Regulatory Pathways for Registration of Seasonal and Pandemic Influenza Vaccines: FDA Approach

6th Meeting with International Partners on Prospects for Influenza Vaccine Technology Transfer to Developing Country Vaccine Manufacturers
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Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration
Department of Health and Human Services
FDA Overview

Office of the Commissioner

Office of Medical Products and Tobacco
- Center for Biologics Evaluation and Research
- Center for Drug Evaluation and Research
- Center for Devices and Radiological Health
- Center for Tobacco Products

Office of Foods
- Center for Food Safety And Applied Nutrition
- Center for Veterinary Medicine

Office of Global Regulatory Operations and Policy
- National Center for Toxicological Research

Office of Global Regulatory Affairs

Office of Regulatory Affairs
CBER Overview

Office of the Director
Karen Midthun, M.D., Director

- Office of Vaccines Research and Review
- Office of Blood Research and Review
- Office of Cellular, Tissue and Gene Therapies
- Office of Biostatistics and Epidemiology
- Office of Compliance and Biologics Quality
- Office of Management
- Office of Communications, Outreach and Development
Stages of Review and Regulation

Clinical Investigational Plan

IND = Investigational New Drug Application;
BLA = Biologics License Application

Phase 1
Safety Immuno-genericity (prelim)

Phase 2
Immuno-genericity Safety Dose Ranging

Phase 3
Efficacy Safety Immuno-genericity

BLA
Data to support licensure; Inspection; Advisory Committee

Phase 4
Inspection Safety Efficacy Lot Release

BLA Supplement
Post-licensure Changes: New Indications Dosing Manufacture Equip./Facilities
IND Role in Biologics Approval Process

- Mechanism and process to collect clinical data to support the license application
  - Demonstrate safety and efficacy
  - Information for the package insert
- Chemistry, manufacturing, and controls (CMC)
  - General biological product standards
  - Process validation
- Assay validation
  - Immunogenicity/activity
  - Product quality control, lot release
- Stability data
**Biologics License Application (BLA)**

- BLA is a marketing application
- Purpose is provide adequate information to allow FDA reviewers to reach a decision
  - Biological product is safe and effective for its proposed use
  - Proposed benefits outweigh risks
  - Labeling is adequate
  - Manufacturing and control methods are adequate
U.S.-licensed Seasonal Influenza Vaccines
Seasonal Influenza Vaccine Licensure Pathways: Biologics License Application (BLA)

• **“Traditional” Approval**
  – 21 CFR 601 Subpart A and C
    • Approval “…based on data… which demonstrate that the manufactured product meets prescribed requirements of safety, purity and potency…”

• **Accelerated Approval**
  – 21 CFR 601 Subpart E
    • Approval “…on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint …reasonably likely…to predict clinical benefit…”
    • Approval “..subject to the requirement that the applicant study the biological product further to verify and describe its clinical benefit…”
Accelerated Approval for Inactivated Influenza Vaccines

- FDA considers influenza vaccines to be in short supply
- CBER will consider anti-HA antibody levels (measured by the hemagglutination inhibition assay) as a likely surrogate marker for efficacy
- 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 be supportive
U.S.-licensed Seasonal Influenza Vaccines

Inactivated, intramuscular
- **Fluzone** Sanofi Pasteur (≥ 6 months)
- **Fluzone High Dose** Sanofi Pasteur (≥ 65 years)
- **Fluvirin** Novartis (≥ 4 years)
- **Fluarix** GSK (≥ 3 years)
- **FluLaval** IDB-GSK (≥ 18 years)
- **Afluria** CSL (≥ 5 years)
- **Agriflu** Novartis (≥ 18 years)

Inactivated, intradermal
- **Fluzone Intradermal** Sanofi Pasteur (18-64 years)

Live Attenuated, intranasal
- **FluMist** MedImmune (2-49 years)

*accelerated approval
Recent Influenza Vaccine Approvals

• FluMist Quadrivalent
  – MedImmune, LLC
  – February 29, 2012
    • First licensed quadrivalent vaccine to prevent seasonal influenza
    • For use in persons ages 2 years through 49 years
    • Contains four strains of the influenza virus, two influenza A strains (H1N1 and H3N2) and two influenza B strains (Yamagata and Victoria lineages)

• Flucelvax
  – Novartis Vaccines and Diagnostics, Inc.
  – November 20, 2012
    • Trivalent vaccine
    • First licensed seasonal influenza vaccine manufactured using cell culture technology (MDCK)
    • For use in persons ages 18 years and older
Recent Influenza Vaccine Approvals – Cont.

