



**OVRR Office Director's MEMORANDUM**

**Date:** November 22, 2013

**From:** Marion Gruber, PhD, Director, Office of Vaccines Research & Review  
Philip Krause, MD, Deputy Director, Office of Vaccines Research & Review

**To:** Biologics License Application (BLA) 125419  
Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (Q-Pan)

**Subject:** Approval of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, (Q-Pan)

GlaxoSmithKline Biologicals (GSK) has submitted a Biologic License Application (BLA) for Q-Pan, Influenza A H5N1 (A/Indonesia/5/2005) Virus Monovalent Vaccine, Adjuvanted for the prevention of influenza disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Prior to administration, the H5N1 antigen component of the vaccine is combined with the AS03 component, an oil-in-water emulsion adjuvant. The vaccine is manufactured using the same process as GSK's licensed seasonal influenza vaccines FluLaval™ and FluLaval Quadrivalent, which are not adjuvanted. FluLaval contains hemagglutinin (HA) from influenza virus strains H1N1, H3N2, and one influenza B strain. FluLaval Quadrivalent contains HA from the same influenza virus strains as FluLaval as well as from a second influenza B strain.

To support licensure of Q-Pan, the applicant has submitted safety and immunogenicity data derived from prelicensure clinical trials using Q-Pan, as well as efficacy data derived from a clinical endpoint efficacy study conducted with FluLaval Quadrivalent.

We concur with the review team that the data submitted with the BLA demonstrate the safety and immunogenicity of Q-Pan. However, we do not concur with the clinical reviewer's and immediate supervisor's views that:

- 1) Licensure of Q-Pan should be granted using the accelerated approval regulations (21 CFR 601 Subpart E) rather than the traditional approval pathway;
- 2) Clinical endpoint efficacy data for FluLaval Quadrivalent are insufficient to verify clinical benefit of Q-Pan for traditional approval; and
- 3) The applicant should be required to conduct a post-marketing effectiveness study of Q-Pan during a pandemic in order to be granted traditional approval.

The purpose of this memorandum is to explain why the Office of Vaccines Research and Review (OVRR) supports verifying the clinical benefit of Q-Pan with vaccine efficacy data from a seasonal influenza vaccine manufactured by the same manufacturing process in order to support a traditional approval.

## **I. Approach to licensure of Q-Pan**

### **1. Licensure pathways for pandemic influenza vaccines**

For vaccines against influenza A subtypes of pandemic potential that are not included in the seasonal influenza vaccines (i.e., other than H1 and H3), clinical endpoint efficacy studies are not feasible in the absence of circulation of the pandemic strain.

As stated in the May 2007 FDA Guidance for Industry “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines” and described in more detail in section 1.1 and 1.2 below, licensure of pandemic influenza vaccines may be sought through the submission of a BLA using either the provisions in 21 CFR 601.2 or the accelerated approval provisions in 21 CFR part 601 Subpart E.<sup>1</sup>

#### **1.1 Approval of pandemic influenza vaccine under 21 CFR 601.2 (herein referred to as traditional approval)**

If a manufacturer holds a U.S. license for a seasonal inactivated influenza vaccine approved under either the provisions in 21 CFR 601.2 or the accelerated approval provisions with the vaccine's clinical benefit having been confirmed in a postmarketing study, and the manufacturing process used for the production of the pandemic vaccine is the same as for the licensed seasonal vaccine, clinical immunogenicity trials would be needed to determine the appropriate dose and regimen of the pandemic influenza vaccine candidate. These trials should also include an assessment of safety. Sponsors are expected to collaborate on plans to collect additional effectiveness and safety information when the pandemic influenza vaccine is used.

#### **1.2 Approval of pandemic influenza vaccine under 21 CFR 601 Subpart E (accelerated approval)**

Accelerated approval may be granted for certain biological products such as pandemic influenza vaccines that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments.<sup>2</sup> For pandemic vaccines, the accelerated approval pathway will be available at least until adequate supplies of such vaccines are available.

