U.S. FOOD & DRUG ADMINISTRATION

CMC Review Memorandum

Date: January 21, 2020

To: Brenda Baldwin, Ph.D., Review Committee Chair, DVRPA

From: Xing Li, Ph.D., DVP, Product Reviewer

Through: Jerry Weir, Ph.D., DVP Director
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Applicant: Seqirus Inc.

STN: BLA 125692/0

Subject: To request licensure of Audenz, the Adjuvanted, Cell-Derived Influenza A (H5N1) Monovalent Vaccine, indicated for active immunization to prevent illness caused by the pandemic influenza A virus H5N1 subtype contained in the vaccine

Submission Reviewed: BLA 125692/0 Original submission and Amendments 2, 4, 7, 9, 14, 16, 19, 21, 24, 26, 28, 29, 33, 34, 38, 39, 40, 41, 42.

Cross references: BLA STN 125408 and BLA STN 125510

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1 EXECUTIVE SUMMARY AND RECOMMENDATION

1.1 Executive Summary

Seqirus Inc. has submitted a Biologics License Application (BLA) for Audenz, an Inactivated Cell-derived Influenza A (H5N1) Monovalent Vaccine, Adjuvanted, indicated for active immunization to prevent disease caused by the pandemic influenza A virus H5N1 subtype contained in the vaccine. Audenz is presented as an emulsion for intramuscular injection in a pre-filled syringe (PFS) containing a minimum of 7.5 µg hemagglutinin (HA) antigen per dose (0.5 ml), intended for persons aged 6 months and older who are at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine. Development of Audenz is under IND 13536.

The influenza component in Audenz, predominantly hemagglutinin (HA) antigen (b) (4) , is produced by the same process as the US licensed seasonal influenza vaccine, Flucelvax (STN 125408). It is prepared from virus propagated in Madin Darby Canine Kidney (MDCK) continuous cell line and chemically inactivated, detergent (b) (4) purified to form the monovalent drug substance. The antigen is formulated with MF59C.1 (b) (4) and then filled into pre-filled syringes (PFS), which is similar to the seasonal influenza vaccine Fluad (STN 125510). The entire manufacturing activities are performed at Seqirus facility located in Holly Springs, North Carolina, United States.

I reviewed the Chemistry, Manufacturing and Controls (CMC) section of this BLA, focusing on Modules 3.2.S Drug Substance, 3.2.P Drug Product, 3.2.A.2 Adventitious Agent Safety Evaluation, and 5.3.1.4 Report of Bioanalytical and Analytical Methods for Human Studies. Several key issues were identified during the review of this submission. The details and the resolution of each issue are summarized as following:

1) **Manufacturing process development - Comparison of Process 3.0, Process 1.1, and Process 2.0**: Process 3.0 is proposed for commercial licensure for the

manufacture of (b) (4) drug substance (DS) for Audenz. It was concerning that the (b) (4) antigen produced by Process 3.0 had not been tested in the clinical studies, given that Audenz Phase I clinical trial material was manufactured with Process 1.0; Phase II trial material was produced with Process 2.0, and Phase III clinical trial material was manufactured with Process 1.1. To support licensing Process 3.0 for Audenz production, Seqirus provided data to demonstrate equivalence between the three manufacture processes and comparability between the quality of DS and final vaccine products manufactured from Process 2.0, Process 1.1, and process 3.0. These data were thoroughly evaluated and deemed acceptable.

2) **Withdrawal of (b) (4) presentation for Audenz drug product:** In the original BLA, Seqirus submitted information to support the (b) (4) presentation for Audenz, which was presented as an emulsion in a (b) (4) glass (b) (4) vial with a 13 mm bromobutyl stopper, labeled as (b) (4) of adjuvanted antigen solution for (b) (4) (0.5 ml per human dose). The vial contained the (b) (4) in addition to the same compositions as Audenz-PFS. The (b) (4) presentation had not been used for the clinical studies. On September 26, 2019, Seqirus submitted Amendment 125692/0.26 to report that (b) (4) were found in the samples of the (b) (4) PPQ (b) (4) batches at the 6-month and 9-month stability timepoints, though all testing results were within specifications for all batches. Seqirus conducted a series of investigations that were still ongoing. The current findings indicated that the particulate formation could be attributed to the coexistence of (b) (4) MF59C.1 that probably reacted with the bromobutyl stopper of the vial, but the results were still inconclusive. On October 9, 2019, Seqirus proposed to withdraw the Audenz-(b) (4) presentation from this BLA in the Late Cycle Meeting.
3) **Tightening certain Audenz (b) (4) /drug product release specifications:** The initially proposed broad specification ranges of Specific Purity for release of H5N1 (b) (4), and non-HA Proteins for Audenz drug product were not reflecting the capability of the manufacturing process that was demonstrated by the clinical trial materials, and were more relaxed than the specifications established for Flucelvax. Given that both Audenz and Flucelvax are produced with the same manufacture Process 3.0, it is not justified to have different acceptable criteria for product purity and quality between these two products. Upon our requests, the company has aligned the release specifications for Audenz (b) (4) /drug product with that for Flucelvax.
4) **Validation of test method for Virus Inactivation Kinetics analysis:** Inactivation of purified virus with β-Propiolactone (BPL) is strain-specific. Inactivation kinetics study is performed on the (b) (4)

(b) (4) . We disagreed company's assay validation report submitted in October 2019 that added a (b) (4) step to all the (b) (4) samples right (b) (4) because it may cause artificial negative results. Through several rounds of communication, including a teleconference, Seqirus committed to accept FDA request to implement a (b) (4) for the (b) (4) samples to get rid of the (b) (4) caused by the (b) (4), and accordingly revised assay validation protocol. On December 16, 2019, Seqirus proposed to take four months to complete the validation study and submit the complete inactivation kinetics validation report as a post-marketing commitment (PMC). However, the Committee Chair decided that this final validation report can be submitted as a Product Correspondence after consultation with OVRR upper management.

5) **Stability data to support Audenz-PFS shelf life:** The proposed shelf life for Audenz-PFS was (b) (4) months when stored at 2-8℃. Currently the stability study of (b) (4) (b) (4) of Audenz-PFS lot manufactured with Process 3.0 is ongoing, and the stability testing results up to 12-month timepoint are all within specifications. Accordingly, a 12-month shelf life for Audenz-PFS is approved in this BLA. The company committed to submit a supplement to provide (b) (4)-month stability data when the stability study is complete. Extension of Audenz-PFS shelf life should be supported by satisfactory stability data.

1.2 Recommendation

Approval

2 REVIEW OF CHEMESTRY, MANUFACTURING AND CONTROLS

2.1 DRUG SUBSTANCE

2.1.1 General Information

1. Nomenclature

AUDENZ, Influenza A (H5N1) Monovalent Vaccine, Adjuvanted, is a MDCK cell-based inactivated subunit vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. This Flu Cell Culture vaccine (FCC) consists of two components, an inactivated influenza vaccine consisting primarily of hemagglutinin and an adjuvant MF59C.1.

2. Structure and General Properties

The drug substance of Audenz predominantly consists of (b) (4) from a H5N1 influenza virus strain identified as pandemic or pre-pandemic by the WHO (World Health Organization), EMA (European Medicines Agency), CBER (Center for Biologics Evaluation and Research), CDC (Centers for Disease Control and Prevention) and other Health Authorities. The quantity of (b) (4) is not monitored in the final vaccine.

(b) (4)

2.1.2 Manufacture

2.1.2.1 Manufacturer(s)

Table 1 Manufacturing Sites and Responsibilities

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

2.1.2.2 Description of Manufacturing Process

The commercial-scale drug substance for Audenz monovalent vaccine is manufactured with Process 3.0 from a (b) (4) infectious MDCK culture at Seqirus Holly Springs facility. The same process has been approved for the production of monovalent bulk for the cell-based seasonal influenza vaccine, Flucelvax.

Description of Manufacturing Process, Process Steps and Control

The Audenz drug substance manufacturing process is (b) (4)

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

(b) (4)

(b) (4)

(b) (4)

Storage and Shipping

The drug substance in the (b) (4) is stored at (b) (4) The shelf life is proposed to be (b) (4) months. The drug substance is formulated at Holly Springs site for drug product manufacture; therefore, shipping is not required.

2.1.2.3 Control of Materials

2.1.2.3.1 (b) (4)

(b) (4)

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

(b) (4)

(b) (4)

2.1.2.3.3 Control of Media, Solutions and Raw Materials

The media, solutions, and raw materials used for H5N1 drug substance manufacture are the same as that used for the licensed seasonal influenza vaccine (Flucelvax). In general, written procedures have been established to describe the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials. Each media, solutions, and raw materials purchased from the approved suppliers is assigned a unique material number and batch number for traceability and control, and then sampled, tested, and dispositioned by the Quality Unit for use according to approved specifications and site procedures. Media or solutions that are manufactured in-house are assigned a unique material number and batch number for traceability and control. The approved sources, part numbers, and release testing/criteria are documented in individual item specifications. All the materials are checked to ensure within expiry prior to use for manufacturing.

Reviewer's comment: *Section 3.2.S.2.3.3 lists the media, solutions and raw materials (including* (b) (4) *used in the drug substance manufacturing process. These documented materials are indicated not containing animal derived contents. The representative Certificates of Analysis (CoAs) for the purchased materials are also included in this submission.*

2.1.2.4 Controls of Critical Steps and Intermediates

To ensure the performance of drug substance manufacturing process and product quality, a planned set of controls is derived from the current product and process,

including related parameters and attributes, as well as the test methods and acceptance criteria.

Process Parameters

A process parameter is an input variable or condition of the manufacturing process that can be directly controlled in the process. The process parameters are classified as following:

Critical Process Parameters (CPP): An input process parameter of that the variability has an impact on a critical quality attribute (CQA), which should be controlled within a narrow operating range to ensure the product quality.

Key Process Parameter (KPP): a process parameter that has a narrow range and/or is difficult to control. An out-of-limit KPP may affect process performance (e.g. yield) and/or a process control but does not affect product quality.

