Summary Basis of Regulatory Action

Date: May 23, 2016

From: Roshan Ramanathan M.D., M.P.H., Committee Chair

BLA/ STN: 125408/101

Applicant Name: Seqirus, Inc.

Date of Submission: November 20, 2014

PDUFA Goal Date: July 22, 2016

Proprietary Name: FLUCELVAX™

Established Name: Influenza Vaccine

Indication: FLUCELVAX is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Flucelvax is approved for use in persons 4 years of age and older.

Dosage Forms: Suspension for injection supplied in 0.5 mL single-dose, prefilled syringes

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

□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.

Specific Documentation used in Developing the SBRA	**Reviewer**
Clinical Review	Gueorgui Dubrocq, M.D. Roshan Ramanathan M.D., M.P.H.
Pharmacovigilance Review	Scott Winiecki, MD
Statistical Clinical Review	Zhong Gao, Ph.D.
CMC/Bioassay Review	Paul Keller, Ph.D.
Bioresearch Monitoring Review	Colonious King
Labeling Review	Gueorgui Dubrocq, M.D. Roshan Ramanathan M.D.,M.P.H. Zhong Gao, Ph.D. Scott Winiecki, M.D. Sonny Saini, PharmD, M.B.A.
Communications and Documentation	Bernard McWatters, Ph.D David Staten, Ph.D.

1. INTRODUCTION

On November 20, 2014, the applicant submitted a supplement to their Biologics License Application (sBLA) for Flucelvax (Influenza Vaccine) to extend the indication for use in children and adolescents 4 to <18 years of age for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. Flucelvax contains the purified surface proteins (hemagglutinin and neuraminidase) from each of the three influenza virus strains recommended annually by the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The antigens contained in Flucelvax are derived from virus propagated in Madin Darby Canine Kidney (MDCK) cells. This preservative-free, non-adjuvanted vaccine is presented in a pre-filled (single-dose) syringe as a suspension for intramuscular injection. The final product contains a total of 45 micrograms (mcg) hemagglutinin per 0.5 mL dose in the ratio of 15 mcg hemagglutinin each of the three influenza strains.

2. BACKGROUND

Flucelvax was approved for active immunization against influenza for use in adults 18 years of age and older on November 20, 2012. The approval was based on the results of seven clinical trials in which a total of 5682 subjects received a single dose of Flucelvax. The efficacy of Flucelvax in adults 18 to <50 years of age (N=11,404) was evaluated in a randomized, observer-blind, placebo-controlled trial which demonstrated 83.8% vaccine efficacy against culture-confirmed symptomatic influenza illness due to antigenically matched strains (lower bound of the one-sided 97.5% confidence interval (CI) was 61%). At the time of approval of Flucelvax for use in adults, the applicant was required to conduct two postmarketing studies (studies V58P12 and V58_31) evaluating the use of Flucelvax in children and adolescents 4 to <18 years of age according to the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

With this supplement, the applicant seeks to: 1) extend approval of Flucelvax for use in children and adolescents 4 to <18 years of age based on the findings from studies V58P12 and V58_31 and 2) fulfill the PREA requirement to conduct a pediatric study to evaluate the safety and effectiveness of Flucelvax in children 4 to <18 years of age (study V58_31). (The PREA requirement to conduct study V58P12 was fulfilled on April 28, 2015 with submission of the final clinical study report for this study to STN 125408/82.)

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

No significant changes to the manufacturing process were made to produce the clinical material used in studies supporting this supplement. Minor changes in manufacturing process and batch information for the formulated trivalent drug product and monovalent bulk drug substance were reviewed and found to be acceptable.

Biopharmaceutical Assays

Hemagglutination inhibition (HI) antibody titers were assessed in both clinical studies using two different assays using either cell culture-derived test antigens or egg-derived test antigens. Validation reports for the HI assays were submitted to the original BLA for Flucelvax (STN 125408/0, approved November 20, 2012) and found to be acceptable. CBER previously agreed that the cell-based HI assay could be used to support immunogenicity in the 4 to <18 year age group.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Nonclinical pharmacology/toxicology data were not required.

5. CLINICAL PHARMACOLOGY

Clinical pharmacology data were not required.

