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8 June 2006

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. 2006D-0088** Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines [71 Federal Register 12366, March 10, 2006]

Dear Sir/Madam,

Sanofi Pasteur Inc. of Swiftwater, Pennsylvania thanks the Food and Drug Administration (FDA) for the opportunity to comment on the above-referenced draft guidance for industry entitled, "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines." Headquartered in Lyon, France, sanofi pasteur is the vaccines business of sanofi-aventis Group. Sanofi-aventis is the world's third-largest pharmaceutical company.

Sanofi pasteur is a world leader in vaccines and produces more than one billion doses of vaccines every year to immunize over 500 million people around the world. Sanofi pasteur, in close consultation with the US public health establishment, including the FDA, and Centers for Disease Control and Prevention (CDC), strives to alleviate the suffering and death resulting from vaccine-preventable diseases.

We offer the following comments for your consideration concerning the FDA's solicitation of responses as they apply to the Biologics (Vaccine) industry.

### **General Comments**

Sanofi pasteur recognizes and appreciates FDA's efforts with respect to development of a pandemic influenza vaccine guidance.

### **Specific Comments**

#### *Section III, B 1. Immunogenicity:*

- In a pandemic strain situation, almost all subjects will be naïve (i.e., HI antibody titer < 1:10) before vaccine administration. Thus, all subjects who reach seroconversion (> 4-fold rise) will also reach seroprotection (HI antibody titer ≥ 1:40), and vice-versa. Considering that these two endpoints will yield similar results, what is the relevance of identifying these two criteria as co-primary endpoints?

- The guidance focuses on the use of HI antibody assays to assess vaccine activity and makes reference to the microneutralization assay as an additional method. It would be helpful if FDA were to include additional guidance on the detailed use of this assay as well.

*Section III, C 1a. Effectiveness:*

- As seroconversion and seroprotection rates will be similar (see above), we request that FDA clarify why there is a large difference in their requirements (*i.e.*, 40% for seroconversion and 70% for seroprotection).
- The criteria for seroprotection as it is specified in this draft Guidance may be difficult to accomplish in the naïve, pre-pandemic population:
  - *The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer  $\geq 1:40$  should meet or exceed 70% and 60% for adults  $<65$  and  $\geq 65$  years of age, respectively.*

It is important to note that a vaccine eliciting a lower immune response may still provide substantial value to public health. Thus, we suggest allowing for appropriately justified criteria for potential approval.

*Section III, C 2. Safety: A total safety database large enough to rule out a serious adverse event that occurs at a rate of 1 in 300 may be adequate.*

- Please clarify this statement, *e.g.*, what statistical power is FDA expecting?

*Section III, D 2. Clinical Lot Consistency:*

- The lot consistency criteria do not present a lower bound. In previous guidance documents, the lower bound has been stated as 0.67.

*Section III, D 3. Adjuvanted Pandemic Vaccines:*

- The guidance proposes a comparative study of adjuvanted vs. non-adjuvanted vaccines of the same dosage with the demonstration of superiority of the adjuvanted vaccine. As stated in the guidance, an adjuvant might reduce the amount of antigen needed to elicit immune responses to protect against influenza. We propose that the clinical investigation might focus on dose sparing, as opposed to demonstration of superiority to the same unadjuvanted dose of vaccine.

On behalf of sanofi pasteur we appreciate the opportunity to comment and thank you for your consideration of these responses. Should you wish to discuss any of our comments or concerns further, please address inquiries directly to Denise Rieker, Deputy Director, Regulatory Policy and Intelligence, by telephone at (570) 895-3465, or me directly at 570-839-4212.

Sincerely,



Kenneth P. Guito  
Sr. Director, Regulatory Policy and Intelligence

KPG/DR/kh