Non-Key Process Parameter (nKPP): A process parameter that does not have an impact on product quality or process performance if a nKPP is out of control limits. nKPP may be monitored as part of normal batch manufacture.

Process Controls

An output variable or outcome that is an indicator of the process performance status. In some cases, a process control can also be considered as a product quality attribute.

In-Process Control (IPC): An IPC is a test performed at critical decision-making steps and the steps where data serve to confirm the consistency of the manufacture process.

Critical Process Controls (CPCs): Release criteria/specifications (critical quality attributes) of the product intermediate and/or final drug substance.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Critical Quality Attribute (CQA)

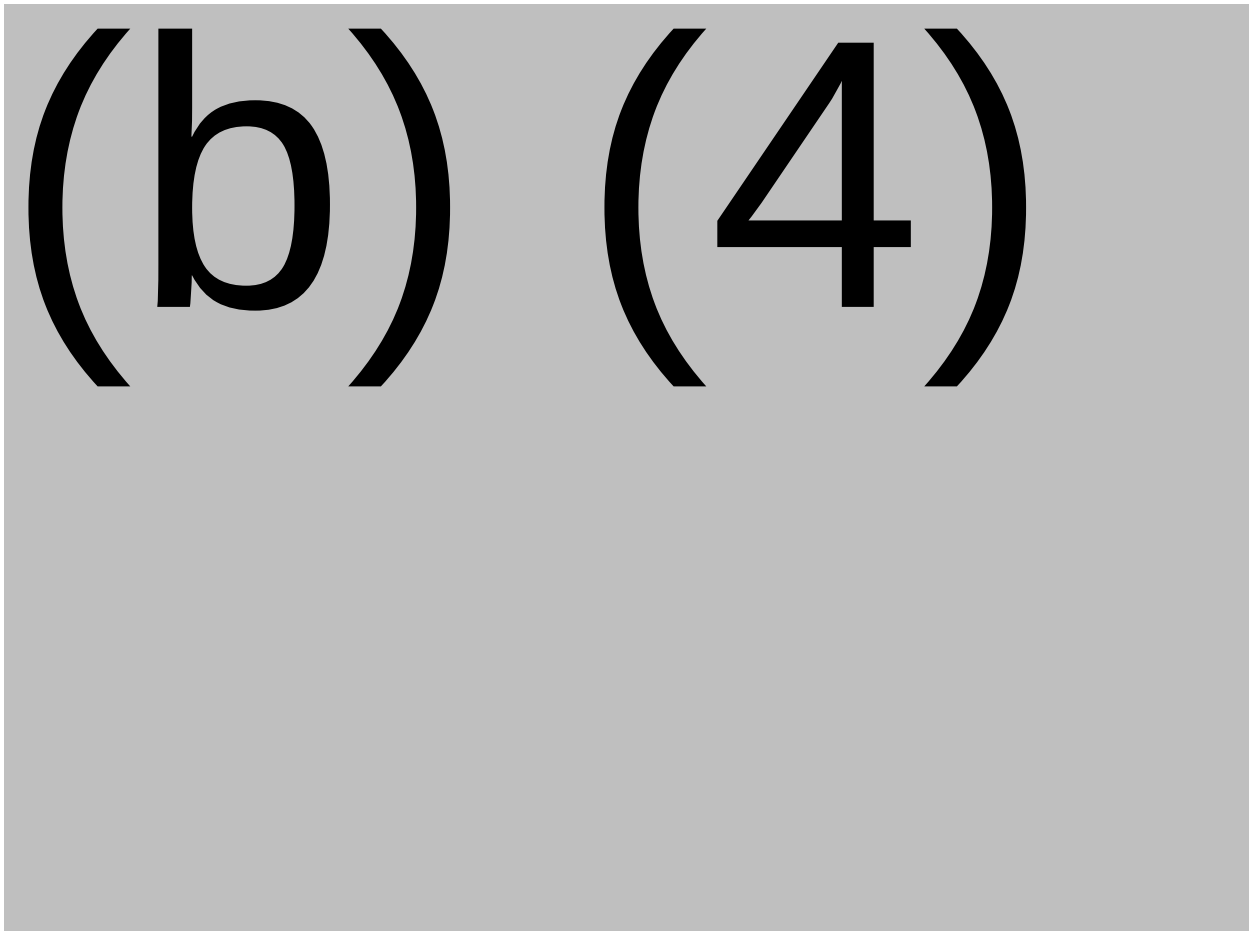
A CQA is a defined physical, chemical, biological, and microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are usually established as release criteria/specifications of the product intermediate and/or final drug substance. The In-Process CQAs for Audenz and test results of the PPQ lots are listed in table 7; the drug substance release specifications are listed in Table 14.

2.1.2.5 Process Validation/Evaluation

The Process Performance Qualification (PPQ) activities were performed under a Drug Substance Process Validation Master Plan throughout the (b) (4) production and drug substance manufacturing process. The process used for the production of this pandemic vaccine is the same as the approved process for US licensed seasonal vaccine, Flucelvax. The process validation for the H5N1 (b) (4) using Process 3.0 was performed at the production scale of (b) (4) and summarized in Table 5:

(b) (4)

(b) (4)



Reviewer's comment: *The subtype-independent steps in the FCC manufacturing process have been validated and approved for Flucelvax (STN 125408/274), and the validated parameters and conditions are applicable to the pandemic FCC manufacturing process. The strain-specific steps are required to be evaluated and optimized for each new strain. Therefore, this memo will focus on evaluating the data generated from H5N1-specific Process Performance Qualification.*

(b) (4)

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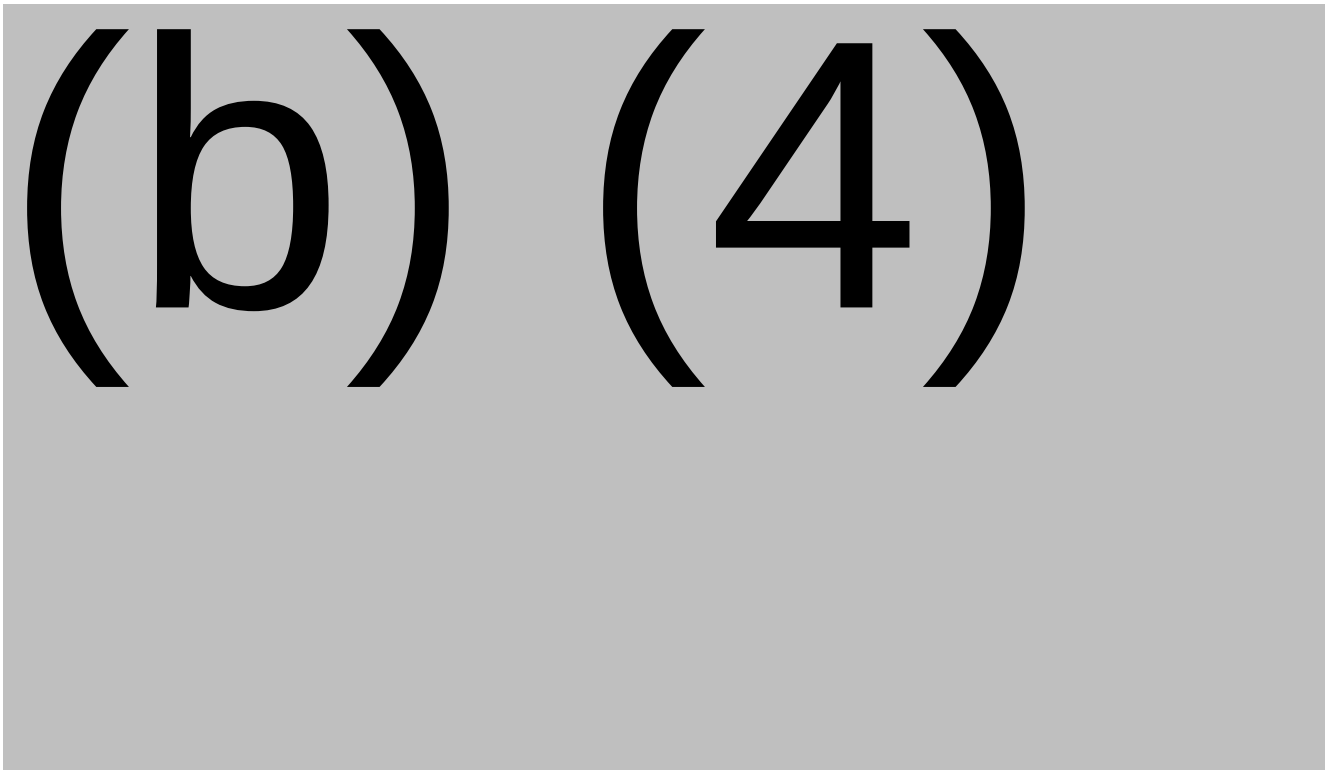
Analytical Comparability

To ensure the manufacturing process changes between Process 2.0, Process 1.1 and Process 3.0 did not adversely impact Safety, Strength, Purity, and Quality of the aH5N1c vaccine, the company presented quantitative and qualitative data generated from routine release and in-process testing to demonstrate that the drug substances produced from different manufacturing processes are comparable. The drug substance release test results are listed in Table 10.



Reviewer's comment: *Both Process 1.1 and Process 3.0 have been approved for the production of FCC seasonal influenza vaccine Flucelvax. In this BLA, Seqirus proposed to license Process 3.0 for commercial production of Audenz, whereas H5N1 Process 3.0 product had not been tested in their clinical studies. H5N1* (b) (4) *manufactured with Process 1.1 was used for Phase III clinical trial and generated satisfactory results in safety and immunogenicity. The product quality comparability between drug substance batches produced by Process 3.0 and Process 1.1 through in-process controls, release specifications, stability profiles, and characterization tests* (b) (4) *to confirm that* (b) (4) *produced by the two processes are comparable, thus supporting Process 3.0 for commercial production of Audenz.*

(b) (4)

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

2.2 DRUG PRODUCT

In the original BLA submission, Seqirus provided information to support licensure of (b) (4) presentations for Audenz drug product**:** (b) (4)) Pre-Filled Syringe (PFS) that was used for all clinical trials under IND 13536; (b) (4) . Due to the observation of (b) (4) in the (b) (4) final containers after six months of storage, Seqirus withdrew Audenz- (b) (4) presentation from this BLA in the late cycle meeting. Thus, this memo only includes review on information to support Audenz-PFS.

