



**DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DVRPA**

Date:

From: **Hector S. Izurieta, MD. MPH**
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Through: **Richard Forshee, PhD**
Associate Director for Research, OBE

Subject: Review of Post-marketing Effectiveness Study for Biologics
License Application for Q-PAN

To: **STN 125419 Q-PAN GSK Adjuvanted H5N1 Vaccine**

Sponsor: ID Biomedical Corporation of Quebec (dba GlaxoSmithKline Biologicals)

Product: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted

Related Documents:

(a) Pivotal study: "Protective effect of single-dose adjuvanted pandemic influenza vaccine in children", by P.G. Van Buynder et al.

(b) Supportive data: Two published effectiveness studies, conducted by Mahmud et al. and Skowronski et al (see references).

Reviewer Name, Division, and Mail Code

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Product Proper Name: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted

Product Formulation: See clinical review.

Pharmacologic Class: Vaccine

Route of Administration: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (Q-PAN) is provided for intramuscular administration

(A) Rationale for use of an observational study and for the use of a test-negative methodology to evaluate effectiveness: There are numerous difficulties for identifying viable ways for the evaluation of efficacy for the Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted Vaccine vaccine to support

traditional approval. (throughout the remaining of this document, the product will be called Q-Pan). Randomized placebo-controlled clinical trials are the gold standard for evaluations of vaccine efficacy. Nonetheless, these trials, for ethical reasons, cannot be conducted using a pandemic vaccine. Also, there are no established correlates of protection or accepted animal models. The chosen alternative for evaluation of pandemic influenza vaccine effectiveness is an observational, case-control study. Given the constraints above, the use of data from observational vaccine effectiveness studies conducted by Canadian public health agencies for *Arepanrix* H1N1, which has the same manufacturing process and formulation as Q-PAN H5N1 but instead uses HA antigen from influenza A/H1N1, appeared as the best available option. Therefore, at a meeting held on February 14, 2011, CBER agreed with GSK's proposal to use evidence of *Arepanrix* H1N1 vaccine's effectiveness obtained from independent studies conducted in children and adults to potentially support the effectiveness of the Q-PAN H5N1 vaccine candidate for prevention of pandemic influenza in a BLA submission. Complete data were submitted for only one of those studies (the Van Buynder study), which was therefore considered the pivotal study. Other two published effectiveness studies were included as supportive evidence. One relevant characteristic of all these studies is that they were not developed or conducted by the Sponsor but, instead, by public health services from Canada.

A potential confounding factor that must be addressed in observational studies of influenza vaccine effectiveness is healthcare-seeking behavior. Compared to individuals who do not seek influenza vaccination, vaccinated individuals in a community may be more likely to seek medical attention for mild or moderate influenza illness. To address this issue, observational "test-negative" case-control studies can be used (Orenstein et al, *International Journal of Epidemiology*, 2007). In these studies, cases and controls are selected from individuals who seek medical care for the same influenza-like illness (ILI). Among them, cases are those who have nasal swab specimens that test positive for influenza and controls are those who have nasal swab specimens that test negative for influenza.

(B) Pivotal Effectiveness Study Conducted with Arepanrix™ ("Q-Pan H1N1") Vaccine

Study: "A Test-negative Case-Control Study to Evaluate the Effectiveness of GSK Biologicals' Adjuvanted Monovalent Inactivated H1N1 Influenza Vaccine (Arepanrix™) in Young Children (6 months to < 10 years of age) (Van Buynder study):

The Van Buynder study became the pivotal effectiveness study for this BLA because it was the only study for which CBER received complete information. For this reason, this review will mainly consider the Van Buynder study. The other two studies (conducted by Mahmud et al. and Skowronski et al), for which the Sponsor was not able to have access to the raw data and study documents, will be included as supportive documents. Both studies have been published.

Van Buynder study design:

The study evaluates the effectiveness of the vaccine using an observational, test-negative case-control design. The comparators will be “test negative no cases”, i.e., subjects who were seen for an influenza-like respiratory infection but who were tested negative for influenza using an RT-PCR test.

