Demonstrating Disease Protection in the Senior Population

See Slides 23-25 for Important Safety Information.
● The Impact of Influenza Disease in Seniors
  ● Older adults suffer disproportionately from influenza-related morbidity and mortality
  ● Influenza-related complications are common

● Influenza Vaccination of Seniors
  ● Influenza vaccination and its impact on major cause-specific mortality
  ● Vaccine effectiveness against influenza-like illness is lower in older vs younger adults

● Fluzone High-Dose Vaccine Licensure
  ● Responding to a need
  ● Antibody response: Fluzone High-Dose vaccine vs Fluzone vaccine

● Efficacy Data on Fluzone High-Dose Vaccine
  ● Primary and secondary results

● Fluzone High-Dose Vaccine: Key Points and Product Information
The Impact of Influenza Disease in Seniors

“Because the proportion of elderly persons in the US population is increasing and because age and its associated chronic diseases are risk factors for severe influenza illness, the toll from influenza can be expected to increase unless control measures are used more vigorously.”

—Centers for Disease Control and Prevention (CDC), 1990

See Slides 23-25 for Important Safety Information.

A Vulnerable Population

- Adults ≥65 years of age are at high risk of influenza-related complications, hospitalization, and death\(^1\)
- Risk is heightened in older people by the likelihood of their having 1, 2, or more underlying medical conditions (heart disease, lung disease, diabetes, etc)\(^1\)
- Age also brings greater susceptibility to infection, reduced capacity to fight it, and a diminished immune response to many vaccines\(^2\)

Older Adults Suffer Disproportionately from Influenza-Related Morbidity and Mortality\textsuperscript{1-3}

Estimated Annual Number of Hospitalizations Due to Influenza in the US: 226,000

Estimated Annual Number of Deaths Due to Influenza in the US: 3000 to 49,000

The greatest burden of influenza disease occurs in persons $\geq 65$ years of age despite achieving an immunization rate of 65\%-70\% in this population

Influenza-Related Complications Are Common\textsuperscript{1,2}

- In otherwise healthy persons, influenza can lead to primary viral or secondary bacterial pneumonia, serious cardiac events, and neurologic complications.

- In persons with comorbidities, influenza often aggravates the underlying chronic illness, such as:
  - Congestive heart failure
  - Chronic obstructive pulmonary disease (COPD)
  - Asthma
  - Diabetes

- Deaths from influenza-related complications are typically attributed to these underlying or secondary illnesses.

Influenza Vaccination and Its Impact on Major Cause-Specific Mortality¹

- Study in Taiwan, 2000-2001, in 102,698 residents ≥65 years of age
- Objective: “To understand more thoroughly whether influenza vaccination was effective for reducing major cause-specific mortality (other than lung diseases) in a county-wide population study with large sample sizes”
- Six of 8 major causes of mortality evaluated were not directly related to lung disease
- >10-month follow-up of 35,637 vaccinated and 67,061 unvaccinated persons ≥65 years of age (prospective and observational)
- High-risk persons were defined as those with a chronic disease, residence in long-term care, or a history of recent (prior 3 years) hospital admissions
  - 80% of the full study population were not classified as high-risk

Influenza vaccine is strongly associated with a lower mortality risk, not only for pneumonia and COPD, but also for other major cause-specific mortalities, which indicates that influenza vaccination might reduce the domino effects of complications from influenza in the elderly.

Influenza Vaccination of Seniors

See Slides 23-25 for Important Safety Information.
Influenza Vaccination Coverage Rates Among Seniors, 2005-2014

Vaccine Effectiveness Against Influenza-Like Illness Is Lower in Older vs Younger Adults\textsuperscript{1,2}

During the influenza seasons shown, the range of vaccine effectiveness was 62\%-76\% in persons 15-64 years of age and 26\%-52\% in persons $\geq$65 years of age

Antibody Responses to Traditional Influenza Vaccine\textsuperscript{a} are Lower in Older vs Younger Adults\textsuperscript{1}

\textsuperscript{a} Fluzone vaccine. \textsuperscript{b} GMT = Hemagglutination inhibition (HAI) geometric mean antibody titer.

Fluzone High-Dose Vaccine Licensure

See Slides 23 and 24 for Important Safety Information
Responding to a Need: Fluzone High-Dose Vaccine

- Licensed in 2009 under the Food and Drug Administration (FDA) Accelerated Approval Pathway
  - Process is designed to help safe and effective products for serious or life-threatening diseases become available sooner
- Objective: Fill an unmet medical need by helping improve protection against influenza in persons ≥65 years of age
- Formulated to contain 4 times the hemagglutinin (HA) content of Fluzone vaccine
  - 60 mcg HA of each strain per dose vs 15 mcg HA per strain
  - Licensure based on data demonstrating immunogenicity comparable or superior to that of Fluzone vaccine and a comparable safety profile

Antibody Response: Fluzone High-Dose Vaccine vs Fluzone Vaccine (Phase III Trial)\textsuperscript{1,2}

Superiority of immune responses achieved for A (H1N1) and A (H3N2); non-inferiority for B. All comparisons, $P < 0.0001$.

\textbf{A (H1N1)}

\begin{itemize}
  \item \textbf{Fluzone High-Dose Vaccine} \textsuperscript{a} = 116
  \item \textbf{Fluzone Vaccine} \textsuperscript{b} = 67
\end{itemize}

\textbf{B}

\begin{itemize}
  \item \textbf{Fluzone High-Dose Vaccine} \textsuperscript{a} = 69
  \item \textbf{Fluzone Vaccine} \textsuperscript{b} = 52
\end{itemize}

\textbf{A (H3N2)}

\begin{itemize}
  \item \textbf{Fluzone High-Dose Vaccine} \textsuperscript{a} = 609
  \item \textbf{Fluzone Vaccine} \textsuperscript{b} = 333
\end{itemize}

\textsuperscript{a} N = 2576 Fluzone High-Dose vaccine. \textsuperscript{b} N = 1275 Fluzone vaccine.

