Summary Basis of Regulatory Action

Date: May 23, 2016

From: Santosh Nanda, DVM, Ph.D., Committee Chair

BLA/ STN: 125408/127

Applicant Name: Seqirus, Inc.

Date of Submission: April 24, 2015

PDUFA Goal Date: May 23, 2016

Proprietary Name: FLUCELVAX™ Quadrivalent

Established Name: Influenza Vaccine

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

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 – Date of Review
Clinical Review	Ralph LeBlanc, M.D., Ph.D. – May 20, 2016
Pharmacovigilance Review	Scott Winiecki, M.D. – February 10, 2016
Statistical Review, Clinical	Lihan Yan, PhD. – January 20, 2016
Statistical Review, Bioassay	Zhong Gao, Ph.D. – February 9, 2016
Biomonitoring Review	Carla V. Jordan – January 14, 2016
Product Review	Wei Wang, Ph.D. – April 25, 2016
Proprietary Name/Labeling Reviews	Ralph LeBlanc, M.D., Ph.D.; Sonny Saini, Pharm.D., MBA; Helen S. Gemignani; Josephine Resnick, Ph.D.; Daphne Stewart, Santosh Nanda, DVM, Ph.D. – November 3, 2015
Testing Method and Analytical Chemistry	Manju Joshi, Ph.D.; Tao Pan, Ph.D., Josephine Resnick, Ph.D. – March 21, 2016
CMC/Facilities and Equipment	Jeremy L. Wally, Ph.D., MA, PMP, CQPA – April 20, 2016
Communication and Documentation	Helen S. Gemignani; Josephine Resnick, Ph.D. – May 23, 2016

Cross referenced applications:

IND 15744, "Influenza Virus Quadrivalent (purified neuraminidase and hemagglutinin glycoproteins; A/A/B/B; Madin-Darby Canine Kidney cells) Vaccine (QIVc)."

STN 125408/101, "To extend the current age indication to include children from 4 to < 18 years of age (to fulfill PMR #2 under 125408/0)."

1. Introduction

On April 23, 2015, Novartis Vaccines and Diagnostics, Inc. (now Seqirus, Inc.) submitted a supplement to their Biologics License Application (sBLA) for Influenza Vaccine, Flucelvax, to include a quadrivalent formulation for intramuscular administration. They proposed a proprietary name Flucelvax Quadrivalent for this formulation. Like the currently approved Flucelvax® trivalent influenza vaccine, Flucelvax Quadrivalent is also for intramuscular injection, and is a "subunit" influenza vaccine prepared from viruses propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line. Flucelvax Quadrivalent (referred to as "QIVc" in this document) contains 15 μg hemagglutinin (HA) antigen per virus strain (A/H1N1, A/H3N2, and two B antigens) per 0.5 mL, for a total of 60 μg HA per mL, is indicated for persons 4 years of age and older and is going to be marketed in single dose syringe presentation.

In this BLA supplement, the applicant, Seqirus, Inc.(formerly known as Novartis Vaccines and Diagnostics, Inc.), has submitted the information on manufacturing facilities, equipment, processes and assay validation studies to provide data demonstrating that the manufacturing process is similar to that of currently approved Flucelvax® vaccine. In addition, the applicant submitted clinical data to demonstrate a similar safety profile and non-inferiority of immunogenicity of the vaccine compared to Flucelvax® vaccine containing either of two lineages of influenza B in the target populations establishing that the presence of a second B strain did not interfere with immune responses elicited by the other B strain or the two A strains.

2. Background

The applicant (Seqirus) submitted the supplemental Biologics License Application (sBLA) to pursue approval of QIVc as a supplement to the existing Flucelvax® license, based on demonstration of noninferior immunogenicity and comparable safety with respect to Flucelvax® (trivalent) vaccine under traditional approval. This supplement is intended to support the use of QIVc for use in the prevention of influenza in persons 4 years of age and older. By adding an additional type B strain of a second lineage to the trivalent influenza vaccine containing a single strain each of H1N1, H3N2 and Type B influenza viruses, the resulting quadrivalent vaccine would provide broader protection against both lineages, B/Yamagata and B/Victoria, of the Type B influenza virus circulating during a particular epidemic season. The original PDUFA goal date for approval was February 22, 2016, it was changed to May 23, 2016 after Seqirus submitted a major amendment to this sBLA requesting accelerated approval for ages > 4 years to <18 years based on 21 CFR 601 Subpart E.