FDA has interpreted the accelerated approval regulation, 21 CFR 601 Subpart E, as allowing accelerated approval of a pandemic influenza vaccine during a vaccine shortage because: 1) pandemic influenza is a serious and life-threatening illness; and 2) providing prophylaxis to those who would not otherwise be immunized provides a meaningful benefit over the existing treatments (i.e., pandemic influenza vaccines which are in short supply).

The accelerated approval regulations (21 CFR 601.41) further establish that FDA may grant marketing approval on the basis of 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. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit. Postmarketing studies must also be adequate and well-controlled and should be conducted with due diligence.

Marketing approval for biological products approved under these regulations may be withdrawn if the postmarketing clinical study fails to verify clinical benefit or the sponsor fails to perform the required postmarketing study with due diligence (21 CFR 601.43(a)(1) and (2)).

Section 1.3 below discusses the surrogate endpoint for influenza and Section 1.4 below discusses approaches to verify clinical benefit of pandemic influenza vaccines.

### **1.3 HI antibody titers as surrogate endpoints**

Influenza virus hemagglutinins, present on viral surfaces, are important for cell-receptor binding. The immune response to these hemagglutinins as measured by the presence of serum hemagglutination inhibition (HI) antibodies is an important protective mechanism following vaccination and/or infection. To date, prospectively designed studies to evaluate the effectiveness of seasonal or pandemic influenza vaccines have not identified a specific HI antibody titer associated with protection against culture-confirmed influenza illness. However, some studies of influenza infection, including human challenge studies following vaccination, have suggested that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects and that protection from illness is increased with higher titers.<sup>3,4</sup> As discussed in the Guidance For Industry, “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines,” for inactivated pandemic influenza vaccines produced by the same manufacturer and process as a licensed seasonal inactivated influenza vaccine, effectiveness may be based on the HI antibody response using endpoints described in that guidance document.<sup>1</sup>

### **1.4 OVRP policy regarding approaches to verify clinical benefit of pandemic influenza vaccines**

Based on scientific evidence and regulatory precedent outlined in Section 3 below, as well as policy stated in the guidance for industry document, “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines,” (Section III. A) OVRP has determined that for manufacturers of U.S.-licensed seasonal influenza vaccines the clinical endpoint effectiveness data accrued with the seasonal influenza vaccine can be used to verify the clinical benefit of influenza A subtype (e.g. H5) unadjuvanted and adjuvanted pandemic vaccines made by the same process. If the corresponding licensed seasonal influenza vaccine was approved under the Traditional Approval pathway on the basis of a clinical endpoint efficacy trial(s), then effectiveness of the new subtype (e.g., H5) unadjuvanted or adjuvanted vaccine is supported by efficacy data derived from studies of the manufacturer’s licensed seasonal influenza vaccine, thereby allowing traditional approval of the pandemic vaccine. If the corresponding licensed seasonal influenza vaccine was approved under the Accelerated Approval Regulations, based on

immunogenicity data, with verification of clinical benefit pending, there are two potential pathways to traditional approval of the pandemic influenza vaccine. In the latter scenario, effectiveness of the pandemic influenza vaccine is considered to be verified using either: a) clinical endpoint efficacy data accrued with the relevant seasonal vaccine made by the same process, when such data become available or b) observational effectiveness data accrued with another influenza vaccine made by the same manufacturer and process, even if not licensed in the U.S. (e.g, case-control effectiveness data on a relevant adjuvanted monovalent H1N1 pandemic vaccine evaluated during the 2009 pandemic).

These clinical pathways to demonstrate effectiveness are applicable only to pandemic influenza vaccines for which it is not feasible for manufacturers to conduct clinical endpoint efficacy studies. Of note, after licensure of a pandemic influenza vaccine and in the event of a pandemic, the manufacturer is expected to work with the FDA and other governmental agencies on plans to collect safety and effectiveness data, such as through epidemiological studies.

