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| Application Type | Original BLA |
| STN | 125692/0 |
| CBER Received Date | Feb 1, 2019 |
| PDUFA Goal Date | Feb 1, 2020 |
| Division / Office | OVRR |
| Committee Chair | Brenda Baldwin, PhD |
| Project Manager | Ed Wolfgang, PhD<br>Belete Teferedegne, PhD |
| Priority Review | No |
| Reviewer Name(s) | Zhong Gao, Ph.D.<br>Mathematical Statistician |
| Review Completion Date / Stamped Date | |
| Concurrence | Lei Huang, Ph.D.<br>Concurring Reviewer, Viral and Bioassay Team, VEB, DB |
| | Tsai-Lien Lin, Ph.D.<br>Chief, Vaccine Evaluation Branch, DB, OBE |
| | John Scott, Ph.D.<br>Director, Division of Biostatistics, OBE |
| Applicant | Seqirus Inc. |
| (Proposed) Trade Name | AUDENZ |
| Pharmacologic Class | Vaccine |
| Formulation(s), including Adjuvants, etc | Each 0.5 mL dose contains at least 7.5 mcg of hemagglutinin (HA) of the influenza virus strain A/turkey/Turkey/1/2005 NIBRG-23 and MF59C.1 adjuvant (MF59) |
| Dosage Form(s) and Route(s) of Administration | Suspension for injection containing 7.5 mcg HA per 0.5mL. For intramuscular injection only. |
| Dosing Regimen | Administer two doses (0.5 mL each) 21 days apart |
| Indication(s) and Intended Population(s) | AUDENZ is a vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine in adults and pediatric persons 6 months of age and older. |

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## 1. EXECUTIVE SUMMARY

Seqirus Inc. submitted an original BLA to pursue licensure of AUDENZ, an adjuvanted Influenza A (H5N1) monovalent vaccine, indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine in adults and pediatric persons 6 months of age and older.

The applicant submitted the validation report of the Hemagglutination Inhibition (HI) assay used for the pivotal Phase 3 study V89_18. The HI assay validation report had been reviewed under IND 13536, and CBER provided comments on Nov. 26, 2018. On June 28, 2019, the applicant submitted their responses to CBER's comments. The applicant proposed to define the assay range as (b) (4) in the linearity series. Accordingly, the applicant proposed a new Upper Limit of Quantification (ULOQ) of (b) (4) for this assay. The applicant indicated that only 6 samples were reported with titers above (b) (4) in study V89_18. The revision caused minor changes in GMT and the 95% Confidence Interval (CI) of aH5N1c Lot #3 at Day 43, i.e., (b) (4) with the revised ULOQ vs. (b) (4) with the initial ULOQ. The proposed revision of ULOQ is acceptable, and the impact of the revision on the interpretation of the pivotal study V89_18 is minimal.

The applicant also conducted validation of the (b) (4) assay. In the (b) (4) validation, the applicant indicated that the (b) (4)

Overall, the HI and (b) (4) assays are acceptable to support the BLA submission from a statistical perspective.

## 2. REGULATORY BACKGROUND

Seqirus Inc. submitted an original BLA to pursue licensure of AUDENZ, an adjuvanted, cell-based Influenza A (H5N1) monovalent vaccine, indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine in adults and pediatric persons 6 months of age and older.

The Hemagglutination Inhibition (HI) assay was used for measuring immune responses to the vaccine during the clinical development. For the pivotal Phase 3 clinical trial (study V89_18), the HI assay was performed on clinical samples using a homologous vaccine strain, i.e., /turkey/Turkey/1/05, at (b) (4) . The validation study of the (b) (4) test method used for the pivotal Phase 3 study was conducted in 2016.

The (b) (4) assay was used to determine specific hemagglutinin (HA) content for testing potency of the pandemic H5N1 vaccine with MF59C.1 adjuvant. The applicant conducted a validation study for the assay in 2018. The applicant intended to use the assay at the Holly Springs site to perform GMP testing on the pandemic A/turkey/Turkey/1/2005 (H5N1) influenza vaccine formulated using Process 3.0 (b) (4)

## 3. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

### 3.1 Review Strategy

This review focuses on the validation study of the HI assay used by (b) (4) for the pivotal Phase 3 study V89_18. The validation studies of the HI assay used in the Phase 2 studies, which was conducted by Novartis Vaccines and Diagnostics Inc (b) (4) were reviewed under IND 13536. This review also focuses on the validation study of the (b) (4) assay.

