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<p>Sponsor: Sanofi Pasteur</p> <p>Drug substance(s): High Dose Trivalent Inactivated Influenza Vaccine</p>	<p>Study Identifiers: IND 4518, NCT00391053</p> <p>Study code: FIM05</p>
<p>Title of the study: Phase III Lot Consistency, Immunogenicity and Safety Study of Three Lots of Fluzone High Dose Trivalent Vaccine Compared with One Lot of Standard Fluzone® in Adults ≥65 Years of Age</p>	
<p>Study center(s): This was a multi-center trial in the United States.</p>	
<p>Study period:</p> <p>Date first subjects enrolled: 09/Oct/2006</p> <p>Date last subjects completed: 09/Jul/2007</p>	
<p>Phase of development: Phase III</p>	
<p>Objectives:</p> <p>Primary Objectives:</p> <p>The following primary objectives were addressed sequentially:</p> <p>1. Immunogenicity - Lot Consistency:</p> <p>To demonstrate lot consistency of the Fluzone High Dose (Fluzone HD) manufacturing process through evaluation of the immune responses elicited by three different lots at one month post-vaccination.</p> <p>2. Immunogenicity - Superiority:</p> <p>To demonstrate the superiority of Fluzone HD vaccine (based on the pooled responses elicited by the three vaccine lots) compared to standard-dose Fluzone vaccine as assessed by the following:</p> <ul style="list-style-type: none"> • The difference in percentage of subjects in each vaccine group who achieve seroconversion (defined as either a pre-vaccination Hemagglutination inhibition (HAI) titer <1:10 and a post-vaccination titer ≥1:40, or a pre-vaccination titer ≥1:10 and a minimum four-fold increase at one month post-vaccination). If one of the three virus strains in Fluzone HD vaccine fails to demonstrate superiority to standard-dose Fluzone, then it must demonstrate non-inferiority, as assessed by seroconversion at one month post-vaccination. • The ratio of the Geometric Mean Titers (GMTs)(GMT2 / GMT1) at one month post-vaccination, where GMT2 is the GMT obtained in the Fluzone HD vaccine group formed by pooling the three lots together, and GMT1 is the GMT obtained in the standard Fluzone vaccine (control) group. If one of the three virus strains in Fluzone HD vaccine fails to demonstrate superiority to standard-dose Fluzone, then it must demonstrate non-inferiority, as assessed by GMT at one month post-vaccination. <p>Secondary Objectives:</p> <p>1. Immunogenicity:</p> <ul style="list-style-type: none"> • To describe the seroprotection of Fluzone HD vaccine (based on the pooled responses elicited by the three lots) compared to that of standard dose Fluzone vaccine, where seroprotection is defined as an HAI antibody titer ≥1:40. <p>2. Safety:</p> <ul style="list-style-type: none"> • To describe the safety profile of Fluzone HD, as assessed by solicited adverse reactions collected for seven days post-vaccination, unsolicited adverse events collected for 28 days post-vaccination, and serious adverse events collected for six months post-vaccination. 	