Post-vaccination Seroconversion\(^a\) Rates (Phase III Trial)\(^1,2\)

- **Fluzone High-Dose Vaccine** (N = 2576)
- **Fluzone Vaccine** (N = 1275)

### Superiority of immune responses achieved for A(H1N1) and A(H3N2); non-inferiority for B\(^b,c\)

<table>
<thead>
<tr>
<th></th>
<th>Fluzone High-Dose Vaccine (%)</th>
<th>Fluzone Vaccine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A(H1N1)</strong></td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td><strong>A(H3N2)</strong></td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>42</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^a\) Seroconversion defined as having paired samples with prevaccination (Day 0) titer <1:10 and post-vaccination (Day 28) titer \(\geq 1:40\) or a \(\geq 4\)-fold rise in serum HAI antibody titers. \(^b\) All comparisons, Fluzone High-Dose vaccine vs Fluzone vaccine, \(P <0.0001\).

Efficacy Data for Fluzone High-Dose Vaccine

See Slides 23-25 for Important Safety Information.
Efficacy Trial for Fluzone High-Dose Vaccine\textsuperscript{1,2}

- On October 31, 2014, the Fluzone High-Dose vaccine Prescribing Information was updated to include results of a post-licensure efficacy trial
  - Efficacy trial results are located in Table 4 of the Prescribing Information.

- The efficacy trial included approximately 32,000 study participants 65 years of age and older. Results from the trial were published in *The New England Journal of Medicine* (August 2014)
  - The efficacy trial was conducted over 2 influenza seasons: 2011-2012 and 2012-2013

- The primary objective of the efficacy trial was to determine relative efficacy against protocol-defined, laboratory-confirmed influenza disease regardless of similarity to the strains in the vaccine

The efficacy trial found that Fluzone High-Dose vaccine was 24.2% more effective than Fluzone vaccine in preventing protocol-defined, laboratory-confirmed influenza disease regardless of similarity to the strains in the vaccine.

The primary result met the FDA-agreed, pre-specified statistical superiority criterion.

Results for a secondary end point from the efficacy trial have also been added to the Prescribing Information for Fluzone High-Dose vaccine.

Located within the text of the Prescribing Information below Table 4

For the secondary end point, relative efficacy was determined against modified CDC-defined, culture-confirmed influenza disease due to influenza strains that were antigenically similar to the strains contained in the vaccine.

Results for the secondary end point indicated that Fluzone High-Dose vaccine was 51.1% more effective at preventing modified CDC-defined, culture-confirmed influenza disease that was antigenically similar to the strains that were contained in the vaccine, compared to Fluzone vaccine.

References:
Fluzone High-Dose Vaccine: Summary of Key Points and Product Information

See Slides 23-25 for Important Safety Information.
Fluzone High-Dose Vaccine: Summary of Key Points

- Adults ≥65 years of age are at increased risk of severe outcomes of influenza infection that may lead to hospitalization and death.

- Due to immunosenescence, older adults do not respond as well as younger adults to influenza vaccine, leaving them more vulnerable to infection and its associated complications.

- In a pre-licensure study, Fluzone High-Dose vaccine was shown to induce superior antibody responses compared to Fluzone vaccine in older adults.

- A post-licensure efficacy study demonstrated superior efficacy of Fluzone High-Dose vaccine over Fluzone vaccine in preventing clinically relevant influenza in this vulnerable population.
Fluzone and Fluzone High-Dose Vaccines: Important Safety Information

Indication
Fluzone and Fluzone High-Dose vaccines are indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in each vaccine.
Fluzone vaccine is indicated for persons 6 months of age and older. Fluzone High-Dose vaccine is approved for use in persons 65 years of age and older.
Safety Information
The most common local and systemic adverse reactions to Fluzone and Fluzone High-Dose vaccines include pain, erythema, and swelling at the injection site; myalgia, malaise, headache, and fever (irritability, abnormal crying, drowsiness, appetite loss, and vomiting in young children receiving Fluzone vaccine). Other adverse reactions may occur. Fluzone and Fluzone High-Dose vaccines should not be administered to anyone with a known hypersensitivity (eg, anaphylaxis) to any vaccine component, including egg protein or thimerosal (the multidose vial is the only presentation containing thimerosal), or to a previous dose of any influenza vaccine.
Fluzone and Fluzone High-Dose Vaccines: Important Safety Information (cont)

Safety Information (cont)
If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone or Fluzone High-Dose vaccine should be based on careful consideration of the potential benefits and risks. Vaccination with Fluzone or Fluzone High-Dose vaccine may not protect all individuals.

Before administering Fluzone and Fluzone High-Dose vaccines, please see full Prescribing Information.
Fluzone High-Dose Vaccine: Product Information

- 60 mcg of HA per strain
- 180 mcg total HA per vaccine dose
  - 4 times the amount of HA compared with Fluzone vaccine
- Single 0.5-mL dose for intramuscular injection
- Provided in prefilled syringes with gray plunger rod
- No preservative
- Not made with natural rubber latex

Share of Fluzone High-Dose Vaccine Among Total Influenza Vaccine Claims (≥65 Years of Age)

Week Ending February 14, 2015
Fluzone High-Dose Vaccine: Reaching the Senior Population

- More than 30 million doses of Fluzone High-Dose vaccine have been distributed in the US since licensure in December 2009
- In the 2014-2015 influenza season, more than 1 in 3 immunized persons ≥65 years of age have received Fluzone High-Dose vaccine

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Questions or Comments?