The trivalent inactivated influenza vaccine (surface antigen, inactivated, cell-based), under the trade name Flucelvax® (referred to as "TIVc" in this document) from Novartis Vaccines and Diagnostics, Inc., was approved for use in adults 18 years of age and older in November 20, 2012 under the original BLA for Flucelvax (STN 125408/0). A supplemental BLA (sBLA, STN 125408/101) to extend the age indication for use in individuals 4 to < 18 years of age (children) was submitted to the agency on November 20, 2014.

Data submitted for the TIVc vaccine to supplement STN 125408/101 did not support traditional approval for individuals 4 to <18 years of age, based on non-inferiority of immunogenicity compared to Fluvirin, a licensed trivalent influenza vaccine. CBER stated during the Type A meeting held on October 29, 2015 that we would consider accelerated approval for an indication in individuals 4 to <18 years of age for both the trivalent (TIVc) and quadrivalent (QIVc) formulations based on the immune response data submitted to STNs 125408/101 and this supplement.

Data in this BLA supplement are based on studies conducted under IND 15744, which went in effect in October 2013. The safety and immunogenicity of Flucelvax QIVc were evaluated in two clinical studies conducted in the United States.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The monovalent bulk is prepared by propagation of influenza working virus seed in MDCK cell suspension culture. The vaccine is prepared by BPL inactivation, detergent disruption, and purification, and formulated to contain 15 μg hemagglutinin (HA)/strain per 0.5 mL dose (similar to the trivalent product), thus totaling 60 μg HA per 0.5 mL dose. The drug product manufacturing process for QIVc is the same as that of the licensed Flucelvax (TIVc), except for the formulation of final bulk (i.e., four influenza strains versus three influenza strains). CBER concluded that the validation of the QIVc final bulk formulation/mixing processes, including stability studies on consistency lots, is sufficient for approval of the QIVc manufacturing process. The Single Radial Immunodiffusion (SRID) assay was used for product characterization and potency assessment. The validation of SRID conducted at the applicant's Holly Springs facility is acceptable. Evaluation of clinical consistency for the QIVc drug product is not required. Stability data is included in the submission to support the requested shelf life of final product for 12 months at 2-8 ^{0}C, and the date of manufacture is designated as the filling date of the final container.

Drug Substance

The upstream manufacturing processes of QIVc and the batch release acceptance criteria are identical to those for approved Flucelvax (BLA 125408, Biologics License # 1751). The descriptions of manufacturing process and process controls, Batch analysis information and stability study information of monovalent lots, provided in the BLA supplement, were acceptable.

Drug Product

The QIVc Drug Product is formulated in the Holly Springs facility by combining the monovalent concentrates of the four influenza virus strains identified for the upcoming influenza season and then diluting to the vaccine strength of 30 µg of HA per strain/ mL for a total of 120 µg HA/ mL. The information provided in the supplement is sufficient to show validity of the QIVc formulation and filling process. There is no impact on the critical quality attributes of the drug product produced by the addition of a fourth strain at both and Holly Springs sites. Formulation and filling processes are comparable between QIVc Phase 3 Process Performance Qualification (PPQ) material from Holly Springs (Batches Three consecutive successful PPQ runs were performed at the routine production batch size of The PPQ runs operated within the defined process parameters and the product met release specifications. There are no significant changes in the formulation and filling processes between trivalent and quadrivalent formulations. There are no changes to the analytical methods used for trivalent and quadrivalent drug product, except the specification change due to the additional strain.

In the original submission 125408/127 Seqirus stated that the monovalent bulks for QIVc were produced at both and Holly Springs sites. Monovalent bulks were mixed and formulated with phosphate buffer saline at the and Holly Springs facilities. The formulated quadrivalent bulks at were transported to for final sterile filling. The formulated quadrivalent bulks at Holly Springs were filled for final product at Holly Springs. Equipment at each site is comparable, and there are no equipment or facility changes between the Flucelvax TIVc and Flucelvax QIVc formulation and filling processes. However, later during the review of the sBLA, Seqirus informed CBER that they had decided that the QIVc drug product will be made only at the Holly Springs facility.