<ul style="list-style-type: none"> Additional clinical information on the number of all-cause hospitalizations, Emergency Room visits, and unscheduled physician visits during the six months following vaccination were collected and analyzed descriptively. 	
<p>Methodology:</p> <p>This was a Phase III, multi-center, randomized, active-controlled, double-blind trial designed to assess the lot consistency between three lots of Fluzone HD vaccine and to compare the immunogenicity and safety of Fluzone HD vaccine to that of standard Fluzone, in adults ≥ 65 years of age.</p> <p>All subjects received a single 0.5 mL dose of influenza vaccine. Subjects were randomized in a 2:1 ratio to receive either Fluzone HD vaccine (60 μg hemagglutinin [HA] per antigen) or standard Fluzone (15 μg HA per antigen). Subjects in the Fluzone HD group were further randomized to receive one of three different lots of the vaccine.</p> <ul style="list-style-type: none"> Group 1: Fluzone HD Lot 1 Group 2: Fluzone HD Lot 2 Group 3: Fluzone HD Lot 3 Group 4: Standard Fluzone <p>All subjects provided a pre-vaccination blood sample on Day 0 and were then injected with the designated vaccine. They received a telephone call on Day 8 for the collection of seven-day safety data; returned on Day 28 for another blood draw; and received a final telephone call six months post-vaccination for collection of serious adverse events and additional clinical information.</p>	
<p>Number of subjects:</p>	<p>Planned: 3896</p> <p>Randomized: 3876</p> <p>Treated: 3837</p>
<p>Evaluated:</p>	<p>Immunogenicity: 3851</p> <p>Safety: 3833</p>
<p>Diagnosis and criteria for inclusion:</p> <p>A potential subject had to meet all of the following criteria to be considered for trial enrollment:</p> <ol style="list-style-type: none"> Aged ≥ 65 years on the day of vaccination. Informed consent form signed. Medically stable. (Subjects may have underlying chronic conditions such as hypertension, diabetes, ischemic heart disease, or hypothyroidism, as long as their symptoms/signs are controlled. If they are on medication for a condition, the medication dose must have been stable for at least 3 weeks preceding vaccination.) Able to attend all scheduled visits and to comply with all trial procedures. 	
<p>Study treatments</p> <p>Investigational Product: Fluzone HD (Influenza Virus vaccine, 2006-2007 strains)</p> <p>An injectable sterile suspension with trivalent inactivated Type A and B influenza antigens, provided in a pre-filled single-dose syringe.</p> <p>Form: Liquid; essentially clear and slightly opalescent in color</p> <p>Composition: Each 0.5 mL dose contained the following:</p> <ul style="list-style-type: none"> A/New Caledonia/20/99/IVR-116 (H1N1) Hemagglutinin: 60 μg A/Wisconsin/67/2005/X-161 (H3N2) Hemagglutinin: 60 μg B/Malaysia/2506/04 Hemagglutinin: 60 μg <p>This vaccine contains no preservative.</p> <p>Route of administration: Intramuscular (IM), to be injected into the deltoid area</p>	

Control Product: Fluzone (Influenza Virus vaccine, 2006-2007 strains)

An injectable sterile suspension with trivalent inactivated Type A and B influenza antigens, provided in a pre-filled single-dose syringe.

Form: Liquid; essentially clear and slightly opalescent in color

Composition: Each 0.5 mL dose contained the following active ingredients:

- | | |
|--|----------------------|
| • A/New Caledonia/20/99/IVR-116 (H1N1) | Hemagglutinin: 15 µg |
| • A/Wisconsin/67/2005/X-161 (H3N2) | Hemagglutinin: 15 µg |
| • B/Malaysia/2506/04 | Hemagglutinin: 15 µg |

This vaccine contains no preservative.

Route of administration: Intramuscular (IM), to be injected into the deltoid area

Duration of participation: The duration of each subject's participation is approximately six months.

Criteria for evaluation:

Primary Endpoints:

The following primary endpoints were addressed sequentially:

1. Immunogenicity - Lot Consistency:

GMTs: The anti-HAI GMTs (for each of the three virus strains) in each of the three lots at one month post-vaccination.

2. Immunogenicity - Superiority:

- Seroconversion: The percentage of subjects who achieved seroconversion one month following vaccination, where seroconversion is defined as either a pre-vaccination HAI titer <1:10 and a post-vaccination titer ≥1:40, or a pre-vaccination titer ≥1:10 and a minimum four-fold increase at one month post-vaccination.
- GMTs: The anti-HAI GMTs (for each of the three virus strains) at one month post-vaccination.

Secondary Endpoints:

1. Immunogenicity:

- Seroprotection: The percentage of subjects who achieved seroprotection one month following vaccination, where seroprotection is defined as an HAI antibody titer ≥1:40.

2. Safety / Reactogenicity:

- **Solicited adverse reactions:** The occurrence, time to onset, number of days of occurrence, and severity of the following solicited reactions between Day 0 and Day 7 after vaccination:

Injection site reactions:

- Injection Site Pain
- Injection Site Erythema
- Injection Site Swelling

Systemic reactions:

