Summary Basis for Regulatory Action (SBRA)

Date: January 31, 2020

From: Brenda Baldwin, Ph.D., Chair of the Review Committee

BLA/ STN#: 125692/0

Applicant Name: Seqirus, Inc.

Date of Submission: Biologics License Application (BLA) (initial portion submitted on December 14, 2018, received on December 17, 2018, and final portion submitted on January 31, 2019, received on February 1, 2019)

Goal Date: February 1, 2020

Proprietary Name/ Established Name: Audenz/Influenza A (H5N1) Monovalent Vaccine, Adjuvanted

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 at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority: Marion F. Gruber, Ph.D., Director, Office of Vaccines Research and Review

□ **I concur with the summary review.**
□ **I concur with the summary review and include a separate review to add further analysis.**
□ **I do not concur with the summary review and include a separate review.**

Document title	Reviewer name, Document date
CMC Reviews • CMC (product office) • CMC (product office) • Facilities review and establishment Inspection Waiver (OCBQ/DMPQ)	Xing Li, Ph.D. – Jan 21, 2020 Marina Zaitseva, Ph.D. – Jan 31, 2020 Obinna Echeozo, Ph.D. – Dec 26, 2019
Clinical Reviews • Clinical (product office) • Postmarketing safety epidemiological review (OBE/DE) • BIMO	Cynthia Nolletti, M.D. – Jan 21, 2020 Christopher Jason, M.D. – Jan 15, 2020 Anthony Hawkins, M.S. – Sep 13, 2019
Statistical Reviews • Clinical data • Non-clinical data	Ye Yang, Ph.D. – Jan 10, 2020 Zhong Gao, Ph.D. – Jan 10, 2020
Pharmacology/Toxicology Review • Toxicology/Developmental toxicology (product office)	Andrew O'Carroll, D.V.M. – Jan 21, 2020
Labeling Reviews • APLB (OCBQ/APLB) • Carton/Container (product office)	Sonny Saini, Pharm.D. – Jan 21, 2020 Oluchi Elekwachi, PharmD, MPH – Nov 15, 2019 Daphne Stewart – Jan 28, 2020
Testing Reviews (OCBQ/DBSQC) • Method and Analytical Chemistry • Results	Selwyn Wilson David, PhD., Simleen Kaur, M.S., Hsiaoling Wang, Ph.D., Manju Joshi, Ph.D. – Dec 17, 2019 Varsha Garnepudi, Ph.D. – Dec 4, 2019 Salil Ghosh, Ph.D. and Emnet Yitbarek, Ph.D. – Oct 25, 2019 Hyesuk Kong, Ph.D. and Josephine Wulu, M.S. – Aug 26, 2019 Darya Melnyk, M.S. and Manju Joshi, Ph.D. – Dec 10, 2019

1. Introduction

Influenza A (H5N1) Monovalent Vaccine, Adjuvanted, also known as Audenz, is indicated for active immunization against 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 who are at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Audenz consists of an inactivated, subunit monovalent influenza virus antigen produced in Madin Darby Canine Kidney (MDCK) cells and an oil-in-water emulsion adjuvant (MF59C.1 adjuvant). The antigen is manufactured in Holly Springs, North Carolina (N.C.) according to the Flucelvax seasonal influenza virus vaccine process licensed in the United States (U.S.). The MF59C.1 adjuvant is manufactured in Holly Springs, N.C. MF59C.1 adjuvant is also present in the seasonal influenza vaccine, Fluad, which has been approved for use in individuals 65 years of age and older in the U.S. since 2015. The final drug product consists of combined antigen and adjuvant that is filled into a 1.0 mL syringe at the Holly Springs, N.C. facility. The dosing regimen in persons ≥ 6 months is two doses of 7.5 μg H5N1 hemagglutinin (HA) (b) (4) MF59 adjuvant (total volume of 0.5 mL per single dose) administered intramuscularly (IM) 21 days apart.

Audenz is an injectable emulsion for intramuscular use supplied in a 1.0 mL single-dose pre-filled syringe. Each 0.5 mL dose contains:

- 7.5 micrograms (μg) hemagglutinin (HA) of influenza – subtype (A/H5N1)
- 9.75 mg squalene
- 1.175 mg sorbitan trioleate
- 1.175 mg polysorbate 80
- 0.66 mg sodium citrate dihydrate
- 0.0425 mg citric acid monohydrate
- (b) (4)

The vaccine does not contain preservative. The dating period for Influenza A (H5N1) Monovalent Vaccine, Adjuvanted shall be 12 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of initiation of final fill of the formulated drug product into final containers.

2. Background

For vaccines against influenza A virus subtypes of pandemic potential that are not included in the seasonal influenza vaccines (i.e., other than H1 and H3), clinical disease endpoint efficacy studies are not feasible in the absence of circulation of the pandemic influenza virus strain. The licensure pathways for pandemic influenza virus vaccines are described in the FDA Guidance for Industry “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines” (May 2007) and can be summarized as follows.

If a manufacturer holds a U.S. license for an approved Biologics License Application (BLA) for a seasonal inactivated influenza vaccine under either the provisions in 21 CFR § 601.2 or the accelerated approval provisions with the vaccine's clinical benefit having been confirmed in a postmarketing study, and the manufacturing process used for the production of the pandemic vaccine is the same as that for the licensed seasonal

influenza vaccine, clinical immunogenicity trials would be needed to determine the appropriate dose and regimen of a pandemic influenza vaccine candidate. These trials should also include an assessment of safety. Sponsors are expected to collaborate with the FDA and other governmental agencies on plans to collect additional effectiveness and safety information when the vaccine is used. This pathway is referred to as traditional approval.

