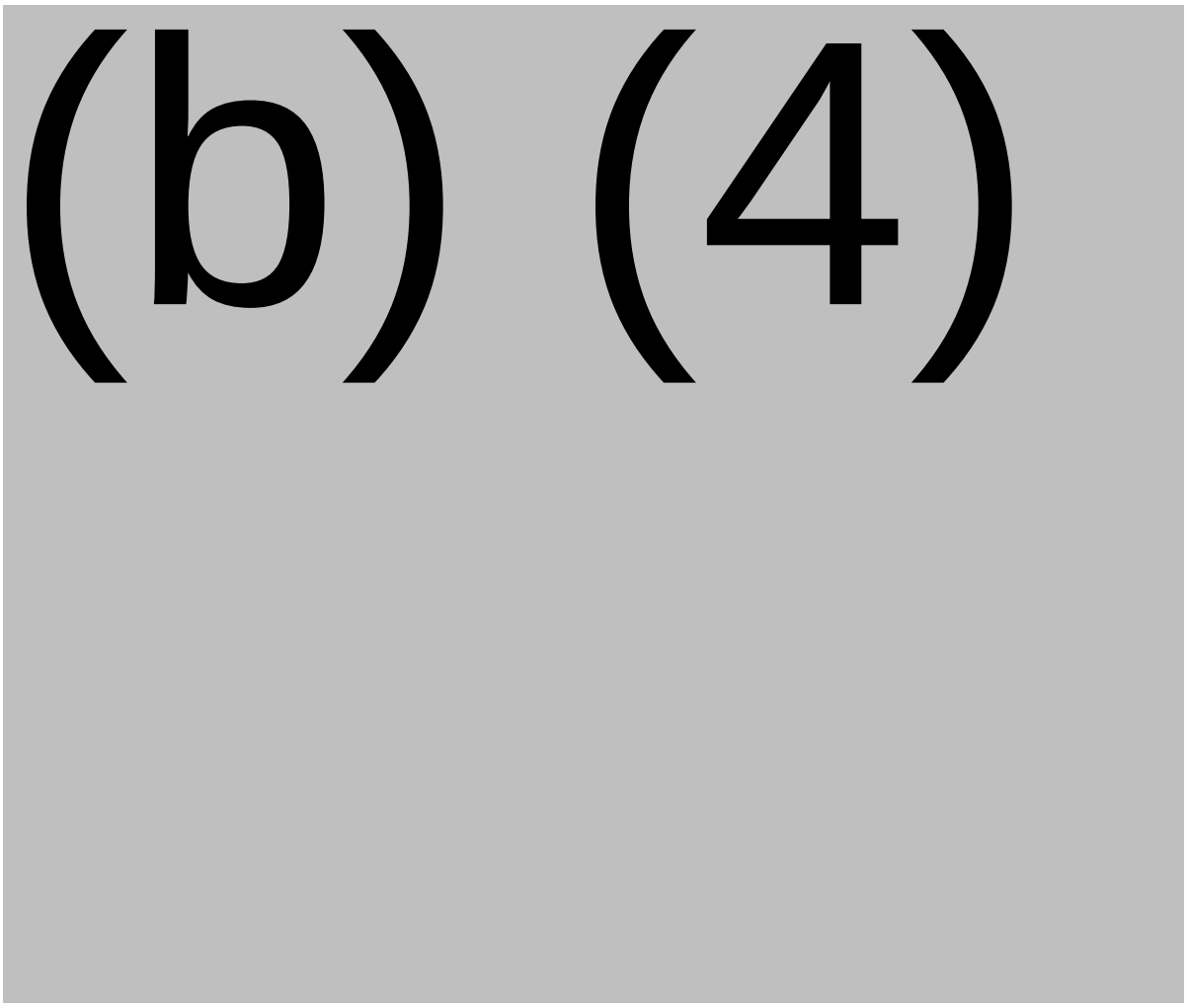
The DP manufacturing process for adjuvanted H5N1c is briefly described below:

1. Formulation

Influenza A (H5N1) Monovalent Vaccine, Adjuvanted DP formulation process consists of (b) (4)

The DP formulation process is performed aseptically in (b) (4)

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



Adjuvanted H5N1c DP is filled into a primary container closure system consisting of 1 mL pre-filled luer lock syringe stoppered with a bromobutyl plunger and (b) (4) tip cap with (b) (4) overseal. This container closure is currently used in the commercial manufacture of Flucelvax. Filling is conducted using a (b) (4)

3. Packaging, Inspection and Labeling

Packaging, inspection and labeling of the PFS is conducted in a (b) (4) area. These processes are either performed (b) (4) .
After filling, a (b) (4)

the filled syringes. Plunger rods are inserted into filled, acceptable syringes(b) (4) inspection. PFS are then labeled and packaged into 10-syringe cartons with product leaflets and are store at 2 – 8ºC until released.

