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9 June 2006

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

Re: Docket No. 2006D-0083 Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines [71 Federal Register 12367, March 10, 2006]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Pennsylvania thanks the Food and Drug Administration (FDA) for the opportunity to comment on the above-referenced draft guidance for industry entitled, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines."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 associated with 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 this trivalent inactivated influenza vaccine guidance document.

In all, we concur with the CBER position as expressed in this document that any new Trivalent Influenza vaccine(s) for target populations should be required to satisfy stringent criteria for co-primary endpoints, seroprotection and seroconversion. The CDC's Advisory Committee on Immunization Practices (ACIP) has in recent years gradually expanded the recommendations for populations who should receive influenza vaccination. While it is accurate to say there have been occasional delays in the availability of influenza vaccines or outright shortages in supply, it is critical that the immunogenicity and safety profile associated with these vaccines over a long history not be compromised in exchange for presumed expanded availability of adequate supplies.

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Due to the unique nature of influenza vaccines, i.e., being administered to large numbers of healthy individuals on a yearly basis, it is essential that all feasible means be employed to ensure continued public confidence in their safety and effectiveness.

In addition, we agree with CBER's recommendation that a Consistency Lot study should be conducted with three consecutively manufactured lots for any new Trivalent Influenza Vaccine. However, we disagree with CBER's statement that "CBER might decide on a case by case basis that lot consistency may be evaluated and incorporated in the post-marketing commitment studies". We believe appropriate Lot Consistency studies should be required as a pre-licensure commitment for any new candidate vaccine for the reasons noted previously.

Lastly, specific guidance on a superiority trial is not provided in this document. This would be useful in terms of potential development of influenza vaccines with a superior immunogenicity/efficacy profile.

Specific Comments

Section III, A 1b. Effectiveness:

- The guidance focuses on culture confirmation for case definition of influenza. We suggest considering inclusion of other options, such as PCR.

Section III, A 2a. Additional Studies to Support the Effectiveness of the Vaccine in Populations Not Included in the Clinical Efficacy Study:

.....While this approach may expand the use of the new vaccine in additional populations, an important consideration is that immune responses in the very young and the elderly might be lower than those observed in healthy adults enrolled in a placebo-controlled clinical efficacy study....

- This statement appears not to be in line with the subsequent recommendations presented in section III B 1b, where you state;
For adults <65 years of age and for the pediatric population:
- *The lower bound of the 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.*
- *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%.*

When we consider, as you appropriately point out, that the antibody response might be lower in the very young, it seems unduly stringent then that the "pediatric population" be required to meet the same requirements as adults < 65 years of age with respect to seroconversion and seroprotection. Rather it would be more consistent to have the pediatric population meet the same requirements as those you specify for adults ≥ 65 years of age.

Section III, A 3. Safety:

- Please clarify if a particular grading scale to describe the severity of adverse events is anticipated as a requirement.

Section III, B. Accelerated Approval of a BLA for a New Trivalent Inactivated Influenza Vaccine: "Thus, suitable controls and assay validation are important for interpreting HI antibody results.

- We would like to add that standardization is also important.

Section III, B 1b. Effectiveness:

- It is well known that the immunogenicity of a vaccine may be strain dependent and that some strains are poorly immunogenic no matter the vaccine formulation used. Thus, for placebo-controlled clinical trials, the criteria for seroprotection as specified by CBER may not be achievable:
The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer >1:40 should meet or exceed 70% and 60% for adults <65 and >65 years of age, respectively.

Section III, B 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.

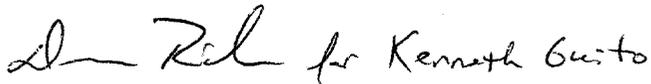
- Please clarify this statement, e.g., what statistical power is CBER expecting?

Section III, C 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.
- *“The two-sided 95% CI on the GMT ratio should not exceed 1.5.”* Does CBER intend this to mean that the two-sided 95% CI should lie entirely between 1/1.5 and 1.5? This is an equivalence test; therefore, both bounds of the 95% CI should be evaluated. Please clarify.

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