6. CLINICAL/STATISTICAL

a) Clinical Program

Two studies were included in this submission:

1) A Combined Phase 2/3, Observer-blind, Randomized, Multi-Center Study to Evaluate Safety, Tolerability and Immunogenicity of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture (Flucelvax) or in Embryonated Hen Eggs (Fluvirin^{TM}) in Healthy Children and Adolescents 3 to <18 Years of Age (Study V58P12, NCT 00645411);

2) A Phase 3, Observer Blind, Randomized, Controlled, Multicenter Study to Evaluate the Safety of Trivalent Subunit Influenza Vaccine Produced either in Mammalian Cell Culture or in Embryonated Chicken Eggs (Fluvirin), in Healthy Children and Adolescents 4 to <18 Years of Age (Study V58_31, NCT 01857206).

Study V58P12 was a phase 3, randomized, observer-blind study of healthy children and adolescents 3 to <18 years of age (N=3140) comparing the immunogenicity of Flucelvax to Fluvirin (U.S.-licensed egg-based influenza vaccine). The study was conducted in the United States and Europe during the 2007-2008 influenza season. The primary endpoint of the study was to demonstrate non-inferiority of Flucelvax compared to Fluvirin in persons 3 to <9 years of age with respect to HI geometric mean titer (GMT) ratio (Flucelvax/Fluvirin) and percentages of subjects achieving seroconversion (SCR). The SCR was defined as pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥ 1:40, or a 4-fold or higher increase from a pre-vaccination HI titer ≥1:10. The pre-specified criteria for success were that the lower bound of the 95% CI for the HI GMT ratio (Flucelvax/Fluvirin) is > 0.67 and the lower bound of the 95% CI for the difference in SCR between Flucelvax and Fluvirin is >-10%. .

As Fluvirin is not approved in the U.S. for use in children younger than 4 years of age, the applicant performed a subgroup analysis of immunogenicity in persons 4 to <9 years of age. Of note, a secondary objective of the study was to describe the immunogenicity of Flucelvax in persons 9 to <18 year of age; no criteria for success were pre-specified in this age group.

The results of the primary endpoint for children 4 to <9 years of age (study V58P12) are shown in Table 1.

Table 1. Study V58P12[1]: Non-inferiority Analysis of FLUCELVAX to a U.S. Licensed Comparator[2] in Children 4 to <9 Years of Age

	Ratio or Difference (95% CI) FLUCELVAX (N=441)[3]; Comparator[1] (N=430)[3]		
	A/H1N1	A/H3N2	B
GMT ratio[4,5] (FLUCELVAX / comparator)	0.89 (0.76-1.04)	0.56 (0.47-0.67)	0.85 (0.68-1.06)
Difference in Seroconversion Rates[4,6] (FLUCELVAX - comparator)	0% (-3% to 2%)	-7% (-12% to -2%)	0% (-6% to 7%)

[1] NCT 00645411
[2] FLUVIRIN (Influenza Vaccine)
[3]Per protocol population
[4]Cell-derived antigen hemagglutination inhibition (HI) assay results
[5]Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) for geometric mean titer (GMT) ratio (FLUCELVAX/comparator) was >0.67.
[6]Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI for difference in percentages of subjects with seroconversion (FLUCELVAX-comparator) was >-10%.

For children 4 to <9 years of age, the pre-specified criteria for demonstration of non-inferiority were met for the A/H1N1 and B influenza strains but not the A/H3N2 influenza strain. The lower bound of the two-sided 95% CI of the HI GMT ratio (Flucelvax/Fluvirin) was 0.47 with respect to the A/H3N2 strain. The lower bound of the two-sided 95% CI of the difference in seroconversion rate (Flucelvax-Fluvirin) was -12%.

A secondary objective of study V58P12 was to evaluate the immunogenicity of Flucelvax according to the 2007 CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines which states that the following criteria may support accelerated approval for the pediatric population: 1) the lower bound of the two-sided 95% CI for the percentage of subjects achieving SCR for HI antibody should meet or exceed 40%; 2) the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI titer ≥ 1:40 should meet or exceed 70%.

These criteria were met for Flucelvax with respect to the influenza A strains in both age groups. The percentage of children 4 to <9 years of age achieving a post-vaccination HI titer ≥ 1:40 to the influenza B strain contained in the vaccine was 66% (two-sided 95% CI: 61-70%).