3.2.P.3.5 Process Validation and/or Evaluation

Process validation for adjuvanted H5N1c was conducted using Phase III clinical lots manufactured using Process 1.1. Process 1.1 is currently approved for the seasonal (b) (4) manufacturing. However, to improve process yields and robustness for both seasonal and pandemic influenza vaccines, Seqirus implemented an upgraded (b) (4) manufacturing process (i.e., Process 3.0) at the Holly Springs manufacturing facility (*Refer to section 3.2. S.2.6*. *"Manufacturing Process Development" of this Review Memo*). Process validation of the seasonal monovalent (b) (4) manufacturing Process 3.0 lots was performed (b) (4) on (b) (4) at the Holly Springs (b) (4) facility and was approved for Flucelvax under STN125408/274.

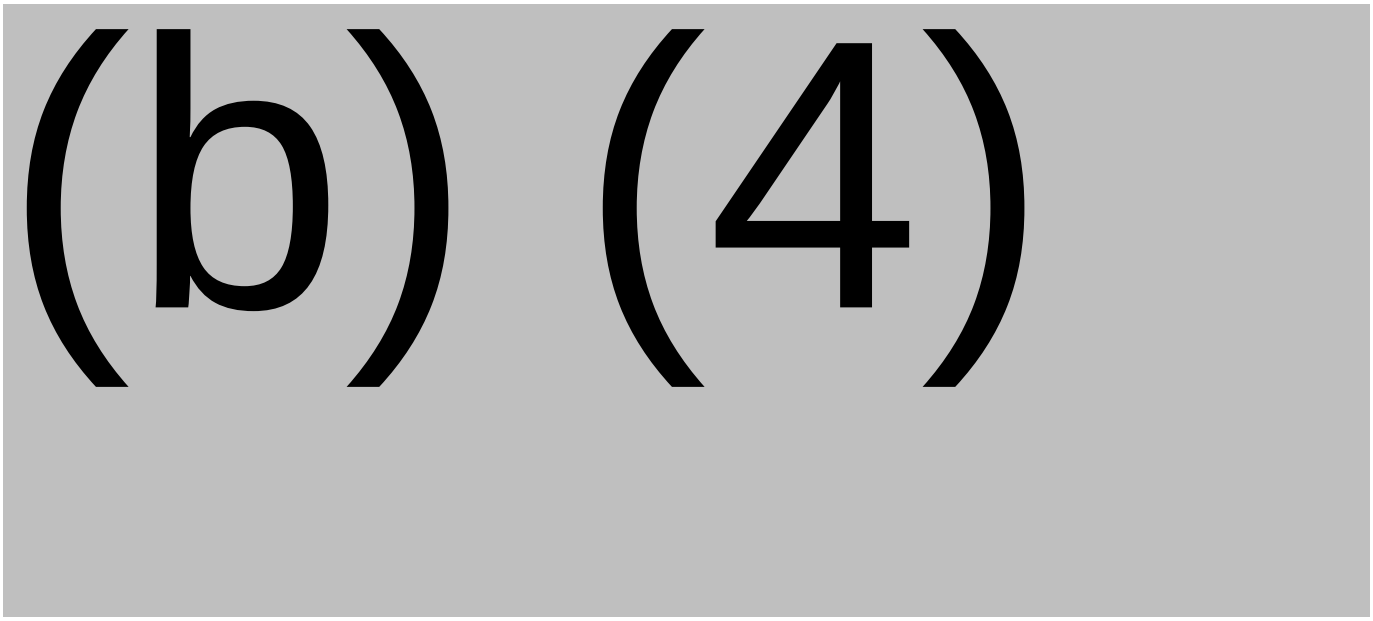
During the May 7, 2014 meeting (CRMTS 9354) between Seqirus and CBER, an agreement was reached to align the pandemic (b) (4) H5N1c Process 3.0 with the seasonal Flucelvax (b) (4) Process.3.0 at the time of the adjuvanted H5N1c BLA filing, if comparability between (b) (4) process versions can be demonstrated. As a result, (b) (4) PPQ batches of H5N1 (b) (4) manufactured using Process 3.0 were compared with H5N1 (b) (4) batches manufactured using Process 1.1. The comparability assessment results (submitted under section 3.2.S.2.6 "Manufacturing Process Development" of the eCTD) conclude that Process 1.1 and Process 3.0 of the H5N1 manufacturing process are comparable. Following comparability of the (b) (4) Process 1.1 to Process 3.0, (b) (4) DP (b) (4) utilizing Process 3.0 H5N1 (b) (4) material and filled into PFS was manufactured and placed on stability.
Note that process validation for MF59 was also submitted within this BLA (*The MF59 process validation is out-of-scope for this review*).

