DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

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FROM: **Gueorgui Dubrocq, MD**
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TO: **BLA STN SUPPLEMENT# 125408/101**

SUBJECT: **Amendment-Complete Response Addendum**
FLUCELVAX (influenza Vaccine)
Human Influenza Virus Type A (H1N1; H3N2) and B Hemagglutinin Vaccine, Purified, Inactivated (Madin Darby Canine Kidney cells)

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APPLICANT: **Seqirus, Inc. (formerly Novartis Vaccines and Diagnostics, Inc.)**

REVIEW: **Chair: Roshan Ramanathan, MD, MPH**

Executive Summary

On September 17, 2015, a complete response (CR) letter was issued to Novartis Vaccines and Diagnostics, Inc. because CBER determined that the data did not support traditional approval as the immunologic non-inferiority of Flucelvax compared to Fluvirin (US licensed comparator) with respect to the A/H3N2 influenza strain was not demonstrated in subjects 4 to <9 years of age. Although immunologic non-inferiority between Flucelvax and a US licensed comparator was not demonstrated, data on the immune response of persons 4 to <18 years of age to Flucelvax (based on hemagglutinin inhibition (HI) geometric mean titer (GMT) ratio (Flucelvax/Fluvirin) and the difference in seroconversion rate) demonstrate that the biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Hence, the data submitted to this supplement support the approval of Flucelvax in persons 4 years of age and older under the accelerated approval regulations (21 CFR 601.40-41). According to these regulations, the applicant is required to perform a clinical endpoint study to verify benefit.

1. Regulatory background

The applicant sought traditional approval for Flucelvax in children and adolescents 4 to <18 years of age based on data from two clinical studies: study V58P12 and study V58_31. As described in the clinical review for STN 125408/101, Study V58P12, which evaluated the immunologic non-inferiority of Flucelvax compared to Fluvirin, did not demonstrate immunologic non-inferiority with respect to the A/H3N2 influenza strain in persons 4 to <9 years of age. Furthermore, a finding of lower immune response for the A/H3N2 strain was also apparent in the descriptive immunogenicity data in subjects 9 to <18 years of age. For this reason, a Complete Response (CR) letter was issued 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. A Type A meeting was held on October 29, 2015 in which CBER indicated that the applicant may consider seeking accelerated (rather than traditional) approval of Flucelvax in persons 4 to <18 years of age based on the studies contained in the submitted supplement. As per the 2007 CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2), accelerated approval can be considered 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 (21 CFR 601.41). For the purposes of accelerated approval of seasonal inactivated influenza vaccines, the HI antibody response criteria described in the 2007 CBER FDA Guidance (2) may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. Approval under this section will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit and such post-marketing studies must also be adequate and well-controlled and should be conducted with due diligence (21 CFR 601.41). On January 20, 2016, Novartis Vaccines and Diagnostics, Inc. submitted their response to the CR requesting 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 using the Flucelvax Quadrivalent (QIVc).

2. Review Strategy

The applicant did not submit new clinical data in the complete response. The clinical review for STN 125408/0 focused on the question of whether the data submitted in the supplement from studies V58P12 and V58_31 supported traditional approval. For this reason, a detailed analysis of the secondary endpoints (which evaluated the immunogenicity of Flucelvax compared to Fluvirin according to the 2007 CBER Guidance which include immunogenicity endpoints to support accelerated approval) was not included in the review (see Section 6.1.1). This addendum to the September 17, 2015 STN 125408/101 Clinical Review (original clinical review) focuses on the question of whether data submitted in this supplement from the same studies support accelerated approval of Flucelvax in in children and adolescents 4 to <18 years of age. Hence, the results of the secondary endpoints (analysis of immunogenicity data according to 2007 CBER Guidance) are discussed here. The safety analysis will be summarized here in the context of the risk-benefit assessment, but for details regarding the safety analysis, please see the original clinical review (Sections 6 and 7).

3. References

1. 2014 FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. Accessible at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.
2. 2007 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. Accessible at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm.
3. 2011 Baylor, Clinical Review STN 125408/0. Flucelvax. Retrieved from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM332069.pdf.
4. May 2015. Flucelvax Package Insert, Novartis Vaccines and Diagnostics, Inc. Retrieved from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM329134.pdf.

4. Study V58P12: Phase 2/3 observer-blind, active-controlled, multicenter study of 3604 subjects 3 to <18 years of age.

Please refer to Section 6 of the original clinical review for details regarding the study design and rationale for including data from persons 4 to <18 years of age in tables below.

Analysis of Secondary Endpoints

As per the 2007 CBER Guidance: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, the following criteria may support accelerated approval for the pediatric population: the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%; the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%. As shown in Table 1, these criteria were demonstrated 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 antibody titer ≥ 1:40 to the influenza B strain contained in the vaccine was 66% (two-sided 95% CI: 61-70%).