## **2. Clinical reviewers' view regarding verification of clinical benefit of pandemic influenza vaccines**

The clinical reviewer and supervisors expressed their opinion that due to “significant antigenic, pathophysiologic and clinical disease differences” between the seasonal influenza viruses and the H5N1 influenza virus, efficacy data for FluLaval Quadrivalent are insufficient to verify clinical benefit of Q-Pan. In their view, the effectiveness of Q-Pan can only be confirmed by conducting a prospective, observational, effectiveness study during an actual pandemic or sustained transmission of the virus. The clinical reviewer and supervisors note that published studies from the 2009 H1N1 pandemic have shown that clinical effectiveness studies during an actual pandemic are feasible. In their view, until such time that a clinical effectiveness study could be conducted with Q-Pan and the results submitted to FDA as a supplement, the application should remain under accelerated approval.<sup>5,6</sup>

## **3. OVR's rationale and justification for policy on verification of clinical benefit of pandemic influenza vaccines**

This section will provide, in detail, OVR's rationale and justification for approaches to licensure of pandemic influenza vaccines outlined in Section 1.4. and also described in the guidance for industry document, “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines,” (Section III. A). Specifically, this section will discuss the approach that is relevant to the Q-Pan BLA, i.e., use of clinical endpoint efficacy data accrued with the same manufacturer's seasonal vaccine made by the same process to support licensure.

### **3.1 Protective mechanism of vaccination against seasonal and pandemic influenza**

Despite differences in receptor-binding specificity and pathogenicity of human and avian influenza viruses, the mechanism of induction of a protective response to these influenza viruses is similar.<sup>7,8,9</sup> Specifically, inactivated pandemic and seasonal influenza virus vaccines mediate protection against influenza through the induction of antibody that is specific to the HA antigen on the virus surface. Inactivated influenza vaccines, both seasonal and pandemic, are formulated to contain a specific quantity of the HA antigen in

each dose. Numerous independent studies have supported that serum HI antibody titers are associated with protection against influenza A viruses. In 1972, from clinical challenge studies, Hobson determined that there is an inverse relationship between the pre-challenge antibody titer and likelihood of infection. He defined the 50% protective antibody level against A and B influenza viruses as being a serum HI titer of 18-36, notably lower than the  $\geq 1 : 40$  titer that is used to evaluate the immunogenicity of influenza vaccines.<sup>1,3</sup> Data from several studies with H1, H2, H3 and B influenza viruses, in which the incidence of natural infection was determined in populations with known pre-existing serum HI antibody titers have been in general agreement with these values.<sup>4, 10, 11</sup> Of note, each current seasonal influenza A virus subtype, as well as the previous H2N2 virus (1957-1968), entered the human population as a pandemic influenza virus to which the population was initially immunologically naïve. In addition, studies of passive transfer of convalescent plasma conducted during previous influenza pandemics showed reduced mortality in patients with severe pandemic influenza A virus infection, indicating the importance of antibodies in protection from disease.<sup>12, 13, 14</sup> Furthermore, published studies show that immunization with an adjuvanted H5N1 vaccine that induced high levels of HI antibodies, including neutralizing antibodies, protected animals from challenge with the H5 influenza virus.<sup>15, 16</sup> In summary, because the biological mechanism for protection from disease is similar between avian and seasonal influenza vaccines, i.e., induction of HI-antibodies, it is reasonable to infer the clinical benefit of Q-Pan using the combination of HI antibody data following Q-Pan vaccination and clinical endpoint efficacy data derived with a seasonal vaccine.

