U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

MEMORANDUM

Date: January 14, 2020

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To: Brenda Baldwin PhD
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Subject: Review of Pharmacovigilance Plan and Clinical Safety

Applicant: Seqirus

Product: aH5N1c influenza vaccine

Application: BLA/STN 125692/0

Proposed Indication: Active immunization of persons 6 months and older for the prevention of disease caused by the influenza A virus H5N1 subtype

Submission Date: January 31, 2019

Action Due Date: February 1, 2020

1 Introduction

1.1 Objective

The applicant is seeking approval to market and distribute aH5N1c, proposed trade name AUDENZ, in the United States. This memo will review the proposed pharmacovigilance plan and safety information from premarket pivotal studies to determine appropriate post approval surveillance and whether any postmarketing studies are necessary for aH5N1c.

1.2 Product Description

aH5N1c, a vaccine for intramuscular injection, is a monovalent, adjuvanted, inactivated subunit, cell-culture derived influenza vaccine that includes the adjuvant MF59C.1 (hereafter referred to as 'MF59'). aH5N1c is propagated in Madin Darby Canine Kidney (MDCK), a continuous cell line adapted to grow freely in suspension in culture medium. aH5N1c comprises surface antigens from a potential pandemic H5N1 strain candidate (A/Turkey/Turkey/1/2005 [H5N1] NIBRG-23 strain). The vaccine also contains MF59 adjuvant (an oil in water emulsion containing squalene), and surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer. Of note, MF59 is the adjuvant in Fluad, an inactivated trivalent egg-based influenza vaccine already available in the US market.

1.3 Proposed Dosing Regimen(s) and Formulation(s)

The intended indication and usage of aH5N1c is active immunization of persons 6 months and older for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. In the event of an H5N1 flu pandemic, it is anticipated that the vaccine would be matched to the circulating A/H5N1 strain and that this modification would be communicated to FDA via a strain change supplement. The applicant is proposing a two-dose vaccination regimen with a recommended 21 days between doses as validated in their premarket trials. The proposed dose for both adults and children is 7.5µg HA and (b) (4) MF59 in 0.5 mL total volume.

1.4 Pertinent Regulatory History

This vaccine shares a common manufacturing process with Flucelvax, approved in its trivalent form on November 12, 2012 and quadrivalent form in May 23, 2016, in that both are expanded in MDCK cells. aH5N1c is currently not approved anywhere in the world.

2 Materials Reviewed

The materials reviewed in support of the assessment are listed in the table below.

Table 1: Materials used in course of review

Source	Document
Applicant	Clinical Overview (125692/0) February 1, 2019
Applicant	Summary of Clinical Safety (125692/0) February 1, 2019
Applicant	Final Integrated Summary of Safety aH5N1c Pandemic BLA (125692/0) February 1, 2019
Applicant	Correspondence RE pediatric study plan (125692/0) February 1, 2019
Applicant	Pharmacovigilance plan for aH5N1c dated May 16, 2019 (125692/0.9) May 22, 2019
Applicant	Integrated Summary of Safety Tables, Listings and Figures Unsolicited Selected Adverse Events (125692/0) February 1, 2019

Applicant	Clinical study report V89_11 (125692/0) February 1, 2019
Applicant	Updated pharmacovigilance plan (125692/0.28) October 3, 2019
Applicant	Proposal for postmarketing pregnancy registry study (125692/0.37) November 20, 2019
Applicant and FDA	Proposed US package insert for AUDENZ (125692/0.35) November 5, 2019

3 Clinical Trials Experience

3.1 Pivotal Trials

3.1.1 Overview

The applicant submitted data from four trials that comprise the analyzed safety population. They are listed in Table 2 below.