b) CBER Lot Release

A testing plan for QIVc was developed by the Division of Biological Standards and Quality Control with concurrence from the review committee, and product testing was performed on final bulk with all specifications being met. Completed lot release protocols were reviewed and approved by CBER. For routine lot release, the applicant will submit samples from final bulk along with a Lot Release Protocol, and QIVc will be released by CBER based upon final bulk testing results.

c) Facilities review/inspection

Facility information and data provided in the Prior Approval Supplement were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of FLUCELVAX Quadrivalent are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 1. Manufacturing Facilities Table for FLUCELVAX Quadrivalent

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Results/ Justification
Novartis Vaccines and Diagnostics 475 Green Oaks Parkway Holly Springs, NC 27540, USA *Drug Substance* Manufacturing *Drug Product* Manufacturing Syringe Filling and Inspection Release Testing	3007867647	080102141	Waived	CBER February 3-14, 2014 VAI
Novartis Vaccines and Diagnostics Limited (b) (4) *Drug Product* Release Testing	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI
(b) (4) *Drug Product* Release Testing	(b) (4)	(b) (4)	Waived	(b) (4) NAI

CBER conducted a Pre-Approval Inspection of Novartis Vaccines and Diagnostics Limited from February 3-12, 2014. The inspection was classified as VAI. All inspectional 483 observations were resolved. Team Biologics conducted a surveillance inspection of Novartis Vaccines and Diagnostics Limited from . The inspection was classified as VAI. All inspectional 483 observations were resolved.

ORA conducted a surveillance inspection of . The inspection was classified as NAI. No issues were identified.

d) Environmental Assessment

The PAS included a request for categorical exclusion from an environmental assessment under 21 CFR 25.31 (c). 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) Container Closure System

The drug product is filled into a pre-sterilized and glass syringe with a tip cap and plunger stopper, and a plastic rigid tip cap overseal Container closure integrity testing was performed using a

Method using [redacted] detection by the service provider [redacted] all acceptance criteria were met.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology data were not provided in the supplement as such data was not needed.

5. Clinical Pharmacology

Clinical pharmacology data were not provided in the supplement as they were not required.

6. Clinical/ Statistical/Pharmacovigilance

a) Clinical Program

The application included safety and immunogenicity data from two clinical trials: 1) Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell- based Trivalent Subunit Influenza Vaccines in adults over 18 years old (V130_01) and 2) Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell- based Trivalent Subunit Influenza Vaccines in children 4-17 years old (V130_03). Across the two studies, 2376 subjects completed the study for QIVc, 1212 subjects received a licensed TIVc, and 1193 subjects received an investigational trivalent influenza vaccine containing an additional lineage influenza B strain. All studies were conducted in the United States. The Hemagglutination Inhibition (HAI) assay was used to assess the immunogenicity of the vaccine. The validation studies of HAI showed that the validation parameters met the acceptance criteria.

Clinical data from studies V130_01 and V130_03 are included in this supplemental application. Their objective was to demonstrate a similar safety profile and non-inferior immunogenicity of the vaccine compared to Flucelvax®, and to establish that the presence of a second B strain did not interfere with immune responses elicited by the other B strain or the two A strains in the target populations.

In Study V130_03, QIVc was compared to TIVc in children ages >4 years to <18 years. The data from V130_03 showed that both co-primary endpoints were met, however these data could not be used to support a traditional approval pathway because Flucelvax® was a licensed seasonal influenza vaccine under accelerated approval at the time of this approval. The first co-primary endpoint was met based on the per protocol population: the GMT of all 4 influenza strains as measured on day 1, day 22 (“previously vaccinated” subjects) and day 50 (“not previously vaccinated” subjects).Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the non-inferiority margin of 1.5.[data not shown]. The second co-primary endpoint was also met based on the per protocol population: percentages of subjects achieving

seroconversion and HI titer ≥1:40 as calculated for all 4 influenza strains on day 1, day 22 ("previously vaccinated" subjects) and day 50 ("not previously vaccinated" subjects).The differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination, criteria for success, was the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%. [data not shown]. These findings indicate that Flucelvax QIVc was immunogenic against influenza strains contained in the vaccine, based on GMTs and HI antibody seroconversion rates and percentages of subjects achieving a HI titer ≥1:40 at three weeks post vaccination. The addition of the second influenza B strain did not cause immunological interference with the other influenza strains contained in the vaccine. Because TIVc was approved for persons 4 to <18 years old under 21 CFR 601.41 (May 23, 2016) and the confirmatory study to verify clinical benefit has not been completed for TIVc, the QIVc data from Study V130_03 could only support accelerated approval based on the CBER immunogenicity criteria as described in the FDA Guidance for Industry "*Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*," in children 4 to <18 years of age. There were no safety concerns identified.

