

**National Institutes of Allergy and Infectious Diseases
National Institutes of Health**

Comments on

***FDA Draft Guidance for Industry: Clinical Data Needed to Support
the Licensure of Pandemic Influenza Vaccines***

General Observations:

1. The use of an immunogenicity endpoint (whether for accelerated approval or for a supplement) ignores the fact that there is a large variability in results of hemagglutination inhibition (HI) assays (Wood et al Vaccine 1994; 12:167.). However, effectiveness judged by immunogenicity could be misleading unless the results are correlated to a clinical effect for each lab performing HI. Contrary to the concern expressed in the guidance document, within a lab HI can be well controlled and highly consistent, so that comparisons made within a study can be valid, but the success or non-success of a vaccine cannot be made in absolute terms by immunogenicity at present.

2. Much of the guidance focuses on HI, but there are other measures of immunogenicity including neutralizing antibodies that might deserve similar consideration. It is noted on page 1 that vaccines not containing hemagglutinin as a component are not addressed, so it is recognized to some extent that there may be alternative ways to identify useful vaccines. It is also noted on page 4 that other immunologic assays, e.g. microneutralization, may also be appropriate. However, microneutralization also has no international standards, so validation of that assay is also difficult, similar to HI as noted below.

Specific Comments:

Page 2, Section II Background – (1) Section notes 15 hemagglutinins - there are now 16 known influenza A hemagglutinin subtypes. (2) Use of the term “epidemic variants” is not clear and may be technically incorrect as described. Epidemic variants do not evolve from reassortment; reassortment may change the hemagglutinin or neuraminidase subtype, but mutations of the proteins are still needed for the proteins to be recognized as variant from a pre-existing virus of the same subtype.

Page 4, Section III Part A -- This section discusses assay validation. No guidance has been provided on how to go about validating the HI assay, which has no international standard reference materials to permit a full validation of the assay. Some recognition needs to be given to the difficulties inherent in trying to validate an assay with no international standard.

Page 4, Section III Parts A1, B1, C1a “immunogenicity” --

a. The guidance document articulates the endpoints that would be relevant for licensure. Recent experience has indicated that the assay status and the performance characteristics are critical in the FDA review of data. It would be of benefit to the industry to state whether the data should be generated with a given assay qualification status and lower limit of detection.

b. With regard to the criteria on rates of seroconversion, NIAID’s recent experience with the FDA has included an additional parameter where a four-fold rise was considered seroconversion as long as the titer was greater than or equal to 1:40.

Page 4, Section III Part A2 “safety” -- The accelerated approval section includes a statement regarding the expected safety database. It would be of value for the FDA to indicate what target safety database would be needed to support approval of the pandemic strain as a supplement.

Page 5, Section III Part A2 "safety" -- Please clarify that the statement, "We assume that approval for use in the adult population, including geriatric population...", means that FDA would require the supplement to include safety packages for both adult and elderly. Would it be acceptable to submit adult data first followed by elderly data when it becomes available, which may occur after submission or approval of the supplement?

Page 5, Section III Part B -- This section reiterates a concern that live vaccines might not be permitted until a pandemic appears because of concerns about reassorting. However, it is too broad a statement of position to declare that the vaccine is anticipated to be labeled for use after the onset of a pandemic outbreak. There may be situations when the vaccine would be recommended by advisory bodies before a pandemic begins. Since it may not be easy to determine what constitutes a "pandemic outbreak," perhaps the definition of pandemic outbreak needs to be made clear.

Page 5, Section III Part B1 "immunogenicity" -- The section on immunogenicity of live vaccine focuses on antibody titers, but antibody titers have not been correlated to vaccine efficacy, and the vaccines appear to be efficacious even when antibody titers are not particularly high. Since there are other immunologic actions of live vaccines compared to inactivated vaccines, the implementation of antibody standards for judging live vaccines seems questionable. It might be better to focus on effective infectious dose, or some other demonstration of vaccine "take."

Page 5, Section III B2 -- With regard to the requirements for conducting clinical studies with live attenuated vaccine platforms, would it be appropriate to indicate whether these studies need to be conducted outside of influenza season?

Page 5, Section III B2 -- Please clarify, "isolated during study period." It would be helpful if "isolation" can be defined. Furthermore, a six-month follow-up period is required as part of the clinical protocol. We assume there will not be a requirement for a six-month isolation for the "study period." It would be helpful if "study period" can be defined as it relates to the requisite isolation.

Page 6, Section III Part C -- This section discusses accelerated approval of vaccine with no existing license and focuses on the strategy being implemented for new inactivated vaccine with an initial immunogenicity study followed by a clinical endpoint study, which seems very appropriate. The reliance on EMEA/CHMP criteria for judging success of vaccine, however, is not scientifically sound because of the variability between labs for HI titers noted above. Use of the criteria may cause rejection of vaccines tested serologically in labs with low absolute titers and acceptance of vaccines tested serologically in labs with high absolute antibody titers, when there might be no difference between the two. A central lab strategy (which FDA cannot endorse) might permit a better standardization of results and a level playing field.

Page 7, Section III Part C -- Any live attenuated data will depend on surrogate markers. The guidance acknowledges that accelerated approval, "will depend on the identification of an immune surrogate that is reasonably likely to predict clinical benefit." It is unclear as to who will sanction the surrogate marker(s).

Page 7, Section III Part C1 "effectiveness" -- Please restate the definition for seroconversion.

Page 8, Section III Part C1b -- What contingency plan will be in place if a pandemic vaccine is licensed, but not available for commercial distribution?

Page 9, Section III Part C3b -- Please comment on the challenges of post-marketing commitments, specifying confirmatory effectiveness studies to verify clinical benefit in the absence of a pandemic outbreak (How can sponsor conduct clinical endpoint efficacy study?).

Page 10, Section III Part D1 "Types of pandemic influenza vaccines" -- There seems to be an inconsistency on the one hand to require some kind of immunogenicity study for licensing of a pandemic vaccine strain change for an existing licensed live vaccine, but then to refuse accelerated approval "until a surrogate endpoint ...reasonably likely to predict clinical benefit is identified."

Page 10, Section III Part D2 "Clinical Lot Consistency" -- Please clarify that clinical lot consistency is not required for supplement to a BLA.

Page 10, Section III Part D3 "Adjuvanted Pandemic Vaccines" -- According to the guidance, it seems that adjuvanted pandemic inactivated vaccines will not qualify for accelerated approval. Please clarify.

The suggestion that a 0.3 log₁₀ difference in GMT ration or a 15 percent difference in seroconversion rate for HI would be a "meaningful" difference seems arbitrary. This relates to the problem of having no standardization for HI with the result being that some labs get higher and some get lower absolute antibody titers. It would be better to know whether adjuvants have any impact on efficacy of vaccines rather than merely increasing antibody response.

Page 11, Section III Part D3 "Adjuvanted Pandemic Vaccines" -- Please clarify if the requirement to demonstrate the benefit of an adjuvant is a clinical requirement. Also, please clarify if the differences in immune response cited are meant to reflect confidence interval bounds or are point estimates.