Objectives: To evaluate Q-PAN effectiveness in children six months to 9 years of age relative to no vaccination against H1N1 pandemic influenza illness

Subject population: Children ages six months to 9 years eligible to receive Q-PAN.

Effectiveness evaluation: A community-based case-control vaccine effectiveness study was conducted in Canada during the 2009-2010 influenza pandemic. Children 6 months through 9 years of age were vaccinated with a single dose of the monovalent influenza A(H1N1) virus vaccine adjuvanted with AS03. In this study, a total of 116 children in the target age group were tested for H1N1 pandemic influenza. Of them, 17 children could not be contacted. In addition, four controls did not meet eligibility criteria for influenza-like illness, three refused to participate and one child was excluded because of ineligibility (immunosuppression). The total number of children finally analyzed was 91 (28 cases and 63 controls). Overall, vaccine effectiveness to prevent laboratory-confirmed influenza in these children (vaccinated at least 14 days prior to disease onset) was statistically significant: 100% (95% CI: 79.5, 100). In a secondary analysis, vaccination was considered effective after 10 days of vaccine administration. In this analysis, VE was 96% but was also statistically significant. Although ecological, an additional evidence of the effectiveness of the vaccine is the short duration and limited number of cases in the New Brunswick outbreak.

Study limitations:

- a. **Data size:** The main study limitation is its size. The total number of children analyzed was 91, which is not sufficient to obtain robust adjusted estimates of vaccine effectiveness. Also, the study was limited to children through age 9 years. Therefore, the results can't be extrapolated to other age groups. Moreover, influenza vaccine effectiveness is usually higher among children than among adults or the elderly.
- b. **Analytical approach:** Case-control studies are particularly susceptible to selection and other types of bias. Nonetheless, the use of the test-negative control design (Orenstein et al, 2007) decreases the likelihood of selection bias. There is a possibility of bias because some influenza case-patients could be tested too late (once the patient is no longer shedding influenza virus). In such a case, the test result would be negative and the patient would be wrongly classified as a control. This would bias results towards finding no difference between the groups (bias towards the Null). A similar bias could occur if the test is insufficiently sensitive. Because date of specimen collection was used as a surrogate for specimen testing, a delay in testing could have increased the likelihood that a patient could be coded

- as protected (tested 14+ days post vaccination) when in fact the real onset was earlier, thus biasing the study towards the Null.
- c. Other sources of bias: One possibility is a potential imbalance favoring vaccinated cases among the 17 children who could not be contacted by the investigators (see statistical review for a full analysis of the bias). Although this possibility exists, there is no particular reason for these individuals (who either had no phone, could not be contacted or for whom the telephone information was wrong) would be more likely to be vaccinated cases. Because of these considerations, although a prudent bias analysis should also include the worst case scenario, such possibility would not be very likely. Because vaccination in this province successfully targeted all children as a priority, the risk of a bias because of a “healthy vaccinee effect” (biasing the study towards vaccination of the healthier cohort, less likely to have serious disease complications) was minimal or non-existing.
 - d. Effectiveness estimate: Because of the Canadian recommendation to prioritize testing for influenza of children with more serious disease, this effectiveness estimate could be assumed to be valid only for serious cases. Nonetheless, many of the children tested had mild disease, thus suggesting that the children tested were likely representative of the ensemble of influenza cases.
 - e. Other considerations: A few mistakes were identified in this paper. For instance, the numbers in figure 1 are not all correct. Given that the numbers in the text are consistent with the data received by CBER, there is no reason to believe this could have affected the study results or its validity. Also, GSK’s re-analysis identified some minor errors in the original New Brunswick data analysis that resulted in a few discrepancies between the outcomes of the two analyses (see clinical review). GSK considered these discrepancies statistically insignificant and biologically irrelevant, with no impact on any of the study conclusions.