Table 2. Study V58P12[1]: Immunogenicity Results[2] Post-Vaccination with Flucelvax in Children and Adolescents 4 to <18 Years of Age (Per Protocol Population)[3]

Children 4 to <9 years of age (Day 50)[4] (N=441)			
	A/H1N1	A/H3N2	B
HI Titer ≥1:40 % (95% CI)	99 (97-99)	99 (97-100)	64 (60-69)
Seroconversion[5] % (95% CI)	96 (94-98)	80 (76-84)	62 (57-66)
Children and Adolescents 9 to <18 years of age (Day 29) (N=142)			
	A/H1N1	A/H3N2	B
HI Titer≥1:40 % (95% CI)	99 (96-100)	100 (97-100)	95 (90-98)
Seroconversion[4] % (95% CI)	74 (66-81)	52 (44-61)	63 (55-71)

Source: Modified from STN 125408/101, CSR for V58P12 Addendum 3, Table 11.4.1-3-5, pages 56-63

[1] NCT 00645411

[2] Cell-derived antigen haemagglutination inhibition (HI) assay results

[3]Pre-specified, non-comparative immunogenicity success criteria were met if the lower limit of the two-sided 95% confidence interval (CI) of the percentage of subjects with HI titer ≥1:40 was ≥70% and the lower limit of the two-sided 95% CI of the percentage of subjects with seroconversion was ≥40%.

[4]Previously unvaccinated children 4 to <9 years of age received two doses of study vaccine, 4 weeks apart. Immunogenicity was assessed 29 days following second vaccination.

[5]Seroconversion is defined as a pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or at least a 4-fold increase in post-vaccination HI titer from a pre-vaccination HI titer ≥ 1:10.

CBER issued a Complete Response (CR) letter on September 17, 2015 informing the applicant that the data in the supplement did not support the effectiveness of Flucelvax in the 4 to <9 age group with respect to the A/H3N2 strain (see Table 1). A Type A meeting was held on October 29, 2015 in which CBER informed the applicant that licensure of Flucelvax in persons 4 to <18 years of age could be considered under the accelerated approval regulations (21 CFR 601.40-46), using the CBER immunogenicity criteria described in the 2007 CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. In addition, a post-approval clinical endpoint study would be required to verify clinical benefit. On January 20, 2016, the applicant requested approval for an indication in individuals 4 to <18 years of age for Flucelvax under the accelerated approval provisions with a proposal to perform a clinical endpoint study (Study V130_XX) to verify benefit which was agreed upon by CBER.

Bioresearch Monitoring (BIMO) Inspection

BIMO inspections of two foreign and one domestic clinical investigator study sites did not raise concerns regarding the data submitted to this BLA.

b) Pediatrics

Pediatric Research Equity Act Requirements (21 U.S.C. 355c)

This supplement included an application for a new dosing regimen (one or two doses in children 4 through 8 years of age depending on vaccination history). For this reason, according to PREA, this supplement was required to contain an assessment of the safety and effectiveness of the product for the claimed indication in children < 4 years of age unless this requirement is waived, deferred, or inapplicable. The review committee presented the pediatric plan to the FDA Pediatric Review Committee (PeRC) on February 10, 2016. The PeRC agreed with CBER on the following plan:

1. The postmarketing requirement to conduct the pediatric study V58_31 to evaluate the safety of Flucelvax in children and adolescents 4 to <18 years of age is fulfilled with submission of this

supplement STN 125408/101. The data from this study supported the safety of Flucelvax for use in children and adolescents 4 to <18 years of age. (See Section 7.)

2. The pediatric study for persons 6 months to 4 years of age is deferred for this application because this product is ready for approval in persons 4 years of age and older and the pediatric studies in persons 6 months to 4 years of age have not been completed.

   The applicant was released from PREA postmarketing requirement #4 identified in the November 20, 2012 Flucelvax approval letter to conduct study V58_35 (deferred study to evaluate the safety and immunogenicity of Flucelvax in persons 6 months to <4 years). This postmarketing requirement was replaced with a new postmarketing study requirement to conduct study V130_10 (deferred study to evaluate safety and immunogenicity of the quadrivalent formulation of Flucelvax in persons 6 months to <4 years of age).

3. The pediatric study requirement for ages 0 to < 6 months is waived because Flucelvax does not provide a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of infants < 6 months of age. Available data indicate that serum antibody responses to inactivated influenza vaccines in infants < 6 months of age are not as robust as in older children due to inherent immaturity of the immune system and interference from maternal antibody.

7. SAFETY

7.1 Safety Data from Clinical Studies and Postmarketing Experience

The safety database (from studies V58_31 and V58P12) included 3346 children and adolescents 4 to <18 years of age who received Flucelvax. The most common (≥10%) local and systemic reactions in children 4 to <9 years of age were pain (29%), erythema (11%) and fatigue (10%). The most common (≥10%) local and systemic reactions in children and adolescents 9 to <18 years of age were pain (34%), myalgia (15%), headache (14%) and erythema (14%). For subjects 4 to <18 years of age, 8 serious adverse events (SAEs) (<1%) were reported by Flucelvax recipients (N=3345) and 5 SAEs (<1%) were reported by Fluvirin recipients (N=1828) within 28 days post-vaccination. None of the SAEs were determined to be related to vaccinations. No deaths were reported in either the Flucelvax or Fluvirin groups in both studies during the treatment or follow up period 6 months after last vaccination.