Table 2: Clinical Trials

Trial Name	N	Description
V89_04	979	This study assessed immunogenicity, dose selection (either 3.75 µg HA or 7.5 µg HA), and safety in healthy adults 18 to <40 years of age
V89_13	1393	This study assessed immunogenicity, dose selection (either 3.75 µg HA or 7.5 µg HA), and safety in healthy adults ≥65 years of age
V89_11	662	This study was a dose selection study with safety and immunogenicity endpoints in healthy children 6 months to ≤17 years of age
V89_18	3196	This study assessed the safety, immunogenicity, and lot to lot consistency of full dose aH5N1c vs placebo in healthy adults ≥18 years of age

3.1.2 Safety

The applicant conducted an integrated review of safety and developed a safety dataset for adults (≥age 18 including V89_04, V89_13, V89_18) comprised of 3579 subjects who received aH5N1c and 796 subjects who received placebo. Additionally, V89_11 was a pediatric study and was excluded from the integrated safety set, but was analyzed separately. In the studies, the applicant provided subjects instructions to record as 'solicited adverse events (AEs)' specific adverse events (local and systemic) occurring in the first 7 days post vaccination. 'Unsolicited AEs' included Serious Adverse Events (SAE), adverse events of special interest (AESI), new onset of chronic disease (NOCD), or adverse events leading to study withdrawal. The two endpoints analyzed for unsolicited AEs were a)any unsolicited AE reported through day 21 for either the first or second vaccination (encompassing the 42-day treatment period), and b) selected unsolicited AEs occurring between day 1 and day 387, including SAEs, Deaths, AE of special interest, new onset chronic disease, AE leading to vaccine study withdrawal, and medically attended AEs.

3.1.2.1 Solicited adverse events

The most common Solicited AE (table 3) was pain, which occurred in 51% of those receiving the vaccine and 14% of those receiving the placebo (normal saline). Induration, erythema, and ecchymosis were also more common with aH5N1c than with placebo, likely due to presence of the MF59 adjuvant and resultant reactogenicity of the vaccine. Regarding the rates of systemic solicited AEs, the rates of malaise and myalgia were higher in the aH5N1c group than in placebo. However, the higher rate of malaise was driven by cases that were "mild" as the rate of moderate (3.5% H5N1 vs 2.9% placebo) and severe malaise (0.6% H5N1 and 1.3% placebo)

were comparable in aH5N1c and placebo (see table 3 below). This also holds true for myalgia as the rates of moderate (2.3% H5N1 vs 2.3% placebo) and severe (0.4% H5N1 vs 0.4% placebo) were comparable.

Table 3: Solicited AEs of Full dose H5N1 vaccine vs placebo

AE		**Any H5N1**	**Placebo**
Local		N= 3518	N=784
Pain		1800 (51.2%)	115 (14.7%)
Induration		46 (1.3%)	0
Erythema		33 (0.9%)	0
Ecchymosis		26 (0.7%)	1 (0.1%)
Systemic		N=3518	N=784
Fatigue		763 (21.7%)	160 (20.4%)
Headache		687 (19.5%)	151 (19.3%)
Malaise	Any	681 (19.4%)	93 (11.9%)
	Mild	537 (15.3%)	60 (7.7%)
	Moderate	122 (3.5%)	23 (2.9%)
	Severe	22 (0.6%)	10 (1.3%)
Myalgia	Any	479 (13.6%)	77 (9.8%)
	Mild	386 (11%)	51 (6.5%)
	Moderate	80 (2.3%)	18 (2.3%)
	Sevewre	13 (0.4%)	3 (0.4%)
Arthralgia		374 (10.6%)	71 (9.1%)
Nausea		304 (8.6%)	67 (8.5%)
Loss of Appetite		225 (7.2%)	59 (7.5%)
Chills		101 (4.3%)	30 (3.8%)
Fever		42 (1.2%)	10 (1.3%)

3.1.2.2 Unsolicited AEs

During the study period the rates of those subjects who received aH5N1c developing an unsolicited AE (920/3579, 25.7%) was similar to placebo (180/796, 22.6%). The most common unsolicited AEs by PT are listed in the table below and the rates of AEs both related and total are similar between aH5N1c and placebo.