(C) Other published vaccine effectiveness studies included in the BLA as supportive evidence:

Two other published vaccine effectiveness studies were included in the BLA as supportive data because GSK was not able to provide the raw data for CBER review:

C.1. Mahmud et al (see reference): This study was sponsored by the Manitoba Winnipeg Regional Health Authority and other Canadian public health institutions. The design was similar to the Van Buynder study. It used a community-based case control test negative design. It included individuals ages 6 months and older. It was much larger than the Van Buynder study (1435 cases and 2309 controls). The overall vaccine effectiveness found was 86% (95%CI 75%-93%)

This case control study used data from Cadham Provincial Laboratory (CPL) and the Manitoba Immunization Monitoring System (MIMS). The study included all Manitoba children ages 6 months who had a respiratory specimen tested for H1N1. The laboratory test was reverse transcriptase-PCR. There were a total of 1435 test positives (cases) and 2309 test negatives (controls). Controls had tested negative for both influenza

A and B. Information on vaccines received was obtained by record linkage with MIMS, the Manitoba immunization registry. Overall, H1N1 VE was 86% (95% CI 75-93%) for laboratory confirmed H1N1 infection for individuals vaccinated 14 days before the specimens were taken for testing. The effectiveness was lower among older (50 years) individuals [51% (-50-84%)] and among the immunocompromised [67% (-3-90%)] compared to young adults and older children [90% (76-96%)] and very young (6-35 months) children [97% (72-100%)] . Vaccine effectiveness, although still high, was lower when vaccination occurred 7-13 days before specimen collection [VE 53%, 95% CI (29-69%)].

Limitations: Case-control studies are particularly susceptible to selection bias, but the use of the test-negative control design decreases the likelihood of selection bias. There is a possibility of bias because some influenza case-patients could be tested too late (once the patient is no longer shedding influenza virus). In such a case, the test result would be negative and the patient would be wrongly classified as a control. This would bias results towards finding no difference between the groups (bias towards the Null). A similar bias could occur if the test is insufficiently sensitive because date of specimen collection was used as a surrogate for specimen testing, a delay in testing could have increased the likelihood that a patient could be coded as protected (tested 14+ days post vaccination) when in fact the real onset was earlier, thus biasing the study towards the Null. Because vaccination targeted higher risk groups, the risk of a bias because of a “healthy vaccinee effect” is decreased. Moreover, the study adjusted for factors that could have accounted for this effect and, also, the TIV vaccine used (subject in theory to a similar bias) was not found effective. Therefore, the likelihood of a “healthy vaccinee effect” bias was low.

Conclusion: Overall, among individuals vaccinated >14 days before specimen collection, the vaccine was highly effective against H1N1 pandemic influenza. Effectiveness among children was the highest.

C.2. Skowronski et al (see reference): Also sponsored by various Canadian public health institutions, the design was similar to the Van Buynder and Mahmud studies (Community based case control test negative design). It used a sentinel physician system to identify cases and controls. It included individuals ages 6 months and older. It was also larger than the Van Buynder study (209 cases and 1435 cases and 343 controls). As in the other studies reviewed, this study used reverse transcription PCR for influenza testing. The overall (adjusted) vaccine effectiveness found was 93% (95% CI 69%-98%). When the analysis was restricted to individuals ages <50 years, the VE estimate changed little, to 91% (95% CI 61-98%). Multiple other subanalyses were performed, and they all provided consistently high VE estimates.

Limitations: Case-control studies are particularly susceptible to selection bias, but the use of the test-negative control design decreases the likelihood of selection bias. There is a possibility of bias because some influenza case-patients could be tested too late (once the patient is no longer shedding influenza virus). In such a case, the test result would be negative and the patient would be wrongly classified as a control. This would bias results

towards finding no difference between the groups (bias towards the Null). A similar bias could occur if the test is insufficiently sensitive. Because date of specimen collection was used as a surrogate for specimen testing, a delay in testing could have increased the likelihood that a patient could be coded as protected (tested 14+ days post vaccination) when in fact the real onset was earlier, thus biasing the study towards the Null. Because vaccination targeted higher risk groups, the risk of a bias because of a “healthy vaccinee effect” is decreased. Moreover, the study adjusted for factors that could have accounted for this effect. Therefore, the likelihood of a “healthy vaccinee effect” bias was low. The proportion of older individuals (age 50 years and older) in the study was not sufficient to obtain a reliable estimate of effectiveness for the age group.

