

Meeting the Challenge of Pandemic Vaccine Preparedness: FDA Perspectives



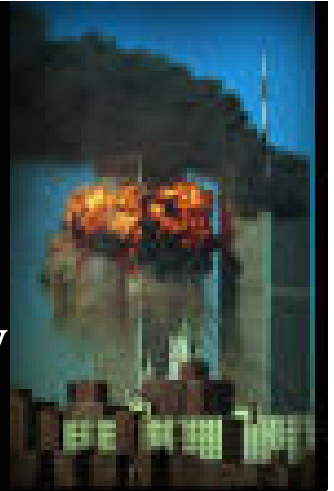
*Jesse L. Goodman, MD, MPH, Director
Center for Biologics Evaluation and Research (CBER)
Presentation to The IOM Symposium on Pandemic
Influenza Research, April 5, 2005*

Or: If pigs (or chickens) can fly –
can we be prepared?



Not Business as Usual

- Since 9/11, CBER has adapted to extraordinary circumstances through extraordinary efforts
 - These include proactive measures w/ sister agencies and industry such as:
 - Meetings to encourage developing new products
 - Early and intensive interactions w/ sponsors
 - Collaboration and rapid turnaround on INDs, EUA
 - Proactive trips to inspect facilities
 - Participation in multiple product development teams
 - Expedited reviews of key product apps.
 - Such approaches were also used in the 2004 flu season and are appropriate, where needed, for pandemic preparedness



Meeting the Pandemic Vaccine Challenge: Overview and Actions

- ✓ Increasing manufacturing diversity and capacity
- ✓ Developing needed pathways and regulatory processes to speed vaccine availability
- ✓ Assuring safety and public confidence
- ✓ Facilitating vaccine manufacturing and availability
 - scientific and related technical needs
 - enabling both current and evolving technologies:
- ✓ Considering pathways to prevent a pandemic
- ✓ Thinking and working globally

Increasing manufacturing diversity and capacity

- Markets (demand and sales) are main driver
- In last 2-3 years, increasing vaccine stimulating interest of global manufacturers in US market
- 2004 shortage further accelerated interest
- FDA and industry interactions helpful:
 - Intensive interactions to assure potential access to vaccine under IND for 2004-5 season: data reviews and facility inspections made 5 mill doses avail, if needed
 - Several manufacturers have expressed interest in US licensure and FDA is interacting proactively with them
 - CBER providing accelerated approval mechanism

Lessons Learned Lead to Other FDA Steps to Strengthen Supply

- Globalization:
 - Information sharing agreements and relationships both completed and being developed
 - Pre and post-licensure
 - Encouraging global vaccine development plans and regulatory cooperation/harmonization
- Annual inspections of flu manufacturers
- GMP initiative
 - Increased communications and enhanced preventive approaches including on vaccine GMPs

Pathways to Speed Availability: Annual US Influenza Vaccine

- Each year, any of the previous three vaccine strains may be replaced with a new strain
- Strain changes based on evaluation of circulating wild-type strains
- Only submission and review of a prior approval manufacturing supplement is needed for strain changes to an existing license
- *FDA does not require clinical data for approval of these annual supplements for licensed manufacturers of inactivated flu vaccine*