- Fever
- Headache
- Malaise
- Myalgia

- **Unsolicited adverse events:** Occurrence, nature (MedDRA preferred term), time to onset, duration, severity, relationship to vaccination, action taken, and seriousness of unsolicited (spontaneously reported) AEs were collected between vaccination (Day 0) and the Day 28 follow-up visit after vaccination.
- **Serious adverse events (SAEs):** The occurrence, nature (MedDRA preferred term), time to onset, duration, severity and relationship to vaccination of any SAEs occurring throughout the trial were collected from vaccination (Day 0) up to six months after vaccination.
- **Additional clinical information:** The following safety information about health care utilization was collected for the duration of the trial and analyzed descriptively:
 - Number of all-cause hospitalizations
 - Number of Emergency Room visits
 - Number of unscheduled physician visits

Statistical methods:

Primary Objectives:

Immunogenicity – Lot Consistency

The primary parameter for lot consistency was the ratio of the anti-HAI GMTs at one month post-vaccination among the three lots for each virus strain.

Let GMT_i denote the anti-HAI GMT in Lot i at one month post-vaccination. A similarity testing approach was performed on the following statistical hypothesis with a two-sided alpha of 5%:

$$H_0: GMT_i / GMT_j \leq 0.67 \text{ or } GMT_i / GMT_j \geq 1.50 \text{ for some } (i, j).$$

$$H_1: 0.67 < GMT_i / GMT_j < 1.50 \text{ where } (i, j) = (1,2), (1,3), \text{ and } (2,3).$$

The statistical methodology was based on a two-sided 95% CI of the ratio of anti-HAI GMTs. The 95% CI was determined using normal approximation. To demonstrate the lot consistency for Fluzone HD, the limits of the calculated two-sided 95% CIs for GMT_1/GMT_2 , GMT_1/GMT_3 , and GMT_2/GMT_3 for each of the three virus strains had to be between 0.67 and 1.50.

Immunogenicity – Superiority

If lot consistency for Fluzone HD was demonstrated, then the three lots were to be pooled together into one group and compared against the standard Fluzone vaccine (control) group.

The first primary parameter was the difference of the percentages of seroconversion (defined as either a pre-vaccination HAI titer $<1:10$ and a post-vaccination titer $\geq 1:40$, or a pre-vaccination titer $\geq 1:10$ and a minimum four-fold increase at one month post-vaccination) between the two groups, $P_2 - P_1$, where P_2 is the rate of seroconversion seen in the pooled Fluzone HD group, and P_1 is the rate of seroconversion seen in the control group.

A superiority testing approach was performed on the following statistical hypothesis, with a one-sided alpha of 2.5%:

$$H_0: P_2 - P_1 \leq 10\%$$

$$H_1: P_2 - P_1 > 10\%$$

The statistical methodology was based on a two-sided 95% CI of the difference of the seroconversion rates.

According to the criteria used in this study, superiority of seroconversion rate for a virus strain is demonstrated if the lower limit of the two-sided 95% CI is greater than 10%. In order for Fluzone HD vaccine to be considered superior to the control vaccine, superiority on the seroconversion measure had to be met for at least two of its three virus strains; and if one of the three strains failed to demonstrate superiority, then it had to demonstrate non-inferiority. Non-inferiority was demonstrated (on the same analysis population used for demonstrating superiority) if the lower limit of the two-sided 95% CI was greater than -10%, where -10% is the non-inferiority margin.

Another primary parameter was the ratio of the GMTs ($\text{GMT}_2 / \text{GMT}_1$) at one month post-vaccination for each virus strain, where GMT_2 is the GMT obtained in the Fluzone HD vaccine group formed by pooling the three lots together, and GMT_1 is the GMT obtained in the standard Fluzone vaccine (control) group.

A superiority testing approach was performed on the following statistical hypothesis, with a one-sided alpha of 2.5%:

$$H_0: \text{GMT}_2 / \text{GMT}_1 \leq 1.5$$

$$H_1: \text{GMT}_2 / \text{GMT}_1 > 1.5$$

According to the criteria used in this study, superiority was demonstrated for a virus strain if the lower limit of the 95% CI for the ratio of $\text{GMT}_2 / \text{GMT}_1$ was >1.5 . In order for Fluzone HD vaccine to be considered superior to the control vaccine, superiority on the GMT measure had to be met for at least two of its three virus strains; and if one of the three strains failed to demonstrate superiority, then it had to demonstrate non-inferiority. Non-inferiority was demonstrated (on the same analysis population used for demonstrating superiority) if the lower limit of the two-sided 95% CI was greater than 0.67, where 0.67 is the non-inferiority margin.

