Workshop on the Development of a Clinical Trial Plan for Pandemic Influenza Vaccines: Regulatory Considerations

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Significant Events in Influenza Vaccine Development and Regulation

- 1930's — Influenza A (H1N1) and B Viruses Isolated from Humans
- 1945 — First Licensed Vaccines (Whole Virus Inactivated Grown in Eggs)
- 1947 — Antigenic Drift with Reduced Vaccine Effectiveness (H1N1)
- 1948 — Global Surveillance Instituted by WHO to Promote Timely Vaccine Changes

Significant Events in Influenza Vaccine Development and Regulation

- 1970's — High Growth Reassortants: Routine Use in Vaccine Production
- 1970's — Development and Licensure of "Split" Virus Inactivated Vaccines
- 1970's — Development of Live Attenuated Influenza Vaccines
- 1978 — Single Radial Immunodiffusion (SRID) Adopted as Potency Test

Significant Events in Influenza Vaccine Development and Regulation

- 1980's — Development of Purified HA Vaccines (Recombinant DNA)
- 1980's — Renewed Interest in Adjuvants
- 1990's — Development of Cell-Culture Grown Influenza Vaccines
- 1990's — Development of DNA Plasmid Influenza Vaccines
- 2003 — Licensure of Live Attenuated Vaccine

U.S. Licensed Influenza Vaccines (currently manufactured)

- Inactivated trivalent vaccines
  - Fluzone (Aventis Pasteur, Inc.)
  - Fluvirin (Evans Vaccines/Chiron)
- Live attenuated trivalent vaccine
  - Flumist (MedImmune)
- Focus of this talk: inactivated vaccines

Inactivated Influenza Virus Vaccines

- Trivalent (influenza A H1N1, influenza A H3N2, and influenza B); vaccine strains selected to match circulating viruses
- Contain at least 15 mcg/dose of each HA (standardized by SRID)
- Vaccine efficacy
  - Potency of vaccine
  - Match of vaccine HAs (and maybe neuraminidase) with circulating viruses

Routine Licensing Actions for Influenza Vaccines in the US

- Each year, any of the three vaccine strains used to manufacture the previous year's vaccine may be replaced with a new strain.
- Strain changes are based on evaluation of circulating wild-type influenza strains and recommendations of the VRBPAC.
- A manufacturing supplement to an existing license is submitted for strain changes, and does not require clinical data for FDA approval.

New Vaccine Strains by Year

Year	H1N1	H3N2	B
1995-96		new	new
1996-97		new	
1997-98	new		
1998-99	new	new	
1999-2000			new
2000-01	new	new	
2001-02			new
2002-03			new

How Does the Routine Process Apply to a Pandemic?

- The new pandemic strain used in a licensed manufacturing process would be reviewed as a manufacturing supplement for strain change.
- Either a wild type or a reassortant virus acceptable to WHO Influenza Centers could be used to produce the vaccine.
- However, will one dose of vaccine containing 15 mcg of HA (as specified for current vaccines) be optimal for a pandemic strain?

How Can We Prepare for a Pandemic?

- Preparations for an influenza pandemic should be made during the interpandemic.
- Manufacturing capacity is being increased by current licensed manufacturers in the interpandemic period in response to perceived demand for vaccine.
- New manufacturers are being encouraged to apply for product approvals in the interpandemic period.

Preparations for the Pandemic That Can Be Done Now

- Investigational vaccines for influenza A subtypes with pandemic potential can be manufactured according to current, licensed processes where feasible.
- Dose-ranging studies can determine the amount of HA and the number of doses needed to induce antibody responses comparable to those induced by a routine, interpandemic vaccine.
- These data can guide vaccine manufacture (e.g., how much HA per dose and the number of doses needed) in the event of a pandemic.

Preparations for the Pandemic That Can Be Done Now (cont.)

- To support the preparation of investigational vaccines with pandemic potential during the interpandemic period, reference viruses and reagents are necessary.
  - Acceptable viruses: wild type (e.g., A/Hong Kong/1073/99 H9N2) or reassortant (e.g., A/Hong Kong/213/03-like H5N1)
  - Strain-specific antigen and antiserum to test potency (by SRID)
  - Libraries of reference viruses and reagents may also be of use for actual pandemic

Antisera Produced at CBER for Potential Pandemic Influenza Vaccines

rHA H5 Antigen

- **A/Hong Kong/156/97*, A/Hong Kong/483/97, A/Hong Kong/213/03***

rHA H9 Antigen

- **A/Hong Kong/1073/99***

Planned for 2003-2004

- **rHA H6, rHA H7**

(* provided by NIAID)

Reagents for Pandemic Influenza Vaccine Production

- **Antisera can be stored liquid and/or lyophilized in freezer indefinitely**
- **Shelf life for lyophilized antigen less certain, but probably years if stored frozen**
- **Currently, CBER has only small amounts of antigen (rHA) for testing potential pandemic vaccines**
- **Large scale vaccine production currently utilizes standardized, strain-specific antigen (whole virus) and antiserum for potency**

How Can an Investigational Inactivated Pandemic Vaccine Be Developed for Licensure?

- To have a licensed vaccine ready for use in a pandemic, the manufacturing process should be developed in advance of the pandemic.
- An investigational vaccine made according to a new process would require product and pre-clinical data, as appropriate, to support the initiation of clinical trials.
- Clinical studies would need to demonstrate safety and efficacy of the new vaccine produced with current circulating strains.

What about Adjuvanted Vaccines?

- Additional pre-clinical studies will be needed, depending on the adjuvant.
- Early studies should demonstrate the rationale for adding an adjuvant (e.g., the adjuvant significantly increases the immunogenicity of the vaccine, and the safety profile is acceptable) and determine the optimal dose.
- Phase 3 studies to evaluate the safety and efficacy of vaccines with adjuvants and licensing should be pursued in the interpandemic period.

Efficacy endpoints for new inactivated influenza vaccines

- The primary endpoint for a new vaccine should be a clinical endpoint.
- Immunogenicity data can be useful:
  - to bridge efficacy data to other populations and to evaluate manufacturing changes.
  - to determine HA dose and number of doses needed for a novel strain
- Under current policy, once a vaccine has been licensed, no additional clinical data have been required for strain changes.

Summary

- When the pandemic arrives, there won't be time to develop new manufacturing processes and the ability to increase the existing capacity will be limited.
- Therefore, the main sources of vaccine will be manufacturers with processes licensed in the interpandemic period.
- Either wild-type virus or high growth reassortants may be used to manufacture vaccine.

Summary (cont.)

- Having data on dosage (amount and number) will help guide vaccine manufacture for the real pandemic.
- Rapid initiation of clinical trials with licensed vaccine containing the actual pandemic strain could help to evaluate the immunogenicity of the vaccine and the need for more than one dose of vaccine. This would be particularly important if the pandemic strain is an influenza A subtype for which there is no clinical study data.

Summary (cont.)

- Other important activities during the pandemic
  - Epidemiological studies to evaluate the impact of the pandemic vaccines on disease burden
  - Surveillance for vaccine-associated adverse events

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