2.2.1 Description and Composition of the Drug Product - PFS

Audenz, the Influenza A (H5N1) Virus Vaccine, cell-derived and adjuvanted with MF59C.1, is an inactivated influenza vaccine containing predominantly hemagglutinin (HA) surface antigen from a MDCK cell-derived H5N1 virus subtype.

MF59C.1 is an oil-in water emulsion containing squalene (b) (4) citrate buffer (b) (4) . The emulsion is stabilized by the inclusion of two non-ionic surfactants.

The potency of the vaccine is expressed as the concentration of the HA protein and is formulated to contain a minimum of 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 adjuvanted antigen solution. The vaccine is milky-white homogeneous fluid in appearance and is preservative-free.

The composition of Audenz-PFS and the assigned Unique Ingredient Identifier (UNII) Codes are listed in Table 18:

Table 18. Composition of Adjuvanted Audenz Influenza Vaccine

Ingredients	Quantity per Adult Dose (0.5 mL/dose)	Function	Reference to Standards	UNII Code
Active Ingredient				
A/turkey/Turkey/1/2005 NIBRG-23 (H5N1) antigen (MDCK cell derived, BPL inactivated)		Antigen (active ingredient)	NIBSC	(b) (4)
(b) (4)				

Adjuvant				
Squalene	9.75 mg	Oil phase	Internal	(b) (4)
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)

Container Closure System of the Final Vaccine

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 (b) (4) and screwed into the luer lock adaptor; the (b) (4) 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 that complies with the (b) (4) for Containers (b) (4) and the (b) (4) for glass containers for injectable preparations (b) (4) The (b) (4) tip cap rubber formulation complies with the requirements of the (b) (4) for (b) (4) (b) (4) and the (b) (4) . for (b) (4) (b) (4)

The syringe plunger stopper is composed of bromobutyl rubber (b) (4) The rubber formulation complies with the requirements of the (b) (4) (b) (4)

(b) (4) (b) (4) and the (b) (4). for (b) (4) (b) (4)

The syringe barrel, tip cap and plunger stopper are product-contact components. Further details are provided in Section 3.2.P.7 Container Closure System - PFS.

2.2.2 Pharmaceutical Development

2.2.2.1 Components of the Drug Product

Drug Substance

An inactivated influenza vaccine containing predominantly HA (b) (4) surface antigens from H5N1 virus derived from MDCK cells.

Adjuvant

MF59C.1, an oil-in-water emulsion, is the adjuvant.

The primary ingredient of MF59C.1 is squalene, a highly unsaturated hydrocarbon found in many animals and in some plants. In humans, squalene is biosynthesized in the liver and is an intermediate in the biosynthetic pathways producing human steroid hormones. It is also the principal hydrocarbon of human surface lipids.

Two surfactants, Polysorbate 80 and sorbitan esters, are included to stabilize the emulsion. Both are commonly used surfactants, which allowed for the production of small, stable emulsion droplets that could be (b) (4) .

The citrate buffer acts as a (b) (4) The MF59C.1 adjuvant is sensitive to light.

Stability studies have shown that the protein antigens formulated with MF59C.1 are not affected by the presence of sodium citrate or the surfactants from the MF59C.1 adjuvant.

Excipients

The formulation of the drug product includes the following excipients:

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

2.2.2.2 Drug Product

Formulation Development

The formulation of the Audenz format drug product is adapted from both the licensed cell-based Flucelvax (STN 125408) and the adjuvanted Fluad (STN 125510) vaccines. The formulation of the (b) (4) product was developed in accordance with the (b) (4) and/or (b) (4) .

The Audenz vaccine, adjuvanted with MF59C.1, contains predominantly hemagglutinin (HA) (b) (4) surface antigens from a MDCK cell-derived H5N1 virus. The (b) (4) The content of HA antigen per dose is (b) (4) 7.5 µg for the H5N1 strain contained in a (b) (4) , also referred

to as (b) (4)

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2.2.2.3 Manufacturing Process Development

(b) (4)

NVD Holly Springs, North Carolina (now Seqirus).

The pandemic adjuvanted monovalent FCC drug product is presented in a single dose syringe that is designed to deliver a 0.5 mL total dose containing 7.5 µg hemagglutinin.

An overview of the (b) (4) drug product batches used to support all three clinical trial phases is provided in Table 19:

Table 19. Overview of Materials used in Phase I, II, and III aH5N1c Clinical Trials

Phase/ Clinical Study	(b) (4) Process/ Strain	Drug Substance Batch	Filled/Finished Product Batch Numbers	(b) (4) Manufacturing Site	MF59C.1 Manufacturing Site	Formulation Site	Filling Site
I/V89P1	1.0/ A/Indonesia [1](H5N1)	(b) (4)	545004011B [3] (15 µg H5N1/dose)	(b) (4)			
			545005011B[3] (7.5 µg H5N1/dose)				
			545006011B[3] (3.75 µg H5N1/dose)				
			545007011B[3] (15 µg H5N1 + 100% MF59/dose)[4]				
			545008011B[3] (7.5 µg H5N1 + 100% MF59/dose)[4]				
			545009011B[3] (3.75 µg H5N1 + 100% MF59/dose)[4]				

II/V89_4	2.0/ A/turkey[2] (H5N1)	(b) (4)	C53D29N1	Holly Springs			(b) (4)
II/V89_11			C53D30N1				
II/V89_13			C53D28N1				
			C53D30N1				
III/V89_18	1.1/ A/turkey[2] (H5N1)		181053	Holly Springs	Holly Springs	Holly Springs	Holly Springs
III/V89_18			181054				
			181675				

[1] A/Indonesia/5/2005 strain was used for the Phase I clinical trials.
[2] A/turkey/Turkey/1/2005 NIBRG-23 strain was used for Phase II and Phase III clinical trials.
[3] Only information for US lots included in the table.
[4]As part of the formulation of the clinical batches, several concentrations of MF59 were used (0, 25%, 50%, and 100%). 100% MF59 in the table above refers to formulations containing the full amount of MF59 in the vaccine, equivalent to 50% MF59 per dose.

2.2.2.3.1 Comparability of Formulation and Filling Processes

The formulation and filling for Phase I and Phase II clinical lots of the aH5N1c drug product using H5N1 (b) (4) MF59C.1 produced in (b) (4) were performed at the (b) (4) site. The Phase III clinical trial material was formulated and filled at the Holly Springs site, using a (b) (4) (from (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 summarized in Table 20:

Table 20. Comparison of Phase II and Phase III Drug Product Manufacturing Steps

Operation	Phase II (b) (4)	Phase III (Holly Springs, NC)	Justification and/or Explanation
			(b) (4)
Drug Product Formulation			(b) (4)

Filling	Aseptic filling in a Grade (b) (4) cleanroom into (b) (4) syringes with (b) (4) plungers	Aseptic filling in a Grade (b) (4) syringes with (b) (4) plungers	No changes were made in the syringes and plungers. Dose targets vary based on the capabilities of the (b) (4) filling lines, but (b) (4) are qualified to deliver the appropriate dose.
Inspection	(b) (4) inspection	(b) (4) inspection by qualified inspectors	(b) (4) inspection of adjuvanted drug product were not completed at Holly Springs when the production began. (b) (4) inspection was used to inspect all syringes sent for clinical packaging QC testing and stability.

2.2.2.3.2 Impact Assessment for Formulation/Filling Changes for Phase III Clinical Trial Materials

Impact assessments were performed to evaluate 1) facilities and equipment; 2) process (including in-process checks, in-process controls and hold times); 3) analytical methods and specifications; 4) stability; and 5) validation (including (b) (4) validations, process qualification, extractables/leachables, (b) (4)), which demonstrated that the proposed 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.

2.2.2.3.3 Comparability Between the Drug Product Formulation and Filling Processes for Phase III (Process 1.1) and Commercial Manufacture (Process 3.0)

There were no differences between the PFS formulation and filling manufacturing processes that were used for the Phase III clinical trial material ((b) (4) Process 1.1) and those proposed for the licensed Audenz pandemic vaccine ((b) (4) Process 3.0). However, two changes were implemented for inspection and packaging: 1) Phase III material was inspected (b) (4) while the commercially produced Audenz pre-filled syringes is inspected with a (b) (4) that was previously qualified for Flucelvax and Fluad inspection. Confirmation of the (b) (4) will be performed for Audenz pre-filled syringes and additional qualification will be completed as required. 2) Packaging of commercially produced Audenz pre-filled syringes will be performed at Seqirus instead of a 3rd party CMO which was used during Phase III trial materials manufacture. The changes made from Phase III to commercial manufacturing for inspection and packaging are considered comparable.

As Process 1.1 and Process 3.0 drug substance materials have been demonstrated to be equivalent (reference Section 3.2.P.2.6 Manufacturing Process Development) and the recently approved PAS for utilizing Process 3.0 for the production of Flucelvax (approved by CBER on July 27, 2018 (STN 125408/274)), Seqirus does not plan to perform

additional process validation studies for the formulation and filling of the final drug product produced by Process 3.0. However, (b) (4) PFS drug product lot has been manufactured with Process 3.0 FCC H5N1 (b) (4) material and has been placed on stability study.

2.2.2.3.4 Comparability of Drug Product

Table 21 lists the release testing results from aH5N1c PFS filled clinical trial materials used for Phase II and Phase III studies.

