Meeting the Challenge of Pandemic Vaccine Preparedness: FDA Perspectives

Jesse L. Goodman, MD, MPH

Director, Center for Biologics Evaluation and Research (CBER), FDA

ACBSA, Arlington, VA, 1/5/2006

FDA
Task Force on Pandemic Influenza

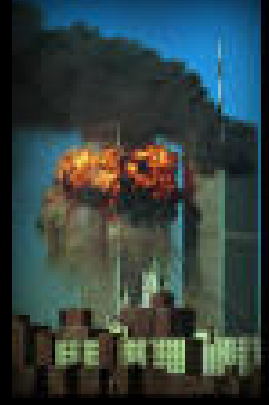
- Commissioner's initiative
  - Announced November 10, 2005

- Will spearhead FDA's participation in inter-agency groups:
  - President's National Strategy for Pandemic Influenza
  - Department of Health and Human Services' Pandemic Influenza Plan and related activities

FDA
Task Force on Pandemic Influenza

- Cross-functional team: 14 Centers/Offices
- Coordinate policy development, planning, priority setting, and communications.
- Focus on accelerated development and production of:
  - Vaccines
  - Antivirals
  - Diagnostics
- Comprehensive plan to include other roles:
  - Management of avian influenza outbreak (USDA)
  - Ensuring the safety of human food and animal feed

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 applications**
    - **Critical Path Research: Targeted to high priority areas for more efficient, rapid product development and availability**
  - Such approaches were used in the 2004 flu season and inform all our activities (for example WNV, pandemic preparedness). Benefits and increased demands/stress.

Meeting the Pandemic Vaccine Challenge: Overview and Actions

- ✓ Increasing manufacturing diversity and capacity
- ✓ Developing needed pathways and regulatory processes to speed vaccine availability
- ✓ Facilitating vaccine manufacturing
- ✓ Assuring safety and public confidence
- ✓ Considering pathways to prevent a pandemic
- ✓ Thinking and working globally

Key concept: Wherever possible, parallel rather than sequenced activities.

Increasing manufacturing diversity and capacity

- Markets (demand and sales) are main driver
- In last few years, increased flu vaccine demand and prices stimulating interest of manufacturers
- 2004 US shortage further accelerated interest
- FDA, industry, and global interactions helpful:
  - Intensive interactions to assure potential access to vaccine under IND for 2004-5 season: data reviews, regulatory information sharing and facility inspections made 5 mill doses avail, if needed

Pathways to Speed Availability: Accelerated Approval

- FDA considers there to be a short supply
- HI anti-HA antibody levels as likely surrogate
- Accelerated approval based on immunogenicity
- GSK data generated/reviewed and approved very rapidly – enhancing annual supply and pandemic preparedness
  - ~ 900 person safety/immunogenicity study planned/reviewed/enrolled in 1 m
- *Indicates that with preparation, substantive and needed data can potentially be rapidly obtained both now and even in evolving pandemic situation*
- *We can consider similar approaches for most pandemic vaccines, including adjuvanted, cell and recombinant*

Pathways to Speed Availability: Licensure of Pandemic Vaccines

- FDA views a pandemic strain used in a licensed manufacturing process as a strain change
  - For licensed manufacturers (inactivated or live vaccine), would not be treated as a *new vaccine* but as a rapid approval supplement with *some clinical data important*
    - *Dosing and immunogenicity, safety if at higher doses*
- Either a wild type or a reassortant virus (including reverse genetics) can be used

Live Attenuated Vaccine (LAIV)

- Currently one approved vaccine, 3m doses/year
- Efficacy in children, young adults: currently uncertain in elderly
- Potential (unproven at present) to induce immunity vs. pandemic strain more rapidly and broadly–H9 study underway, H5 planned
- Given adequate clinical/immune data, FDA can handle as strain change to current licensed vaccine
- Infection control/gene reassortment issues make studies cumbersome; vaccine unlikely to be used until a pandemic occurs – not for pre-vaccination