### 3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- Hemagglutination Inhibition (HI) assay
  Client Specific Method Validation Report Hemagglutination Inhibition Assay for Detecting Antibody Responses Following Influenza A (H5) Virus Infection (b) (4) Report Number: RPT-RD-VAL060)
- Seqirus response to CBER regarding the Hemagglutination Inhibition assay validation study, dated June 28, 2019, under IND 13536.
- (b) (4) assay
  Validation Report for The Determination of HA Content by (b) (4) For Testing FCC PANDEMIC H5Nl With MFS9C.l Adjuvant (Protocol Number: VAL-000083837 Version 1; Report Number: VAL-000086628)
- Seqirus response to CBER regarding the (b) (4) assay validation study, dated September 25, 2019, submitted to STN 125692/0.25.

## 4. DISCUSSION OF INDIVIDUAL STUDIES

### 4.1 Validation of Hemagglutination Inhibition (HI) Assay

Seqirus Inc. submitted a report for the validation study conducted by (b) (4) for the hemagglutinin inhibition assay to detect antibody levels following influenza A (H5) virus infection or vaccination.

(b) (4)

(b) (4)

(b) (4)

1 Page has been determined to be not releasable: (b)(4)

***Reviewer Comments:***
*Under IND 13536, the validation report had been reviewed, and the following CBER comments and questions had been provided to the applicant before this submission.*

1) *You determined the ULOQ based on the upper limit of the expected GMT (i.e., (b) (4) which was (b) (4) of the expected GMT. In this validation study, there were no samples with true titers around this level evaluated for accuracy, precision, and linearity. Additionally, the accuracy acceptance interval (b) (4) although may be reasonable for individual replicate titers, is too wide for GMTs. If you intend to set ULOQ at (b) (4), please provide adequate evidence to support accuracy, precision, and linearity around this level.*
2) *In your dilutional linearity analysis, the samples with low titers, especially those with dilution factor of (b) (4), showed a trend of deviating away from the linear regression line. Additionally, as discussed in the comment above, the accuracy acceptance criterion (b) (4) appears to be too wide for GMTs. Please comment.*

On June 28, 2019, the applicant submitted their responses to IND 13536 regarding CBER's comments dated November 26, 2018.

- Response to CBER comment (1)

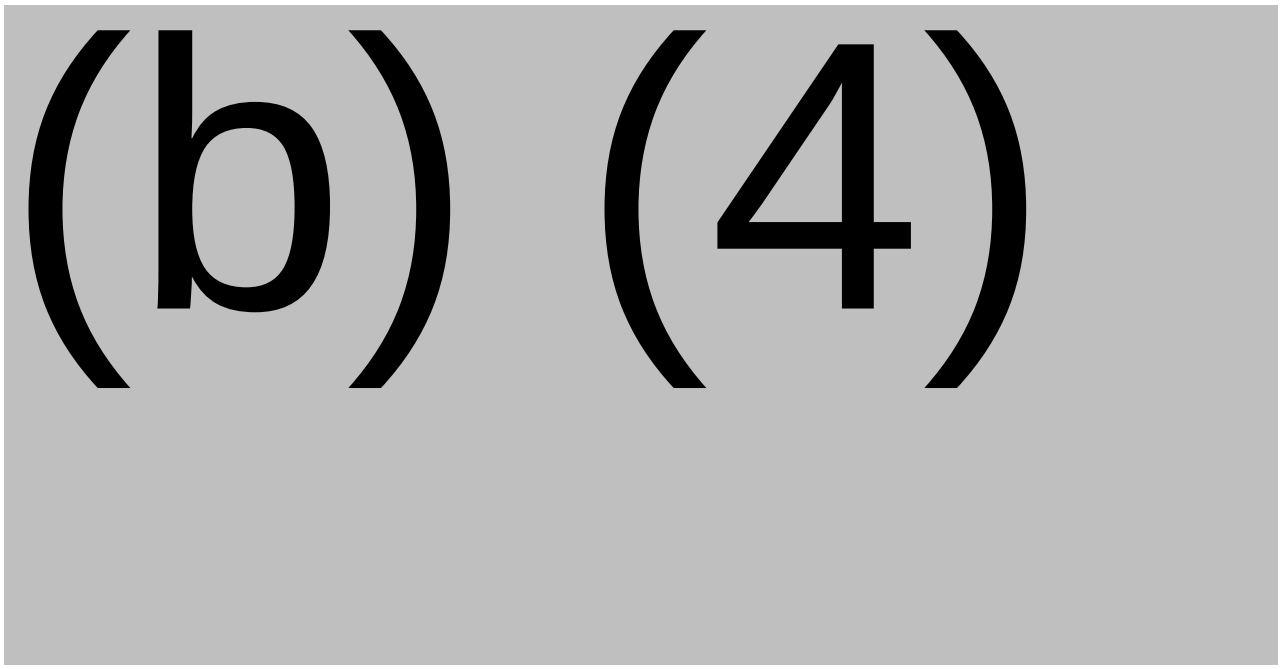
Seqirus indicated that the linearity, precision and accuracy results met the acceptance criteria across a range of samples with expected GMTs spanning from a titer of (b) (4) The applicant suggested that the Upper and Lower Limits of Quantification can be based on the validated range of expected GMT samples. The applicant proposed to define the validated range as (b) (4) in the linearity series. Therefore, the applicant proposed a new ULOQ of (b) (4) for this assay.