• Fluarix Quadrivalent
  – GlaxoSmithKline Biologicals
  – December 14, 2012
    • First licensed quadrivalent inactivated vaccine to prevent seasonal influenza
    • For use in persons ages 3 years and older
    • Contains four strains of the influenza virus, two influenza A strains (H1N1 and H3N2) and two influenza B strains (Yamagata and Victoria lineages)

• Flublok
  – Protein Sciences Corporation
  – January 16, 2013
    • Trivalent vaccine
    • First licensed influenza vaccine manufactured using an insect virus (baculovirus) expression system and recombinant DNA technology
    • For use in persons ages 18 through 49
U.S.-licensed Seasonal Influenza Vaccines: Routine Licensing Actions

- Each year, one or more of the vaccine strains may be replaced with a new strain.
- Each year, submission of a prior approval manufacturing supplement to an existing biologics license application (BLA) is required for annual influenza strain change.
  - “Strain change supplement”
- Clinical Data
  - Inactivated vaccines: No clinical data
  - Live attenuated: Limited clinical data
WHO recommendations for Influenza Vaccine Composition
Northern Hemisphere: 2013-2014

• Recommended that the following viruses be used for influenza vaccines in the 2013-2014 influenza season (NH winter):
  – An A/California/7/2009 (H1N1) pdm09 – like virus
  – A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011
  – B/Massachusetts/2/2012-like virus (B/Yamagata lineage)
• It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus (B/Victoria/2/87 lineage vaccine virus)
• As in previous years, national or regional control authorities approve the composition and formulation of vaccines used in each country
CBER is a WHO Essential Regulatory Laboratory (ERL): Influenza product quality laboratories

- CBER’s ERL activities include:
  1. Yearly Strain Selection
     - Antigenic characterization of circulating influenza isolates for strain selection purposes
  2. Generation of high-growth reassortant viruses (reference strains) suitable for use in vaccine production
  3. Production, calibration (cross-calibration) and provision of SRID reference reagents to measure vaccine potency
  4. Antigenic confirmation of production seeds
  5. Lot Release including potency testing
# Influenza Vaccine Timetable

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Seasonal vaccine

* - FDA involvement
U.S.-licensed Pandemic Influenza Vaccines
Selected Influenza A (H1N1) Events

- April 21: CDC Report - 2 Cases of Illness Due to Influenza A (H1N1) Virus
- April 26: DHHS Acting Sec: Public Health Emergency
- May 19: > 9,000 Cases of H1N1 Disease in 40 Countries (79 deaths)
- June 11: WHO Phase 6 Pandemic Declared
- July 23: VRBPAC on H1N1 Vaccine Regulatory Approach and Clinical Studies
- July/August: Pilot Vaccines Available for Testing
- September 15: FDA Approves Four H1N1 Vaccines
Influenza A (H1N1) 2009 Vaccines

• Approved as strain change supplements to the seasonal influenza virus vaccine BLAs
• Consistent with licensure of annual strain changes to seasonal vaccines
• Consistent with past regulatory actions
  – 1986 - Influenza A/Taiwan/1/86 H1N1
  – Supplemental monovalent vaccines licensed as strain change supplements
  – No clinical data
Influenza A (H1N1) 2009 Vaccines: Strain Change Supplements

• Manufacturers utilized same egg based manufacturing process as for their licensed seasonal vaccines
• Vaccines contained the same quantity of antigen as a single strain of seasonal vaccine
• Same population usage as the licensed seasonal vaccine
• Same clinical data requirements as for seasonal influenza vaccine strain change supplements
  ➢ Inactivated vaccines: No clinical data
  ➢ Live attenuated: Limited clinical data
• However, clinical data obtained to verify approach (e.g., dose and dosing regimen)
Influenza Vaccine Timetable

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Seasonal vaccine

Pandemic vaccine (2009)

* - FDA involvement
Influenza A (H1N1) 2009 Vaccine Strain Change Supplements

• Approval: September 15, 2009
  – Sanofi pasteur
  – Novartis
  – CSL
  – MedImmune (LAIV)

• Approval: November 10, 2009
  – IDBiomedical/GSK
Influenza A (H1N1) 2009 Vaccines

- Licensed for use in the same populations as each manufacturer’s seasonal influenza vaccine:
  - Sanofi pasteur ≥ 6 months of age
  - Novartis ≥ 4 years of age
  - CSL ≥18 years of age (>6m Nov. 10)
  - IDB/GSK ≥18 years of age
  - MedImmune 2-49 years of age
Pandemic Vaccine – Challenges

• Regulatory:
  – Pathways and regulatory processes to speed vaccine availability
  – Assuring safety and public confidence
  – Facilitating vaccine manufacturing and availability