Secondary Objectives:

Immunogenicity – Seroprotection

The secondary endpoint for immunogenicity was the percentage of subjects who achieved seroprotection one month following vaccination, where seroprotection is defined as an HAI antibody titer $\geq 1:40$

The difference of the seroprotection rates between the two vaccine groups was based on $P_2 - P_1$, where P_2 was the seroprotection rate of the Fluzone HD vaccine group (formed by pooling the three lots together), and P_1 was the rate of the standard Fluzone vaccine group. The 95% two-sided CIs were calculated.

For each virus strain, the difference of the percentages of seroconversion/seroprotection, $P_i - P_j$, between Lot i and Lot j, and its 95% two-sided CI were calculated.

Immunogenicity – Additional Analyses

Within-Group GMT Analyses:

Within-group analyses included the ratio of GMTs using $\text{GMT}_{\text{post}} / \text{GMT}_{\text{pre}}$ and its associated 95% CI, where GMT_{pre} and GMT_{post} are the GMTs obtained at pre- and one-month post-vaccination, respectively.

For each group, the GMTs, the percentages of seroconversion and seroprotection, and their associated 95% CIs were calculated for each virus strain at baseline and at one month post-vaccination. Reverse cumulative distribution of \log_{10} titers were plotted graphically by vaccine group.

Analyses According to EMEA Criteria:

The results of this study were also evaluated using criteria provided by the EMEA (European Medicines Evaluation Agency) Note for Guidance CPMP/BWP/214/96 for the immunological evaluation of influenza vaccines for adult and elderly populations. These criteria are: 1) seroprotection rate post-vaccination, 2) the mean geometric increase between pre- and post-vaccination, and 3) the seroconversion rate or significant increase of titer post-vaccination.

Post Hoc Analyses:

Post hoc analyses were conducted in order to determine whether the following factors played any role in the immune response: age, gender, medical history, and history of previous vaccination against influenza. In addition, an analysis was conducted on the number of subjects achieving post-vaccination antibody titers of 1:80 and 1:160.

Safety

Safety was described for each lot of Fluzone HD. Once lot consistency with respect to immunogenicity was established, the solicited adverse events of Fever, Headache, Malaise, and Myalgia were to be assessed across pooled lots.

Safety as Assessed by Descriptive Analyses:

1. Solicited reactions were reported for seven days post-vaccination and summarized by group and time. Each solicited reaction was categorized as None, Mild, Moderate, or Severe, and was further classified as “Any”, “Any Injection Site Reaction”, and “Any Systemic AE”. The aforementioned reactions were reported for combined time intervals (Days 0-3, Days 4-7, and Days 0-7 post-vaccination).
2. Unsolicited AEs and SAEs reported post-vaccination were summarized by vaccine group.
3. The following clinical information was collected for the duration of the trial and analyzed descriptively:
 - Number of all-cause hospitalizations
 - Number of Emergency Room visits
 - Number of unscheduled physician visits

Safety as Assessed by Hypothesis Testing:

The solicited systemic reactions of Fever, Headache, Malaise, and Myalgia were used to test the hypothesis that the safety of Fluzone HD vaccine is non-inferior to that of standard-dose Fluzone vaccine. The percentages of subjects reporting moderate or severe occurrences of these four events, as well as the percentages reporting any occurrences, were compared between the two groups. Data from the groups receiving three different lots of Fluzone HD were pooled and compared against the group receiving standard-dose Fluzone. Non-inferiority would be demonstrated if the upper limit of the 95% two-sided CI of the ratio (of Fluzone HD to standard-dose Fluzone) of the two proportions was < 3 .

Populations to Be Analyzed:

Full Analysis Set (FAS)

The FAS was defined as subjects who met the following conditions:

- Received a study vaccine
- Provided data on at least one post-vaccination assessment

The analyses were performed on the FAS population as follows:

- For safety, the analysis was performed on the FAS according to the vaccine actually received by the subjects.
- For immunogenicity, the analysis was performed on the FAS according to the vaccine the subjects were randomized to receive.

