Telephone Conference Memorandum - 7/30/2007 - AFLURIA

TELEPHONE CONFERENCE MEMORANDUM

STN 125254/0: CTD BLA for Influenza Virus Vaccine
SPONSOR: CSL Limited
PRODUCT: Influenza Virus Vaccine
DATE: July 30, 2007

CBER REPRESENTATIVE:
Katherine Berkhousen

CSL REPRESENTATIVE:
Paul Hartman
Tel: 610-878-4644
Fax: 610-878-4182

SUMMARY:

We have the following comments regarding your July 17, 2007 submission that contained a response to our questions about submission of studies to be conducted after a potential accelerated approval licensure:

1. After CBER review of your original IND submitted on April 10, 2006, the following clinical comments were conveyed to you in a June 12, 2006 correspondence:

   The study might support licensure of CSL influenza vaccine under accelerated approval regulations where successful HAI antibody assay results for all three vaccine strains would be reasonably likely to predict clinical benefit as a surrogate endpoint. However, we remind you that other provisions of the accelerated approval regulations are applicable, such as whether or not a shortage of influenza vaccine is documented at the time of the accelerated approval.

   We request the commitment to conduct a clinical endpoint efficacy study during the influenza season following accelerated approval that would be designed to confirm the clinical benefit of the CSL influenza vaccine. We refer you to the FDA Draft Guidance for Industry document "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines".

1. One of the other provisions of the accelerated approval regulations includes a commitment to continue product development towards full licensure "with due diligence". We reference 21 CFR 601.41: "Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence."

   Your proposed timelines for initiation of the culture confirmation study in February/March 2009 in the Southern Hemisphere, initiation of the safety and immunogenicity study in an at-risk adult population in October 2008 in the Northern Hemisphere, and no provision for initiation of pediatric studies, do not represent due diligence and have important considerations under these accelerated approval regulations. Please provide the draft protocol of a culture confirmation study to be initiated in February/March 2008 in the Southern Hemisphere. Please also provide your draft protocols for the safety and immune response studies in the at-risk adult population and in pediatric populations. The studies in at-risk adults and in pediatrics should also be initiated in the influenza season following accelerated approval, initiated either in October 2007 in the Northern Hemisphere, or February/March 2008 in the Southern Hemisphere. Please submit the three or more draft protocols to the IND for review by close of business August 31, 2007. For study design and consideration of endpoints to be used in a culture confirmation study, we refer you to the final Guidance Document http://www.fda.gov/cber/gdlns/trifluvac.htm, as well as recent publications of completed culture confirmation studies [1.) Ohmit SE, Victor JC, Rotthoff, JR et al. Prevention of Antigenically Drifted Influenza by Inactivated and Live Attenuated Vaccines. New Engl J Med 2006; 355:2513-2522. 2.) Belshe RB, Edwards KM, Vesikari T, et al. Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children. New Engl J Med 2007; 356:685-696.]

2. During our review, we noted lower immune responses among subjects $\geq$65 years of age, in particular immune responses from studies 04-99 and 05-13. Please provide summary immune response data from all of the studies in subjects >60 years of age that were used to support yearly licensure in European countries by using the following table:

Study title and year	**% 4-fold inc. HI titer (95% CI)**	**% HI titer $\geq$ 1:40 post-vac (95% CI)**
H1N1 strain		
H3N2 strain		

Study title and year	% 4-fold inc. HI titer (95% CI)	% HI titer ≥ 1:40 post-vac (95% CI)
B strain		

3. Regarding your post-marketing experience, please provide the following data:
   a. The total number of doses of CSL inactivated influenza vaccine distributed since 1968.
   b. The total number of doses of CSL inactivated influenza vaccine distributed since January 2002, and the countries of distribution.

4. Regarding Pediatric Study CSLCT-NHF-04-05:
   a. Please provide the case report forms for the three reported SAEs.

5. Please provide your response to items 2, 3, and 4 by the close of business August 10, 2007.