Safety and Efficacy of Seasonal and Pandemic Influenza Vaccines: U.S. Perspective

Global Action Plan for Influenza Vaccines Meeting (GAP-II)
July 12-14, 2011
Geneva, Switzerland

Karen Midthun, MD
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
U.S.-licensed Seasonal Influenza Vaccines
# U.S.-licensed Seasonal Influenza Vaccines

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

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

## Live Attenuated, intranasal
- MedImmune: FluMist (2-49 years)
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 Required Clinical Studies

<table>
<thead>
<tr>
<th>Age of subjects</th>
<th>CCI VE “matched” strains (LB 95-97.5% CI)</th>
<th>CCI VE “matched” and “unmatched” strains (LB 95-97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluarix (GSK)</strong></td>
<td>18-64y</td>
<td>66.9% (51.9%)</td>
</tr>
<tr>
<td><strong>Agriflu (Novartis)</strong></td>
<td>18-49y</td>
<td>78.4% (52.1%)</td>
</tr>
</tbody>
</table>

VE = vaccine efficacy; CCI = culture confirmed influenza
U.S.-licensed Seasonal Influenza Vaccines: Routine Licensing Actions

• Each year, one or more of the three 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
U.S.-licensed Influenza A (H1N1) 2009 Vaccines
Selected Influenza A (H1N1) 2009 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 6: 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)
U.S.-Licensed Influenza A (H1N1) 2009 Vaccines

Licensed for use in the same populations as each manufacturer’s seasonal influenza vaccine

• Sanofi Pasteur ≥ 6 months
• Novartis ≥ 4 years
• CSL ≥18 years (≥ 6m Nov. 2009)
• IDB/GSK ≥18 years
• MedImmune 2-49 years
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
Influenza Vaccine Safety Profile

• Known adverse effects include:
  ➢ Fever
  ➢ Injection site reactions (including whole limb swelling)
  ➢ Syncope (including rare serious injury from falls)
  ➢ Rare anaphylaxis (very rarely including death)
  ➢ Live attenuated vaccine: Wheezing in individuals with asthma or children < 5 years old with recurrent wheezing

• Guillain-Barré Syndrome (GBS)
  ➢ 1976-1977 U.S. influenza vaccine associated with increased risk of GBS
  ➢ 1992–1993 and 1993–1994 U.S. influenza vaccines found to have one excess case of GBS per million people vaccinated in one study
  ➢ U.S. Institute of Medicine Immunization Safety review in 2004 stated that evidence was inadequate to accept or reject a causal association of GBS with influenza vaccine formulations after 1976–1977
  ➢ Subsequently published study of 2000 and 2001 U.S. influenza vaccines in U.S. Medicare population did not support an association with GBS
U.S. Vaccine Adverse Event Reporting System (VAERS)

• VAERS is U.S. spontaneous reporting system
  ➢ Used for hypothesis generation
  ➢ Generally cannot be used to determine causal associations because of limitations of spontaneous reporting systems

• A review of all adverse events (AE) reported after influenza vaccines from 1990-2005 revealed no safety signals¹
  ➢ No unusual patterns in reported deaths or serious AE reports
    ▪ Distribution of causes of death consistent with general population mortality data
  ➢ Serious AE reports: GBS most frequently reported AE
  ➢ Nonserious AE reports: Local reactions and constitutional symptoms (e.g. fever, headache, myalgia) most frequently reported
  ➢ No data mining signals