For pandemic influenza vaccines manufactured by a process that is not licensed in the U.S., the accelerated approval pathway (21 CFR § 601.41) is another option described in the FDA Guidance for Industry. Accelerated approval will be based on adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Approval under this pathway will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit. Postmarketing studies must also be adequate and well-controlled and should be conducted with due diligence.

The Biomedical Advanced Development and Research Authority (BARDA) of the U.S. Department of Health and Human Services (DHHS) contracted Novartis Vaccines (transitioned to Seqirus, Inc., November 2015) to develop and submit for licensure a cell culture-derived H5N1 influenza virus vaccine with antigen-sparing potential for inclusion in the U.S. National Stockpile. The clinical development of this MF59-adjuvanted cell culture-derived H5N1 influenza virus vaccine was conducted under IND 13536, which was submitted on October 24, 2007. Fast Track designation was granted in December 2015.

At a Type C meeting between the Center for Biologics Evaluation and Research (CBER) and Novartis Vaccines on May 7, 2014, it was agreed that development of the pandemic H5N1 (b) (4) process (Process 2.0 for the Phase 3 clinical trial material) could be aligned with the seasonal (b) (4) Flucelvax process 1.1 to support submission of the Audenz BLA, if comparability between the drug substance processes was demonstrated.

On June 21, 2018, CBER held a pre-BLA meeting with Seqirus to discuss the manufacturing, pre-clinical and clinical information to be included in the BLA submission for the Audenz vaccine. Seqirus indicated that the plans had changed since the May 7, 2014, Type C meeting and the BLA would include H5N1 drug substance data for product made by Process 3.0 to be consistent with the Flucelvax current manufacturing Process 3.0 licensed on July 27, 2018 (STN 125408/274). It was agreed that comparability between Phase 3 drug substance manufactured using Process 1.1 and drug substance manufactured by Process 3.0 would be provided, as well as data demonstrating comparability between Processes 2.0 and 3.0 (see comparability discussion below in Section 3.e.). During this meeting, CBER also outlined licensure options for the approval of Audenz and use in various age ranges as follows. If licensed based on immunogenicity data alone to support vaccine effectiveness, approval of

Audenz for use in adults ≥18 years would be granted according to the traditional regulatory pathway because seasonal Flucelvax (trivalent formulation, TIVc) and Flucelvax Quadrivalent (QIVc) have full or "traditional" approval. However, because seasonal TIVc and QIVc were approved in children and adolescents 4 years to <18 years of age according to accelerated approval regulations (21 CFR 601.41) and because seasonal TIVc and QIVc are not approved in children <4 years of age, approval of Audenz in persons 6 months to <18 years would be granted according to accelerated approval regulations. CBER also agreed to a rolling BLA in this meeting.

On February 1, 2019, CBER received the final submission of the rolling BLA for Audenz, which was assigned the STN 125692. The PDUFA Goal Date is February 1, 2020. The BLA submission includes the following clinical data:

- immunogenicity and safety data from one phase 3 clinical trial (V89_18 conducted under IND 13536) in adults 18 years of age and older;
- immunogenicity and safety data from two phase 2 studies and one phase 1/2 study (V89_04, V89_13 and V89P1) conducted in adults; and
- immunogenicity and safety data from a third phase 2 trial (V89_11) conducted in children 6 months to < 18 years of age.

A summary of the issues and considerations raised by the various reviewers and how they were resolved can be found below in the relevant sections.

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

The Process 2.0 lots of Influenza A/turkey/Turkey/1/2005 are in the current HHS Stockpile which may or may not be used during a declared pandemic. Upon request of the U.S. Government and receipt of a new candidate vaccine virus (CVV) during a declared pandemic, Seqirus will commence manufacture of the drug substance (according to Process 3.0) and drug product in accordance with the information provided in this BLA. MF59C.1 adjuvant is stored separately at (b) (4) in sterile (b) (4) . It is anticipated that the vaccine strain would be matched to the circulating A/H5N1 strain via a strain change supplement.

Upon release of the adjuvanted vaccine, the finished, labelled, packaged product will be shipped via a temperature-controlled truck, which is validated for pharmaceutical transport, to destinations as directed by the Centers for Disease Control and Prevention (CDC), which has the authority for distributing and allocating pandemic vaccines in the U.S.

a) Product Quality

The information provided in the BLA for Audenz demonstrates that the manufacturing process is well controlled with appropriate validations. Moreover, adequate quality control testing has been conducted and stability data have been accrued with Audenz.

Antigen Drug Substance (DS)
The antigen DS consists of a (b) (4)

Control of Materials and Critical Steps: Critical elements of the product information included in the BLA are related to the inactivation of the influenza virus, determination of the HA potency for formulation, validation of the manufacturing process for the final vaccine product, development of appropriate quality control testing plan to ensure manufacturing consistency and final container product quality, (b) (4) and to support the requested dating period for the product once released for distribution. Data and information included in the BLA demonstrate that the manufacturing process is well controlled. (b) (4) .

Cell Production: The MDCK (b) (4) cells were derived from canine kidney cells. (b) (4) The safety and quality of the cell banking system was thoroughly evaluated by the FDA under the Flucelvax BLA (STN 125408).

CVV Production: The influenza reference virus NIBRG-23 used for manufacture of lots evaluated in clinical trials submitted to this BLA is a reverse genetics virus containing (b) (4) HA genes from A/turkey/Turkey/1/2005 (H5N1) and

(b) (4)

Influenza Working Virus Seed: (b) (4)

Storage of Working Virus Seed: The WVS is stored at (b) (4) .

