

Final Q-Pan clinical review concurrence memo, August 14, 2013 - Q-Pan

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| Date: | August 14, 2013 |
| To: | STN 125419: Glaxo Smith Kline Biologicals Influenza A (H5N1) Virus Monovalent Vaccine |
| From: | Lewis Schragger, M.D. Chief, Clinical Review Branch 2 Division of Vaccines and Related Product Applications OVRRCBER |
| Through: | Wellington Sun, M.D. Director, DVRPA OVRRCBER Marion Gruber, Ph.D. Director, OVRRCBER |
| Subject: | Branch Chief Concurrence with Clinical Review |

Conclusion:

I concur with the assessment of Dr. Andrea James, the clinical reviewer, that the data included in the Biological Licensing Application (BLA) submission STN 125419 provides sufficient evidence of the safety and effectiveness of Q-Pan H5N1(A/Indonesia/5/2005 made in eggs with ASO3 adjuvant) for use in an H5N1 pandemic, and that the immunogenicity of Q-Pan H5N1 is a surrogate that is reasonably likely to predict protection against H5N1 infection and support the approval under 21 CFR 601 Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (21 CFR 601.40-46).

I also concur with Dr. James's assessment that confirmation of clinical effectiveness of Q-Pan H5N1 in an actual pandemic or during a period of sustained transmission of the virus is the appropriate approach to verify effectiveness under 21 CFR 601.41, while granting traditional approval under PHS Act Sec. 351, based on the clinical effectiveness of a seasonal influenza virus vaccine manufactured via the same process as that used to manufacture Q-Pan H5N1 does not take into consideration the significant biological differences between the H5N1 influenza virus subtype and seasonal influenza viruses (H1N1, H3N2 and types B)

Background:

H5N1 avian influenza is distinct from any of the circulating seasonal influenza strains. H5N1 avian influenza infection manifests a case-fatality rate of 59% as of 15 February 2013 according to the WHO, markedly higher than the case-fatality rate seen in association with seasonal influenza virus infections. From a physiological perspective, H5N1 influenza virus utilizes a different receptor and binding site than that used by

seasonal influenza strains. H5N1 primarily utilizes the α 2,3-linked sialic acid receptors located on ciliated respiratory epithelia deep in the lower respiratory tract. In comparison, human seasonal influenza viruses preferentially utilize the α 2,6 sialic acid receptors located on non-ciliated respiratory epithelial cells situated in the upper respiratory tract. This difference in preferential receptor utilization likely explains at least some of the striking clinical differences noted following infection with H5N1 as compared to infection with seasonal influenza strains.

In February 2012 GlaxoSmithKline Biologicals (GSK) submitted the BLA for Q-Pan H5N1 for the prevention of influenza disease in persons 18 years and older at increased risk for exposure to H5N1 subtypes contained in the vaccine. In her review of this BLA, Dr. James reaches the following conclusions:

1. Q-Pan H5N1 has been demonstrated to be sufficiently immunogenic to permit a conclusion that the vaccine would be reasonably likely to protect adults ages 18 and older against pandemic influenza H5N1 infection, thereby satisfying the efficacy requirement for licensure under 21 CFR 601.40-46 (21 CFR 601 Subpart E): Accelerated Approval for Biological Products for Serious or Life-Threatening Illnesses;
2. Q-Pan H5N1 has been demonstrated to be sufficiently safe to permit licensure for the purposes of protecting against pandemic influenza H5N1 infection should a pandemic occur, and for use in persons currently deemed to be at increased risk of contracting H5N1 infection, under the conditions of potential use set forth in her review (Clinical Review, Section 2);
3. While licensure under the accelerated approval regulations is supported by the safety and immunogenicity data submitted, the verification of clinical effectiveness of Q-Pan H5N1 in adults based on the pediatric efficacy data of FluLaval quadrivalent, an unadjuvanted seasonal influenza vaccine with the antigen components (H1N1, H3N2 and influenza B – Yamagata and Victoria lineage viruses), manufactured using the same process as the H5N1 antigen component of Q-PAN H5N1, requires extrapolation of effectiveness across subtypes that is not supportable given the important differences between H5N1 influenza and seasonal influenza strains noted above. Clinical efficacy of Q-Pan H5N1 in support of licensure under the traditional approval regulations must be confirmed directly via studies of the vaccine's effectiveness conducted at the time of an actual H5N1 pandemic or during sustained transmission of the virus.

Discussion:

I concur with Dr. James that the data presented in this BLA demonstrate the safety and immunogenicity of Q-Pan H5N1. Q-Pan H5N1, once licensed, will be used to prevent infection with H5N1 avian influenza, a life-threatening disease, during a pandemic, and is reasonably likely to provide meaningful therapeutic benefit over existing therapy, fulfilling the criteria for accelerated approval under 21 CFR 601 Subpart E. The shortage of the only H5N1 pandemic influenza vaccine currently available, the unadjuvanted H5N1 (Vietnam/1203/2004) vaccine by Sanofi Pasteur (SP) licensed in 2007 for storage in the strategic national stockpile until an H5N1 pandemic occurs, and the dose-sparing properties of Q-Pan H5N1, provide additional reasons supporting Q-PAN H5N1 licensure.

21 CFR 601.41 states that the FDA may grant marketing approval for a biological product 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 to predict clinical benefit. The hemagglutination inhibition (HI) antibody titer against subtypes of influenza A viruses is a surrogate used by CBER to infer influenza vaccine effectiveness, meeting the requirements of 21 CFR 601.41 (see the 2007 CBER Guidance for Industry, Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines).