Table 4: Top 10 most common unsolicited AEs by PT during entire time period[i]

AE (N = 3579 aH5N1c) (N= 796 placebo)	**All AEs H5N1**	**All AE placebo**
Any	920 (25.7)	180 (22.6)
Headache	77 (2.2)	17 (2.1)
Injection site bruising	64 (1.8)	13 (1.6)
Fatigue	59 (1.6)	12 (1.5)
Arthalgia	56 (1.6)	10 (1.3)
Upper Respiratory Tract Infection	55 (1.5)	6 (0.8)
Viral Upper Respiratory Tract Infection	45 (1.3)	3 (0.4)
Myalgia	44 (1.2)	8 (1.0)
Back Pain	31 (0.9)	10 (1.3)
Urinary Tract Infection	27(0.8)	12 (1.5)

3.1.2.3 Serious AEs

During the treatment period (days 1-21 after each vaccination, total 42 days), there were 13 serious AEs after the 1st vaccination and 9 after the second vaccination with aH5N1c (Table 5).

[i] not mutually exclusive

The majority of AEs during the treatment period in those vaccinated with aH5N1c were in the SOC 'infections and infestations.'

Table 5 Serious AEs in treatment group during treatment period by PT

PT	1st vaccination (N=3579)	2nd vaccination (N=3579)
Appendicitis	2 (0.1)	
Pyelonephritis	1 (0.0)	
Shigella infection	1 (0.0)	
Wound infection	1 (0.0)	
Diverticulitis		1 (0.0)
External Ear Cellulitis		1 (0.0)
Cerebral Hematoma	1 (0.0)	
Presyncope	1 (0.0)	
Nerve compression		1 (0.0)
Atrial Flutter	1 (0.0)	
Atrioventricular block	1 (0.0)	
Acute Myocardial infarction		1(0.0)
Atrial fibrillation	1 (0.0)	
Acute Kidney Stone	1 (0.0)	
Hospitalisation	1 (0.0)	
Non cardiac chest pain	1 (0.0)	
Anemia		1 (0.0)
Breast cancer		1 (0.0)
Cholecystitis		1 (0.0)
Hyponatremia		1 (0.0)
Asthma		1 (0.0)

During the entire study period (days 1-387) for the unsolicited safety set (N=3579), there were 225 (6.3%) serious AEs in the aH5N1c group and 74 (9.3%) SAEs in the placebo group. The majority of SAEs were related to chronic conditions and there was no clustering or concerning patterns in the SOCs or PTs of the AEs. It is difficult from submitted information to attribute their onset to the study vaccine.

3.1.2.4 Deaths

In the combined safety set (studies V89_04, V89_13, V89_18) there were 18 deaths. None of these deaths were in the treatment period (day 1-42) and medical officer assessment of the case narratives determined that none of the deaths (Table 7) is likely related to the vaccine.

Table 7 Deaths in safety set

Subject	Age (years)	Sex	Study/ Study Group	Cause of death	Onset day (duration in days) after vaccination
(b) (6)	27	M	V89_04 / Full dose	Cerebral Hemorrhage due to car accident	330 (b) (6)
	59	M	V89_04 / Full dose	Myocardial infarction due to atherosclerotic coronary artery disease	113
	53	F	V89_04 / Full dose	Acute Respiratory failure and sepsis due to unknown organism (presumed bacterial) in HIV patient	166
	62	M	V89_04 / Full Dose	Sepsis due to unknown organism complicated by bacterial pneumonia	341
	70	F	V89_13 / Full Dose	Acute myocardial infarction and cardiac arrest, found dead, no autopsy	162
	67	M	V89_13 / Half Dose	Lung Adenocarcinoma leading to pneumonia, transitioned to palliative care	142