Raw Materials: The virus is produced in animal-derived MDCK cells which has negligible risk of TSE contamination. The other raw materials used in the manufacture of the antigen DS are from non-animal origin.

Specifications and Methods: The proposed tests, specifications and methods for the release of the antigen DS are presented in Table 1 and are similar to those applied for the Flucelvax seasonal vaccine (b) (4) approved under BLA 125408.

Table 1. Tests, Methods, and Specifications for Routine Control of the Audenz Antigen Drug Substance

(b) (4)

(b) (4)

(b) (4)

MF59C.1 Adjuvant

Manufacturing: The MF59C.1 adjuvant is an oil-in-water emulsion composed of an oil phase containing one biodegradable oil, squalene, mixed with an aqueous phase consisting of sodium citrate dehydrate and citric acid monohydrate. Polysorbate 80 and sorbitan trioleate are used as surfactants to stabilize the oil/water interface. The emulsion is (b) (4) The only component of animal source is squalene, which is prepared from shark liver oil by (b) (4) Shark liver does not fall under the scope of the Transmissible Spongiform Encephalopathy (TSE) guidelines (according to EMA's guidance 410/01, fish is not considered a TSE-relevant animal species).

(b) (4)

(b) (4)

Drug Product (DP)
The final formulation of Audenz DP, 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 (involves (b) (4)) with the addition of the (b) (4) water for injection (WFI); pH (b) (4) required volume of WFI and MF59C.1 (b) (4) Final filling of the vaccine into 1.0 mL syringes is performed in an aseptic manner.

Controls for (b) (4) Production: (b) (4) are characteristics of the product that are defined and measured through appropriate validation and control of operational parameters and performance attributes.

Stability of DP (b) (4): The DP (b) (4) may be (b) (4) (referred to as the DP Final Container, DP FC).

Product Quality: The analytical methods and their validations and/or qualifications reviewed for the Audenz (b) (4) drug product were

found to be adequate for their intended use. The proposed specifications and testing methods for the routine control of Audenz DP (b) (4) FC are shown in Table 2.

Table 2. Tests, Methods, and Specifications for Quality Control Release of the Audenz Drug Product (b) (4) Final Container

Test (Method)	(b) (4)	**Audenz Drug Product Final Container (PFS) Specifications**
HA Antigen (b) (4)	(b) (4)	(b) (4)
Total DNA Content (b) (4))	(b) (4)	N/A
Squalene (b) (4)	(b) (4)	Confirmed
Squalene (b) (4)	(b) (4)	(b) (4)
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Appearance (Visual Inspection)	(b) (4)	White homogeneous suspension
Visible Particulates (b) (4)	(b) (4)	Essentially free of visible particulates
Sub-Visible Particles (b) (4)	(b) (4)	(b) (4)
pH (b) (4)	(b) (4)	Between 6.5 and 7.7
(b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)	(b) (4)	Absence of growth

Test (Method)	(b) (4)	Audenz Drug Product Final Container (PFS) Specifications
(b) (4)		
(b) (4)	(b) (4)	(b) (4)
Endotoxin Content	(b) (4)	(b) (4)
(b) (4)		
Extractable volume	(b) (4)	(b) (4) 0.50 mL
(b) (4)		

N/A = not applicable; NLT = no less than; NMT = no more than

(b) (4)

Final Container: The drug product is filled into single-dose (b) (4) 1 mL (b) (4) glass syringes with (b) (4) (styrene-butadiene rubber formulation (b) (4) The syringe and (b) (4) are closed with (b) (4) bromobutyl plunger stoppers (b) (4). 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 (b) (4) is lodged in a (b) (4) which protects the tip cap from damage, and it is screwed into the (b) (4) adaptor. The tip cap is supplied (b) (4).

This container closure and its qualification (via (b) (4) CCIT method) 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.

The packed product release test includes HA identity (b) (4). Table 3 shows the composition of the Audenz DP FC per 0.50 mL dose.

Table 3. Quantitative Composition of the Audenz DP FC per 0.50 mL Dose

INGREDIENTS	QUANTITY per 0.50 mL	FUNCTION
Antigen: Split-virion Monovalent, A/H5N1	7.5 µg HA	Antigen
Adjuvant: MF59C.1		
Squalene	9.75 mg	Oil
Polysorbate 80	1.175 mg	Surfactant
Sorbitan Trioleate	1.175 mg	Surfactant

Sodium Citrate Citric Acid	0.66 mg 0.04 mg	Buffer Buffer
(b) (4) Water for Injection	(b) (4)	(b) (4) Diluent

(b) (4)

Residuals: Audenz DP FC (in single dose pre-filled syringe) may contain trace amounts of protein other than HA (≤ 30 μg) including MDCK cell protein (< 3.15 μg), MDCK cell DNA (≤ 10 ng), additional PS80 (≤ 0.375 mg), CTAB (≤ 4.5 μg), and BPL (≤ 0.1 μg), all of which are used in the manufacturing process of the Monovalent (b) (4).

Extractables/Leachables: No extractables or leachables study in the syringes was performed with the Audenz DP because previous (b) (4)-month leachable study analyses with Fluad in the glass syringe with (b) (4) plunger stopper and (b) (4) tip cap raised no safety concerns. The (b) (4) tip cap to be used in commercial lots has been determined to be equivalent to the (b) (4) tip cap used in the phase 3 clinical trials and approved for Fluad use on September 29, 2017 (125510/48).