Table 21. Comparison of Release Results for aH5N1c Phase II and Phase III Clinical Finished (Filled) Lots

Test	Specification	Phase II Lots (n = 3)	Phase III Lots (n = 3)
Sterility	Sterile	Pass	Pass
pH	6.5– 7.7	(b) (4)	(b) (4)
Endotoxin	(b) (4)		
Appearance	White homogeneous suspension	Conforms	Conforms
HA (b) (4)	(b) (4)		
Extractable volume	(b) (4) 0.50 mL	(b) (4) 0.50 mL	(b) (4) 0.50 mL
Squalene (b) (4)	(b) (4)		
Squalene (b) (4)	(b) (4)		
Number of large particles	(b) (4)		
Visible particles	(b) (4)		
Subvisible particles	(b) (4)		
Mean particle size	(b) (4)		
	(b) (4)		

Reviewer's comment: *The release testing results indicated that the aH5N1c vaccine-PFS lots used in both Phase II and Phase III clinical trial studies were comparable.*

2.2.2.4 Container Closure System

The vaccine is presented in 1 mL (b) (4) colorless glass syringes with (b) (4) and with a grey stopper. This container closure system is also used for Flucelvax and Fluad.

To meet extractable volume requirements, an appropriate (b) (4) in the 1 mL syringe without a needle has been selected as per (b) (4) Therefore, no needle is present on the syringe.

Container Closure Integrity Test (CCIT) Validation Study

Container closure integrity testing (CCIT) is performed to demonstrate that a sterile boundary can be maintained for a closure component system throughout the shelf life of the product. The CCIT study evaluated the ability of a (b) (4) for the 1 mL (b) (4) glass syringes with (b) (4) tip caps and (b) (4) plunger stoppers (including Audenz product). All the positive and negative controls were found to be acceptable and all samples passed both the (b) (4) indicating the container closure using the (b) (4) tip cap is acceptable at the 0, 6, 12 (b) (4) month time points.

Reviewer's comment: *Evaluation of CCIT study is deferred to DMPQ reviewers.*

Extractables and Leachables

The (b) (4) glass syringe barrel did not require an extractables and leachables assessment due to its non-reactivity. An extractables and leachables assessment was performed for the bromobutyl plunger stopper and tip cap, receiving an overall rating risk of medium which were required further evaluation.

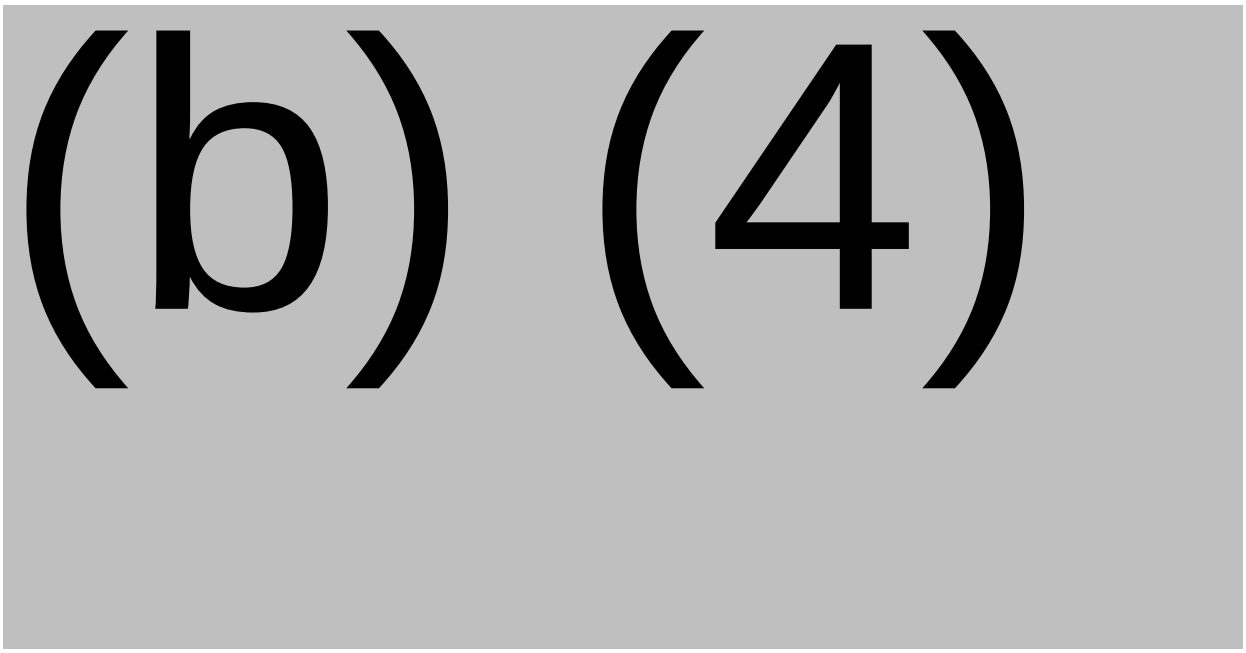
The material of construction of the (b) (4) plunger stopper is latex-free bromobutyl rubber which is the same component used in the currently licensed product, Fluad, a MF59C.1-adjuvanted egg-based influenza vaccine in pre-filled syringes. The leaching characteristics of the stopper material has been previously evaluated in leachable studies for Fluad. The results indicated that there was no safety concern regarding the plunger stopper rubber bromobutyl formulation.

There is no study that has directly evaluated adjuvanted monovalent FCC vaccine in a syringe with the (b) (4) tip cap, the risk of leachables migrating from the (b) (4) to the drug product is low because the (b) (4) tip cap has been determined to be equivalent to the (b) (4) tip cap and a long-term study executed with Fluad (aTIVe) trivalent adjuvanted drug product (a worst-case product compared to Audenz) using the (b) (4) tip cap demonstrated no safety issues due to leachable migration. Therefore, this syringe with (b) (4) tip cap is deemed suitable as a primary container closure element for adjuvanted monovalent FCC product.

2.2.2.5 Microbiological Attributes

Audenz is a sterile parenteral solution without addition of preservatives. Formulation is performed as a closed aseptic process using sterilized equipment and sterile disposable components. Table 22 provides the microbiological control for the formulation and filling:

(b) (4)



The MF59C.1 adjuvant is produced, (b) (4) and stored at Holly Springs facility.

2.2.2.6 Compatibility

The compatibility of the drug product with the container has been demonstrated through the monitoring of critical quality attributes during stability studies. Compatibility continues to be supported by the (b) (4) stability program.

2.2.3 Manufacture

2.2.3.1 Manufacturer

Seqirus, Inc., located at 475 Green Oaks Parkway, Holly Springs, NC 27540, USA, is the only manufacturing site and responsible for the entire manufacturing process to produce Audenz drug product in pre-filled syringe, including MF59C.1 manufacture, Production of (b) (4), Filling, Inspection and Packaging, and QC testing.

2.2.3.2 Batch Formula

The final formulation of Audenz PFS drug product, batch size of (b) (4) is prepared in a (b) (4) to target the strength of 7.5 µg of HA antigen per 0.5

ml dose (or 15 µg/ml) with the addition of the calculated amount of formulation (b) (4) and WFI based on the required volume of H5N1 (b) (4) in addition to the adjuvant MF59C.1 that accounts for (b) (4) .

2.2.3.3 Description of Manufacturing Process

Formulation Process

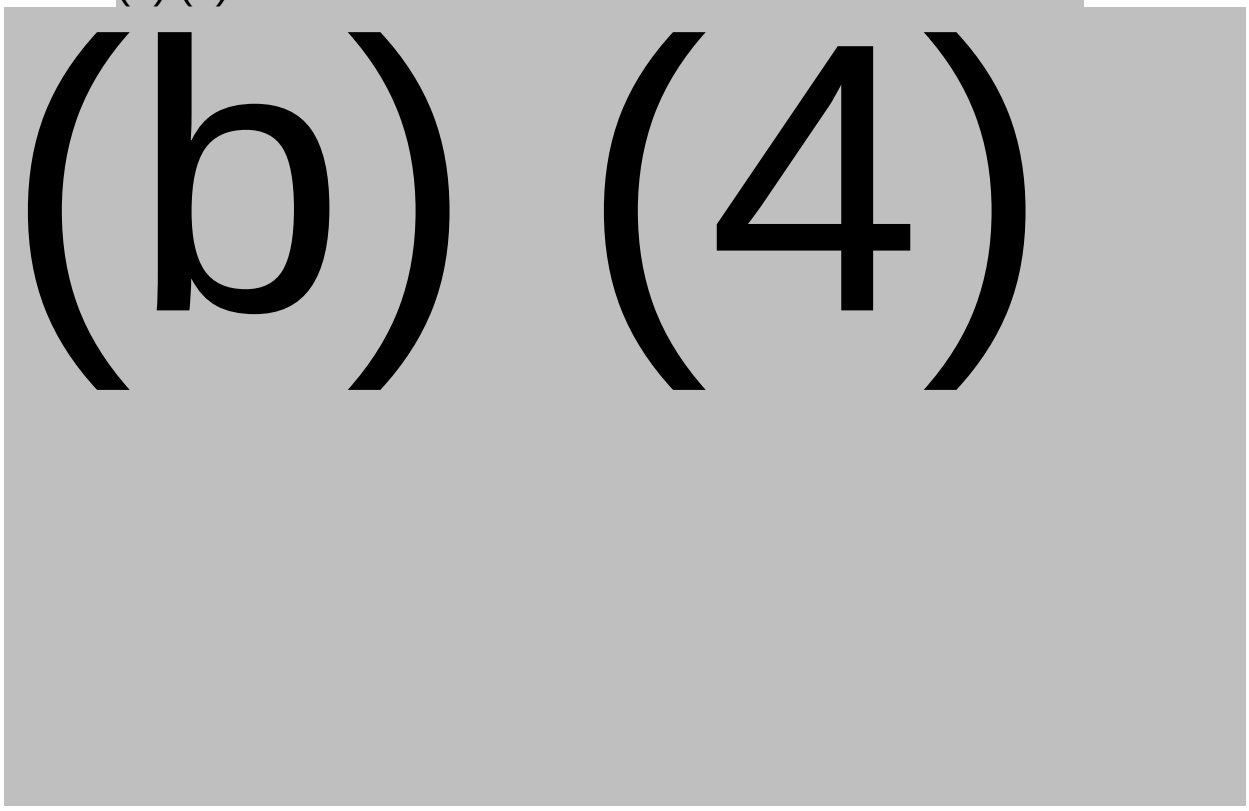
Formulation of the monovalent Audenz drug product consists of (b) (4) of HA antigen (H5N1) (b) (4) WFI, and (b) (4) MF59C.1 adjuvant to the final required antigen concentration. The formulation antigen target is evaluated to provide sufficient coverage for a potency decrease over the shelf life of the product (the targeted dose (b) (4) The proposed drug product nominal batch size is (b) (4)

The formulation process is performed in a (b) (4) room at Holly Springs as an aseptic addition of sterile materials in closed system using sterilized components, where the Audenz Drug Product is formulated as an aseptic formulation in a sterile (b) (4) with the following components:

Filling and Packaging Process

The filling and packaging process as well as critical process parameters, in-process controls and release testing is summarized in the following flowchart:

(b) (4)



(b) (4)

.