The CBER Guidance criteria for seroconversion and for the percentage of subjects achieving HI titers ≥1:40, 3 weeks after vaccination, were met following QIVc, TIV1c and TIV2c vaccination, respectively (Table 2). This was a secondary endpoint in the Study and is the basis for the accelerated approval pathway for the Flucelvax Quadrivalent vaccine.

Table 2. Number (%) of Subjects with Seroconversion and HI Titer ≥1:40 (95% CI), 3 Weeks After the Last Vaccination, HI Assay - Full Analysis Set

	QIVc	TIV1c/or/TIV2c[a]
H1N1 Seroconversion Day 22 or day 50[b]	N=1113 812 (73%) (70%-76%)	N=566 417 (74%) (70%-77%)
HI titer ≥1:40 Day 22 or day 50[b]	N=1113 1104 (99%) (98%-100%)	N=566 563 (99%) (98%-100%)
H3N2 Seroconversion Day 22 or day 50[b]	N=1112 527 (47%) (44%-50%)	N=566 287 (51%) (47%-55%)
HI titer ≥1:40 Day 22 or day 50[b]	N=1112 1109 (100%) (99%-100%)	N=566 563 (99%) (98%-100%)
B1 Seroconversion Day 22 or day 50[b]	N=1112 743 (67%) (64%-70%)	N=566 371 (66%) (61%-69%)
HI titer ≥1:40 Day 22 or day 50[b]	N=1112 1028 (92%) (91%-94%)	N=566 525 (93%) (90%-95%)
B2 Seroconversion Day 22 or day 50[b]	N=1108 809 (73%) (70%-76%)	N=556 401 (72%) (68%-76%)
HI titer ≥1:40 Day 22 or day 50[b]	N=1108 1009 (91%) (89%-93%)	N=556 504 (91%) (88%-93%)

Source: *Adapted from sBLA 125408.127, CSR for V130_03, Table11.4.1-3, p.110*

[a]*For H1N1, H3N2 and B1 influenza strains TIV1c data is presented, whereas for B2 influenza strain TIV2c data is presented.*

[b]*Analysis was performed on day 22 for previously vaccinated subjects and on day 50 for not previously vaccinated subjects.*

Results: *CBER immunogenicity criteria were met: The percentage of subjects achieving seroconversion for HI antibody was >40%. The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 was >70%.*

The data from Study V130_01 in adults ages 18 years and above support the approval of Flucelvax QIVc under traditional approval pathway and the non-inferiority criteria for the co-primary endpoints were met for all four influenza vaccine strains.

The first co-primary endpoint for Study V130_1 was the demonstration of non-inferiority of antibody responses of QIVc to comparator TIV1c based upon the ratio of GMT for each of the 4 vaccine strains, separately, after vaccination. These results are

presented in Table 3. The second co-primary endpoint was the demonstration of the non-inferiority of QIVc compared to TIVc as determined by seroconversion rates for each of the 4 vaccine strains and these results are presented in Table 4.

Table 3. Geometric Mean Titers (95% CI), and Vaccine Group Ratios, 3 Weeks After the Vaccination, HI Assay-Per Protocol Set

	QIVc	TIV1c/or/TIV2c[a]	Vaccine Group Ratio
H1N1	N=1250	N=635	
Day 22	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9-1.1)
H3N2	N=1250	N=635	
Day 22	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9-1.1)
B1	N=1250	N=635	
Day 22	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8-1.0)
B2	N=1250	N=639	
Day 22	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9-1.0)

Source: *Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.3, p.521*
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
[a]*For H1N1, H3N2 and B1 strain ratio of GMTs was calculated as TIV1c/QIVc, whereas for B2 strain ratio of GMTs was calculated as TIV2c/QIVc.*
Result: *The non-inferiority criteria were met; The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the non-inferiority margin of 1.5.*

Table 4. Number (%) of Subjects with Seroconversion (95% CI) and Vaccine Group Differences, 3 Weeks After the Vaccination, HI Assay – Per Protocol Set