(b) (6)						(b) (6)
	56	M	V89_18 / Full Dose	Found deceased, death thought to be due to hypertensive Heart disease	282	
	67	M	V89_18 / Full dose	Cardio-Respiratory Arrest had arrest due to unknown cause but had multiple chronic conditions, HTN, Af b and cerebral vascular disorder contributed	243	
	70	F	V89_18 / Full dose	Death due to unknown cause, found deceased, multiple chronic conditions, coronary artery disease, COPD contributed to death	393	
	73	M	V89_18 / Full dose	Patient found deceased, believed to have died from Myocardial infarction	232	
	71	F	V89_18 / Full dose	Respiratory Failure with legionella, complicated by renal failure	362	
	70	F	V89_18 / Full dose	Hospitalized 8 days after vaccination for small bowel obstruction and found to have Crohns Disease, rehospitalized and died 1 month later with large colon cancer and perforation with peritonitis and death	34 (	
	72	M	V89_18 / Full dose	Patient died of an MI while driving vehicle, felt hypertension was contributory	53 (	
	85	F	V89_18 / Full dose	Renal Failure and HTN leading to cardiac arrest, subject died in ER	163	
	79	M	V89_18 / Full dose	Cerebral Infarction (MCA) and respiratory distress leading to death	125	
	83	M	V89_18 / Full dose	Cardiogenic Shock due to complications form triple bypass due to severe CAD complicated by renal failure, CML	226	
	94	M	V89_18 / Full dose	Patient hospitalized with pneumonia leading to sepsis and died 1 month after starting palliative care	343	
	90	M	V89_18 / Full dose	Patient fell out of bed and found bleeding, found to have Subdural Hematoma discharged to hospice and died	276	

3.1.2.5 Adverse events of special Interest, New onset Chronic disease

A group of immune mediated diseases were retrospectively assigned to the term Adverse Events of Special Interest (AESI) in the pooled data group because, though potential immune mediated diseases were assessed in each of the studies, the PTs used to classify these AEs were not identical. The PTs designated as AESIs also include the terms in important potential risks in the PVP below (neuritis, convulsions, encephalitis, vasculitis, Guillain-Barre Syndrome, demyelination, Bell's Palsy, syncope, and hypersensitivity reactions). Review of adverse event data of the AESIs disclosed no concerning signals. Only one subject had an AESI that was also listed in the PVP: in the treatment group there was one case of chronic inflammatory demyelinating polyradiculopathy. Otherwise, none of the potential adverse events noted in the PVP were seen in the treatment group.

During the study there were 23 events (0.6%) that qualified as new onset of chronic disease in the aH5N1c group after the first vaccination (day 1-21), 17 (0.5%) after the second (day 22-42), and 320 (8.9%) during the follow up period (day 42-387). In the placebo group there were 3 (0.4%) after the first vaccination, 3 (0.4%) after the second, and 68 (8.5%) during follow up. The rates of new onset of chronic disease were similar between aH5N1c and placebo and there was no clustering or concerning patterns in the SOCs or PTs of the AEs. Furthermore, during the entire study period, no new vasculitis or rheumatologic disease was noted.

4 Pediatric Study and Pregnancy Data

4.1 Pediatric Study: V89_11

The applicant and FDA agreed in the Pediatric Study Plan that the applicant would perform an immunogenicity and safety study in children. The applicant conducted study V89_11 to satisfy this agreement, testing low (3.75 µg HA and 0.125mL MF59) or high dose aH5N1c (7.5 µg HA and 0.25 mL MF59) (2 injections) in subjects >6 months to 17 years. A total of 662 subjects

were randomized 1:1 to receive 2 vaccinations 3 weeks apart (no placebo comparator was used). The study time periods were treatment period day 1 through 42 and follow up period day 43 to 387. 658 subjects were exposed to the vaccine and included in safety analysis. A dose tolerability study was conducted that assessed immunogenicity and safety in children; this study yielded safety information relevant to use of the 7.5 µg HA (b) (4) MF59 dose (b) (4) that was eventually chosen as the final product. Given this, only the proposed final dose will be discussed. The most common solicited local AEs in age < 6 years (N=159) were tenderness in 89 subjects (56%) and erythema in 4 subjects (3%) which was similar in the age 6-17 years group (N=163) that reported pain in 111 (68%) and erythema in 2 (1%). The most common solicited systemic AEs in age <6 (N=159) were irritability in 47 subjects (30%) and sleepiness in 40 subjects (25%). In children aged 6-17 (N=163), the most common solicited AEs were myalgia in 49 subjects (30%) and fatigue in 43 subjects (27%). Overall, the AE reports in this trial were not suggestive of new safety issues related to the vaccine, and they were similar to the AEs seen in the adult studies. There was no concerning clustering or patterns of solicited AEs in children.

