DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
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Division of Dockets Management (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

June 1st 2006

Re: **Docket No. 2006D-0088**

Madam/Sir,

Please find enclosed written comments on the above referenced Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, published in March 2006.

Sincerely,

Kanta Subbarao, MD, MPH (Senior Investigator)
Brian Murphy MD (Laboratory Co-Chief)
Catherine Luke Ph.D. (Staff Scientist)

Laboratory of Infectious Diseases,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health

2006D-0088 C3

Comments on Docket No. 2006D-0088,

Draft Guidance 'Guidance for Industry. Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines'

Page 5.

Section B Approval of a Pandemic Influenza Vaccine as a Supplement to a U.S. Licensed Trivalent Live Attenuated Influenza Vaccine

1. Immunogenicity

The basis for the use of an hemagglutination inhibition (HI) titer as a recommended endpoint in studies to support licensure of pandemic influenza vaccines is not clear. The ability of antibodies to neutralize infectivity of a virus is a functional test that is likely to have biological significance. In HI tests, serum antibodies that bind to the hemagglutinin (HA) of an influenza virus block agglutination of red blood cells. An HI titer of ≥ 1:40 was found to be a surrogate for neutralization of infectivity of human influenza viruses and was predictive of protection from human influenza in experimental challenge studies (Potter et al. J Hyg 79: 321.[1977[). There is insufficient experience with vaccines against influenza viruses of pandemic potential in humans and neutralization and HI titers against these viruses may not correlate well. For example, an H5N1 virus vaccine generated against a 2003 human influenza A H5N1 virus isolate elicits neutralizing antibody but does not elicit HI antibody (Hoffmann et al PNAS 102: 12915. [2005]). There are no data to support the use of HI titers and specifically, an HI titer of ≥ 1:40, as a correlate of protection against avian influenza virus infections. As stated in a reference cited in the Draft Guidance (Ref. 20, de Jong et al. 2003), the HI test is 'not a functional test for measuring immunity and suffers from a number of serious technical drawbacks'.

It is also becoming apparent that the HI test is not sensitive or reliable for avian influenza viruses. Use of horse erythrocytes instead of turkey erythrocytes appeared

to increase the sensitivity of the HI test for detection of antibodies in sera from volunteers who had been immunized with an inactivated avian H5 influenza vaccine (Stephenson et al. Virus Res 103: 91 [2004]). However, these tests have not been standardized and the biological significance of specific HI titers with horse erythrocytes have not been established. In Phase 1 studies conducted on vaccines for avian influenza viruses of the H5 and H9 subtypes, it was found that the microneutralization test is more sensitive than HI. Both assays were used to measure immunogenicity in a recent Phase 1 study of an inactivated vaccine against H5N1 influenza (Treanor et al. NEJM 354: 1343 [2006]). However, there are no data to support the use of an HI titer of ≥ 1:40 as an endpoint for immunogenicity of H5 vaccines or by which to set the bounds of the confidence intervals for HI antibody titers.

Thus, HI titers should not be recommended as an endpoint for immunogenicity of vaccines in the absence of data that indicates 1) that HI titers correlate with neutralizing antibody titers for influenza A viruses of all subtypes and 2) the level of serum HI antibody that is likely to be protective against avian influenza viruses. Instead, the recommendation should be restated as 'an HI antibody assay or other appropriate functional assay of immunogenicity may be used to measure the immune responses and a four-fold rise in titer should be the minimum acceptable evidence of a serological response to a vaccine'.

The Agency does not give specific information on 'other assays' or those assays that 'assess mucosal immunity' which they suggest may be appropriate if they are predictive of protection. Assays for mucosal immunity, such as measurement of IgA in nasal wash specimens, have not been validated for the LAIV for seasonal influenza. To establish such correlates of protection would require large clinical studies, and as in the case of the serum antibody response, it is not clear whether information gathered on the mucosal antibody response to human influenza viruses would be predictive of protection against influenza viruses of pandemic potential. These comments also apply to Page 7, Paragraph 3 in the section '**Accelerated Approval of a BLA for a Pandemic Influenza Vaccine (i.e., Not as a BLA Supplement to an Existing U.S. Licensed Influenza Vaccine**).

2. Safety

While we appreciate the concern that live attenuated vaccines based on influenza viruses of pandemic potential present a theoretical risk of reassortment with circulating influenza viruses, and agree that initial studies of any such vaccine candidate be conducted in an inpatient setting, we believe that the data generated from initial evaluations should guide further studies. Data on shedding of the vaccine virus from subjects in initial studies in isolation units may suggest that it is safe to proceed to outpatient studies in the summer, when human influenza viruses are not circulating.

Isolation requirements for further evaluation of a particular candidate live attenuated vaccines for pandemic influenza should be reconsidered when data are available from the first set of inpatient studies that were conducted in isolation units. If data on virus shedding and respiratory symptoms in vaccinees demonstrate that the vaccine virus is highly restricted in replication, the risk of transmission of the vaccine virus is remote. This would be especially true if the candidate vaccine virus is shed at titers lower than that seen in studies with LAIV vaccine viruses against human influenza. There is only one documented case of transmission of vaccine virus following administration of LAIV, in a childcare setting and, if the investigational vaccine virus replicates to titers lower than the licensed LAIV, it would be reasonable to conclude that the risk of transmission of the vaccine virus will be lower than that of the licensed LAIV. If the vaccine virus is highly attenuated and fails to replicate to titers likely to be infectious for contacts, this would suggest that the risk of transmission is extremely low, and this in turn reduces the risk of reassortment with circulating influenza viruses. To further mitigate the risk of reassortment, outpatient studies with candidate live attenuated pandemic influenza vaccines could be conducted in the summer months when human influenza viruses are not circulating in the community.

A requirement to conduct all studies of live attenuated pandemic influenza vaccine candidates to isolation units will severely impede progress in studying the safety, infectivity and immunogenicity of such vaccines in large numbers of subjects. We strongly suggest reconsideration of this part of the Draft Guidance to allow flexibility in

conducting outpatient trials if indicated by the infectivity data obtained in initial inpatient studies.

Page 10 D. Additional Considerations

2. Clinical Lot Consistency

Since the HI antibody assay may not be appropriate for the evaluation of live attenuated vaccines against pandemic influenza, the wording should be changed to 'The HI asntibody assay or other appropriate measure of immunogenicity may be used to assess the immune responses'.