Overall, the safety findings were consistent with those previously described in the prescribing information for Flucelvax and for other trivalent inactivated influenza vaccines. No new safety signals were identified in the review of this supplemental BLA and the safety profile of Flucelvax was acceptable for approval of this application.

Pharmacovigilance Plan

No safety signals were identified in the pre-licensure data. The applicant's plan to establish routine pharmacovigilance was found to be acceptable.

8. ADVISORY COMMITTEE MEETING

The review committee determined that presentation of the supplement to the VRBPAC was not required because the data submitted to the supplement did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

There are no other relevant regulatory issues of note.

10. LABELING

The review committee requested that the applicant revise the label to include percentages of children 4 to <8 years of age reporting moderate and severe adverse reactions (Section 6 of the package insert for

Flucelvax). The review committee determined that results of the non-inferiority analysis of Flucelvax to Fluvirin according to vaccine strain in addition to the results of the immunogenicity analysis (percentage of subjects with HI ≥ 1:40 and percentage of subjects with seroconversion) to support accelerated approval should be included in the package insert. Section 1(Indications and Usage) of the package insert was revised to explain that data demonstrating a decrease in influenza disease after vaccination of children and adolescents 4 to <18 years of age with Flucelvax are not available. Additional editorial changes were made to improve the clarity of the package insert. These changes were accepted by the applicant.

Pregnancy and Lactation Labeling Rule (PLLR)
The applicant is required to submit labeling that conforms to the Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling by June 30, 2019.

11. **RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT**

a) Recommended Regulatory Action: Based on review of the product and clinical data, the review committee recommends licensure of Flucelvax for use in persons 4 to <18 years of age under the accelerated approval regulations (21 CFR 601.40-46).

b) Risk/Benefit Assessment: The risk:benefit assessment of Flucelvax for use in the pediatric population 4 to <18 years of age is favorable. The immunogenicity data submitted to this supplement indicate that Flucelvax has an effect on a surrogate marker of activity (HI titer) that is reasonably likely to predict clinical benefit. The most common adverse reactions associated with Flucelvax identified pre-licensure are local and systemic adverse reactions; no serious adverse events or deaths attributable to vaccination were reported.

c) Recommendation for Postmarketing Risk Management Activities: Postmarketing risk management activities (such as Risk Evaluation and Mitigation Strategies) are not recommended.

d) Requirement for Postmarketing Activities:
Accelerated Approval Postmarketing Requirement (21 CFR 601.41)
Products approved under the accelerated approval regulations require that the applicant study the product further to verify and describe clinical benefit. The applicant is required to conduct the following study: A Phase III, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of the Quadrivalent Formulation of Cell-Based Influenza Vaccine Compared to a Non-Influenza Comparator Vaccine in Persons ≥4 to <18 Years of Age.
Final Protocol Submission Date: September 30, 2016
Study Completion Date: March 30, 2017
Final Report Submission: August 30, 2018

PREA Postmarketing Requirements (Section 505B(a) of the Federal Food, Drug and Cosmetic Act)
The applicant is released from the PREA postmarketing requirement identified in the November 2012 Flucelvax approval letter to conduct a safety and immunogenicity study in subjects 6 months to <4 years of age to compare the antibody of Flucelvax to a U.S. licensed control using a non-inferiority study design (study V58_35). This postmarketing requirement is replaced with the requirement to conduct a safety and immunogenicity study in children 6 months to < 4 years of age (Study V130_10).
Final protocol submission date: June 30, 2019
Study completion date: August 30, 2020
Final report submission: February 28, 2021

Concurrence Page

Application Type and Number: BLA*/* STN: 125408/101

COMMUNICATION TYPE: Summary Basis of Regulatory Action

History: Drafted By: R. Ramanathan 4/18/2016

Revisions by: Zhong Gao 4/19/2016, Gueorgui Dubrocq 4/22/2016, Rakesh Pandey 5/9/2016, Douglas Pratt 5/16/2016, Wellington Sun 5/19/2016, Marion Gruber 5/17/2016

Concurrence:

Office/Division	**Name/Signature**	**Date**
OVRR/DVRPA	**Roshan Ramanathan**	**5/23/2016**
OVRR/DVRPA	**Jeff Roberts**	**5/23/2016**
OVRR/DVRPA	**Wellington Sun**	**5/23/2016**