Adjuvanted monovalent FCC vaccine is filled into 1 mL (b) (4) syringes with (b) (4) tip cap and (b) (4) overseal. The syringes are closed with (b) (4) bromobutyl plungers. The target fill quantity is (b) (4) per syringe, with an in-process (b) (4) per syringe. The target (b) (4) (b) (4) per syringe to account for (b) (4) and needle hold up, and extractable volume release test variation. This ensures a delivery volume of (b) (4) 0.5 mL per syringe. The product density for pandemic vaccine is (b) (4)

(b) (4)

Inspection, labeling, and packaging of the filled syringes are performed in a (b) (4) area, and can be performed (b) (4) . Acceptable filled syringes undergo a (b) (4) visual inspection by a qualified (b) (4) inspection to detect defects. Syringes that do not meet the visual inspection criteria are rejected and separated from the acceptable syringes according to internal procedures. The acceptable syringes are (b) (4)

After inspection, (b) (4) the acceptable syringes using (b) (4) and the labels are applied. Batch number and expiration date are added to the label. The syringe label information and placement are confirmed using visual systems.

Pre-filled syringes are placed into 10-syringe cartons with product leaflets during the packaging process. Visual systems confirm that the syringes and leaflet are present with each filled packing container. Sealed cartons are packed into a case for final storage at 2 – 8 °C until released.

2.2.3.4 Controls of Critical Steps and Intermediates

A quality risk analysis (QRA) assessment was performed to determine critical quality attributes and critical process parameters for the formulation manufacturing process. The CQAs for Audenz Drug Product-PFS are provided in the following table:

Table 23. Critical Quality Attributes for Audenz Drug Product-PFS

Critical Quality Attributes	Acceptance Criteria
H5N1 antigen	(b) (4)
Adjuvant: (b) (4) MF59C.1	(b) (4)
Excipient	(b) (4)
Dose	(b) (4) 0.5 mL extractable volume
Sterility of Final Dose	Sterile

(b) (4) ; NLT: Not less than

Formulation

Table 24. In-Process Controls for Formulation

Parameter	Acceptance Criteria
(b) (4)	

Filling and Packaging

The critical process parameters (CPP) for the Audenz Drug Product-PFS are listed in Table 25:

Table 25. Critical Process Parameters for Audenz Filling and Packaging

Process Parameter	Range
(b) (4) (dose)	(b) (4) 0.50 mL/syringe

The in-process controls for the filling and packaging process are provided in Table 26:

Table 26. In-Process Controls for Audenz Filling and Packaging

Process Parameter	Acceptance Criteria
(b) (4)	

2.2.3.5 Process Validation and/or Evaluation

2.2.3.5.1 (b) (4) of MF59C.1

(b) (4) process validation for the adjuvant MF59C.1 has been reviewed by Dr. Marina Zaitseva.

2.2.3.5.2 Audenz Formulation Process Validation

The formulation process validation activities for Audenz PFS included:

- Process Performance Qualification (PPQ)
- (b) (4) Validation
- (b) (4) Validation
- Extractables/Leachables
- Aseptic simulation
- Hold Time Validation

Process Performance Qualification of Phase III Clinical Lots (PFS) Formulation/Filling Process

The PPQ study was executed under Protocol 323009 "Process Performance Qualification Protocol for Adjuvanted Monovalent FCC Flu Vaccine in (b) (4) to validate a formulated (b) (4) batch size of (b) (4) and a filling batch size of not more than (b) (4) which was determined by the number of syringes required for Phase III clinical trial. A minimum fill target of (b) (4) syringes) was filled and inspected.

(b) (4) batches in total were manufactured to support this PPQ study. (b) (4) products failed to meet acceptance criteria and were deemed to be invalid. (b) (4) was successfully formulated but never filled or inspected, as it was placed on hold to investigate a gross leak that occurred on the (b) (4) was manufactured to timely provide the Phase III trial material when the investigation on (b) (4) was ongoing. PPQ (b) (4) were successfully executed. All acceptance criteria outlined by Protocol 323009 were successfully met. The overall status of the PPQ is deemed to be valid passing, and the (b) (4) process for Adjuvanted (b) (4) (H5N1) Flu vaccine is considered fully validated at the pre-defined scale. The PPQ lots are summarized as following:

Table 27. Summary of Process Performance Qualification Runs (Phase III Clinical Lots)

(b) (4)

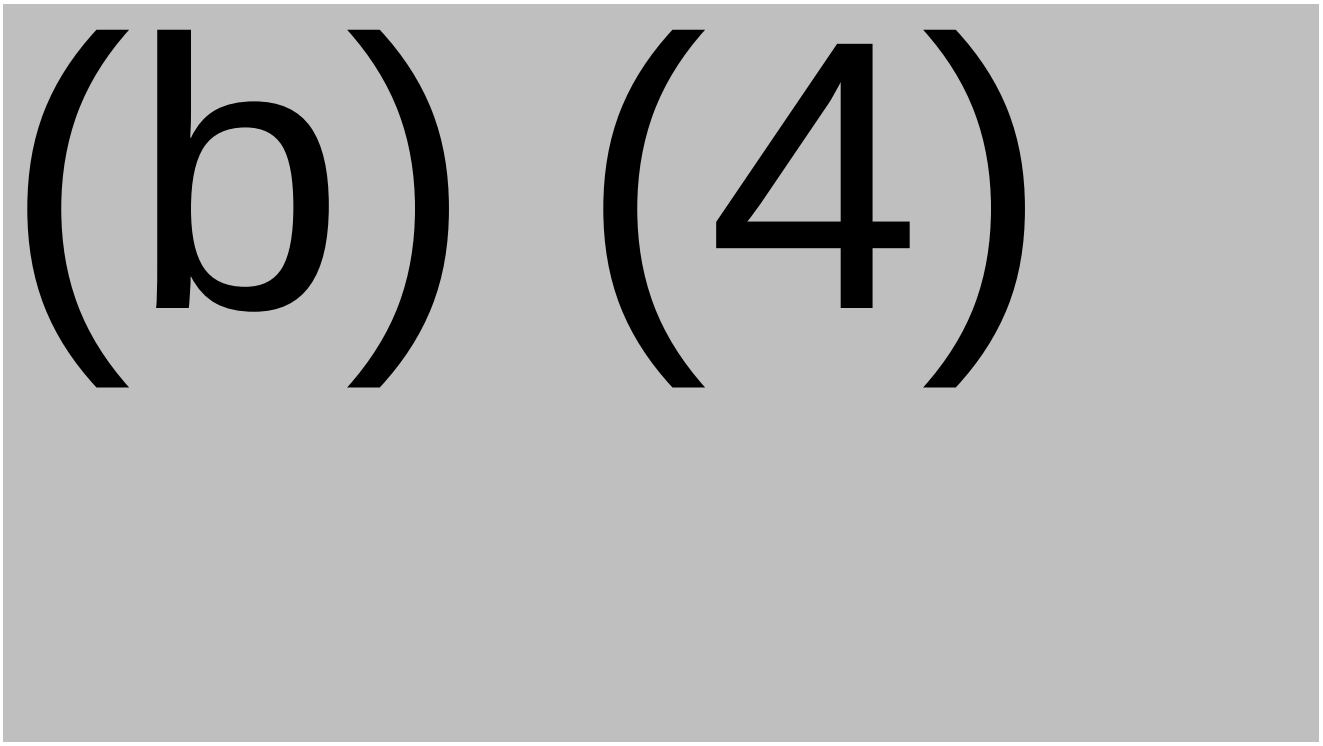
(b) (4)

Reviewer's comment: *PPQ Report 336408 (VAL-000075247) indicated* (b) (4) *invalid PPQ Runs but did not provide the root cause that resulted in the invalidity. In response to FDA's Request, Seqirus provided the following information on May 17(Amendment 9): "Batches* (b) (4) *failed to meet acceptance criteria due to issues with input materials that were outside the scope of the PPQ. The* (b) (4) *material used for these* (b) (4) *PPQ batches was well beyond the age of a typical seasonal* (b) (4) *. As*

a result, there was no experience formulating material of this age (the (b) (4) *was* (b) (4) *months old)." The company's response indicated that the invalid PPQ runs resulted from the aged* (b) (4) *months), though the Process 2.0 HHS Stockpile lots demonstrated a stable HA antigen potency trend up to* (b) (4) *months.*

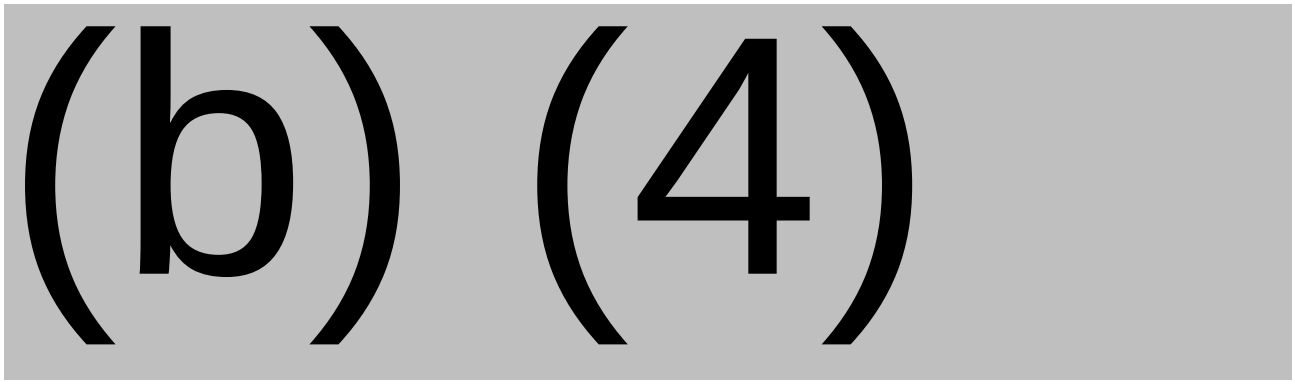
Formulation Performance Parameters are listed in Table 28:

Table 28. Summary of Formulation Performance Parameters (Outputs) for Phase III Clinical PPQ Lots



Filling Performance Parameters are listed in Table 20:

Table 29. Filling Performance Parameters (Outputs) for Phase III Clinical PPQ Lots



(b) (4)

Inspection Performance Parameters are listed in Table 30:

Table 30. Defect Classifications of Rejected Syringes for Phase III PPQ Lots

(b) (4)

Analytical Results

Three types of samples were collected during PPQ execution: 1) routine in-process and release testing as per the formulation and filling batch production records (BPRs), 2) enhanced validation sampling to demonstrate fill uniformity, and 3) stability samples. All testing was performed at Holly Springs unless indicated otherwise. Release test sampling is performed from samples collected from the (b) (4) of filling batch and then randomly issued to the testing labs, with the exception of sterility which is tested from each of the fill segments.