4.1.1 Serious AEs

In the study time period (day 1 – day 387) there were 8 serious unsolicited AEs in 8 pediatric patients. The majority of SAEs were infectious in nature but there were 2 reports of convulsions in the study subjects. There were no deaths in the study and 3 cases of new onset chronic disease (one case each of bone cyst, ADHD, and dyspepsia).

4.2 Pregnancy Data

During V89P1, V89_04, V89_11, and V89_18, a total of 55 pregnancies were reported in subjects receiving aH5N1c (N=3579) and 5 in subjects receiving placebo (N=796) (see table 10 for information). Despite the imbalance in occurrence of pregnancy, the number of spontaneous abortions in each arm was comparable (4 in vaccine arm vs 2 in control arm). There were no congenital anomalies diagnosed in the infants/fetuses.

Table 10 pregnancy outcomes by study

Study	Group	Time period	Total pregnant	Live birth	Spontaneous abortion	Planned abortion	Congenital anomaly	No info available
V89P1	aH5N1c	Days 1-42	8	2	0	6	0	0
	aH5N1c	Days 43-387	19	12	0	3	0	4
V89_04	aH5N1c	Days 1-42	7	2	2	0	0	3
	aH5N1c	Days 43-387	8	2	1	0	0	5
V89_11	aH5N1c	Days 1-387	2	2	0	0	0	0
V89_18	Placebo	Days 1-42	2	0	2	0	0	0
	aH5N1c	Days 43-387	6	5	1	0	0	0
	Placebo	Days 43-387	3	1	0	2	0	0

5 Postmarketing Data

The vaccine aH5N1c is not approved anywhere in the world. As such, there are no postmarketing events that occurred.

6 Pharmacovigilance plan

6.1 Safety Issues

The applicant provided a pharmacovigilance plan (PVP) for aH5N1c on May 16, 2019 (updated plan submitted October 3, 2019). In it, the applicant reported on the risks (identified, potential,

missing information) of the vaccine (summarized in table 11 below). The submitted PVP is similar to the most recent Flucelvax PVP submitted in 125408/177 which is appropriate as they share a manufacturing process and will likely have a similar risk profile.

Table 11: Risk assessment of 125692 Pharmacovigilance plan as submitted by applicant 125692/0

Safety Concerns	Planned Action
Important identified risks	
• None	none
Important potential risks	
• Neuritis • Convulsions • Encephalitis • Vasculitis • Gullain-Barre Syndrome • Demyelination • Bell's Palsy • Syncope • Hypersensitivity reactions	Routine Pharmacovigilance
Important missing information	
• Safety During Pregnancy or lactation	Routine Pharmacovigilance
• Safety and Immunogenicity in infants <6 months of age	A study in this population (protocol V89_19) will be conducted in the event of an H5N1 pandemic

6.2 Definition of Routine Pharmacovigilance

Per the PVP, the applicant reports that all case reports of adverse events (AE) are processed and all suspected adverse reactions are reported per the regulatory guidelines. The applicant's Pharmacovigilance and Risk Management (PVRM) headquarters are in the UK and responsible for the overall safety of influenza vaccine manufactured by the applicant. Individual case safety reports (ICSR) received by the company are processed by a third party (b) (4) is responsible for hosting, operating, validating, and maintaining the database. The PV plan includes monitoring spontaneously reported AE cases, literature cases, and AR reports from clinical trials and non-interventional organized data collection system cases.

In addition, the applicant's pharmacovigilance activities involve submitting periodic surveillance update reports (PSURs) per the FDA regulations. The applicant submitted a waiver to be exempt from submitting lot distribution reports until the vaccine is distributed.

7 Integrated Risk Assessment

7.1 Identified Risks

There were no identified risks noted in the trials for approval.

