Manufacturer’s View of H1N1 Vaccine Development, Licensure, and Manufacturing - Obstacles and Opportunities

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Influenza
Highly contagious respiratory illness caused by frequently changing virus
2009 A(H1N1) Pandemic Timeline

**Surveillance**

- Reference labs around the world collect wild virus carried by humans and characterize the genetic makeup.
- Influenza viruses are continually monitored and tracked by health authorities.

Influenza Vaccine Production Process
**Strain Selection**

- World health officials analyze and identify the dominant circulating strain.
- Health officials select virus strains and submit them to contracted laboratories to prepare seed virus.
- Laboratories distribute seed viruses to manufacturers to begin the production process.

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**Preparation of Seed Virus**

- Seed virus is prepared by contracted laboratories using conventional reassortment or reverse genetics methods.
  - Conventional reassortment: Two flu strains with the preferred features for a new vaccine are injected into an egg and the genes reassort naturally.
Seed Passaging and Selection
- Once the seed virus is received, vaccine manufacturers begin passaging the seed virus in eggs to determine the optimum growth conditions and to improve virus yield by acclimating the virus to growing in eggs.
- The working seed developed by the manufacturer is certified by the FDA.

Bulk Manufacturing and Production
- Millions of specially-prepared chicken eggs are used to produce the vaccine. Throughout the year, fertilized eggs are delivered to the manufacturer. Each egg is injected with the working seed.
- The eggs are incubated for several days to allow the virus to multiply.
- After incubation, the virus-loaded fluid is harvested.
- Key processing steps of the harvested fluids include virus inactivation and sterile filtration.
**Purification and Testing**

- Manufacturers test the vaccine concentrate with specially prepared reagents provided by the FDA to determine the potency of the vaccine for immunization.
- Each batch is additionally tested to confirm it meets strict acceptance criteria including virus inactivation and sterility.

**Formulation, Filling and Packaging**

- Viral fragments from strains are collected from different batches, and combined upon completion of quality control tests.
- Upon FDA approval and licensing, the vaccine is released for distribution in time for immunization.
- Manufacturers begin filling the doses into vials and syringes, which are then sealed and carefully inspected before labels are applied to show the vaccine batch, lot numbers and expiration date.
- Each lot must be specifically “released” by the FDA before manufacturers can ship supplies.
Shipping
- Vaccine shipments take place over time as vaccine is produced.
- Health authorities determine the distribution process for pandemic vaccine.

Regulatory Procedures for Approval

**U.S.**
- If manufacturers utilize their current seasonal flu vaccine production, may be regarded as a “strain change” (e.g., supplement to the seasonal flu vaccine license)
- Expedited approval of new pandemic influenza vaccines in U.S. when utilizing same manufacturing process (e.g. H5N1)
- Emergency Use Authorization
**Regulatory Procedures for Approval**

**Europe**

- Variation to the seasonal flu vaccine registration
- “Mock-up” vaccine dossier
  - Contains results of advance studies using a virus strain that has not circulated recently in human populations to mimic novelty of pandemic virus
- EMEA has ‘emergency procedure’ for fast-track approval of new vaccine developed after the start of the pandemic

**WHO Prequalification**

- **Category I** (1 working day)
  - Manufacturers whose seasonal influenza vaccine is prequalified and both seasonal influenza vaccine and pandemic vaccine are licensed by the NRA
- **Category II** (10 working days)
  - Seasonal influenza vaccine has not been prequalified by WHO
  - Seasonal and pandemic are licensed by the NRA
  - Other vaccines from same company are prequalified
- **Category IIIa** (Full assessment process on fast track basis, 20 working days)
  - Seasonal influenza vaccine has not been prequalified by WHO, but manufacturer has experience in the production of flu vaccines
  - Seasonal and pandemic are licensed by the NRA
  - No other vaccine from same company is prequalified
  - NRA meets WHO criteria
- **Category IIIb** (Full assessment process on fast track basis, 6 months)
  - Seasonal influenza vaccine has not been prequalified by WHO, and manufacturer has no prior experience in the production of flu vaccines
  - Pandemic vaccine is licensed by the NRA
  - No other vaccine from same company is prequalified
  - NRA meets WHO criteria
- **Category IV** – not acceptable for prequalification evaluation
  - NRA does not meet WHO criteria
Sanofi Pasteur presentations of A(H1N1)2009 vaccine

- **HUMENZA**: Monovalent vaccine (A/H1N1) 3,8 or 7,5 µg HA, adjuvanted (AF03)
  - 10 doses vials
  - Registration via a Centralized Procedure
  - PEI and MHRA as reporter and co-reporter respectively

- **PANENZA**: Monovalent vaccine (A/H1N1) 15 µg HA, non adjuvanted
  - 2 presentations:
    - 10 dose vials (with thimerosal)
    - 2 dose syringes (without thimerosal)
  - Registration via a Decentralized Procedure
  - France (RMS) + Germany, Spain, Luxembourg, Belgium and Italy (CMS)

- Monovalent vaccine 15 µg HA non adjuvanted approved on 15/09/09 based on a variation of seasonal vaccine file

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2009 A(H1N1) Pandemic Timeline

- **Global**
  - Earliest case in Mexico
  - World health emergency meeting to consider declaring an international public health emergency
  - WHO calls on governments to ensure adequate supplies of smallpox antiviral stockpiles
  - WHO declares a public health emergency
  - WHO declares a pandemic (stage 6)
  - Australian human clinical studies begin
  - First batches of A(H1N1) vaccine available in US
  - President Obama declares national emergency