# U.S. Postmarketing Safety Monitoring System Developed for the 2009 H1N1 Vaccine*

<table>
<thead>
<tr>
<th>Vaccine Safety Program</th>
<th>Outcome Monitored</th>
<th>Population Monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>All health events</td>
<td>US population</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>Pre-specified outcomes</td>
<td>9.5 million</td>
</tr>
<tr>
<td>Defense Medical Surveillance System (DMSS)</td>
<td>Pre-specified outcomes</td>
<td>1.4 million</td>
</tr>
<tr>
<td>Veteran’s Affairs (VA) Signal Detection</td>
<td>Pre-specified outcomes</td>
<td>918,000</td>
</tr>
<tr>
<td>Centers for Medicare and Medicaid Services (CMS)</td>
<td>Guillain-Barré syndrome</td>
<td>38 million</td>
</tr>
<tr>
<td>Indian Health Services (IHS)</td>
<td>Pre-specified outcomes</td>
<td>1.4 million</td>
</tr>
<tr>
<td>Post-Licensure Rapid Immunization Monitoring System (PRISM)</td>
<td>Pre-specified outcomes</td>
<td>30 million (17 million registry enhanced)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome enhanced surveillance by Emerging Infections Program (EIP)</td>
<td>Guillain-Barré syndrome</td>
<td>45 million</td>
</tr>
</tbody>
</table>

*H1N1 VSRAWG Report, June 2010. The H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG) was established by the National Vaccine Advisory Committee (NVAC) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines.
2009 H1N1 Pandemic Vaccine Safety: H1N1 VSRAWG Report - June 2010

• As of April 28, 2010, approximately 127 million doses of H1N1 vaccine distributed through the immunization program
  ➢ 105,211,620 doses of inactivated H1N1 vaccine
  ➢ 21,755,200 doses of live attenuated H1N1 vaccine

• During vaccination season, safety monitoring conducted in multiple U.S. systems focusing on multiple rare and serious outcome events
2009 H1N1 Pandemic Vaccine Safety: H1N1 VSRAWG Report - June 2010

- Weak safety signals (low level risk and/or substantial methodological limitations in data or study design) detected for 3 outcomes of interest
  - Guillain-Barré syndrome (GBS)
    - Weak signal detected in the Emerging Infections Program (EIP) but not 6 other systems
  - Bell’s palsy
    - Weak signal in IHS and Vaccine Safety Datalink (VSD)
  - Thrombocytopenia/idopathic thrombocytopenia (TP/ITP)
    - Weak signal detected in 3 systems, including Defense Medical Surveillance System (DMSS), Veteran’s Affairs (VA), and Indian Health Service (IHS)

- Final “end of season” analysis in progress
  - Includes medical record review of claims data
Febrile Reactions in 2010–2011 Southern Hemisphere Trivalent Influenza Vaccine

- Using enhanced passive surveillance, the Australian TGA reported febrile seizures (~9 per 1,000 doses of CSL trivalent vaccine) in children under five years old in the 2010 Southern Hemisphere formulation\(^2\)
- CSL is working with TGA and FDA to determine a root cause
- The 2010 Northern Hemisphere formulation is antigenically equivalent
  - In July 2010, the U.S. FDA placed a warning on the Afluria package insert referring to the southern hemisphere postmarketing reports
  - In August 2010, the U.S. Advisory Committee on Immunization Practices recommended that Afluria not be administered to children nine years old and younger and the Vaccine Information Statement was updated\(^3\)
  - U.S. 2010-2011 influenza safety monitoring included active and passive surveillance for febrile convulsions


\(^3\) [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm)
Febrile seizures after 2010-2011 Northern Hemisphere Trivalent Influenza Vaccine

• On December 3, 2010, the U.S. FDA and CDC determined that a safety signal existed for febrile seizures after Fluzone based on data from both VAERS and the Vaccine Safety Datalink (VSD)
• Fluzone, a TIV, is the only influenza vaccine recommended for 6-23 mo old children in the U.S.
• Cases of febrile seizure after TIV in the VSD have been chart confirmed; the majority received concomitant PCV13 and/or DTaP vaccines
• As of June 2011, it appears that the largest attributable risk, 0.42 per 1,000 vaccinations, is found among 12-23 month old children who received both TIV and PCV13
• Further work is needed to elucidate the possible contribution of DTaP vaccines and is underway
• Febrile convulsions have been added to the Postmarketing Experience section of the Fluzone package insert
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. H5N1)
    ▪ Subtype in seasonal: Strain change supplement to seasonal (e.g. H1N1)
  ➢ 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
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)