Other Steps to Strengthen Supply

- Globalization:
  - Information sharing agreements and relationships put into place
    - Pre and post-licensure
  - Encouraging global vaccine development plans
  - Annual inspections of flu manufacturers
- GMP initiative
  - Increased communications and enhanced preventive and collaborative approaches to vaccine GMPs

Thinking ahead: facilitating manufacturing and availability of licensed pandemic vaccines

- Preparation of qualified seed strains and high growth reassortant library representing major known and evolving pandemic antigens
- Studies of strain cross-protection within 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/release

Thinking Ahead: Enabling New Approaches and Technologies: Overview

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

Adjuvant to Extend Vaccine Supply

- Some recent clinical results promising but some past studies negative
- Adjuvants may increase immune response and, in some cases cross-protective properties - but also adverse events
  - *Same issues with "whole" virus flu vaccines historically*
- Adjuvant addition requires changes in manufacturing that may affect vaccine and its stability –new product (BLA)
- FDA may use accelerated approval for adjuvanted vaccine based on rapid generation and assessment of immunogenicity, manufacturing and safety data
- *If proof-of-concept studies favorable, Phase 3 studies of immunogenicity and safety should be rapidly pursued*
- *How we approach pandemic vaccines should be data driven, and such data can be soundly and rapidly obtained and shared –research agenda to drive policy*

New Delivery Approaches

- Limited data suggest that intradermal delivery might reduce amount of vaccine needed
- Can be given into the skin by syringe or by various to date unproven devices, patches, injectors
- FDA in most cases could evaluate use rapidly as clinical supplements to licensed vaccines; would require dose, immunogenicity and some safety data

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- Significant potential advantages in flexibility
- FDA has licensed many other cell culture and recombinant based vaccines and has no special regulatory concerns with these technologies for flu
  - We are encouraging their development and providing intensive interactions with sponsors –VRPAC on MDCK
- Several in development but ***limited manufacturing, clinical experience to date***
- Potential for considering accelerated approval: based on immune response - cannot compromise on safety

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 routine influenza immunization?
- Transparency, public dialogue, a non-crisis environment, and acceptance/demand would be important for any such approaches to be considered

Relevant Lessons of Swine Flu

- Communication re: benefit/risks of vaccine critical
  - Includes balanced communication of uncertain risk of pandemic as vaccine benefit depends on it
- Public's safety concerns and expectations are important and significant (and even more so today) and can affect, even derail, vaccination plans
- Confidence in vaccines, governments, industry and public health systems will be on line

Relevant Lessons of CT Efforts

- **Vaccine production complex, time consuming, not always predictable-** ***vaccines are not widgets.***
- ***Short-cuts seldom are.***
  - Most delays have been in making a workable product, not clinical studies
- ***Less expensive seldom is.***
- FDA and other global regulatory counterparts can play important and facilitating roles
  - Help facilitate production, maximize the efficiency of investments
  - ***Rapidly <u>and</u> objectively evaluate scientific findings re: safety, manufacturing and efficacy in face of urgency***

Why is global regulatory convergence desirable?

- It should be possible to generally agree upon a reasonable science based dataset needed to assess various potential pandemic vaccine types
- This may make development faster and more efficient for manufacturers and government
- In urgent situations it may be possible to share regulatory resources, information and reviews, as well as safety and effectiveness monitoring in use
- Convergence, including defining and where possible resolving true differences is desirable
- ***Plans and priorities:***
  - ***1) CBER concept papers/pandemic vaccine guidance***
  - ***2) FDA/WHO/HC global regulators meetings (Q1&Q2 '06)***

Summary

- We are working with partners to diversify and strengthen influenza vaccine manufacturing, and provide flexible and rapid regulatory pathways – *progress has been made*
- Scientific data needs for evaluating antigen sparing approaches and non-egg based technologies are critical for policy decisions and best addressed before a pandemic – *several key studies underway*
- Further advance preparation and improvement of strains, reagents, assays and standards would be beneficial
- Consider benefits and risks of early intervention vs. virulent potential pandemic strains, including potential integration into routine public health
- Regulatory convergence being encouraged