Basis for Use of Accelerated Approval Authorities

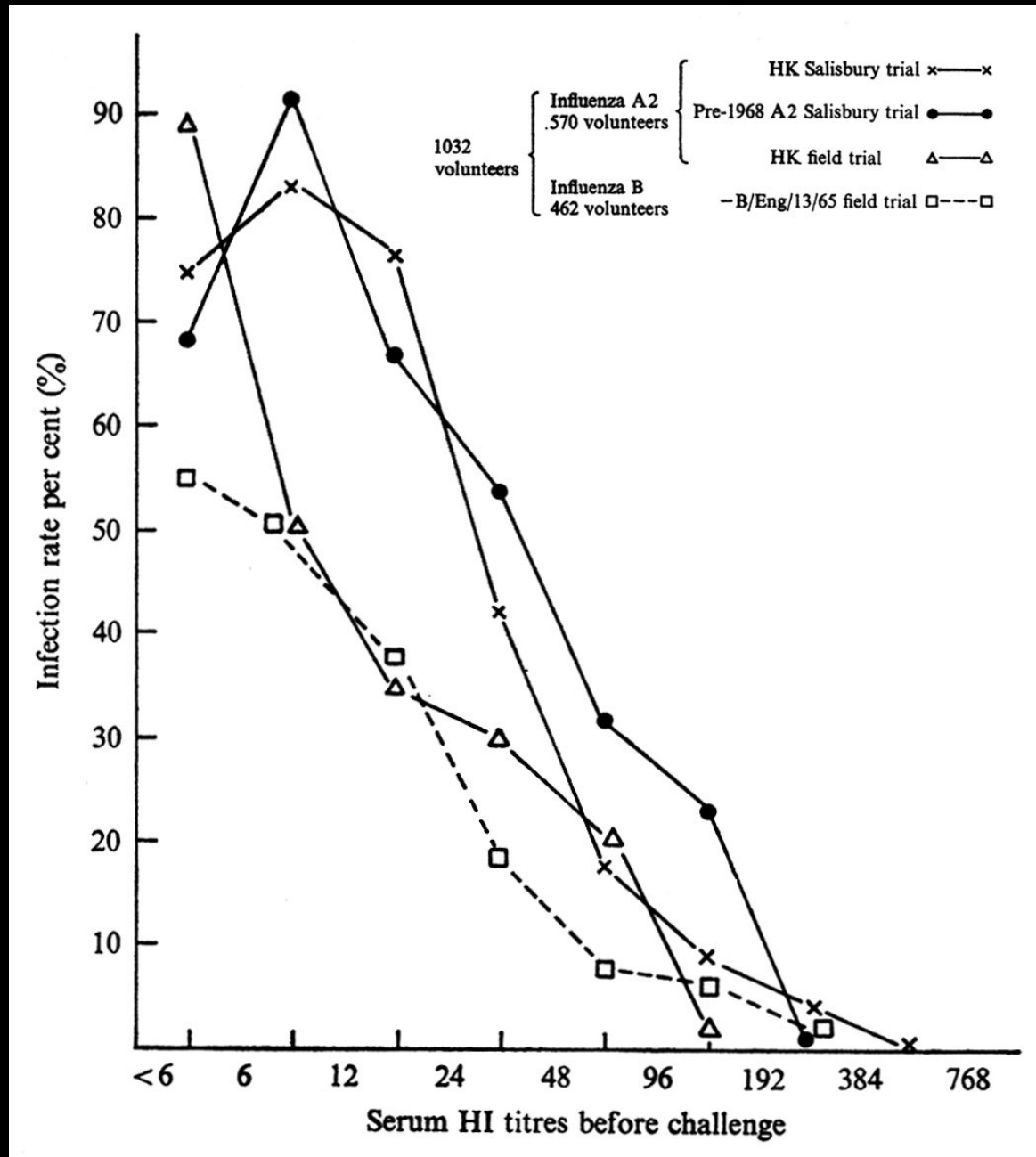
- 21 CFR 601.40
 - Meaningful therapeutic benefit
 - Serious or life-threatening conditions
 - Lack of available alternative therapies
 - Influenza vaccine shortage applicable
 - CDC population of benefit ~ 185 million doses
 - For pandemic strains, unmet medical need per se
- 21 CFR 601.41
 - Surrogate endpoints
 - Reasonably likely to predict clinical benefit
 - Clinical endpoint studies to confirm

Pathways to Speed Availability: Accelerated Approval for Inactivated Flu Vaccines

- FDA considers there to be a short supply
- CBER will consider HI anti-HA antibody levels as a likely surrogate marker for efficacy
- Therefore, accelerated approval can be sought based on immunogenicity provided:
 - validated assays
 - post-approval studies of clinical efficacy
 - complete manufacturing data, controls & inspections
 - satisfactory safety data; clinical trials and data from experience with same vaccine under foreign licensure can contribute

Potential Surrogate: Infection Rate of Volunteers Challenged with Influenza Viruses in Relation to Pre-Challenge HI Titers

From: Hobson et al
J Hyg, Camb 1972



Pathways to Speed Availability: Accelerated Approval for Inactivated Flu Vaccines II.

- GSK and ID Biomedical have, to date, each indicate that they will seek licensure under this accelerated approval mechanism (others may in future) – shortening time to potential approval by 1-2 years
- Immunogenicity data can also be useful:
 - to bridge efficacy data to additional populations and to evaluate manufacturing changes
 - to determine HA dose and number of doses needed for a novel strain (e.g. For pandemic strains)

Need for Valid and Standardized Methods: Comparison of HI Titters for H1N1 Flu in Two Labs with Same Sera

Lab	Serum Source	Pre % >40	Post % >40	Pre GMT	Post GMT	4 Fold Rise
A	EU	13	88	9	195 ⁽³⁾	83
B		4	58	7	25 ⁽³⁾	58
A	USA	68	96	46	202 ⁽²⁾	27
B		20	75	11	39 ⁽²⁾	40
A	AUS	50	100	20	216 ⁽¹⁾	79
B		17	88	7	68 ⁽¹⁾	83
A	JAP	50	92	34	93 ⁽⁴⁾	25
B		16	32	7	16 ⁽⁴⁾	48

Pathways to Speed Availability: Licensure of Pandemic Vaccines

- FDA views a pandemic strain used in a licensed manufacturing process as a strain change
 - Biologically, a new HA antigen is just that, another HA antigen, such as used in routine strain changes
 - For licensed manufacturers using licensed processes, would not be treated as a *new vaccine* but as a supplement with *some clinical data important*
- Either a wild type or a reassortant virus (including virus derived by reverse genetics) can be used
 - FDA has no problems with use of recombinant or cell culture based technologies in strain production so long as adequate controls and characterization