Dating Period Evaluation: The proposed expiry dating period for Audenz DP FC was (b) (4) months from the date of filling when stored at 2 to 8ºC, protected from light; however, because Seqirus only had 12 months of stability data at the time of this approval, the expiry dating period of Audenz DP FC is 12 months when stored at 2 to 8ºC. (b) (4) PFS drug product lot has been manufactured with Process 3.0 (b) (4) material and has been placed on stability study. Acceptable (b) (4)-month stability data from the Process 3.0 stability batch would be required to support a supplement to the BLA to extend the expiry dating period to (b) (4)-months. If additional batches of DP FC are manufactured for a pandemic, Seqirus proposes to place at a minimum (b) (4) lots of Audenz DP PFS into a stability program at 2 to 8ºC for up to (b) (4) months with the sampling time points at 0, 3, 6, 9, 12 (b) (4) months. The evaluation under the stability program will consist of the following parameters: (b) (4)

Cartons/Containers: Audenz is pre-filled into syringes, each containing a 0.5 mL single dose. The syringes are labeled and packaged into a carton that contains 10 syringes. Final cartons of Audenz are stored at 2 to 8°C until release and shipment for distribution.

The following section describes CMC issues identified during CBER's review and how they were resolved:

- In the original BLA, Seqirus submitted information to support a (b) (4) vial (b) (4) presentation for Audenz, which was to be presented as a liquid ready for injection in a (b) (4) glass (b) (4) vial with a (b) (4) bromobutyl stopper, labeled as (b) (4) mL of adjuvanted antigen solution for (b) (4) doses (0.5 mL per human dose), and would contain the (b) (4) in addition to the same concentration of components as in the PFS. This (b) (4) presentation was not used for the clinical trial material nor was it used in the DART study. Seqirus reported that at the 6-month and 9-month stability timepoints for the (b) (4) PPQ (b) (4) batches, (b) (4) were found in the (b) (4) samples, though all testing results were within specifications for all batches. Seqirus conducted a series of investigations that indicated that the particulate formation could be attributed to coexistence of (b) (4) MF59C.1 adjuvant which was probably reacting with the bromobutyl stopper of the vial, but that results were inconclusive to date. Because Seqirus did not have sufficient time to resolve this issue, the (b) (4) was withdrawn from consideration in the original BLA on October 22, 2019.
- During the BLA review, the (b) (4) method for (b) (4) of viral inactivation was improved for the H5N1 virus and a validation report was provided; however, it was determined that the test lacked a (b) (4) We suggested that the (b) (4) without compromising the assay (b) (4) Seqirus agreed that if (b) (4) An acceptable validation protocol was provided on January 14, 2020. Seqirus has agreed to implement the (b) (4) following successful validation of the revised method. The validation report is (b) (4)
- The Drug Substance Release Specification (b) (4) However, this hypothetical assumption was not acceptable as supportive data. Upon FDA's request, Seqirus eventually revised the Specification for (b) (4)

- (b) (4)
- For the post-approval stability protocol for a commercial pandemic (b) (4) CBER agreed with this approach.
- The proposed Specification for (b) (4) Upon FDA's request, Seqirus revised the Specification for (b) (4) consistent with that for Flucelvax.
- Potency Evaluation: (b) (4)

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facility Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of Audenz is listed

in Table 4 below. The activities performed and inspectional histories are also noted in Table 4.

Table 4: The Facility Responsible for the Manufacture of Audenz

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
Drug Substance Manufacturing and Testing. *Drug Product Formulation, Fill/Finish, Labeling, Packaging and Testing* Seqirus, Inc. 475 Green Oaks Parkway Holly Springs, NC 27540 United States	3007867647	080102141	Waiver	Team Biologics, June 11-18, 2018 VAI

CBER waived the pre-license inspection based on the compliance history of the facility, and the manufacturing process similarities between Audenz and the already licensed Flucelvax. Both products are manufactured at the Seqirus Holly Springs facility using the same critical equipment. Team Biologics performed surveillance inspections of the facility from June 11-18, 2018. All FDA 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

d) Environmental Assessment

A request for a Categorical Exclusion from an Environmental Assessment under 21 CFR § 25.31(c) was submitted to the BLA. The 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.

e) Product Comparability

Process 3.0, the licensed third generation manufacturing process for cell-based drug substance production, is to be used for commercial Audenz DS manufacture. This process is slightly different from the processes used for the Phase 1 clinical trial material (Process 1.0, first generation process), the Phase 2 trial material (made with Process 2.0), and the Phase 3 clinical trial material (made with Process 1.1, a second-generation process that was also used in the original licensed Flucelvax under STN 125408).

To support licensing Process 3.0 for Audenz production, Seqirus provided data from (b) (4) full-scale H5N1 PPQ batches to demonstrate equivalence between the processes and comparability between products from the different processes. The comparability assessment results concluded that Process 1.1 and Process 3.0 of the H5N1

manufacturing processes were comparable, and also that Process 2.0 was comparable to Process 3.0.

The development of the pandemic (b) (4) (Drug Substance) initially started with Process 1.0 (b) (4) Due to significant (b) (4) several modifications were needed. The modified process, Process 1.1, was initially implemented for the seasonal influenza vaccine, Flucelvax. Despite improvements at (b) (4) continued for the pandemic vaccine which prompted the development of an alternative (b) (4) step that did not have (b) (4) was implemented for the pandemic (b) (4) process as the (b) (4) This change resulted in Process 2.0.