Runs (b) (4) successfully met acceptance criteria for in-process and release testing. Run (b) (4) successfully met the acceptance criteria for release testing, but did not meet (b) (4) (b) (4) IPC acceptance limit of (b) (4) with the results of (b) (4) determined that the root course was process-related, i.e. the (b) (4) . But the IPC limit is set as an alert instead of a specification for the (b) (4) . The (b) (4) The investigation concluded that there was a high probability that the (b) (4) as designed and validated, therefore the out-of-limit (b) (4) did not impact batch (b) (4) or the PPQ.

Uniformity testing was executed on Runs (b) (4). Acceptance criteria for Runs (b) (4) were successfully met.

The overall acceptance criteria pre-defined in Protocol 323009 were met for the PPQ Runs (b) (4). All the deviations were investigated and concluded no impact on the PPQ or product.

Reviewer's comment: *A* (b) (4) *Audenz drug product-PFS "stability* (b) (4) *) was manufactured on* (b) (4) *with Process 3.0 PPQ* (b) (4) *using the same formulation and filling/packaging process as that for Phase III clinical lots produced with Process 1.1. The release test results were all comparable with that from the Phase III clinical lots, and the stability study is ongoing. Data from the drug product PPQ lots produced with both 1.1 and 3.0 processes are acceptable to support that the Formulation and Filling/Packaging process was validated and suitable for the manufacture of Audenz vaccine-PFS.*

(b) (4) Validation

The Audenz formulation process step requires (b) (4)

(b) (4)

(b) (4)

(b) (4) Validation and Aseptic Simulation will be reviewed by DMPQ reviewers.

Hold Time Validation

The hold time limits have been demonstrated by (b) (4) hold duration and (b) (4) . The hold time demonstrated at Holly Springs facility are indicated as:

(b) (4)

2.2.4 Control of Excipients

All excipients used in the manufacture of Audenz are (b) (4)

2.2.4.1 Specifications

The (b) (4) , is produced as part of the Audenz drug product formulation process. (b) (4) for the Audenz process. The ingredients used in the production of (b) (4) is provided in Table 32:

(b) (4)

(b) (4)

All components comply with the current edition of the (b) (4) , as applicable. Except for Water for Injection, which is manufactured on site, all ingredients are sourced from the supplier with Certificates of Analysis. All ingredients used to prepare the (b) (4) Therefore, the specifications comply with the (b) (4) .

(b) (4) .

2.2.4.2 Excipients of Human or Animal Origin

Squalene is the only substance of animal origin used in the drug product. It is derived from shark liver and it is the main component of MF59C.1 adjuvant. Squalene is a well

characterized biological substance. The chemical structure is 2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexane.

2.2.5 Control of Drug Product

2.2.5.1 Specification(s) and Justification of Specification(s)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

.

Table 34. Release Specifications for Filled Audenz Product

Test	Method	Requirements
Sterility	(b) (4)	No evidence of microbial growth
Endotoxin	(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)
Hemagglutinin antigen (HA; potency)	(b) (4)	
pH	(b) (4)	6.5 – 7.7
Squalene (b) (4)		
Squalene (b) (4)		
Number of Large Particles	(b) (4)	
Mean Particle Size	(b) (4)	

		(b) (4)

(b) (4)

Table 35. Release Specifications for Packaged Audenz Product

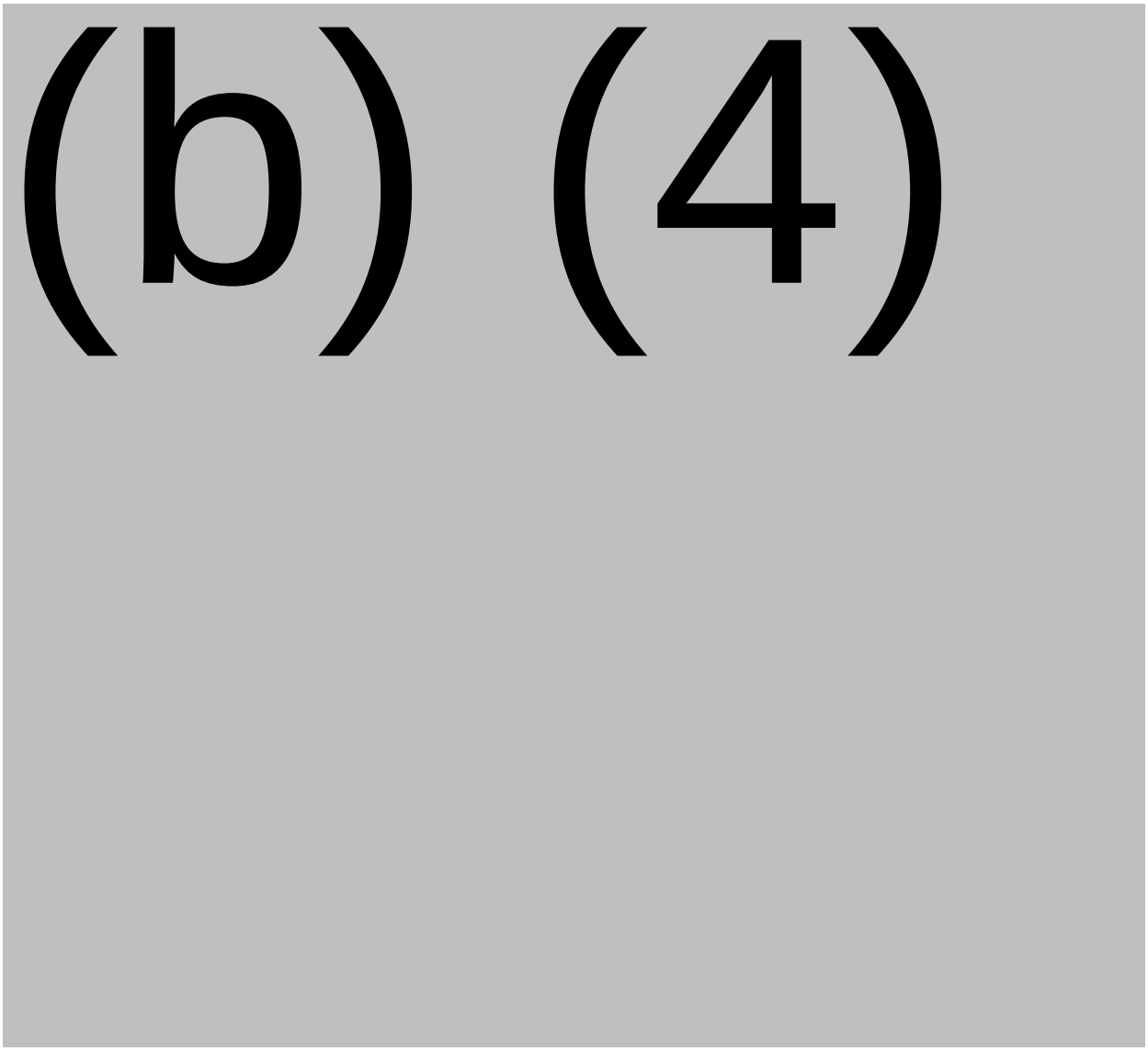
Test	Method	Requirements
HA Identification	(b) (4)	Identity Confirmed

2.2.5.2 Analytical Procedures for the Testing of Drug Product and Validation

2.2.5.2.1 Hemagglutinin antigen Assay (b) (4)

(b) (4)

:



Reviewer's comment: *The Audenz drug product is formulated with MF59C.1 adjuvant with HA at the concentration of 15 µg/ml. Seqirus indicated that* (b) (4)

Collaborated with DBSQC reviewers, we requested additional information regarding the sample preparation and the assay method validation for evaluation. Seqirus confirmed that the (b) (4)