Per Protocol Analysis Set (PP)

The PP analysis set for immunogenicity was defined as those subjects who met the following conditions:

- Satisfied the inclusion and exclusion criteria
- Received a study vaccine correctly according to randomization
- Provided blood samples pre- and one month post-vaccination
- Completed Visit 2 within the specified time window

The FAS analysis set was used for the primary and secondary immunogenicity analyses, and the PP analysis set was used for the exploratory immunogenicity analysis.

Summary:**Population characteristics:**

A total of 3,876 elderly adults were randomized in the study. Of this number, 3,837 were vaccinated: 2,575 with Fluzone HD and 1,262 with standard Fluzone. Twelve Fluzone HD subjects and 10 control subjects withdrew prior to Visit 2. Two of the Fluzone HD withdrawals and four of the control group withdrawals were due to SAEs; however, none of these SAEs was considered related to vaccination.

Females represented 51.3% of subjects who received Fluzone HD and 54.6% of those who received standard Fluzone. The mean age in all groups was 72.9 years, with a range from 65 to 97 years. The majority of subjects were Caucasian, constituting 91.7% of the subjects in the Fluzone HD group and 92.9% in the control group; other racial groups each represented less than 5% of the total. Sex, age, and race all had similar representations across the three Fluzone HD lots.

Primary Immunogenicity Objective #1: Lot Consistency

The primary objective of determining lot consistency was assessed by comparing the post-vaccination GMT for each virus strain in each lot of Fluzone HD vaccine against those seen in the other two lots. The analyses were conducted only on the Immunogenicity Analysis Set. Results were comparable across the three lots. For the A/H1N1 strain, the ratios of Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3 were 0.98, 0.94, and 0.96, respectively; for A/H3N2, they were 0.95, 0.99, and 1.04; and for B, they were 1.00, 1.00, and 1.00. The limits of the two-sided confidence intervals were all between 0.67 and 1.50, which met the pre-defined criterion for demonstrating lot consistency.

Primary Immunogenicity Objective #2: Superiority Over Standard Fluzone

The second primary objective was to demonstrate the superiority of Fluzone HD vaccine over standard Fluzone, as assessed by 1) seroconversion rates and 2) GMT ratios. For these measures, the results from the three Fluzone HD groups were pooled. The analyses were conducted only on the Immunogenicity Analysis Set.

For the A/H1N1 strain, the percentage of subjects who reached the criterion for seroconversion was 48.56% in the Fluzone HD group compared to 23.14% of control subjects; for A/H3N2, it was 69.10% compared to 50.72%; and for B, it was 41.76% compared to 29.94%. A strain was considered superior if the lower limit of the 95% CI of the difference of the seroconversion rates was greater than 10%, and was considered non-inferior if this value was greater than -10%. In order for Fluzone HD vaccine to be considered superior to standard-dose Fluzone, at least two of the three virus strains had to demonstrate superiority, and if one strain failed, it had to demonstrate non-inferiority. The criterion of superiority was met for the A/H1N1 strain (lower limit of the 95% CI = 22.38) and the A/H3N2 strain (lower limit =15.08); and the criterion of non-inferiority was met for the B strain (lower limit =8.63).

Pre-vaccination GMTs were comparable between the groups: for A/H1N1, they were 28.5 for the Fluzone HD group and 29.36 for the control group; for A/H3N2, they were 74.60 and 74.74, respectively; and for B, they were 19.32 and 18.96, respectively. In contrast, the post-vaccination GMTs were higher for the Fluzone HD group than for the control group for all three strains: 115.79 compared to 67.29 for A/H1N1; 608.87 compared to 332.46 for A/H3N2; and 69.06 compared to 52.34 for B.

For the A/H1N1 strain, the GMT value was 115.79 for the Fluzone HD group compared to 67.29 for the control group; for A/H3N2, it was 608.87 compared to 332.46; and for B, it was 69.06 compared to 52.34. A strain was considered superior if the lower limit of the 95% CI for the GMT ratio was greater than 1.5, and was considered non-inferior if it was greater than 0.67. In order for Fluzone HD to be considered superior to standard-dose Fluzone, at least two of the three virus strains had to demonstrate superiority, and if one strain failed, it had to demonstrate non-inferiority. The criterion of superiority was met for the A/H1N1 strain (lower limit of the 95% CI = 1.61) and the A/H3N2 strain (lower limit =1.70); and the criterion of non-inferiority was met for the B strain (lower limit =1.24).