The key changes to the (b) (4) process from Process 1.1 to Process 3.0 included the change in (b) (4) , implementation of (b) (4) . In addition, the in-process controls and critical quality attributes were maintained to mitigate the potential risks to product quality and safety. The (b) (4) manufacturing key changes included the (b) (4) to improve product quality and safety.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Pre-clinical toxicity studies were conducted in order to identify and evaluate any toxicity findings following the administration of Audenz. These included a GLP-compliant repeat-dose toxicology study and a developmental and reproductive toxicity (DART) study performed in rabbits to evaluate the vaccine formulation considered in this BLA. No clinically-significant toxicological findings were found which would preclude the use of this vaccine in its intended human population at the intended human dose. In the repeat-dose study, treatment-related findings were limited to mild increases to fibrinogen and globulins on clinical pathology assessments, minimal to mild splenic follicular hyperplasia and minimal evidence of inflammation at injection sites. These findings were all considered anticipated sequelae of the intended immune response rather than as a sign of toxicity and none had any clinical effect on the study rabbits. In the DART study, there was no treatment-related mortality or any treatment-related effects on female fertility and mating performance, fetal development, parturition or postnatal development up until 29 days postpartum.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology or pharmacokinetic studies were performed as part of the clinical development program for Audenz.

6. CLINICAL/STATISTICAL

a) Clinical Program

Five clinical studies were conducted to support licensure of Audenz (Table 5):

Table 5. Clinical Studies Supporting Licensure of Audenz

Study	N	Age	Description
V89P1 (NCT00812019) 2008/2009 season	753	18 to 40 years	A Phase 1/2, randomized, observer-blind, 12-arm multicenter dose-ranging study to select one of 12 antigen-adjuvant combinations
V89_04 (NCT01776541) 2013/2014 season	979	18 through 64 years	A Phase 2, randomized (1:1), observer-blind, two-arm multicenter study to select one of two, half (3.75 μg HA/0.125 mL MF59) vs. full (7.5 μg HA/ 0.25 mL MF59) doses
V89_11 (NCT01776554) 2013/2014 season	662	6 months through 17 years	A Phase 2, randomized (1:1), observer-blind, two-arm multicenter study to select one of two (half vs. full) doses
V89_13 (NCT01766921) 2013/2014 season	1393	≥65 years	A Phase 2, randomized (1:1), observer-blind, two-arm multicenter study to select one of two (half vs. full) doses
V89_18 (NCT02839330) 2016/2017 season	3196	≥18 years	A Phase 3, randomized (1:1:1:1), observer-blind, placebo-controlled multicenter study to evaluate lot consistency, and immunogenicity and safety of 2 full doses of Audenz

As mentioned previously, the monovalent antigen suspension of Audenz is manufactured according to the same process as that used to produce the antigens contained in Flucelvax, a U.S.-licensed seasonal influenza virus vaccine. The effectiveness of Audenz was inferred from serum hemagglutination inhibition (HAI) antibody responses induced by vaccination with Audenz, as well as clinical disease endpoint efficacy results in adults 18 through 49 years of age obtained in Flucelvax Study V58P13 (under STN 125408).

The HAI assay was used to detect HAI antibodies in serum samples from trial participants. The HAI assay used for the evaluation of clinical trial specimens was adequately validated and was performed using appropriate controls. Blood samples for

HAI titers were collected prior to each vaccination (Day 1 and Day 22) and on Days 43 and 183 or 366/387.

V89P1
Twelve different formulations of vaccine (3.75, 7.5 or 15 μg HA adjuvanted with 0%, 25%, 50% (half dose), or 100% (full dose) MF59) were evaluated. The study was performed with a different H5N1 vaccine virus strain from the other studies submitted to this BLA, i.e., A/Indonesia/5/2005/PR8-IBCDC-RG2. All adjuvanted groups except the 3.75 μg HA/25% MF59 met the seroconversion rate (SCR) endpoint. None of the unadjuvanted groups achieved seroconversion. None of the treatment groups achieved a lower bound (LB) of the two-sided 95% CI for % HAI ≥1:40 of ≥70%.

V89_04
The study supported the need for two doses, as well as evaluation of the 7.5 μg dose for adults in Phase 3.

V89_13
The study supported the need for two doses, as well as evaluation of the 7.5 μg dose for adults in Phase 3.

V89_18
The co-primary immunogenicity objectives to be analyzed in a stepwise fashion were lot-to-lot consistency, and then % of subjects with post-vaccination HAI titer of ≥ 1:40 on Day 43. The pre-specified criteria for demonstration of equivalency of three lots of Audenz and % of subjects with post-vaccination HAI titer of ≥ 1:40 met CBER criteria on Day 43 (21 days after 2nd dose) in both age groups (Table 6).

Table 6: Percentage of Subjects with HAI Titer ≥1:40 at Day 1 and Day 43 by Age Group, V89_18 (Per Protocol Set)

Age Group	**18 to <65 years**	**18 to <65 years**	**≥65 years**	**≥65 years**
Treatment	**Audenz N=1116**	**Placebo N=372**	**Audenz N=1133**	**Placebo N=367**
Day 1, N	N=1116	N=372	N=1133	N=367
Day 1 % HAI ≥1:40 (95% CI)	13.0 (10.7, 15.6)	15.0 (11.5, 19.4)	27.8 (24.9, 30.9)	24.5 (20.1, 29.6)
Day 43, N	N=1076	N=349	N=1080	N=351
Day 43 % HAI ≥1:40 (95% CI)	95.0 (93.4, 96.2)	8.5 (5.9, 12.1)	85.7 (83.3, 87.9)	20.8 (16.6, 25.8)

HAI=hemagglutinin inhibition; %HAI ≥1:40=percentage of subjects with post-vaccination HAI titer of at least 1:40; N=number of subjects in the Per Protocol Set at the specified time points; CI=confidence interval.HAI=hemagglutinin inhibition; % HAI ≥1:40=percentage of subjects with post-vaccination HAI titer of at least 1:40; N=number of subjects in the Per Protocol Set at the specified time points; CI=confidence interval.