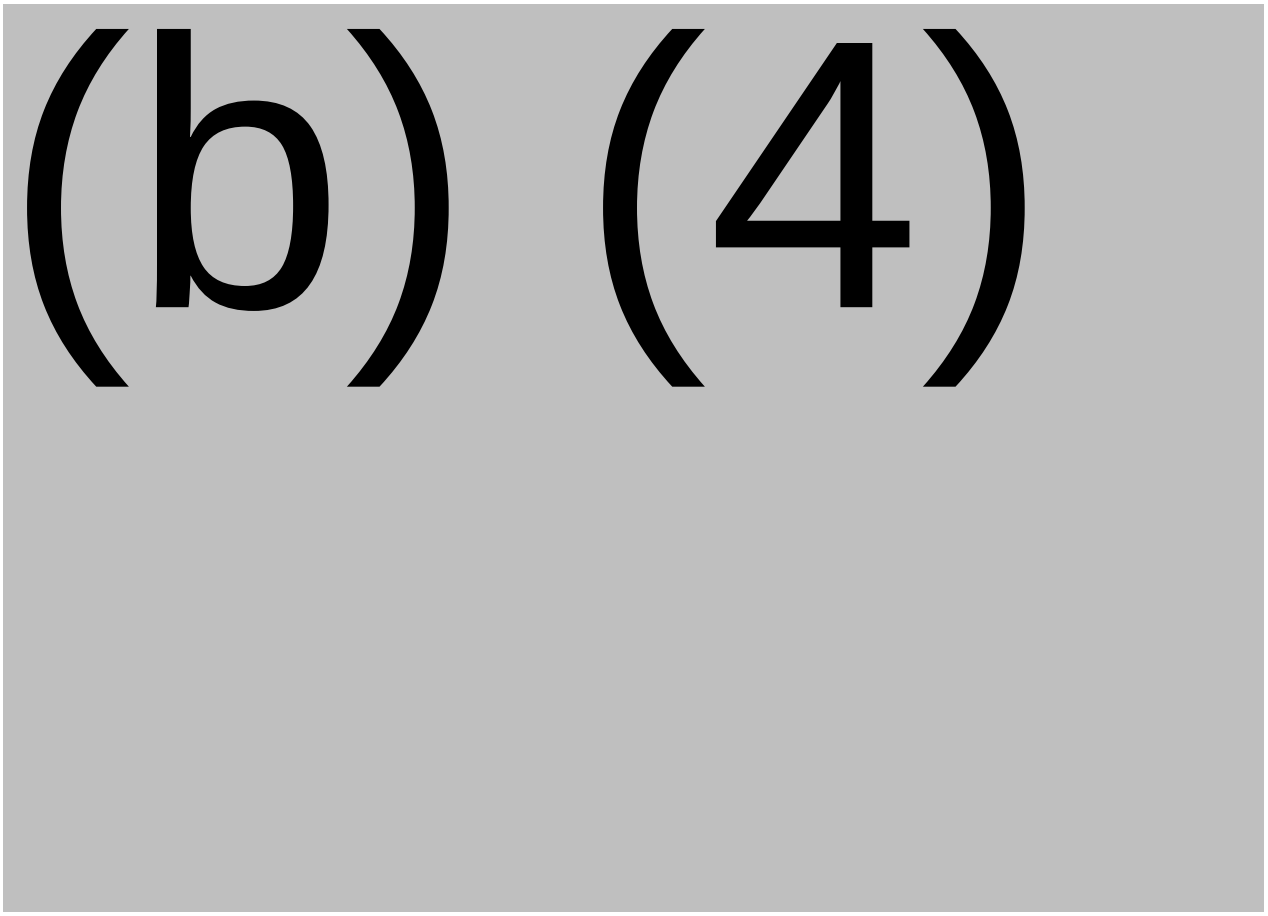
(b) (4)

The company's response in addition to the method validation data are acceptable.

Additionally, Seqirus submitted (b) (4) *of Audenz PFS samples for FDA confirmation potency testing. In CBER DBSQC laboratory, the PFS filled vaccine samples was prepared for* (b) (4) *as per Seqirus' SOP, and then* (b) (4) *was performed as per CBER test method. The potency results for the AUDENZ PFS* (b) (4) *obtained in DBSQC lab is in good agreement with that reported by Seqirus.*

2.2.5.2.2 Total DNA Content

Total DNA content is tested for release of the Audenz (b) (4) with the specification of (b) (4) using the (b) (4) method. The (b) (4) Drug Product manufactured with Process 3.0 (b) (4) was previously validated in Report Val-000082754. The attached Report VAL-000092735 summarized the results of the execution of Comparability Study for the Quantification of Residual DNA by (b) (4) for FCC Adjuvanted Drug Product under Protocol VAL-0000883840, which assessed the addition of MF59C.1 adjuvant (b) (4) DNA content compare to the previously validated matrix of the Drug Product formulated with Process 3.0 (b) (4) . The results are listed in Table 37:



Reviewer's comment: *As part of an investigation of a protocol deviation that indicated that the MF59C.1 adjuvant in matrix interfered with the* (b) (4) *for DNA quantitation in Audenz drug product,* (b) (4) *. However, this* (b) (4) *was not described in the 3.2.P.5.2 Analytical Procedures-Total DNA Content, or indicated in 3.2.P.5.3 Validation of Analytical Procedures. Upon FDA's request, Seqirus confirmed that samples and controls are each tested* (b) (4) *. The* (b) (4) *will be performed with the* (b) (4) *for all samples and controls as a* (b) (4) *, and updated the Section 3.2.P.5.2 Analytical Procedures-Total DNA Contents.*

2.2.5.4 Batch Analyses

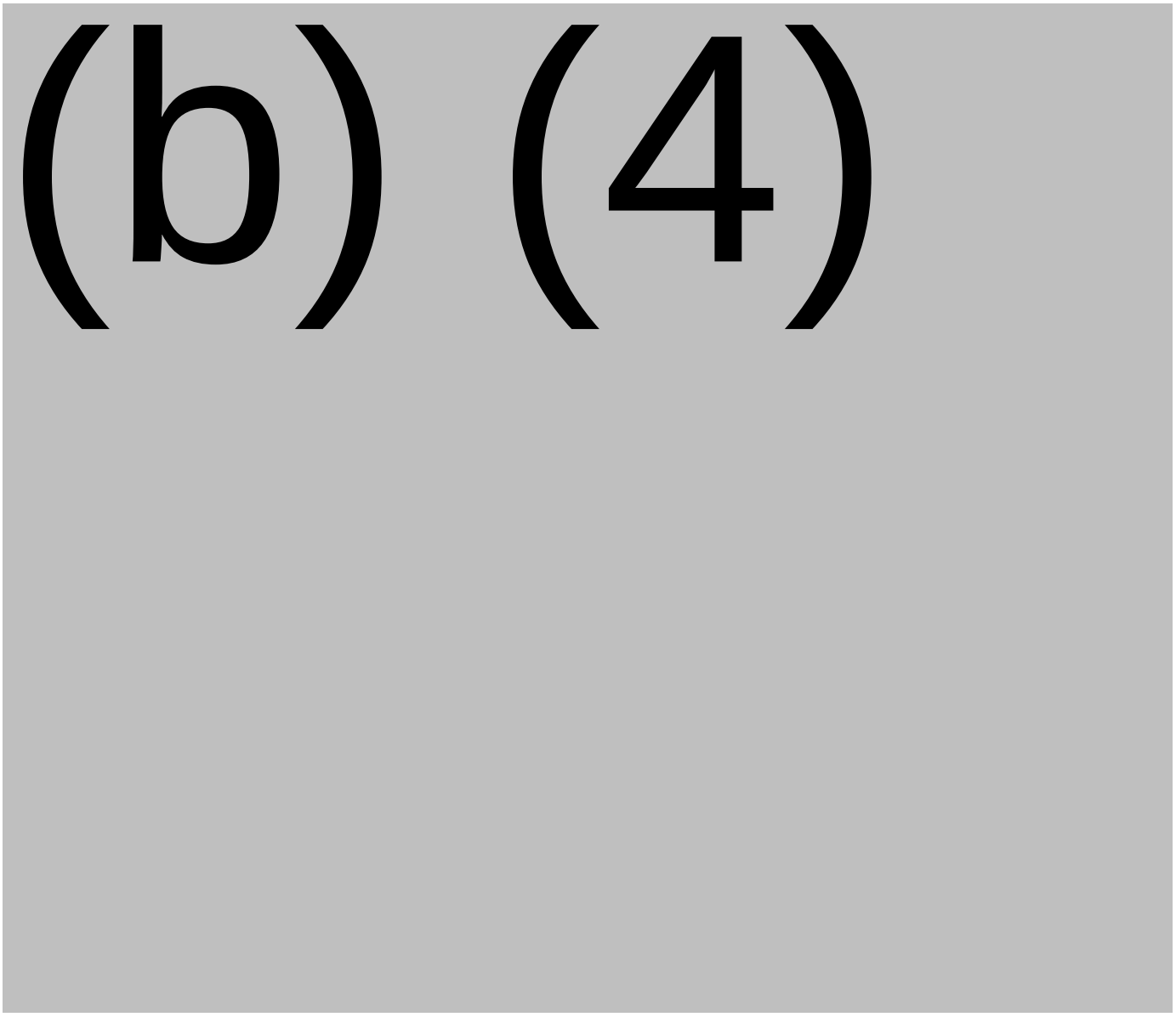
Three consecutive lots (181053, 181054, and 181675), formulated, filled and packaged in pre-filled syringes at the Holly Springs site, were used to support the Phase III clinical trial for Audenz pandemic influenza vaccine. These three clinical lots also served as the PPQ lots for the Audenz pandemic influenza vaccine.

With the new manufacturing process 3.0 for the (b) (4) of drug product (b) (4) was formulated/ filled into PFS and put on stability. The (b) (4) manufacturing process and the final container closure (except tip cap) of the PFS remain the same as in the production of the Phase 3 clinical trial materials.

Batch analysis data for the three Phase III clinical lots and the Process 3.0 Stability (b) (4) are provided in Table 38 and 39.