7.2 Potential Risks

7.2.1 Neuritis

"Neuritis" is a broad set of conditions including ocular neuritis, brachial neuritis, and lumbosacral neuritis with a possible association with influenza vaccines[1,2]. There is no clear mechanism for the cause of neuritis, though an Institute of Medicine report postulated that autoantibodies, T cells, immune complexes, and molecular mimicry may contribute to symptoms[1]. Neuritis is recognized as an adverse event possibly related to flu vaccination and is listed in section 6.2 "Postmarketing Experience" in the US package insert for the flu vaccine FLUAD[3], manufactured by Seqirus and containing the adjuvant MF59. In the studies submitted for approval, there was 1 reported case of hypoasthesia categorized as "mild" and 1 case of "moderate" cervical radiculopathy. Though neuritis was not seen in significant numbers in the pivotal studies for aH5N1c, given the putative mechanism and reports in other influenza vaccines, there remains a potential risk. Given the lack of safety information suggestive of a signal, monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.2 Convulsions

There have been multiple reports of seizures in those that receive flu vaccine, though several meta analyses[1,6] have looked for links between influenza vaccine and seizures and have not discerned a definitive association. The mechanistic cause for seizures in relation to vaccination is also unclear, though febrile seizures occur in a subset of children with fevers in the general population and thus febrile seizures may be tied to the immunogenicity of the vaccine causing fever rather than a direct effect of the vaccine[1]. During the aH5N1c trials, there were no "convulsions" in the adult studies; only 2 children experienced this AE, including 1 child with "convulsions" and 1 with "febrile convulsions." Given the reports of seizures post vaccination in other vaccines, including FLUAD[3], and lack of clear signal in the pivotal trials, monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.3 Encephalitis

Encephalitis is a known complication from influenza virus infection and has been reported in the literature, thought to be related to high levels of systemic immune activation during acute infection[7]. There have also been isolated reports of encephalitis following influenza vaccination, however a metanalysis conducted in 2011 determined that there was insufficient evidence to determine an association. In the studies in this submission, there was one serious adverse event of encephalopathy but there was no encephalitis noted. Given the lack of safety information suggestive of a signal, monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.4 Vasculitis

Various types of vasculitis (including multiple types of large and small vessel both ACNA associated and not) have been reported after influenza vaccination, though the onset is rare with only case reports or series reported[8]. Per a 2011 metanalysis, "it is unclear what is the predominant mode in patients or if the same mechanism occurs in a majority of cases of vasculitis."[1] During the pivotal trials of aH5N1c, 2 cases involving possible vasculitis developed. One subject developed polymyalgia rheumatica, a systemic inflammatory disease that overlaps with giant cell arteritis[9] , 6 months after vaccination. Another patient developed Raynaud's phenomenon, blanching of the skin due to temperature changes that may be associated with a variety of rheumatologic and vascular diseases[10], 281 days after vaccination. Otherwise, no

new diagnoses of vasculitis occurred in the study. Given the lack of clear signal, monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.5 Guillain-Barre Syndrome

Guillain-Barre Syndrome is an acute, immune mediated, demyelinating disease that has been reported after the administration of influenza vaccines[11]. The pathogenesis is thought to be related to immune attack by macrophages and antibodies against neuronal proteins. Several studies have shown that the attributable risk of vaccination for GBS is roughly 1-3/1,000,000 based on prior studies[6]. There were no cases of Guillain Barre Syndrome during the trials for the vaccine. However, there was one case of chronic inflammatory demyelinating polyradiculopathy seen in the full dose aH5N1c vaccine group. This occurred 310 days after vaccination. Given the potential risk but lack of clear signal, monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.6 Demyelination