	QIVc	TIV1c/or/TIV2c[a]	Vaccine Group Difference
H1N1 Day 22	N=1250 615 (49.2%) (46.4%-52.0%)	N=635 309 (48.7%) (44.7%-52.6%)	-0.5% (-5.3%-4.2%)
H3N2 Day 22	N=1250 479 (38.3%) (35.6%-41.1%)	N=635 226 (35.6%) (31.9%-39.5%)	-2.7% (-7.2%-1.9%)
B1 Day 22	N=1250 457 (36.6%) (33.9%-39.3%)	N=635 221 (34.8%) (31.1%-38.7%)	-1.8% (-6.2%-2.8%)
B2 Day 22	N=1250 497 (39.8%) (37.0%-42.5%)	N=639 226 (35.4%) (31.7%-39.2%)	-4.4% (-8.9%-0.2%)

Source: *Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.2., p.435*
Abbreviation: *CI-confidence interval, HI- hemagglutination inhibition*
[a]*For H1N1, H3N2 and B1 strain differences in seroconversion was calculated as TIV1c/QIVc, whereas for B2 strain differences in seroconversion was calculated as TIV2c/QIVc.*
Results: *The non-inferiority criteria were met; the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%.*

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient is submitted, unless the requirement for assessment has been deferred or waived. A waiver from conducting studies with QIV in children from birth to <6 months of age was granted because available data in infants in this age group indicate that serum antibody responses to inactivated influenza vaccines are not as robust as in older children, likely due to the inherent immaturity of the immune system and interference from maternal antibody. Thus, use of Flucelvax QIVc in infants <6 months of age would provide no meaningful therapeutic benefit over initiating vaccination at 6 months of age, and the vaccine is not likely to be used in a substantial number of infants < 6 months of age.

The Study V130_03 was submitted in response to a PREA requirement under the original BLA 125408 and the data contained in this application fulfill PREA requirements for children and adolescents 4 to <18 years of age.

The pediatric studies for ages 6 months to 4 years of age are deferred because the product is ready for approval in persons 4 years of age and older and the pediatric studies (6 months to 4 years of age) have not been completed. The sponsor is expecting to use the results of an ongoing TIVc dose-finding study in children 6 months to <4 years to formulate the dose in QIVc for children in this age group. This application is subject to PREA because the addition of a second B strain is considered a new active ingredient. A PMR has been established and need to be fulfilled with the planned Flucelvax QIVc study in children 6 months to <4 years age using Flucelvax QIVc. The results from this QIVc study will complete the pediatric assessments for infants and children 6 months to 4 years of age (Study V130_10) for both Flucelvax (TIVc) and Flucelvax QIVc.

The applicant will also conduct a post-marketing pediatric study in >4 to < 18 years age group using Flucelvax QIVc to further clarify and confirm clinical benefit, as required for the accelerated approval of QIVc. This will be a clinical efficacy endpoint study with Flucelvax QIVc as the active influenza vaccine and meningococcal vaccine as the non-influenza comparator vaccine.

The pediatric development plan for Flucelvax QIVc was presented to the Pediatric Review Committee on February 10, 2016 and the Committee concurred with CBER's assessment.

Bioresearch Monitoring Inspection
A total of eight Bioresearch Monitoring (BIMO) inspections of clinical investigators were conducted in support of this supplement. The inspection reports did not reveal problems that impact the validity of the data submitted in the application.

7. Safety

Safety data showed that solicited adverse reactions associated with QIVc occurred at similar rates compared with TIVc formulation for all age groups.

In children ≥4 through <18 years of age, the most common injection-site reaction was pain (59%); tenderness for subjects ≥4 to <6 years of age (55%). Most of the solicited local AEs had their onset from 6 hours to 2 days after the vaccination and were mild to moderate in severity. The most common solicited systemic adverse events in children >4 years to < 18 years, that occurred at rates >10% were myalgia, headache, fatigue, sleepiness and irritability. Fevers ≥38.0 °C occurred in 3% of QIVc subjects, 4% of TIV1c subjects and 2% of TIV2c subjects, and one subject who received QIVc had a febrile convulsion. The rates of unsolicited AEs and the types of these events are within the range typically seen with routine childhood vaccinations and do not raise any concerns from a safety perspective. In adults 18 years and older, the most common injection-site reaction was pain

(33.6% in ≥18 years; 45.4% in ≥18 years <65 years); the most common solicited systemic adverse events were head ache (14% in ≥18 years; 18.7% in ≥18 years <65 years) and fatigue (13.5% in ≥18 years; 17.8% in ≥18 years <65 years). In adults >65 years of age, the most common injection-site reaction was pain (21.6%); the most common solicited systemic adverse event were head ache (9.3%) and fatigue (9.1%).