### **3.2 Regulatory precedent**

Furthermore, this approach is consistent with previous regulatory decisions related to pandemic influenza virus vaccines. In April 2007, CBER licensed a monovalent H5N1 vaccine (Influenza Virus Vaccine, H5N1) manufactured by Sanofi Pasteur Inc. for use in persons 18 through 64 years of age who are at increased risk of exposure to the H5N1 influenza virus subtype included in the vaccine. This vaccine is included in the Strategic National Stockpile. This vaccine was discussed by the VRBPAC in February 2007, and the committee recommended that the available data were sufficient to support safety and effectiveness of the product.<sup>17</sup> Safety and immunogenicity data supported the dose of antigen (90 ug/1 mL dose) and dosing regimen (2 doses approximately 28 days apart) in persons 18 through 64 years of age. The vaccine is manufactured by the same process as the seasonal influenza vaccine manufactured by Sanofi Pasteur, Inc. (Fluzone) which is approved for use in persons 6 months of age and older. Implicit in the approval of the H5N1 vaccine was that effectiveness data for Fluzone provided support for the effectiveness of H5N1 vaccine. Verification of clinical benefit of Q-Pan with clinical endpoint efficacy data from a study with a seasonal influenza vaccine made by the same process as Q-Pan follows this approach.

### **4. Studies submitted by GSK to support effectiveness of Q-Pan**

Data from prelicensure clinical trials showed that Q-Pan induced an HI antibody titer that exceeded the  $\geq 1 : 40$  threshold in 90.8% of subjects 18 through 64 years of age and in 74.5% of subjects 65 years of age or older.<sup>5</sup>

In addition, GSK presented data to show that an adjuvanted H1N1 pandemic vaccine made by the same process (Arepanrix) induces an immune response (the proportion of subjects achieving an HI antibody titer > 1 : 40 and seroconversion) that also meets the criteria for establishing effectiveness described by CBER.<sup>1</sup> Three observational studies conducted with Arepanrix during the 2009 H1N1 pandemic suggested that Arepanrix was effective in preventing influenza.<sup>18, 19, 20</sup>

Moreover, studies conducted by GSK using mice and ferrets show that immunization with adjuvanted H5N1 vaccine induced high level of HI antibodies and that animals were protected from challenge with the H5 influenza virus (data submitted to the BLA).

Together, these data further support that HI antibody titers can provide protection from influenza disease.

## **5. Feasibility of conducting effectiveness studies during a pandemic**

On November 14, 2012, CBER convened its Vaccines and Related Biologic Products Advisory Committee (VRBPAC) as part of its ongoing review of BLA STN 125419 to receive the committee's input on a non-voting question related to the licensure pathway for Q-Pan H5N1. In November 2012, FluLaval Quadrivalent had not yet been licensed, so the appropriate pathway for approval of Q-Pan, at that time, would have been accelerated approval. CBER requested a discussion regarding whether the effectiveness of Q-Pan H5N1 for "traditional" approval should be a) confirmed with efficacy data generated with a U.S.-licensed seasonal influenza virus vaccine made according to the same manufacturing process or b) confirmed by conducting an effectiveness study (or studies) during an H5N1 influenza virus pandemic. At this meeting, the feasibility of conducting studies during an influenza pandemic with the goal of obtaining vaccine specific effectiveness data for the pandemic influenza vaccine was discussed.<sup>21</sup> The Centers for Disease Control and Prevention (CDC) presented plans to estimate the overall and age group-specific vaccine effectiveness (VE) for pandemic vaccines during the next pandemic using primarily existing seasonal influenza program platforms. CDC commented on the low feasibility of obtaining product-specific effectiveness data, a prerequisite if GSK would be required to verify the clinical benefit of Q-Pan by conducting adequate and well-controlled studies during a pandemic under the accelerated approval provisions (21 CFR 601.41) and as requested by the clinical reviewer and supervisor. CDC stated that it would likely be infeasible using currently available systems, to obtain product-specific VE estimates during a pandemic because CDC's current vaccine distribution system would not assure that a particular vaccine is administered at CDC study sites. Obtaining product specific VE estimates during a pandemic would require the development of a different distribution system. Notably, current CDC systems do not involve manufacturers' input or funds.