Disorders involving "demyelination" span a broad range of neurologic syndromes characterized by their chronicity and pathogenic lesions in the central nervous system and can include acute disseminated encephalomyelitis (ADEM), transverse myelitis, and multiple sclerosis (MS). There are reports of both ADEM and transverse myelitis occurring after influenza vaccination, though there is no clear association[1]. In addition "encephalomyelitis" is listed in section 6.2 of the Fluad package insert[3]. The pathogenesis is possibly related to autoimmune response to some antigen, but animal models have not reproduced the syndrome through vaccination[6]. There were no cases of demyelination that occurred in the pivotal studies with aH5N1c. Given the potential risk but lack of clear signal, monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.7 Bell's Palsy

Bell's palsy is an acute, isolated palsy (nerve paralysis) of a branch of the 7th cranial nerve that occurs unilaterally. Case reports involving Bell's palsy after influenza vaccine have been published but a review by the IOM in 2011 rejected a causal relationship between influenza vaccination and Bell's Palsy[1]. A 2015 Institute for Vaccine Safety White paper agreed that, "*the available evidence does not indicate an increased risk in adults and overall evidence does not support an increased risk in any age group*," though the authors acknowledge that "*some signals suggested the possibility of an increased risk of Bell's palsy*."[6] In the pivotal trials of aH5N1c, there was one report of Bell's palsy (PT "facial paralysis"), a 71-year-old female developed it 39 days after vaccination. The investigator attributed the cause in the report to be a concomitant vaccine, Fluvax, administered at the same time as aH5N1c. Based on available data there appears to be no causal association between Bell's Palsy and influenza vaccination, and there was no concerning cluster of events during preapproval studies. However, Bell's palsy has been reported in association with influenza vaccination and a possibility of risk is not completely eliminated. Given this, the sponsor's listing of Bell's Palsy as an "Important Potential Risk" in their Pharmacovigilance Plan is reasonable and monitoring this potential adverse event with routine pharmacovigilance is appropriate.

7.2.8 Hypersensitivity Reactions

"Hypersensitivity reactions" was not listed on the applicant's initial pharmacovigilance plan, but was added at the request of the FDA. Hypersensitivity or anaphylaxis is a potential risk of any biologic, and in a review by the Institute of Medicine from 2011 the committee felt that "the evidence convincingly supports a causal relationship between influenza vaccine and

anaphylaxis[1]." The committee noted that many allergic reactions occurred in egg allergic individuals. Flucelvax and aH5N1c are both egg free vaccines, so this risk should be diminished. However, allergic reactions remain a concern for Flucelvax, a vaccine sharing a common manufacturing process intended for vaccination against the seasonal Flu. In the Flucelvax Package Insert, anaphylaxis is addressed as follows:

> *"Warnings and Precautions*
> *Section 5.3 Preventing and Managing Allergic Reactions*
> *Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine."*
>
> *6.2 Postmarketing Experience*
> *Immune system disorders: Anaphylactic reaction, angioedema."*

In the unsolicited safety set in preapproval trials, there were 4 events (0.1%): 2 episodes of hypersensitivity that were mild, one episode of moderate drug hypersensitivity and one type IV hypersensitivity reaction all occurring during the treatment period. Additionally, hypersensitivity has been documented during the postmarket period with Flucelvax[12]. Therefore, as with Flucelvax, it is appropriate to monitor hypersensitivity as a potential risk using routine surveillance.

7.2.9 Syncope

Syncope was not listed on the applicant's initial pharmacovigilance plan, but was added at the request of the FDA. Syncope, or sudden loss of consciousness, has been associated with vaccines of any type including influenza vaccines, with the main cause being a vasovagal reaction to the injection itself rather than the contents of the vaccine[1]. Therefore, aH5N1c could potentially pose a risk of syncope related to vaccination. Syncope has also been seen in the postmarketing review of Flucelvax and section 6.2 of the Flucelvax PI mentions syncope as an adverse event seen in the postmarket setting. In the pivotal trials, there were 3 episodes (0.1% of the unsolicited safety set) of presyncope that occurred during the treatment period, 2 mild and one severe. Though cases did occur, there is no clear signal in the clinical trials. Therefore, it is appropriate to monitor hypersensitivity as a potential risk using routine surveillance.