Reviewer's comment*: Review of the Comparability Assessment for H5N1c (b) (4) manufactured using Process 1.1 and Process 3.0 is deferred to the Product Office.*

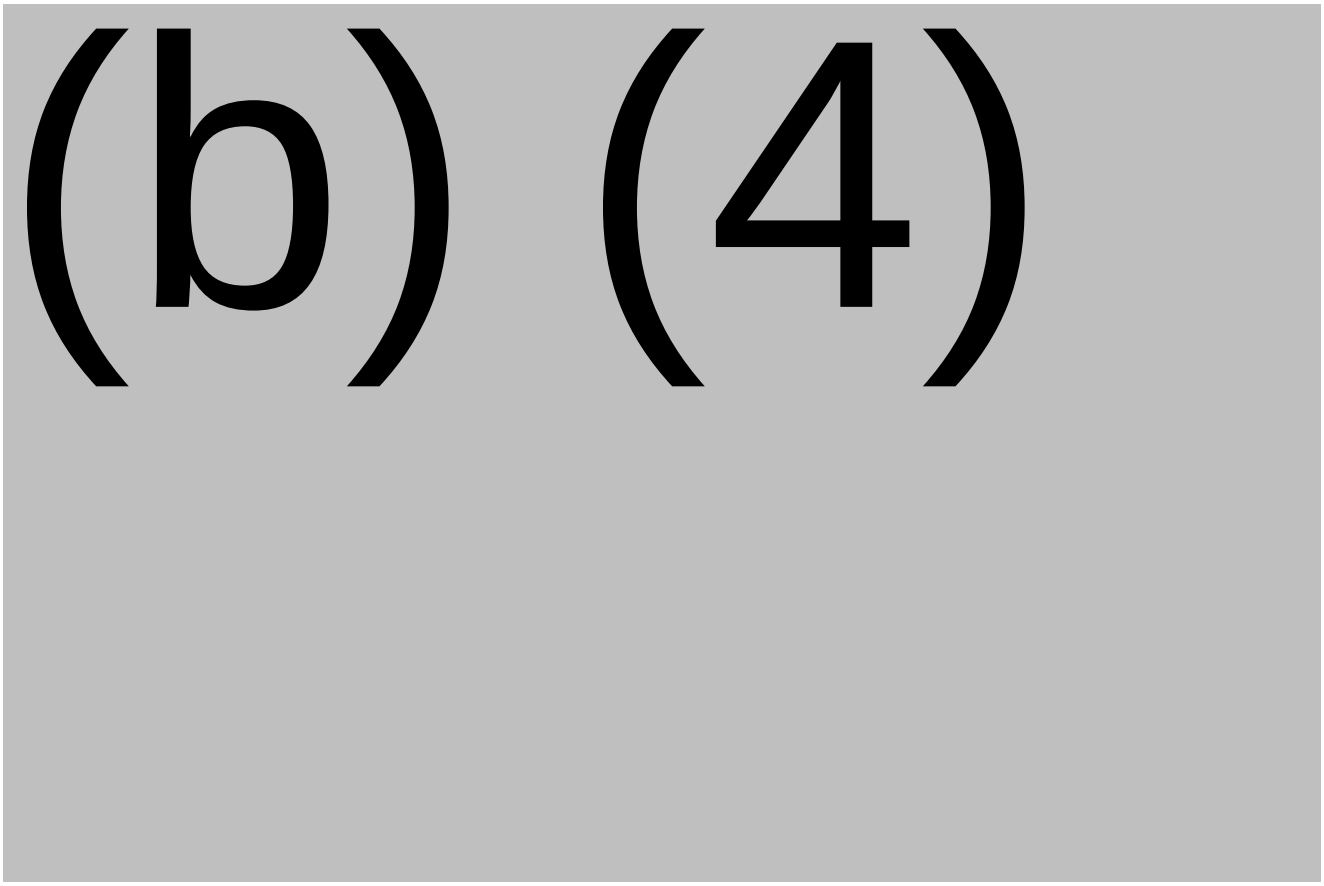
1. PPQ

Three consecutive H5N1 Phase III clinical lots (181053, 181054 and 181675) manufactured in (b) (4) runs, using Process 1.1 were implemented towards PPQ. A (b) (4) lot (lot # (b) (4)) was deemed invalid (*See the deviation section below for* details). PPQ was executed according to Seqirus' document #336408, *"Process Performance Qualification Report for Adjuvanted Monovalent FCC Flu Vaccine in* (b) (4) *Manufacturing at Holly Springs (Batches* (b) (4) " PPQ data covered manufacturing from the (b) (4) was applied towards PPQ. A minimum fill target volume of (b) (4) (approximately (b) (4) syringes) was used instead of the fill batch size of (b) (4) due to the small number of syringes needed for Phase III clinical trials. Key and critical parameters with normal operating ranges, including operational parameters were evaluated during the PPQ runs. The table below

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



In-scope routine in-process and release testing results for the PPQ Phase III clinical lots are presented in Table 9. With the exception of one deviation, all acceptance criteria for routine in-process and release testing for the three PPQ lots were met.

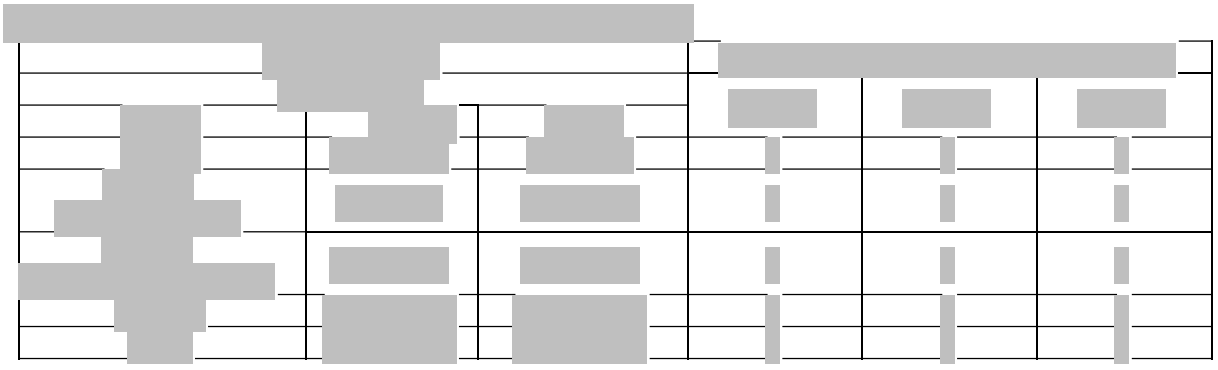


1 Page has been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment*: The firm's explanation is acceptable since the immediate corrective actions taken was rejection of underfilled or overfilled syringes by the filler.*

(b) (4)