Moreover, experience with the 2009 H1N1 pandemic showed that during a pandemic, it is challenging to conduct VE studies that are adequate to support regulatory approval of pandemic influenza vaccines.<sup>5, 22</sup> Specifically, GSK had originally proposed to verify the clinical benefit of Q-Pan with effectiveness data using an unlicensed adjuvanted pandemic influenza A H1N1 subtype vaccine made by the same process, Arepanrix. These data were derived from a case-control, test negative, retrospective, vaccine effectiveness observational study carried out by the New Brunswick Department of Public Health in Canada during the 2009 H1N1 pandemic. Following review of the study report CBER reviewers concluded that

although results suggested that the vaccine was effective in preventing laboratory confirmed pandemic H1N1 influenza during the 2009/2010 H1N1 pandemic, study limitations precluded use of the study in a regulatory setting as the basis to verify clinical benefit, and thus, support traditional approval of Q-Pan. Thus, it is not certain whether data from a clinical effectiveness study conducted during a future pandemic would be acceptable to verify the clinical benefit of the vaccine and thus, support traditional approval of Q-Pan.

In addition, OVRP has learned, in discussions with vaccine manufacturers and the Biomedical Advanced Research and Development Authority (BARDA), that in the event of a pandemic, the manufacturers will not control distribution and use of the pandemic influenza vaccine, as these are controlled by the US government. This poses challenges on the part of the vaccine manufacturer to comply with the accelerated approval regulations in 21 CFR 601.41, namely, that the clinical benefit confirmatory study(ies) should be adequate and well-controlled and that the applicant has to carry out such studies with due diligence.

## **6. VRBPAC Deliberations**

On February 29, 2012, prior to the November 14, 2012 VRBPAC meeting to specifically discuss Q-Pan, CBER convened the Committee to discuss pathways to licensure of pandemic influenza vaccines, in general, with particular emphasis on types of data that can be used to support effectiveness of such vaccines prior to licensure.<sup>23</sup> The VRBPAC consensus was that it is important to have safety and immunogenicity data accrued with the adjuvanted pandemic vaccine and that it was reasonable to infer effectiveness of the pandemic influenza vaccine from the efficacy of the seasonal influenza vaccine made by the same manufacturer and process. At the subsequent November 14, 2012, meeting of VRBPAC to specifically discuss Q-Pan, some committee members stated that use of data derived from a clinical endpoint efficacy study of a US licensed seasonal influenza vaccine made by the same manufacturing process is a reasonable and pragmatic approach to verify the clinical benefit of Q-Pan H5N1. These members noted that it is not reasonable to require GSK to confirm the clinical benefit of Q-Pan H5N1 during a pandemic, and that fulfilling such a requirement is not feasible. On the other hand, a number of committee members stated a preference for licensing Q-Pan under the accelerated approval provisions and that the effectiveness of Q-Pan be confirmed during an H5N1 influenza pandemic. However, specifics of the accelerated approval regulations, including the requirement to conduct confirmatory studies with due diligence, were not discussed by the committee. Of note, members stressed the importance of confirming effectiveness during a pandemic. In accordance with the Committee's view, GSK has committed to collaborate with the U.S. government to collect additional effectiveness and safety data in the event that the vaccine is used during a pandemic, regardless of the approach to licensure.

## **II. Conclusion**

GSK has demonstrated that Q-Pan induces a robust HI antibody response that substantially exceeds the  $\geq 1 : 40$  criterion for HI titer in a high proportion of vaccines. Furthermore, GSK has verified the clinical benefit of Q-Pan using clinical endpoint efficacy data accrued with its U.S.-licensed seasonal influenza vaccine, FluLaval quadrivalent that is made by the same manufacturing process as Q-Pan. Therefore, and in accordance with the May 2007 FDA

Guidance for Industry “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines”, Q-Pan was granted traditional approval. Of note, GSK has committed to collaborate with the Food and Drug Administration and other governmental agencies in the United States on plans to collect additional safety and effectiveness data in the United States, when Q-Pan is used.

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