(b) (4)

(b) (4)



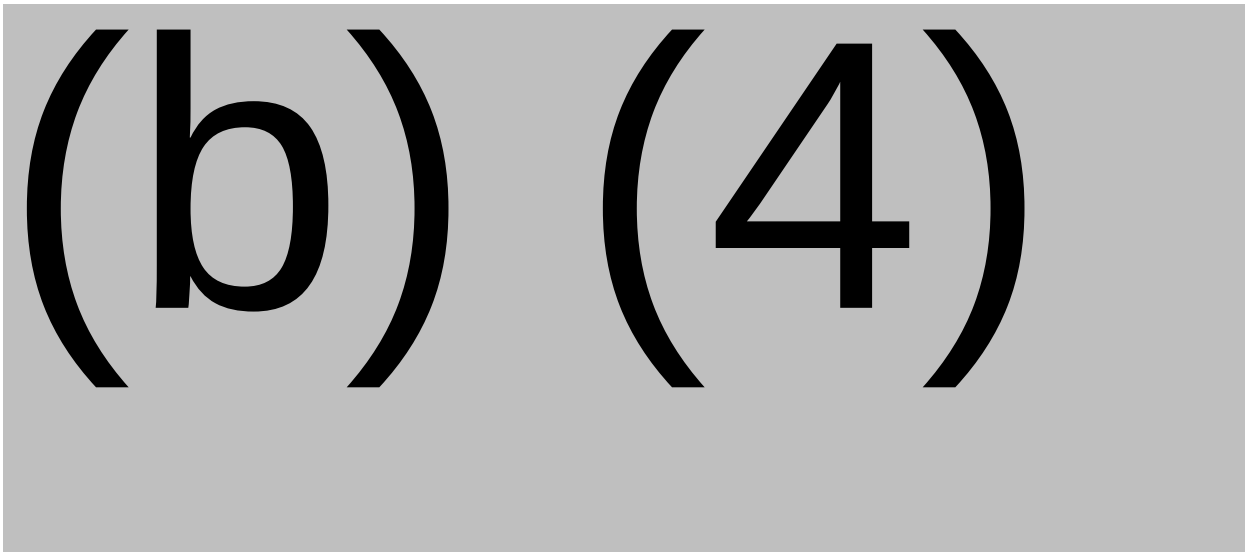
2.2.5.5 Characterization of Impurities

The Audenz drug product has been evaluated for impurities that could affect identity, strength, quality, purity, and potency of the vaccine. The only process- and product-related impurities in the drug product are those carried over from the manufacture of the H5N1c (b) (4) and MF59C.1.

Process-related impurities for FCC H5N1 (b) (4) (manufacturing process (b) (4) are evaluated in (b) (4) MF59C.1 has no process-related impurities since all raw materials added during the manufacturing process are components of the formulated adjuvant. Squalene is the primary component of MF59C.1. No solvents are used during the (b) (4) of squalene from crude shark liver oil and, being a physical process, there is no exogenous chemical impurities being introduced into

the product. Impurities inherent in squalene (not introduced during the (b) (4) process of squalene or during the MF59C.1 manufacturing process) are considered to be product-related. The MF59C.1 product-related impurities are provided in Table 40:

Table 40. Product-Related Impurities



2.2.7 Container Closure System

The Audenz vaccine is supplied as single dose pre-filled glass syringe. 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) (not made with 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 primary packaging components, which do not contain any materials of animal origin, are described in Table 41:

Table 41. Description of the Audenz PFS Primary Packaging Components

Component	Supplier	Description	Product Contact	Master File
Syringe with (b) (4)	(b) (4)	(b) (4) borosilicate glass, colorless, (b) (4) (b) (4)	Yes	DMF (b) (4)
Tip Cap	(b) (4)		Yes	DMF (b) (4)
Plunger Stopper	(b) (4)	Bromobutyl rubber (b) (4)	Yes	DMF (b) (4)

Additionally, (b) (4) the barrel and the stopper to provide easy and smooth plunger stopper motion. The (b) (4) used for stopper is a (b) (4) , conforming to the (b) (4)

2.2.8 Stability

2.2.8.1 Stability Summary and Conclusion

Stability studies were performed on three Audenz Phase III clinical trial lots (181053, 181054 and 181675) using drug substance manufactured under Process 1.1 and (b) (4) drug product (b) (4) using drug substance manufactured with Process 3.0, and filled in 1.0 mL (b) (4) syringes to support licensure of the Audenz pandemic influenza vaccine and to confirm the (b) (4)-month shelf life when stored at 2 - 8°C.

In addition, the drug product (b) (4) was served to demonstrate comparability between drug product batches formulated with (b) (4) lots manufactured with different processes (1.1 and 3.0).

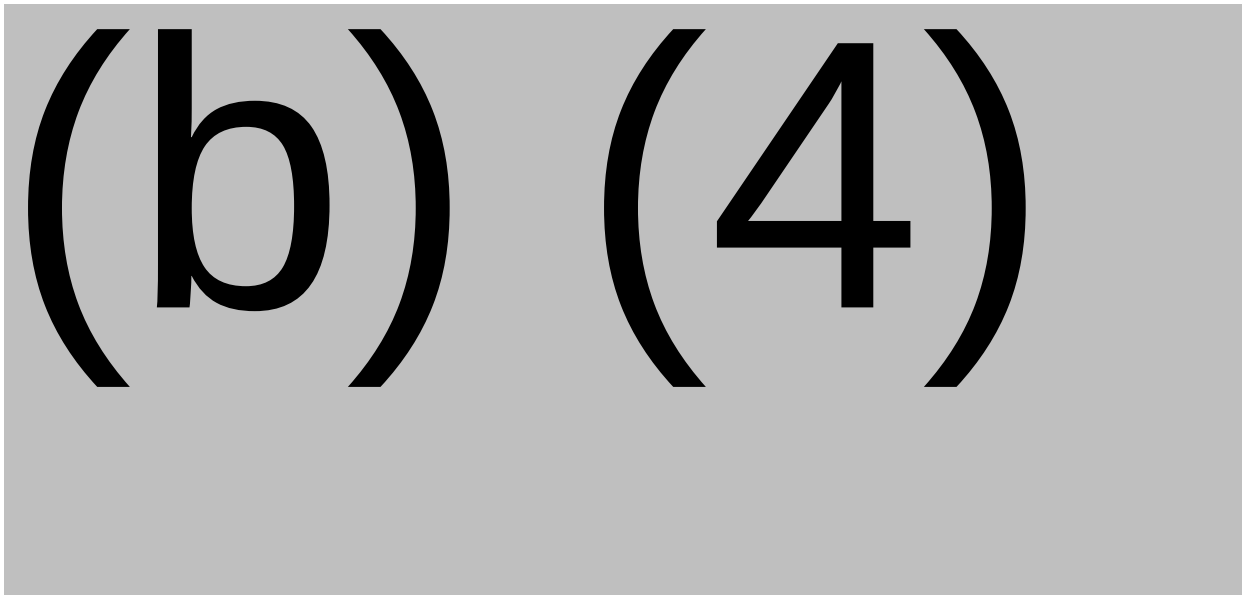
Container for Phase III Clinical Lots: 1 mL (b) (4) syringe with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal.

Container for drug product Lot (b) (4) : 1 mL (b) (4) syringe with (b) (4) tip cap, (b) (4) bromobutyl latex-free plunger stopper and (b) (4) overseal.

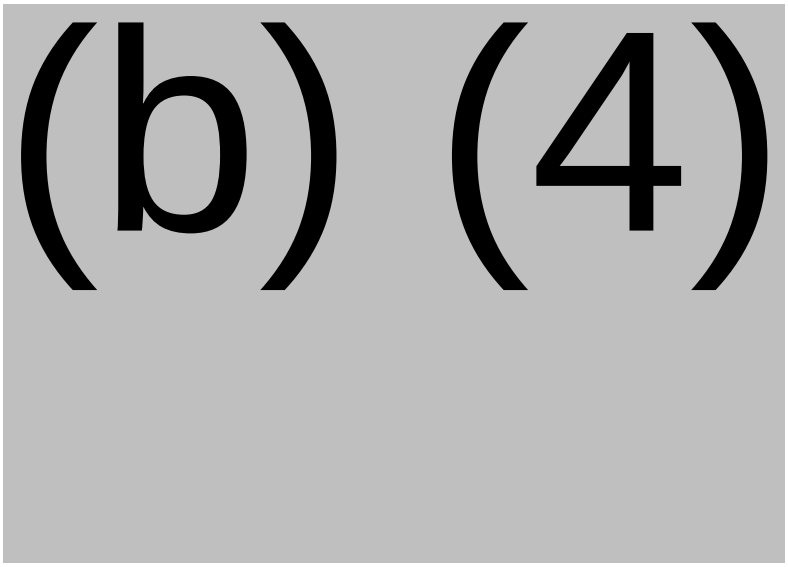
Stability Storage Conditions: Long-term storage at 2 - 8°C for up to (b) (4) months; accelerated storage at (b) (4) for up to 6 months.

Stability indicating Parameters: Current analytical procedures and specifications in Stability Study to evaluate the safety and quality of Audenz pandemic vaccine are listed as following:

Table 42. Stability-Indicating Parameters



2.2.8.3 Stability Data



Reviewer's comment: *The initially proposed shelf life for the Audenz pandemic influenza vaccine in PFS is* (b) (4) *months. To support the shelf life,* (b) (4) *-month stability data from the three Phase III trial PPQ lots are included in this BLA submission. The stability study for the Process 3.0 lot is ongoing, and 12-month stability data was provided in Amendment 125692/0.21 (August 2, 2019), indicating that all the stability test results were within specifications. However, the* (b) (4) *-month shelf life must be supported by satisfactory* (b) (4) *-month stability data from the Process 3.0 stability batch. In the late cycle meeting with FDA on October 9, 2019, the company committed to submit a supplement to update FDA with the* (b) (4) *month stability dada when the study result is available. The shelf life for Audenz is currently approved as 12 months.*

2.2.8.2 Post-Approval Stability Protocol and Stability Commitment

A minimum of (b) (4) Audenz commercial pre-filled syringe (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 - 8°C. The stability testing plan is presented in Table 43:

Table 43. Stability Test Plan for (b) (4) Commercial Batches

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: *The Post-Approval Stability Protocol Plan is acceptable.*

3 ENVIRONMENTAL ASSESSMENT

A request for a Categorical Exclusion from an Environmental Assessment under 21 CFR § 25.31(c) was submitted to the BLA. FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4 VALIDATION OF HEMAGGLUTINATION INHIBITION (HAI) ASSAY

Seqirus conducted clinical studies in support of the BLA for Audenz. The primary endpoints for the immunogenicity were measured by a titer of hemagglutination inhibition (HAI) assay conducted at (b) (4) .

In the Amendment 59 to IND 13536, Seqirus submitted the HAI assay validation protocol. On May 8, 2018, the assay validation report (b) (4) was included in Amendment 76 to IND 13536. The results of the validation studies were listed in the following table:

(b) (4)

(b) (4)

:

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