Reviewer's comment*: Overall, the PPQ conducted by Seqirus using the H5N1 Phase III clinical lots seems satisfactory. Evaluation of the minimum fill target volume used (i.e.,* (b) (4) *is deferred to the Product Office. The deviations encountered during PPQ do not appear detrimental to the process.*

2. Aseptic Process Validation

Reviewer's comment*: In the original BLA submission, Seqirus did not provide aseptic process simulation report covering the H5N1* (b) (4) *filling unit operation. An information request was sent to the firm on July 19, 2019 (Question #27), to submit the most recent aseptic process simulation summary report covering the filling step of DP manufacturing process. Seqirus provided their response on August 02, 2019 and is reviewed in the section below.*

DP Aseptic Process (b) (4)

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

(b) (4)

(b) (4)

(b) (4)

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3.2.P.7 Container Closure System

The final DP 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 (b) (4) syringe which contains no needle. An elastomeric tip cap with rubber formulation (b) (4) (not made with natural rubber) seals the end of the syringe. The tip cap is lodged in a (b) (4) (which protects the tip cap from damage) and screwed into the (b) (4) adaptor. The tip cap is supplied (b) (4) This supplier also supplies the syringe and the plunger stopper. The syringe is also supplied from (b) (4)

This container closure and its qualification (via CCIT) have been approved for Flucelvax (approved on May 23, 2016 under STN 125408/127) and no changes were made to the container closure within the current BLA.