Secondary Immunogenicity Objective: Seroprotection

The secondary immunogenicity objective was to describe the seroprotection of Fluzone HD vaccine (based on the pooled responses elicited by the three lots) compared to that of standard dose Fluzone vaccine, where seroprotection was defined as an anti-hemagglutinin antibody titer $\geq 1:40$. For the A/H1N1 strain, seroprotection was achieved by 89.9% of subjects in the Fluzone HD group compared to 76.8% of controls; for A/H3N2, by 99.3% compared to 96.5%; and for B, by 79.3% compared to 67.6%.

Within-Group GMT Ratios and EMEA Criteria

Within-group GMT ratios (GMTRs) compared the post-vaccination GMT value for each strain to the pre-vaccination value for those subjects who contributed both pre- and post- results for each strain. The ratios for the Fluzone HD group were 3.77 for A/H1N1, 7.73 for A/H3N2, and 3.10 for B. For standard-dose Fluzone, they were 2.16 for A/H1N1, 4.23 for A/H3N2, and 2.43 for B.

The results of this study were also evaluated using criteria provided by the EMEA (European Medicines Evaluation Agency) Note for Guidance CPMP/BWP/214/96 for the immunological evaluation of influenza vaccines for adult and elderly populations. The criteria for adults >60 years old are: 1) seroprotection rate post-vaccination of >60%, 2) mean geometric increase between pre- and post-vaccination of >2.0, and 3) seroconversion rate or significant increase of titer post-vaccination of >30%.

Post Hoc Immunogenicity Analyses

Post hoc analyses were conducted in order to determine whether various factors played any role in the immune response. Fluzone HD recipients in both age groups (younger than 75 years, or 75 years or older) had comparable seroconversion and seroprotection rates. The immune response for both age groups was significantly greater than that seen in subjects in the same age who received standard Fluzone. Female subjects had a greater response to both vaccines than did male subjects, but both males and females had a greater response to Fluzone HD than to standard Fluzone vaccine. Both subjects with and without cardiopulmonary disease showed a greater immune response to Fluzone HD than to standard Fluzone. Finally, significantly more subjects receiving Fluzone HD had post-vaccination titers of 1:80 and 1:160.

Secondary Objective: Safety

No deaths were reported between Day 0 and Day 28 post-vaccination. A total of 23 deaths were reported during the follow-up period (Day 29-Day 180) of the study: 16 (0.62%) among Fluzone HD recipients and 7 (0.56%) among standard-dose Fluzone recipients. All fatal SAEs were deemed by the site Investigators to be unrelated to vaccination.

Information on serious adverse events (SAEs) was collected and assessed throughout the trial, from inclusion until six months after vaccination. The reporting rates were comparable between the two groups of subjects. A total of 249 (6.50%) subjects reported SAEs: 156 (6.06%) in the Fluzone HD group and 93 (7.38%) in the control group. Two of the SAEs were deemed to be related to vaccination: exacerbation of Crohn's disease in a Fluzone HD recipient and myasthenia gravis in a control subject.

At Day 180, adverse events leading to discontinuation had occurred in 16 (0.6%) of Fluzone HD subjects and in 11 (0.9%) control subjects.

Adverse events occurring in the 30 minutes following vaccination were reported by 14 (0.5%) Fluzone HD recipients and by 6 (0.5%) control subjects. Of these, the events experienced by 8 (0.3%) Fluzone HD recipients and 4 control subjects (0.3%) were considered to be related to vaccination. In the Fluzone HD group, the reactions were Stomach discomfort (n = 1), Chills (n = 2), Dizziness (n = 3), Dysgeusia (n = 1), Hypoaesthesia (n = 1), Cough (n = 1), and Pharyngolaryngeal pain (n = 1). In the control group, they were Nausea (n = 1), Fatigue (n = 1), and Dizziness (n = 2).

Rates of solicited reactions within the first seven days post-vaccination were higher in the Fluzone HD group. At least one solicited reaction of any type was reported by 1,378 (53.6%) Fluzone HD recipients, compared to 556 (44.1%) controls. The difference was greater for injection site reactions, which were reported by 1,076 (41.8%) of Fluzone HD recipients compared to 394 (31.3%) controls, while systemic reactions were reported by 882 (34.3%) and 370 (29.4%), respectively. Most of the reactions resolved within three days following vaccination.