Interestingly, although subjects were considered immunologically naïve to the H5N1 virus, baseline GMTs were above zero, possibly explaining why % HAI ≥1:40 and SCRs were not equal within treatment and age groups and were higher in subjects ≥65 years than in subjects 18 to <65 years.

Secondary immunogenicity endpoints, also based on HAI antibody responses, included GMTs, % HAI ≥1:40, and SCRs, measured in each treatment group (pooled Audenz or placebo), at different time points post-vaccination, overall, and by age sub-groups, sex, race, and ethnicity. Both age groups met secondary endpoint criteria for the SCR after two vaccinations, but not after a single vaccination. GMTs, % HAI ≥1:40, and SCRs all decreased toward baseline at six months after the first vaccination. Exploratory analyses, performed in the full dose group at Day 43, showed some cross-reactive immune responses to heterologous influenza A/H5 strains, with the highest responses observed for A/Egypt/2010, A/Hubei/2010, and A/Vietnam/1203/2004, although clinical benefit is uncertain.

Unadjusted analyses of % HAI ≥1:40 also met immune response criteria. The sponsor chose to only adjust Day 43 % HAI ≥ 1:40 used to evaluate CBER criteria, everything else, including SCR, was unadjusted in the package insert (PI). Because differences between adjusted and unadjusted results were small and not clinically significant, the statistical reviewer stated that either result would be appropriate to use in the PI.

V89_11

Co-primary immunogenicity endpoints including SCRs and % HAI ≥1:40 at Day 43 were met for both half or full dose. Higher immune responses were noted in subjects receiving the full dose. In both dose groups, subjects 6 to <36 months had higher immune responses relative to the other two age subgroups (3 to < 9 years and 9 to < 18 years). The explanation for this observation is unclear. Secondary endpoints showed that only the full dose group met SCR criteria after a single vaccination or at twelve months following the second vaccination. Neither group met the % HAI ≥1:40 success criteria after a single vaccination or at twelve months after the second vaccination. At Day 387, GMTs in both half and full dose groups declined but remained ~5.6 and 12 times the baseline level, respectively.

In V89_11, a total of 25% and 28% of subjects in the half and full dose groups, respectively, had major protocol deviations, primarily due to missing serologies. It was found that serology results were missing for some samples that were actually collected. During inspection by the Bioresearch Monitoring Program (BiMo), the Applicant indicated that the serology results were missing in part due to a lack of sufficient serum to conduct analysis or inability to obtain a confirmatory result. Based on the Applicant's justifications and additional statistical analysis, it was concluded that the missing serology data did not impact study conclusions.

Bioresearch Monitoring Review: The Bioresearch Monitoring Branch issued inspection assignments for three clinical trial sites that participated in the conduct of

Protocol V89_18 and two clinical trial sites that participated in the conduct of Protocol V89_11. The inspections did not reveal problems that impacted the data submitted in the BLA.

b) Pediatrics

A presentation of Seqirus' Pediatric Plan was made to the FDA Pediatric Review Committee (PeRC) on October 29, 2019. The committee agreed with the recommendation for deferral of submission of the trial for infants 0 to < 6 months of age for this application because this product is ready for approval for use in individuals 6 months of age and older and the pediatric trial in ages 0 to < 6 months has not been completed. The Pediatric Research Equity Act (PREA) required trial specified in the approval letter and agreed upon with Seqirus is trial V89_19 to evaluate the safety and immunogenicity of Audenz when administered to infants 0 to < 6 months of age.

7. SAFETY/PHARMACOVIGILANCE

Across the phase 2 and 3 clinical trials noted above, the overall safety database (total exposure) for the full dose of Audenz vaccine selected for licensure was comprised of 3579 adults and 329 children and adolescents, for a total of 3908 subjects exposed to full dose vaccine, and 796 placebo recipients. An additional 1179 adults and 329 children and adolescents (total 1508) were exposed to and contributed safety data for the half dose vaccine.

Adults
A total of 18 deaths were reported in the expanded pooled analysis of all subjects ≥18 years (full dose n=16, half dose n=1, and placebo n=1). No deaths were assessed as related to study treatment. No clear safety concerns in SAEs (Serious Adverse Events) and MAAEs (Medically Attended Adverse Events) were observed between treatment groups. Two SAEs had a close temporal relationship to Audenz vaccination making it difficult to completely exclude causality: 1) acute myocardial infarction in a 60-year old female (b) (4) hours following the second vaccination and 2) cerebral haematoma in a 75-year old female following a fall (b) (4) after the first vaccination. The rates of AESIs (Adverse Events of Special Interest) and NOCDs (New Onset of Chronic Diseases) were low and no patterns or clusters were observed that would support an assessment of causality. Details can be found in the clinical review.

Overall, the ISS reflected safety profiles observed in the individual BLA studies and identified no new safety concerns. Solicited local AEs following any vaccination in adults ≥ 18 years of age were reported by 51.6%, 48.5%, and 14.7% of full dose, full or half dose, and placebo recipients, respectively. Solicited systemic AEs following any vaccination in adults ≥ 18 years of age were reported 39.0%, 38.7%, and 32.8% of full dose, full or half dose, and placebo recipients, respectively. Solicited local AEs were almost twice as likely in subjects 18-64 years than subjects ≥ 65 years. The most frequent solicited AEs were injection site pain, fatigue, headache, and malaise. While local pain and malaise were reported more frequently by Audenz vaccine recipients

than placebo recipients (51.2% of full dose and 14.7% of placebo; and 19.4% of full dose and 11.9% of placebo, respectively), rates of other solicited AEs were generally similar between treatment groups. Rates decreased following the second vaccination (34.8% for local and 21.6% for systemic) as compared to the first vaccination (44.9% for local and 31.8% for systemic). Solicited AEs were mostly mild to moderate and of short duration. Unsolicited AEs occurred in ~25% of all subjects in the ISS, with similar rates of events between Audenz vaccine and placebo recipients. No unusual patterns or imbalances or safety signals were identified. Therefore, the safety profile of Audenz was acceptable for approval of this application in adults, given the overall favorable benefit-risk balance.