Pathways to Speed Availability: Licensure of Pandemic Vaccine; II

- Conduct clinical studies for pandemic vaccine during interpandemic period to extent possible
 - NIAID studies (e.g. of H5N1) will provide critical information on dose and schedule
 - Future generalizability of such data to other strains unclear: immunogenicity of various pandemic strains may differ
- Assuring safety and public confidence
 - Clear communication: full transparency and continuing discussions re: risks/uncertainties of pandemic vs. vaccine safety/effectiveness
 - Where time permits, obtain additional safety database on several thousand individuals pre-licensure
 - Facilitate AE reporting & surveillance through VAERs & other databases

Thinking ahead: facilitating manufacturing and availability of licensed pandemic vaccines

- Preparation of qualified seed strains and high growth reassortants representing major known and evolving pandemic antigens
- Studies of strain cross-protection in HA types, methods to predict based on sequence analysis
- Advance preparation of needed reagents for manufacturing: e.g. antigens & antisera
- Evaluation of existing assays and consideration of development of new technological approaches (e.g. to potency, Abs, sterility) that may speed manufacturing and regulatory review

Thinking Ahead: Enabling New Approaches and Technologies: Overview

- Even with aggressive and successful efforts to diversify and strengthen US inter-pandemic production, capacity may still be inadequate for true widespread pandemic in US, and, almost certainly, for global needs
- Antigen sparing and other new technologies should be evaluated before a pandemic

Enabling New Technology - Scientific Needs

- Addition of adjuvant to vaccine formulation.
 - Results (published and unpublished) in past have been conflicting: adequate studies are needed before adopting
 - Would be considered a new product (requiring BLA)
 - Safety and efficacy (immunogenicity) data required
 - Simplest - aluminum (extensive experience in licensed vaccines)
 - Early studies should demonstrate rationale (e.g., *significant* increases in immunogenicity with acceptable safety profile) and determine dose
 - Novel adjuvants or those with previous safety signals would require more safety data
 - Supporting manufacturing and product information also needed
 - If proof-of-concept and other studies favorable, Phase 3 studies should be pursued in interpandemic period

Antigen Sparing Strategies

- Changing route of vaccine delivery
 - Simplest change might be i.d. using needle and syringe but raises practicality issues
 - Safety and efficacy (immunogenicity) data needed
 - Other delivery methods promising: need data
- Use of immune stimulators, (e.g. use of patch with heat-labile toxin).
 - Safety and efficacy data required
 - Such strategies are in relatively early development; lack of experience will require safety testing

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- There are significant potential advantages in flexibility afforded by non-egg based technologies
 - Despite problems, egg based manufacturing has been successful & cost effective and, to date, other technologies have not been marketed or widely used
 - FDA has licensed other cell culture derived and recombinant based vaccines and has no special regulatory concerns with these technologies for flu
 - We encourage their development and provide intensive interactions with sponsors
 - Scientific/technical challenges include:
 - Cell based: usual safety issues (i.e. tumorigenicity, adventitious agents), sufficient yield, manufacturing scale & cost
 - Recombinant: Antigenicity and protective immune response

Other New Technologies

- Cross-protective antigens
- Live attenuated vaccines
 - Provide multiple immunogens, some may be cross-protective
 - May enhance more rapid development of immunity
 - May raise potential containment issues for public health and agriculture

Considering Potential Future Pathways to Preparedness?

- For a pandemic to be a pandemic a prerequisite is the lack of population immunity
- Can we conceptualize pandemic preparedness in a routine prevention rather than crisis mode?
- Should we consider earlier building of immunity against evolving virulent pandemic threat strains?
- Should we consider the potential for integration of such preparedness into more routine influenza immunization, as we do for emerging epidemic strains?
- Transparency, public dialogue, a non-crisis environment, and acceptance/demand would be important for any such approaches to be considered

Thinking globally and acting both locally and globally

- Work with public health and industry partners to facilitate building global vaccine capacity – benefits all
- Regulatory and other cooperation to facilitate potential sharing and transnational use of vaccines
 - Payoffs in both pandemic and interpandemic settings
- Potential to vaccinate at geographic site(s) of evolving virulent pandemic strain transmission threat, even prior to widespread human to human spread
 - May slow or halt pandemic – modeling may be helpful
 - May allow better understanding and additional modeling of unique scientific and non-scientific challenges in early intervention against pandemic threat strains

Summary

- FDA is working with partners to diversify and strengthen influenza vaccine manufacturing, and providing flexible rapid regulatory pathways – *progress has been made*
- FDA views pandemic vaccines made using licensed processes as supplements rather than new vaccines – *this can speed & reduce the burden and costs of pandemic response*
- Further advance preparation and improvement of strains, reagents, assays and standards would be beneficial
- Scientific needs in manufacturing and in evaluating safety and effectiveness of antigen sparing approaches, and of new vaccines as well as of non-egg based technologies is best addressed before a pandemic – key studies are beginning
- Pathways exist to allow consideration of benefits and risks of early intervention against virulent potential pandemic strains, including potential integration into public health preparedness, as we do for annual influenza strains.

"The roosters of America are ready to do their duty"

Secretary of Agriculture as quoted in Neustadt and Fineberg – "The Swine Flu Affair"
USDHEW, 1978

Are we?



Can we learn from the Swine Flu experience *and still*
work to meet the challenge of pandemic preparedness?

We welcome your ideas and input....