Shipping of the Final Container

The final DP is supplied as a 0.5mL PFS. Shipping validation of palletized PFS final products shipped from the Holly Springs facility has been previously approved for the seasonal strain (Flucelvax Quadrivalent) under STN 125408/127. The validation included testing of filled/finished syringes in a (b) (4) presentation. (b) (4) testing was performed on the Holly Springs facility by the service provider, (b) (4), and consisted of (b) (4) No shipping modifications were made within the current BLA.

Reviewer's comment*: Shipping validation has been previously approved for the PFS DP.*

3.2.P.8 Stability

Stability studies were performed on the three Influenza A (H5N1) Monovalent Vaccine, Adjuvanted Phase III clinical trial lots used for PPQ (i.e., lots 181053, 181054 and 181675) and (b) (4) stability (b) (4) utilizing (b) (4) manufactured under Processes 1.1 and 3.0, respectively. These lots were filled into the PFS described under section 3.2. P.7. The stability samples were placed on long-term storage conditions at 2 – 8ºC for (b) (4) months and accelerated storage conditions at (b) (4) for up to 6 months, to support the proposed (b) (4)-month shelf life when stored at 2 - 8°C.

The container closure for the Phase III Clinical lots is: 1mL (b) (4) syringe with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal while the stability lot container closure is: 1 mL (b) (4) syringe with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal. A total of (b) (4) PFS of the stability lot# (b) (4) were placed on stability studies. The number of Phase III Clinical lots placed on stability studies include: (b) (4) syringes (lot# 181053), (b) (4) syringes (lot# 181054) and (b) (4) syringes (lot# 181675).

Reviewer's comment*: The same container closure system used for the stability lot (lot#* (b) (4)*) will be used in the commercial production of Influenza A (H5N1)*

Monovalent Vaccine, Adjuvanted. The detailed review of stability is deferred to the product office.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

1. Facilities

Facilities table for this submission is provided in Table 13

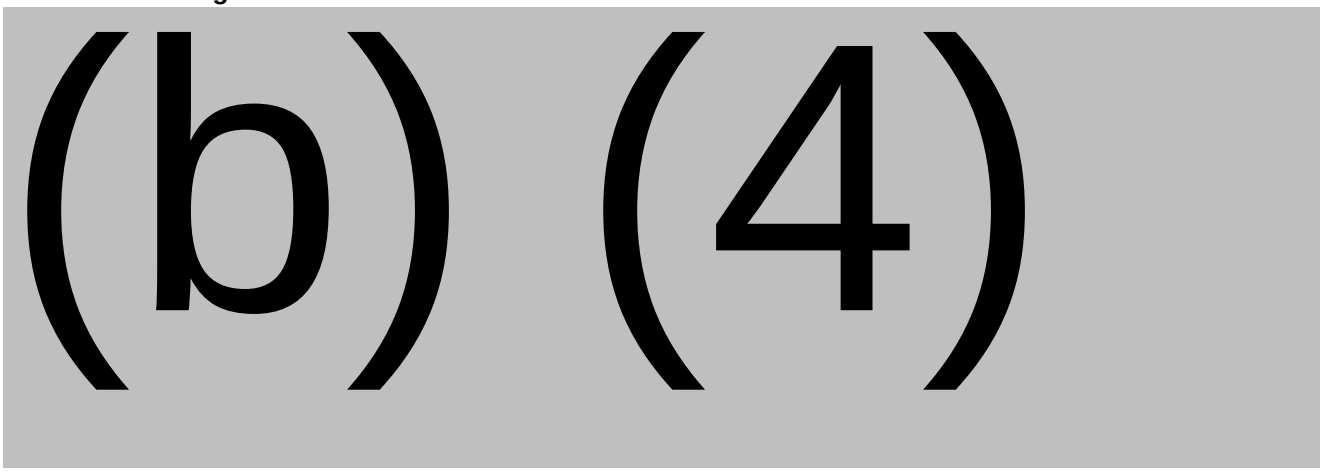
Table13: Facilities Table

Manufacturing/ Testing activities and facilities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
DS Manufacturing: (b) (4) **Facility:** Seqirus Inc 475 Green Oaks Pkwy Holly Springs, NC 27540 (**FEI#**: 3007867647)	Waiver	Yes	Yes	Team Bio Inspection, VAI, June 11 – 18 2018
Manufacture of MF59C.1 Adjuvant[1] **Facility/FEI#**: Same as above	No	No	Yes	Same as above
DP Manufacturing (for Pre-filled Syringes): Formulation[2], Fill/Finish, Release Testing **Facility/FEI#**: Same as above	Waiver	Yes	Yes	Same as above