Conclusion: Overall, among individuals vaccinated >14 days before specimen collection, the vaccine was highly effective against H1N1 pandemic influenza. Because of sample size limitations, the estimate for individuals ages <50 years (91%) appears to be the most reliable.

(D) Reviewer comments: Although the hemagglutination-inhibition antibody responses following 2 doses of Influenza A (H5N1) Virus Monovalent Vaccine were similar to those seen following a single dose of influenza A (H1N1) virus monovalent vaccine, there are no established valid correlations between immunogenicity tests for influenza vaccines and vaccine efficacy. In this BLA, the effectiveness of Influenza A (H5N1) Monovalent Vaccine is inferred based on monovalent influenza A (H1N1) vaccine effectiveness data obtained during the 2009-10 pandemic. The Influenza A (H5N1) Virus Monovalent Vaccine and the influenza A (H1N1) virus monovalent vaccine studied are produced by the same manufacturing process and both contain the AS03 adjuvant. Nonetheless, there are differences between both vaccines that make an extrapolation difficult. Some important differences include the fact that the H1N1 antigen is of swine origin and the H5N1 is of avian origin, and that the case-fatality rate for H5N1 human infections, at least as of now, is higher than that for H1N1 infections. While accepting these limitation, the analysis of effectiveness of the H1N1 vaccine is still very informative.

The pivotal effectiveness study was the the Van Buynder study. The study, implemented among children ages 6 months to 9 years, found a high vaccine effectiveness. Unhappily, the study has a number of limitations that make it unsuitable as a definitive study to establish vaccine effectiveness against the H1N1 pandemic virus.

As information regarding two other published vaccine effectiveness Canadian studies was also available as supportive evidence, this reviewer has decided to also consider these studies in his overall evaluation of vaccine effectiveness.

Taken together, the three studies support this reviewer’s conclusion that the monovalent adjuvanted vaccine is significantly effective against the pandemic H1N1 virus. Effectiveness is higher for younger age groups.

(E) Reviewer recommendations: This reviewer suggests that licensure of this H5N1 vaccine should be contingent upon implementation of additional observational effectiveness studies performed during an H5N1 pandemic. The pivotal study is not

sufficient to reach definitive conclusions regarding effectiveness of this vaccine, although the ensemble of the information provided in the BLA (including not only the small pivotal study but also the two published studies included as supportive evidence) suggests that the vaccine is effective against a swine H1N1 pandemic virus. This body of evidence supports consideration of an approval process other than a traditional approval for this product. Also, the finding that the vaccine is effective against a swine H1N1 pandemic virus is, by itself, not sufficient evidence that an H5N1 vaccine will be as effective against both disease and mortality caused by an avian H5N1 influenza virus, particularly if we take into account existing differences in the severity of human disease. Well designed observational studies performed during an H5N1 pandemic would address most of these concerns.

(F) Significant Findings from Other Review Disciplines:

Please see individual review memos of the statistical review (Dr. Tsai-Lien Lin), and clinical review (Dr. Andrea James).

(G) References:

Van Buynder PG, Dhaliwal JK, Van Buynder JL, Couturier C, Minville-Leblanc M, Garceau R, et al. Protective effect of single-dose adjuvanted pandemic influenza vaccine in children. *Influenza Other Respi Viruses*. 2010;4(4):171-178.

Mahmud S, Hammond G, Elliot L, et al. Effectiveness of the pandemic H1N1 influenza vaccines against laboratory-confirmed H1N1 infections: Population-based case-control study. *Vaccine* 29(2011):7975-7981

Orenstein EW, DeSerres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, Orenstein WA. Methodological issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *International Journal of Epidemiology*. 2007;36:623-631.

Skowronski DM, Janjua NZ, DeSerres G, Hottes TS, Dickinson JA, Crowcroft N, et al. Effectiveness of AS03 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. *BMJ*. 2011;342:c7297.