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June 2, 2006

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

Re: Comments on Dockets 2006D-0083 and 2006D-0088; Draft Guidance for Influenza Vaccines

Dear Sirs;

Novartis Vaccines is submitting comments on the two draft guidance documents on influenza vaccines recently published by CBER and announced in the Federal Register/ Vol. 71, No. 47/ Friday, March 10, 2006, pages 12366-12367. Comments on each guidance document are attached under the title for each document.

If you have questions or require clarification please do not hesitate to contact me by phone at (215) 255-4218 or by facsimile at (215) 255-4222.

Sincerely,

Maurice W. Harmon, Ph.D., RAC
Senior Director, Regulatory Affairs
Novartis Vaccines
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2006D-0083

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Docket 2006D-0083, Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines

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Comment 1

In discussing the information needed to support an adjuvanted vaccine, we note that CBER has requested that sponsors should demonstrate the added value of the adjuvant given with the antigen. CBER has advised that the immune response elicited by the adjuvanted antigen should be significantly better than that elicited by the same antigen without adjuvant. The guidance specified a two-fold increase in the GMT ratio and a 15% increase in seroconversion rates as examples of meaningful differences.

Novartis has considerable experience with at least one adjuvant, MF59, in primed and naïve populations. Based upon that experience we conclude that a two-fold increase in the GMT ratio and a 15% increase in seroconversion rate are more likely to be achieved when the population being vaccinated is immunologically naïve to that particular antigen, as might be expected with an avian influenza virus strain that begins to circulate in the general population or any influenza strain with infants. However, in a population that is primed and/or immunized to circulating, interpandemic influenza strains, such as the majority of people in most populations, such differences may not be fully evident, due to the pre-existing immunity. Our experience indicates that with interpandemic vaccines containing the standard 15 μg dose, the GMT ratio would be in the range of 1.1 to 1.4 and the seroconversion rate increase generally in the range of ≤ 10%. In light of considerable evidence that sponsors would not be able to meet FDA criteria for the interpandemic vaccine, FDA might consider a statistically significant increase in antibody titer to be evidence of a "significantly better" vaccine when adjuvanted. Additionally, it would be useful to clarify if the increased immunogenicity should be demonstrated for at least one strain or for the three of them altogether.

Also, it may be valuable to consider such parameters as the breadth of antibody responses to the multitude of strains circulating and/or consideration of responses less than 4-fold as being significant. MF59-adjuvanted interpandemic vaccines induce seroprotective antibody titers against heterovariant strains (e.g. against H3N2 A/Fujian using an A/Panama strain as the vaccine) in nearly all vaccinated individuals, versus 80% of those receiving non-adjuvanted vaccine (Del Giudice et al, Vaccine 24: 3063-3065, 2006). Using an MF59-adjuvanted pandemic (H5N3) vaccine, cross-reactive protection against H5N1 heterovariants that emerged in 2003 and 2004 was evident in 45% to 65% of individuals versus none in subjects receiving the non-adjuvanted vaccine (Stephenson, J Infect Dis 191: 1210-1215, 2005). In addition, cell mediated immune responses may be important to consider when evaluating adjuvanted vaccines.

Therefore, to be successful, we suggest that this guidance consider broader criteria or definitions of significant differences in immune response that could provide clinically meaningful benefits when adjuvants are used. In addition, the immune status of the population being studied (naïve vs. primed) is also an important consideration, and may require further adjustments in these criteria.