Table 1. Study V58P12: Analysis of Immunogenicity Results Post-Vaccination with Flucelvax, According to the CBER Immunogenicity Criteria, Children and Adolescents 4 to <18 Years of Age (Per Protocol Population)

Children 4 to <9 years of age (Day 50)[1]						
	Flucelvax			Fluvirin		
	N=441			N=430		
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
GMT (95% CI)	609 (540-686)	976 (855-1114)	60 (51-71)	685 (608-773)	1743 (1527-1989)	71 (57-66)
% with HI Titer ≥ 1:40 (95% CI)	99% (97-99%)	99% (97-100%)	64% (60-69%)	98% (97-99%)	97% (95-98%)	66% (61-70%)
Seroconversion rate (95% CI)	96% (94-98%)	80% (76-84%)	62% (57-66%)	97% (94-98%)	87% (84-90%)	62% (57-66%)
Children and Adolescents 9 to <18 years of age (Day 29)[1]						
	Flucelvax			Fluvirin		
	N=141			N=144		
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
GMT (95% CI)	1076 (886-1307)	676 (585-783)	136 (113-163)	1296 (1069-1571)	1651 (1429-1908)	186 (155-222)
% with HI Titer ≥ 1:40 (95% CI)	99% (96-100%)	100% (97-100%)	95% (90-98%)	98% (94-100%)	100% (97-100%)	94% (89-94%)
Seroconversion rate (95% CI)	74% (66-81%)	52% (44-61%)	63% (55-71%)	74% (66-81%)	78% (70-84%)	69% (61-76%)

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

[1] Cell-derived antigen hemagglutination inhibition (HI) assay results

[2]Seroconversion is defined as a negative 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.

Reviewer Comment :

The accelerated approval pathway is one of four FDA programs intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition (1). This program is also intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks. An additional qualifying criteria for accelerated approval is the availabiltiy of a surrogate endpoitn reasonably likely to predict clinical benefit.

Data to support accelerated approval is 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 (21 CFR 601.41). Based on the 2007 CBER Guidance the HI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit (2). Flucelvax is manufactured in MDCK cells instead of eggs and the manufacturing process may be useful in the event that there is a need for a rapid scale up of influenza vaccine (for example, in the event of a highly pathogenic pandemic strain), the availability of a pediatric formulation of Flucelvax would be beneficial to public health (3).

The data from V58P12 support accelerated approval of Flucelvax in this age group for the following reasons :

1) **The CBER immunogenicity criteria were met for both influenza A strains in persons 4 to <18 years of age.**

2) **The CBER immunogenicity criteria were met with respect to the influenza B strain in children 9 to <18 years of age. For children 4 to <9 years of age, the CBER immunogenicity criteria were met with respect to seroconversion, although the percentage of subjects achieving an HI titer ≥ 1:40 did not meet or exceed 70%.**

Study V58P12 demonstrated non-inferiority of Flucelvax compared to Fluvirin (a US licensed product) with respect to the influenza B strain in terms of day 50 post-vaccination HI GMT and seroconversion rates in children 4 to <9 years of age (lower limit of the two-sided 95% CI for the ratio of GMT Flucelvax/Fluvirin was >0.67 and the lower limit of the two-sided 95% CI for the difference between seroconversion rates Flucelvax-Fluvirin was >-10%) (See Section 6.1.13.1of the clinical review).

Although the pediatric data submitted in this supplement did not demonstrate immunogenicity non-inferiority with respect to the A/H3N2 strain (see Section 6 of original clinical review), the data support accelerated approval.

5. Confirmatory Efficacy Study

For the required study to verify clinical benefit the applicant submitted a synopsis of the clinical protocol for Study V130_12) , a phase III, randomized (1:1), observer-blind, multicenter study. The primary objective of Study V130_12 is to demonstrate the absolute vaccine efficacy of Flucelvax Quadrivalent (QIVc) compared to meningococcal vaccine as the -comparator determined by prevention of RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in 6367 children and adolescents 4 to <18 years of age. The influenza cases will be assessed from 14 days to 180 days after last vaccination or through the end of the influenza season, whichever is longer. The estimated study initiation date is September, 2016.

Reviewer Comment: The results of a confirmatory clinical endpoint study verifying clinical benefit of Flucelvax Quadrivalent can be used to support traditional approval of Flucelvax (trivalent) because the two products are manufactured by the same process. The general contours of the proposed study design are acceptable. The details of the protocol will be negotiated in a separate submission to the IND for this product.

6. Labeling

Revisions to the Flucelvax package insert were negotiated with the applicant. The revisions to the package insert primarily related to characterization of the clinical data to support the safety and effectiveness of Flucelvax in children 4 to <18 years of age (Sections 6 and 14). With respect to safety (Section 6), CBER requested the applicant to provide percentages of subjects reporting any, moderate and severe adverse reactions. In Section 14, CBER provided the results of the non-inferiority analysis of Flucelvax to Fluvirin according to vaccine strain as well as the results of the immunogenicity analysis (percentage of subjects with HI ≥ 1:40 and percentage of subjects with seroconversion) that were used to support accelerated approval. The package insert additionally indicates 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.

7. Risk-Benefit Assessment

The most common risks associated with Flucelvax are pain and erythema at the injection site, headache, induration, swelling, malaise, myalgia and fatigue in the week after vaccination. These adverse reactions are mild and resolve within days. No safety signals were apparent in the review of the safety data submitted to this supplement (See Sections 6 and 7 of the original clinical review). The data submitted in this supplement indicate that Flucelvax has an effect on an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. The risk:benefit assessment of Flucelvax for use in the pediatric population 4 to <18 years of age is favorable.

8. Recommendation

The data submitted to this supplement support the approval of Flucelvax in persons 4 to <18 years of age under the accelerated approval regulations.