There were no deaths in the Study V130_03 in the children and 12 deaths occurred in Study V130_01, with 11 in the ≥ 65 years of age group but none were related to the study vaccine. No imbalances in the frequency or severity of unsolicited adverse events were observed among the treatment arms within each study, and there were no serious adverse events or New Onset of Chronic Disease (NOCD) cases related to the study vaccine.

CBER agreed that a clinical lot consistency evaluation is not required because the chemistry, manufacturing, and controls of the QIVc manufacturing processes are same with that of approved TIVc product.

Pharmacovigilance Plan
No safety signals were identified in the pre-licensure data. The applicant's pharmacovigilance plan, which establishes routine pharmacovigilance, is acceptable.

There are two populations (subjects < 4 years of age and pregnant women) in which important pharmacovigilance information does not exist. In order to address the use of QIVc in subjects 6 < 48 months of age, the sponsor proposes to conduct Study V130_10. The sponsor has also proposed to conduct a Pregnancy Registry for Flucelvax Quadrivalent to assess the safety of QIVc in pregnant women.

8. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee meeting was not held for Flucelvax Quadrivalent, as there were no novel issues that required additional expert advice, and the vaccine does not involve a new manufacturing process or indication. Moreover, the inclusion of an additional B strain in seasonal influenza vaccines has been discussed in previous advisory committee meetings, and four other quadrivalent influenza vaccines have already been approved.

9. Other Relevant Regulatory Issues

The indication for Flucelvax Quadrivalent in individuals 18 years of age and older is recommended for approval under the traditional approval process and for individuals 4 to <18 years of age in accordance with the accelerated approval regulations (21 CFR 601.41).

10. Labeling

To be consistent with similar US-licensed quadrivalent influenza vaccines, the proprietary name Flucelvax Quadrivalent was recommended and Seqirus agreed to it. The carton and syringe labels were reviewed and found to be acceptable after several minor changes. The

proposed package insert required some modifications and was reviewed in conjunction with the Flucelvax TIVc package insert. After negotiations with the applicant, the review committee reached a conclusion that the Prescribing Information for Flucelvax Quadrivalent is acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

Based on the review of the data provided regarding manufacturing process, as well as safety and effectiveness information on Flucelvax QIVc, the review committee recommends approving the sBLA for Flucelvax QIVc, for use in 18 years of age and older population under traditional approval pathway and for use in 4 to < 18 years of age population under accelerated approval pathway.

b) Risk/ Benefit Assessment

Flucelvax QIVc presents a favorable overall risk-benefit profile. There were no safety signals. The clinical and manufacturing information submitted in this sBLA support the safety and effectiveness of Flucelvax Quadrivalent for persons 4 years and older for the prevention of influenza (due to A and B types contained in the vaccine). Because clinical benefit for individuals 4 to <18 years of age is inferred from immunogenicity as a surrogate, clinical benefit is required to be confirmed by a clinical endpoint study.

d) Recommendation for Post-marketing Activities

The pediatric Study V130_10 in 6 months to 4 years of age for this application has been deferred and the deferred pediatric study is required under 505B(a) of the Federal Food, Drug, and Cosmetic Act (a required PREA post-marketing study).

Study V130_12 is a required post-marketing study to verify and confirm clinical benefit. This will be a clinical efficacy endpoint study to assess vaccine efficacy to prevent influenza in children >4 years to <18 years, where Flucelvax QIVc will be used as the active influenza vaccine and a non-influenza vaccine will be the control vaccine.

Seqirus agreed to establish a pregnancy registry as a post-marketing commitment that will enroll adult women vaccinated with Flucelvax QIVc during pregnancy and will collect data from vaccinated pregnant women at enrollment in the registry, at the end of the second trimester of pregnancy, and at delivery for the outcome of the pregnancy for both mother and infant. Seqirus will collect the data on a minimum of 600 prospectively enrolled and evaluable pregnant women. Seqirus will submit a study report for this product to CBER and continue enrollment pending CBER review and discussion of results with Seqirus as request by CBER. The estimated end of data collection will be August 31, 2020.