The applicant indicated that only a total of (b) (4) samples were reported with titers above (b) (4) in study V89_18. The applicant compared the data from Table 14 in the V89_18 CSR and the updated data using the new ULOQ of (b) (4). The revision will cause minor changes in GMT and 95% CI of aH5N1c Lot #3 at Day 43, i.e., (b) (4) with the revised ULOQ vs. (b) (4) with the initial ULOQ. The applicant indicated that the revision of the ULOQ will have minimal impact on the overall results of study V89_18.

Regarding the accuracy acceptance interval (b) (4) the applicant noted that accuracy of biological assays is difficult to be assessed where there is no available reference material of known value/concentration. Nevertheless, the applicant acknowledged the CBER comment and will take it into account in future work.

***Reviewer Comments****: Ideally, the determination of LLOQ and ULOQ should be supported by data generated in the validation and/or qualification study. The highest sample had a GMT of (b) (4) in the validation study, supporting a ULOQ of (b) (4) In study V89_18, the proportion of subjects with Day 43 titers (b) (4) in the per-protocol set. Based on internal discussion, the proposal of offsetting the ULOQ at*

(b) (4) *does not appear to have impact on study conclusion for V89_18. I defer to the clinical statistics reviewer on evaluation of the revision of the clinical study data.*




- Response to CBER comment (2)

The applicant indicated that some extreme data points were below the LLOQ and in the region where data values had been arbitrarily assigned as a titer (b) (4) (Figure 1). Therefore, the applicant suggested that the extent of deviation of some data from the line of best fit for these preparations is uncertain, of minimal impact and an artefact of the proximity of the true GMT for these samples to the LLOQ of the assay.

***Reviewer Comments:*** *The relative accuracy data showed that % recovery was* (b) (4) *and* (b) (4)*, respectively, for the* (b) (4) *dilutions. Although the % recovery met the acceptance interval of* (b) (4) *set by the applicant, the acceptance interval was wide, as commented in the November 26, 2018 IR, and the result might indicate a lower level of relative accuracy at these dilution levels. Some of the data points at these dilution levels had a titer* (b) (4) *and were replaced with an arbitrary value of* (b) (4) *in the GMT calculation. This may contribute to the differences between the observed and expected GMT. Nevertheless, since the %recovery was less than* (b) (4) *(i.e. the measured titer is on average below the expected titer) and success criterion for the primary immunogenicity endpoint in study V89_18 is based on the percentage of subjects achieving an HI antibody titer ≥1:40, it appears to be unlikely that the reported proportion of subjects achieving an HI titer ≥1:40 based on this HI assay would overestimate the actual proportion, making it conservative to draw the conclusion that the immunogenicity has met the success criterion. Hence, the uncertainties around the LLOQ appears to have minimal impact on the conclusion of the study.*

### 4.2 Validation of the (b) (4) Assay

The applicant performed a validation study to assess the (b) (4) assay for the determination of hemagglutinin potency. Table 2 summarizes the experimental design, acceptance criteria, and results of the study.

2 Pages have been determined to be not releasable: (b)(4)

# 5. CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

1. The applicant submitted the validation report of the Hemagglutination Inhibition (HI) assay used for the pivotal Phase 3 study V89_18. In response to CBER comments, the applicant proposed to define the assay range as (b) (4) in the linearity series. Accordingly, the applicant proposed a new ULOQ of (b) (4) for this assay. The applicant indicated that total of only (b) (4) samples were reported with titers above (b) (4) in study V89_18. The revision caused minor changes in GMT and 95% CI of aH5N1 Lot #3 at Day 43, i.e., (b) (4) with the revised ULOQ vs. (b) (4) with the initial ULOQ. The proposed revision of ULOQ is acceptable. The impact of the revision on the interpretation of the data from the pivotal study V89_18 is minimal.

2. In the (b) (4) validation, the applicant indicated that the (b) (4), indicating that the test sample preparation process is likely adequately controlled for its intended use.

## 5.2 Conclusions and Recommendations

The Hemagglutination Inhibition assay and (b) (4) assay are acceptable to support the BLA submission from a statistical perspective.