21 CFR 601.41 also requires that the applicant conduct, with due diligence, a post-marketing, adequate and well-controlled study to verify the clinical benefit of the product. According to this regulation, such a study usually would be underway at the time of the licensing action. Applying the accelerated approval pathway to Q-Pan H5N1 presents unique challenges, foremost being that the H5N1 virus is not currently circulating widely in humans to allow direct verification of clinical benefit through a controlled clinical study. Accordingly, CBER considered several options in how Q-Pan H5N1 clinical effectiveness could be verified:

1. Inferring clinical effectiveness by a test-negative case-control observational study of GSK's H1N1 AS03-adjuvanted influenza vaccine conducted during the 2009 H1N1 pandemic in Canada (antigen from different subtype virus and same adjuvant made by same manufacturing process).
2. Inferring clinical effectiveness by FLU-Q-QIV-006, a phase 3 randomized, active control clinical efficacy trial, conducted in children, of GSK's unadjuvanted quadrivalent seasonal influenza vaccine, FluLaval, with antigens which includes the four seasonal influenza strains A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage) and B/Florida/4/2006 (Yamagata lineage); (antigens from different subtypes of virus made by the same manufacturing process, no adjuvant).
3. Demonstrate clinical effectiveness directly by a prospective, case-control, observational study or studies to be conducted during an H5N1 pandemic or during a period of sustained transmission of the H5N1 influenza virus if it occurs (antigen from the same subtype virus and same adjuvant made by the same manufacturing process).

Regarding Option 1, Dr. James did not accept the premise that an inference of clinical effectiveness of the H5N1 vaccine drawn from the observational study of the 2009 H1N1 AS03-adjuvanted vaccine during the 2009 H1N1 pandemic was appropriate, given the marked antigenic, clinical and physiological differences between H5N1 infection and H1N1 infection described above and further elucidated in the assessment of option 2, below. I concur with this assessment. Additionally, the epidemiology and statistical reviewers of the BLA found the observational study conducted by Van Buynder, et. al., during the 2009 H1N1 pandemic in Canada (Option 1) to be inadequate to support traditional approval, resulting in the dismissal of this option.

Regarding Option 2, Dr. James concluded that a demonstration of clinical efficacy of FluLaval quadrivalent, an unadjuvanted seasonal influenza vaccine is not sufficient to confirm the clinical efficacy of the Q-Pan H5N1 vaccine, even though the antigen components were manufactured by the same process as that of Q-Pan H5N1 (Clinical Review, Section 5.4.1, Reviewer Comment). She noted that there are significant

antigenic, pathophysiologic and clinical differences between the H5N1 influenza virus and the four seasonal influenza viruses included in FluLaval quadrivalent. Accordingly, Dr. James concluded that the clinical effectiveness of FluLaval quadrivalent cannot verify the clinical effectiveness of Q-Pan H5N1 at the level of certainty to support traditional approval. I concur with this conclusion. Additionally, Dr. James noted that, although the antigenic components of both vaccines are made using identical manufacturing process, this only provides confidence in the manufacturing consistency of Q-Pan H5N1 *vis a vis* FluLaval quadrivalent but does not permit a determination of Q-Pan H5N1 clinical effectiveness by an extrapolation from the FluLaval quadrivalent clinical efficacy data. The FluLaval the package insert supports this perspective, stating that “antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype.” Given these limitations in confirming the effectiveness of Q-Pan H5N1 from efficacy studies of a quadrivalent vaccine against seasonal influenza subtypes, Option 2 cannot be supported, even though the antigen components of Q-Pan H5N1 and Flulaval quadrivalent are made using identical manufacturing processes.

I concur with Dr. James’s rationale, set forth in Section 11.3 of the clinical review, that the most scientifically supportable approach to the verification of Q-Pan H5N1 clinical effectiveness is to conduct a study or studies to evaluate effectiveness during an actual H5N1 pandemic or sustained transmission of the virus. Numerous published studies from the 2009 H1N1 pandemic, including the study by Van Buynder, et. al., have shown that such studies are feasible in the setting of a pandemic. Additionally, as Dr. James noted in Section 11.3 of her clinical review, the FDA has granted accelerated approval to two antibiotics for use against a life threatening disease which was non-exigent and therefore was not amenable to a controlled clinical efficacy trial conducted at or around the time of marketing approval. When approving both these products, the Agency interpreted the requirement for due diligence in the conduct of a post-marketing effectiveness study to be fulfilled with the initiation of such a study if or when the disease actually occurs. Dr. James concluded that this solid Agency precedent, interpreting the due diligence requirement of 21 CFR 601.41 in the setting of a licensing action for an intervention against a non-exigent disease, should be applicable to the licensure of the Q-Pan H5N1 vaccine. I concur.

Finally, it is important to consider the outcome of the discussion of the Q-Pan H5N1 BLA at the November 2012 Vaccines and Related Biological Products Advisory Committee (VRBPAC). Subsequent to the VRBPAC’s favorable votes on the applicant’s demonstration of the vaccine’s safety and immunogenicity, the committee was asked to discuss Options 2 and 3 for the verification of clinical effectiveness. Many of the committee members expressed concerns about the antigenic diversity and unpredictable nature of a H5N1 pandemic, and about verifying effectiveness using an unadjuvanted seasonal vaccine. While there was no vote on which of the two options would be preferred, it was clear from the discussion that the majority of the members favored Option 3, verification of effectiveness by studying Q-Pan H5N1 during a pandemic. VRBPAC members recognized that feasibility of an intrapandemic effectiveness study was a significant but not insurmountable obstacle. Additionally, following the discussion of the importance of and challenges involved in confirming

pandemic vaccine effectiveness at the November VRBPAC, the Biomedical Advanced Research and Development Authority (BARDA) initiated a cross-Agency working group on developing options for conducting effectiveness studies during a pandemic. An FDA requirement to conduct post-marketing effectiveness studies during a pandemic likely would spur further efforts to address this public health need.