The solicited reactions of fever, headache, malaise, and myalgia were used to test the hypothesis that the safety of Fluzone HD is non-inferior to that of standard Fluzone. The percentages of subjects reporting moderate or severe occurrences of these events, as well as the percentages of subjects reporting any occurrences, were compared between the two groups. The systemic safety of Fluzone HD is non-inferior to that of standard Fluzone if the upper limit of the two-sided 95% CI is <3.

In general, Fluzone HD is non-inferior to standard Fluzone for any solicited systemic reaction and moderate or severe systemic reaction. The relative risk was below the set limit for any fever, headache, malaise, and myalgia, and for moderate or severe headache, malaise, and myalgia.

Fluzone HD is inferior to standard Fluzone for moderate or severe fever, with a relative risk of 3.55. However, the number of subjects with moderate or severe fever was relatively low. There were 29/2569 subjects (1.1%) in the Fluzone HD group and 4/1258 subjects (0.3%) in the standard Fluzone group with moderate or severe fever. Most of these subjects had moderate fever. There were only 2 subjects with severe fever: one in the Fluzone HD group and the other in the standard Fluzone group.

Rates of unsolicited adverse events within 28 days of vaccination were comparable for the two groups, reported by 789 (30.7%) Fluzone HD subjects and 385 (30.6%) control subjects. Of these, 129 (5.0%) Fluzone HD subjects and 58 (4.6%) control subjects experienced unsolicited reactions (i.e., adverse events deemed related to vaccination).

With regard to the timing of occurrence of adverse events, the majority of solicited reactions occurred within three days of vaccination. Among the Fluzone HD recipients, solicited injection site reactions were reported by 1071 (41.6%) subjects between Days 0 and 3 post-vaccination compared to 185 (7.2%) between Days 4 and 7, while for controls, the numbers were 390 (31.0%) compared to 61 (4.8%). Solicited systemic reactions were reported by 807 (31.4%) Fluzone HD subjects between Days 0 and 3 compared to 307 (11.9%) between Days 4 and 7; for controls, the numbers were 319 (25.3%) compared to 162 (12.9%).

Rates of unsolicited injection site events were low, reported by no more than 2.3% of Fluzone HD recipients and 2.2% of control subjects at any time interval. For Fluzone HD recipients, they were reported by 47 (1.8%) subjects between Days 0 and 3 post-vaccination, by 50 (1.9%) between Days 0 and 7, by 58 (2.3%) between Days 0 and 28, and between Days 0 and 180. For controls, they were reported by 24 (1.9%) subjects between Days 0 and 3 post-vaccination and between Days 0 and 7; and by 28 (2.2%) between Days 0 and 28, and between Days 0 and 180.

Rates of unsolicited systemic events were similar between the groups, reported by 29.3% of Fluzone HD recipients and 29.2% of control subjects at any time interval. For Fluzone HD recipients, they were reported by 175 (6.8%) subjects between Days 0 and 3 post-vaccination, by 253 (9.8%) between Days 0 and 7, by 523 (20.3%) between Days 0 and 28, and by 755 (29.3%) between Days 0 and 180. For controls, they were reported by 76 (6.0%) subjects between Days 0 and 3 post-vaccination, by 119 (9.4%) between Days 0 and 7, by 257 (20.4%) between Days 0 and 28, and by 368 (29.2%) between Days 0 and 180.

The majority of serious adverse events were reported more than a week after vaccination. For Fluzone HD recipients, SAEs were reported by 2 (0.1%) subjects between Days 0 and 3 post-vaccination; by 5 (0.2%) subjects between Days 0 and 7; by 26 (1.0%) subjects between Days 0 and 28; and by 156 (6.1%) between Days 0 and 180. For controls, they were reported by 3 (0.2%) subjects between Days 0 and 3 post-vaccination; by 8 (0.6%) subjects between Days 0 and 7; by 22 (1.7%) subjects between Days 0 and 28; and by 93 (7.4%) between Days 0 and 180.

The onset of all reported events was comparable at all time intervals among the three different Fluzone HD lots.

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