• Manufacturing:
  – Seed virus development
  – Potency testing reagents

• Clinical data:
  – Antigen dose
  – Number of doses
  – Antigen sparing: use of oil–in-water adjuvants
  – Timing of availability of clinical data

• Public health:
  – Vaccine use
  – Distribution
  – Assuring safety and public confidence
Expediting Influenza Vaccine Availability: Collaborative work underway

- Develop and optimize high yielding and highly immunogenic vaccine reference strains
- Develop alternatives for rapid preparation and calibration of vaccine reagent standards
- Work towards standardization of current SRID potency assay
  - Could include the use of harmonized global reagents
- Develop new potency assays with improved accuracy and sensitivity
  - Some assays might not require new reagent production
- Accelerate sterility release testing from current 14 days
  - Proposed Rule to amend the sterility test requirements for biological products (June 21, 2011)
  - Possible faster availability of vaccine during pandemic or emergency
Pandemic Vaccines: International Collaborations

• Existing relationships/activities key to success regarding pandemic
  – Confidentiality agreements with a number of regulatory agencies

• Worldwide communications/collaborations
  – Global dialogue facilitated by WHO
  – Dedicated routine and on-going confidential regulatory discussions with foreign counterparts
  – Seed virus development
  – Potency testing reagents
  – Technical assistance to developing countries via WHO
  – CBER agreed to be Reference NRA for WHO vaccine prequalification for multiple H1N1 vaccines
Preparing for the Next Pandemic Based on Experience with 2009 H1N1 Vaccines
Preparing for the Next Pandemic

- Regulatory pathways defined before the pandemic
  - Unadjuvanted (seasonal influenza manufacturer)
    - New subtype: BLA (e.g. Sanofi Pasteur’s Influenza Virus Vaccine, H5N1)
    - Subtype in seasonal: Strain change supplement to seasonal (e.g. Influenza A (H1N1) 2009 monovalent vaccines)
  - Adjuvanted (seasonal influenza manufacturer)
    - No U.S-licensed seasonal
- Preliminary immunogenicity data (+/- adjuvant) with subtypes of pandemic potential before a pandemic
  - Clinical studies with the pandemic strain vaccine will likely be needed to verify dose and dosing regimen
    - Develop a concept protocol
- Develop plans for post-marketing safety surveillance
Preparing for the Next Pandemic (con’t)

• Vaccine availability
  – Explore options to make vaccine available sooner
    • Alternative manufacturing technologies/platforms (e.g., cell-based or recombinant vaccines)
  – Progress in developing a correlate of protection

• Reagents/potency testing
  – Develop alternatives to SRID

• Expect manufacturing challenges
  – Experienced manufacturers likely have knowledge and capacity to address these challenges
    • Yield
    • Potency testing reagents
  – Stability – collect data with monovalents
Preparing for the Next Pandemic (con’t)

- Public health
  - Assuring safety and public confidence
    - Effectively communicate severity of pandemic and the uncertainty of predictions
    - Effectively communicate manufacturing issues and the impact on supply
  - Build on the surveillance systems developed and used in 2009 H1N1 pandemic
- International collaboration (WHO, regulatory and public health agencies, etc.) essential
EUA of Medical Products

• The Secretary of DHHS can authorize use of medical products in a declared emergency under an Emergency Use Authorization (EUA).
  • This ability has been delegated to the FDA Commissioner.

• During a pandemic emergency in the U.S., the FDA Commissioner may authorize:
  – Use of an unapproved product
  – Unapproved use of an approved product if the statutory criteria for issuance of an EUA are met.
Summary

• In the U.S. experience, influenza vaccines have a long track record of safety and effectiveness
• A strong post-marketing safety evaluation system is important, both for seasonal and pandemic vaccines, and for older as well as newly introduced influenza vaccines
• Seasonal influenza vaccine manufacturing capacity and experience form an important basis for pandemic response
• Influenza pandemics will continue to challenge public health officials globally to make critical decisions about vaccine approval, use and distribution
• National regulatory authorities must be prepared to respond with regulatory pathways to expedite the availability of vaccines
• Novel vaccine approaches may provide important alternatives (e.g., cell-based and recombinant manufacturing technologies, novel adjuvants and delivery systems)
FDA guidance documents on seasonal and pandemic influenza vaccines

Foreign Regulatory Seminar (Web-based): CBER’s Regulation of Biologics

- [http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm272086.htm](http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm272086.htm)
Acknowledgements

• CBER & FDA colleagues
• DHHS partners

CBER vaccines website:  http://www.fda.gov/BiologicsBloodVaccines/default.htm
HHS influenza website:  www.flu.gov