Facility Overview

The manufacture of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted DS and DP are performed at the Holly Springs, North Carolina, USA facility, which is also the currently approved manufacturing facility for Flucelvax [approved under STN 125408/41(May 16, 2014) and STN 125408/51(June 13, 2014)]. The facility is designed for both multi-antigen (primary) manufacturing operations and multi-product (secondary) manufacturing operations, centered on seasonal, pre-pandemic, and pandemic influenza cell culture vaccines. A summary of the facility areas for the various Influenza A (H5N1) Monovalent Vaccine, Adjuvanted manufacturing steps are provided in Table 14.

Table 14: Overview of Seqirus Holly Springs Influenza A (H5N1) Monovalent Vaccine, Adjuvanted manufacturing areas



Reviewer's comment*: Seqirus did not indicate if any changes, that have not been approved under the Flucelvax submission (STN 125408), were made to their manufacturing facility as a result of the current BLA. CBER sent an information request for clarification (Question #22) on April 3, 2019 and received response from the firm on April 25, 2019 under amendment STN 125692/0.4:*

> ***CBER's information request:***
> ***Please clarify if any facility and/or room modifications were made at Holly Springs as a result of the subject of this BLA. If so, please provide a detailed description of these changes and submit their qualification reports.***
>
> Seqirus' Response: No facility or room modifications were made at Holly Springs as a result of the manufacture of Adjuvanted H5N1c Influenza Vaccine.
>
> ***Reviewer's comment:*** *The firm's response appears acceptable since they confirmed that no facility changes have been made under this BLA. Additionally, the DS and DP manufacture of Flucelvax (which follows the same manufacturing process as Influenza A (H5N1) Monovalent Vaccine, Adjuvanted) is currently being performed at Seqirus Holly Springs and a recent surveillance inspection*

completed by Team Bio (June 2018) was classified VAI. Therefore, facility pre-license inspection was waived via an Inspection Waiver Memo.

2. Equipment

Reviewer's comment*: It was not clearly stated if any modifications, that have not been previously approved, were made to equipment used in the manufacture of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted at the Holly Springs facility. CBER sought clarifications in an information request sent to Seqirus on April 3, 2019 (Question #19). The firm responded on April 25, 2019 under amendment STN 125692/0.4, stating that all the equipment used in the manufacture of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted DP is approved for use in the manufacture of Flucelvax and Fluad except for the* (b) (4)

(b) (4)

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

Reviewer's comment*: Overall, the cleaning validation strategy implemented by Seqirus appears acceptable.*

(b) (4)

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Reviewer's comment*: In their response to an information request (sent by CBER on July 19, 2019 and response received under amendment 125692/0.21 on August 02, 2019), Seqirus submitted their changeover and line clearance procedures for manufacturing between the seasonal and pandemic strains, documented in the firm's SOP* 000081370, *"Strain Changeover and Area Clearance Procedure." A summary of the SOP is provided below:*

(b) (4)

(b) (4)

4. Utilities

Reviewer's comment*: It was not clear from the submission if changes (not approved under STN 125408) were made to the utility system due to the subject of this BLA. An information request was sent to Seqirus on April 3, 2019 for clarification (Question #23). The firm sent their response on April 25, 2019 under amendment STN 125692/0.4:*

> Seqirus' Response: No utility modifications were made at Holly Springs as a result of the manufacture of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted.
>
> ***Reviewer's comment****: The firm's response is acceptable.*

5. Computer Systems

Reviewer's comment*: Seqirus did not submit information regarding their computer systems under this BLA. In response to CBER's information request of April 3, 2019 (Question #24) provided on April 25, 2019 under amendment STN 125692/0.4, Seqirus stated the following:*

> Seqirus' Response: The computer systems were reported to the Agency as part of the Fluad BLA (STN 125510/48).
>
> ***Reviewer's comment****: The firm's response appears acceptable. The computer systems information was submitted and approved on September 30, 2017, under STN 125510/48.*

OTHER eCTD MODULES
Module 1

A. Environmental Assessment or Claim of Categorical Exclusion
Seqirus submitted a Categorical Exclusion (CE) from the requirement to prepare an Environmental Assessment (EA) in accordance with 21 CFR 25.31(c). Seqirus states that to their knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA.

Reviewer's comment*:* The FDA concluded that this request is justified and agrees that the CE is appropriate for the product and the change.