Children/Adolescents
A total of 24 SAEs (all non-fatal) occurred, including 14 SAEs reported by 11 subjects (3%) in the half dose group and 10 SAEs reported by 8 (2%) subjects in the full dose group. All SAEs were considered unrelated to study vaccine. No deaths occurred during the trial. Discontinuations were infrequent and did not significantly impact the evaluation of safety; however, three subjects were discontinued from the second vaccination due to AEs assessed as possibly or probably related to study vaccine: irritability; severe urticaria at the vaccination site; and severe pyrexia. Unsolicited AEs including SAEs were typical of a pediatric population without unusual patterns.

In children 6 months to <6 years of age, injection site tenderness was the most frequently reported local AE following any vaccination (56% in both dose groups) with most being mild to moderate; 1% experienced severe tenderness. Among children 6 years through 17 years, injection site pain was the most frequently reported local AE following any vaccination (half dose 72%, full dose 68%) with most being mild to moderate; 1% experienced severe pain. Among children 6 months to <6 years, the most frequently reported solicited systemic AEs (≥10%) following any vaccination (half vs full dose) were irritability (28 vs 30%), sleepiness (25%) and change in eating habits (12% vs 18%), with most events assessed as mild to moderate in severity. Among children 6 years through 17 years, the most frequently reported solicited systemic AEs (≥10%) following any vaccination (half vs full dose) were fatigue (30% vs 27%), headache (29% vs 22%), myalgia (28% vs 30%), malaise (24 vs 25%), nausea (16% vs 13%), arthralgia (12% vs 13%), and loss of appetite (11% vs 14%), with most events assessed as mild to moderate in severity.

The occurrence of fever in the seven days following vaccinations was examined closely. Higher rates of fever were observed in younger age groups following the full dose. Among children 6 months to < 6 years, solicited fever (≥38.0°C, ≥100.4°F) in the seven days following any vaccination occurred in 8% of half dose and 16% of full dose vaccine recipients. Four (2%) half dose and 3 (2%) full dose recipients had fever ≥102.1°F. Full dose Audenz was associated with higher rates of fever among children 6 months to <3 years and 3 years to <6 years (21% and 7%, respectively) as compared to half dose recipients (9% and 7%, respectively). Among children 6 through 17 years, fever following any vaccination occurred in 3% of half dose and 4% of full dose vaccine recipients. One (1%) half dose and 1 (1%) full dose recipient had fever ≥102.1°F. In

both age groups, most fever occurred within 2-4 days of vaccinations and resolved within 1-2 days. No febrile seizures or convulsions were reported in the 21 days following any vaccination. Given the high mortality associated with influenza A/H5N1 infection and an expectation that higher immune responses may be more protective, the higher rates of fever and only slightly higher rates of other systemic symptoms were acceptable to the review team and support the use of full dose Audenz for children 6 months to < 6 years.

Pregnancy
Pregnancy was an exclusion criterion in all five trials supporting licensure. Thus, the Audenz vaccine has not been evaluated systematically in pregnant females. However, during the course of these trials, a total of 25 subjects receiving Audenz (half or full dose) reported pregnancies. Thirteen resulted in a healthy infant, four resulted in spontaneous abortions, with the remaining eight not reporting the outcome. These results are consistent with the rate of spontaneous abortion in early pregnancy (<20 weeks gestation) in females <35 years of age, i.e., approximately 15%.

Postmarketing
No previous postmarketing human experience exists for Audenz. However, Audenz is related to other seasonal, pandemic and pre-pandemic vaccines manufactured and distributed by Seqirus including Flucelvax, Fluad, Focetria (egg-derived monovalent H1N1 vaccine with MF59); Aflunov (pre-pandemic egg-derived H5N1 vaccine with MF59); and Celtura (pandemic, cell culture-derived H1N1 vaccine with MF59, licensed in Germany, Switzerland and Japan during the 2009 H1N1 pandemic).

Potential risks identified in the Applicant's Pharmacovigilance Plan (PVP) include uncommon or rare AEs associated with other influenza vaccines: convulsion, neuritis, encephalitis, vasculitis, Guillain Barre Syndrome (GBS), demyelination, Bell's palsy, syncope and hypersensitivity reactions.

8. ADVISORY COMMITTEE MEETING

An Advisory Committee meeting was not held for Audenz since relevant issues regarding licensure of pandemic vaccines were discussed previously at Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings held on February 29, 2012, and November 14, 2012; and because our review of information submitted in the BLA did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable.

10. LABELING

The proposed proprietary name, Audenz, was reviewed by the APLB on November 15, 2019 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on December 17, 2019.

Seqirus submitted revised versions of the PI as well as carton and container labels in response to comments provided by CBER during labeling negotiations. The revised PI and carton/container labels were reviewed by the Chair and members of the Review Committee [clinical, statistical, non-clinical, product, pharmacovigilance, and Advertising and Promotional Labeling Branch (APLB) reviewers], as appropriate.