Comment 2

The guidance has mentioned that antigen sparing may be an outcome of an adjuvanted vaccine. Our interpretation of this remark is that antigen sparing could be considered an added value of an adjuvanted vaccine since it would contribute to vaccine supply. However, this would probably be at the expense of a superior antibody response compared to the non-adjuvanted vaccine. To take advantage of this feature, the sponsor would reduce the antigen dosage to a point that the adjuvanted, reduced-antigen content vaccine induced a rate of seroconversion and percent of subjects achieving an HI antibody titer of ≥ 40 that is high enough to satisfy the criteria noted in the guidance. Another way of looking at this is that the superior antibody response possible with the adjuvanted vaccine is sacrificed for an "adequate" antibody response using significantly less antigen than would be required without an adjuvant. Such consideration – lowering the administered dose to produce a comparable "take" rate – was given to the smallpox vaccine when the supply of that vaccine was deemed limited. Does FDA consider this interpretation valid or is the interpretation such that the added benefit is considered only if directly benefiting the individual vaccinated subject?

Comment 3

In the interests of developing an improved immune response to influenza, sponsors that have licensed influenza vaccines on the market are most likely to re-formulate that vaccine with an adjuvant. The guidance states that all adjuvanted vaccines must be the subject of a new Biologics License Application which implies a clinical endpoint efficacy study requirement. Can sponsors assume that the basis for licensure of such "newly adjuvanted" formulations of previously licensed vaccines, which are already considered efficacious, will be an improved antibody response as a correlate of efficacy and that they will not be required to perform a clinical endpoint efficacy trial as a licensing requirement?

Comment 4

In the interests of facilitating influenza vaccine development, not to mention harmonization, it would be a meaningful advance if the FDA would consider adopting the same clinical criteria as specified by the EU guidance (CPMP/BWP/214/96) for vaccine requirements.

Comment 5

The terminology used in the draft guidance that refers to clinical efficacy/effectiveness is somewhat different from our understanding of these terms. It would be appreciated if the guidance documents would provide an interpretation of clinical effectiveness and clinical efficacy in order to avoid any confusion in this regard.

Comment 6

The guidance documents contain the phrase "the timing of the clinical development and the size of the safety database to support use in the pediatric age groups warrants discussion with CBER". It would be very helpful if the guidance documents could provide a proposal for stratifying by age bands for safety purposes, including high-risk subgroups.

Comment 7

It would be helpful to sponsors if the Agency could give some indication as to the size the required safety database. There is considerable human experience with several influenza vaccines. While we recognize that there will be case-by-case judgments that will be made, we would think that sufficient data exist where a common baseline figure could be indicated in the guidance as a general guide.

Docket 2006D-0088, Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

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Comment 1

The draft guidance states that a pandemic influenza vaccine may be granted accelerated approval based upon the HI antibody response and a commitment to conduct confirmatory post-marketing studies. The post-marketing confirmatory studies can be either development of a trivalent inactivated influenza vaccine using the same manufacturing process or field effectiveness studies to confirm clinical benefit.

The regulations for accelerated approval (21 CFR 601.41) require that confirmatory trials be executed with due diligence. The field effectiveness confirmatory trial will require the pandemic strain to be circulating in order to collect the effectiveness data. The timeline for circulation of a pandemic virus is unknown and is also out of any control by the sponsor. The question relates to the timeframe the Agency is likely to allow following accelerated approval of an adjuvanted, pandemic vaccine for the sponsor to complete the confirmatory trials before FDA considers that the sponsor was not proceeding with due diligence and proceeds to revoke the license for the pandemic vaccine?

Comment 2

The guidance documents contain the phrase "the timing of the clinical development and the size of the safety database to support use in the pediatric age groups warrants discussion with CBER". It would be very helpful of the guidance could provide a proposal for stratifying by age bands for safety purposes, including high-risk subgroups.

Comment 3

It would be helpful to sponsors if the Agency could give some indication as to the size the required safety database. There is a considerable amount of human experience on several influenza vaccines. While we recognize that there will be case-by-case judgments that will be made, we would think that sufficient data exist where a common baseline figure could be indicated in the guidance as a general guide.

Comment 4

In the interests of facilitating influenza vaccine development, not to mention harmonization, it would be helpful if the FDA would require the same clinical criteria as specified by the EU guidance (CPMP/BWP/214/96) for vaccine requirements.