- **US**
  - CDC confirms 5 US cases
  - HHS Sec. Sebelius announces preparations underway for vaccine production
  - Sanofi Pasteur begins large scale A(H1N1) production
  - FDA approves four manufacturers A(H1N1) vaccines
  - President Obama declares national emergency
Clinical Studies

- Designed to evaluate safety and determine optimum dosing in each population
- CSL began study in Australia end of July
- Manufacturers and NIH began studies in U.S. in early August
- First data available early September
  - Studies show one dose sufficient in adults
- Pediatric data shows two doses protect children 6 months to 9 years of age; one dose protects children 9 years of age and older

Sanofi Pasteur A(H1N1)2009 pandemic vaccines safety monitoring

- Extensive experience gained with seasonal trivalent inactivated vaccines
  - Long term safety and Pharmacovigilance databases of both (Fluzone® and Vaxigrip®) licensed in more than 100 countries and more than 1 billion doses distributed in all populations from 6 mo of age
- Pre license, more than 6000 volunteers included in A(H1N1)2009 clinical trials
  - In all populations from 6 mo of age
- Post licensure commitments in Europe
  - Risk management plan, which includes a large scale safety surveillance on 9000 subjects
  - Population based effectiveness studies implemented by the ECDC in 10 European countries
- CDC and its partners will use multiple systems to monitor the safety of A(H1N1)2009 pandemic vaccines in the US:
  - Vaccine Adverse Event Reporting System (VAERS) jointly operated with FDA
  - Vaccine Safety Datalink (VSD) Project = vaccine safety system used to both identify and confirm adverse outcomes after immunization
  - Collaboration between CDC and 8 large managed care organizations, in which comprehensive medical information is collected on approximately 9 million people
  - Weekly monitoring for certain adverse events that could be associated with newly licensed vaccines
  - Department of Defense, Veteran’s Administration, Centers for Medicare and Medicaid Services, Indian Heath Service, Post-licensure Rapid Immunization Safety Monitoring (PRISM), Real Time Immunization Monitoring System (RTIMS), collaboration with the American Academy of Neurology (GBS).
Production Challenges

- Seasonal flu vaccine production continued
- Production yield of strain initially significantly lower than standard
- Initial biocontainment level of BSL2+
- Potency reagent availability
  - Reagents not available at time of clinical trial vaccine formulation led to alternative potency assays
- Finalization of labeling was dependent upon first data from clinical trials

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Production Challenges

- Shift from HHS’s initial plan for multidose vials to single dose syringes
  - Required adjustments to initial filling and packaging schedules
  - Worked with FDA to accelerate approval of additional filling lines
  - Contract fill and packaging to supplement internal resources
- Numerous GMP Inspections and HHS Audits
- Recruitment and training of 100+ personnel
- Media requests for tours and interviews
  - sanofi pasteur agreed in order to reassure public that vaccine made same as seasonal flu vaccine and expected to be as safe
  - Ensuring full GMP compliance
Success!!

- Sanofi pasteur is expert in influenza virus vaccine production
- “the vaccines FDA has approved are made with a method that is tried and true” -Jesse Goodman before the Subcommittee on Health and the Subcommittee on Oversight and Investigations Committee on Energy and Commerce
- Expansion of production facilities
- Expedited review of multiple supplements by CBER
- H5N1 vaccine production experience
- Commitment of sanofi pasteur employees
- Regular communication between industry and agencies

Backup Slides –Clinical
Sanofi Pasteur clinical development plan overview in the US

Clinical Trial 18-65y and >65y
Non adjuvanted vaccine (7.5, 15 and 30 µg HA per dose)

Clinical Trial 6mo - 9y
Non adjuvanted vaccine (7.5 and 15 µg HA per dose)

Clinical Trial 18-65y and >65y
Adjuvanted vaccine (3.8 and 7.5 µg HA per dose with AFO3)

Q3 2009 | Q4 2009

Sanofi Pasteur announces results of U.S. clinical trials in adults after 1 dose of A(H1N1) 2009 vaccine

- One dose of sanofi pasteur A(H1N1) 2009 monovalent vaccine (15µg, non-adjuvanted) induces a robust antibody response that is considered protective 21days after one dose in:
  - 98% of adults 18 years of age through 64 years of age
  - 93% or more of adults 65 years of age and older.
- No serious adverse events have been observed to date in this clinical trial
- Local injection site redness, swelling and pain and systemic complaints of mild fever, headache and fatigue were reported
- Overall, the safety profile observed to date is very similar to that of the seasonal influenza vaccine

**Sanofi Pasteur clinical development plan overview in the EU**

**Vaccine formulation tested:**
- Non adjuvanted vaccine (15 µg HA per dose)
- Adjuvanted vaccine (3.8 and 7.5 µg HA per dose with AFO3)

**Clinical Trials:**
- Clinical Trial 18-60y and >60y
- Clinical Trial 3-17y
- Clinical Trial 6-35M

**Post authorization safety study**

**Panenza® and Humenza® A(H1N1)2009 vaccines demonstrate robust immune response after 1 dose**

**Interim data from European studies**

- One dose of Panenza® (15 µg dose, non-adjuvanted) or Humenza® (3.8 µg dose, adjuvanted) Influenza A (H1N1)2009 monovalent vaccine induces a robust antibody response that is considered protective in:
  - 93% or more of adults 18 to 59 years old
  - 83% or more of adults 60 years of age and older
  - 94% or more of children 3 years of age through 17 years of age

- Both vaccines tested met the three European Medicines Agency’s (EMEA) criteria

- No serious adverse events have been observed to date in these clinical trials. Local injection site (redness, swelling and pain) and systemic complaints of mild fever, headache and fatigue were reported

- Safety and tolerability profiles were as expected