7.3 Missing Information

7.3.1 Safety During Pregnancy or lactation and pregnancy registry

As described above, there were 55 women who became pregnant during the studies submitted for approval. Though there were no congenital abnormalities reported, a significant number of patients were lost to follow up (12 of 55 [22%]). Because of the need to assess safety of the vaccine in pregnant women, the FDA requested the sponsor develop a pregnancy registry as a postmarketing commitment. The sponsor agreed to the FDA request to develop a pregnancy registry as a postmarketing commitment in submission 125692/0/37 (submitted November 20, 2019). In order to develop the registry, the sponsor requested a post approval meeting with CBER, BARDA, and CDC. The sponsor also committed to submitting a draft concept protocol for the in-pandemic registry by December 31, 2020. In the event of a H5N1 pandemic, the FDA would notify the sponsor to submit the protocol. The sponsor would then submit the final protocol within 90 days after notification by the FDA to finalize the protocol. The sponsor would initiate the registry within 60 days after this FDA notification. The sponsor would complete the

study within 24 months after initiation of the registry and submit the final clinical study report 12 months after final data is collected.

7.3.2 Safety and Immunogenicity in infants <6 months of age

On February 21, 2015, the FDA granted a deferral for the applicant for patients <6 months of age with the agreement that the applicant would initiate a trial in the postmarket setting to study vaccine immunogenicity and safety for infants <6 months. The purpose of the study V89_19 would be to use half dose vaccine to observe safety and immunogenicity. The applicant would enroll 200 subjects <6 months of age and give half dose 3.75 µg with (b) (4) MF59. The subjects would be followed for solicited and unsolicited adverse events.

8 Section 6.2 Labeling

Though aH5N1c has not been approved anywhere in the world, Seqirus has other vaccines that either contain the same adjuvant (Fluad) or have the same manufacturing process (Flucelvax) as aH5N1c. Given that the postmarketing experience of these vaccines may be useful for patients receiving aH5N1c, the FDA asked the sponsor to submit language for the aH5N1c US Package Insert *Section 6.2 Postmarketing Experience* detailing AEs seen for the vaccines above. Because of the vaccines' similarity to aH5N1c, knowledge of these AEs would make clinicians aware of AEs that potentially could occur following receipt of aH5N1c. The sponsor submitted proposed language on November 20, 2019, and after review, the FDA is proposing adding the below language to *Section 6.2 Postmarketing Experience* of the US Package Insert for AUDENZ.

> "*There is no postmarketing experience following administration of AUDENZ.*
> *The following adverse events have been reported during postmarketing use of U.S.-licensed*
> *seasonal influenza vaccines and pandemic influenza vaccines used outside of the U.S. during*
> *the Influenza A 2009 (H1N1) pandemic. Because these vaccines either contain the same MF59 adjuvant or share the same manufacturing platform as AUDENZ, similar adverse events may be seen in post-marketing experience with AUDENZ.*
> *Because spontaneously reported events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence or to establish a causal relationship to the vaccine.*
> *Blood and lymphatic system disorders: Lymphadenopathy.*
> *Immune system disorders: Hypersensitivity reactions including angioedema and anaphylaxis.*
> *Nervous system disorders: Bell's Palsy, convulsions, including febrile convulsion, demyelination, encephalitis, Guillain-Barré Syndrome, neuritis, paresthesia, syncope.*
> *Skin and subcutaneous tissue disorders: Urticaria, pruritis, non-specific rash.*
> *Musculoskeletal and connective tissue disorders: Muscular weakness*."

The language is reasonable and appropriately describes AEs seen with other influenza vaccines either containing MF59c (Fluad) or sharing the same cell-based manufacturing process (Flucelvax).

9 Recommended Pharmacovigilance actions

Should this product be approved, DE agrees with the pharmacovigilance activities proposed by the applicant in the PVP (version 1.0, dated October 2, 2019) submitted under original BLA 125692/0.28, including routine pharmacovigilance with adverse event reporting as required under 21 CFR 600.80. DE agrees with the sponsor's proposed timeline for a pregnancy registry as a postmarketing commitment and will review the protocol when submitted by the sponsor.

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