Major changes recommended for product labeling included:

- Section 1 – added wording regarding accelerated approval in children 6 months through 17 years of age and stated that continued approval in this age group may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Section 6.1 – additional text added to better describe adverse events. In order to avoid an implied indication for a half dose of Audenz, references to the half dose and description of safety data for the half dose were removed.
- Section 6.2 – although no postmarketing experience exists for Audenz, the sponsor was asked to identify for inclusion in the PI potential risks based on the postmarketing experience for seasonal and pandemic influenza vaccines that contain the same MF59 adjuvant or share the same manufacturing platform as Audenz.
- Section 11 – updated residuals and included reference to Flucelvax.
- Section 14 – references to and description of immunogenicity results for the half dose of Audenz were removed from this section to avoid an implied indication for the half dose. If this information is of interest in the event of a pandemic, it may be found in the clinical review which will be available in the public domain.

Final versions of the PI, carton, and container labels were agreed upon through communications with Seqirus. The APLB found the PI and package/container labels to be acceptable from a promotional and comprehension perspective. The Applicant will be advised to submit the final content of labeling in Structured Product Labeling (SPL) format after approval.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the review committee recommends approval of Audenz for the proposed indication and usage.

Moreover, based on the previous discussions held between CBER and Novartis/Seqirus throughout the clinical development phase of Audenz; current policy stated in the Guidance for Industry "Clinical Data Needed to Support the Licensure of Seasonal Influenza Vaccines"; and the combined manufacturing, pre-clinical, and clinical data submitted in the BLA, the Chair recommends licensure of Audenz via the traditional approval pathway for adults 18 years and older and accelerated approval pathway for children/adolescents 6 months through 17 years of age.

b) Risk/Benefit Assessment

In view of the data submitted to support the safety and effectiveness of Audenz that have been presented and discussed in this document, as well as the high degree of morbidity and mortality associated with pandemic influenza virus illness, the review committee is in agreement that the benefit/risk profile for Audenz is favorable with respect to the intended indication and usage.

c) Recommendation for Postmarketing Activities

Because seasonal Flucelvax (TIVc and QIVc) were approved in children and adolescents 4 years to <18 years according to accelerated approval regulations (21 CFR 601.41) and are not approved in children <4 years, approval of the Audenz vaccine in persons 6 months to <18 years will be granted according to accelerated approval regulations. Seqirus is currently finalizing the results from a confirmatory absolute efficacy trial for Flucelvax quadrivalent (QIV) as compared to a non-influenza comparator vaccine in children/adolescents 4 years to < 18 years of age Once these results are deemed acceptable and traditional approval is granted for Flucelvax in children/adolescents 4 years to < 18 years, traditional approval for Audenz will be possible in this age group. For traditional approval of Audenz in children 6 months to < 4 years, Seqirus will need to successfully demonstrate vaccine effectiveness in V130_10, an immunogenicity and safety study of Flucelvax QIV intended to support traditional approval in children 6 months to < 4 years. Traditional approval in children 6 months to < 4 years will also be contingent on successfully demonstrating clinical disease endpoint efficacy of Flucelvax in children 4 years to 17 years (in the previously mentioned study V130_12).

The postmarketing activities which Seqirus has committed to and are to be included in the approval letter are shown below:

POSTMARKETING STUDIES SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR § 601.70

ACCELERATED APPROVAL REQUIREMENTS

1. To conduct a study (V130_12) to evaluate the efficacy, safety and immunogenicity of Flucelvax Quadrivalent compared to a non-influenza comparator vaccine in persons 4 years to <18 years of age.

Final Protocol Submission: December 13, 2018
Study Completion: September 30, 2019
Final Report Submission: July 31, 2020

2. To conduct a study (Study V130_10) to evaluate the safety and immunogenicity of your quadrivalent formulation of Flucelvax Quadrivalent in pediatric subjects 6 months to < 4 years of age.

Final Protocol Submission: June 30, 2019
Study Completion: August 30, 2020
Final Report Submission: February 28, 2021

PEDIATRIC REQUIREMENTS

3. Deferred pediatric study V89_19 under PREA to evaluate the safety and immunogenicity of Audenz when administered to healthy infants 0 < 6 months of age.

Final Protocol Submission: 60 days after notification by the FDA to finalize the protocol, which will be related to an imminent H5N1 influenza virus pandemic (sustained human-to-human H5N1 transmission)
Study Completion: 24 months after initiation of the study
Final Report Submission: 8 months after completion of data collection

P<u>OSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B:</u>

4. To establish a pregnancy registry in the U.S. that is able to prospectively collect data on an actively recruited cohort to study the safety of Audenz Vaccine during pregnancy. A draft protocol for this pregnancy registry will be prepared under the assumption that the vaccine would be distributed to the general population in the U.S. in an officially-declared H5N1 influenza virus pandemic. Once the circumstances of vaccine usage in an officially-declared H5N1 influenza virus pandemic are determined by the U.S. Government, Seqirus will work with the FDA, in coordination with BARDA (Biomedical Advanced Research and Development Authority) and CDC (Center for Disease Control), to finalize the protocol and initiate the registry.

   Draft Protocol Submission: December 31, 2020
   Final Protocol Submission: 90 days after notification by the FDA
   Initiate Registry: 60 days after notification by FDA
   Study Completion Date: 24 months after initiation of the registry
   Final Report Submission: 12 months after completion of data collection

AGREEMENTS:

Furthermore, Seqirus has agreed to the following:

1. To collaborate with the government on plans to collect additional safety and effectiveness data when Audenz is used. Furthermore, if Audenz is used in another country and Seqirus obtains additional safety and effectiveness data, Seqirus will provide these data to the Food and Drug Administration.

2. To acknowledge that Seqirus does not intend to market Audenz for commercial distribution in the U.S. since it will be produced and distributed under contract to the U.S. Government as part of national pandemic preparedness initiatives. Thus, Seqirus does not intend to distribute promotional advertising or promotional labeling materials for Audenz.