



Pharmacovigilance Review Memorandum
Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE)

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Through: Wei Hua, MD, PhD, MS, MHS
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David Martin, MD, MPH
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Subject: Pharmacovigilance Plan Review
(BLA STN 125510)

Applicant: Novartis Vaccines and Diagnostics, Inc

Product: Adjuvanted, Formaldehyde Inactivated, Trivalent Seasonal
Subunit (A/A/B hemagglutinin and neuraminidase; embryonated
hen's eggs) Influenza Vaccine (Fluad[®])

Influenza vaccine, surface antigen, inactivated, adjuvanted with
MF59.C.1(Fluad[®])

Proposed Indication: Active immunization of persons 65 years of age and older against
influenza disease caused by influenza virus subtypes A and B
contained in the vaccine.

Submission type: Original BLA (STN 125510)

Submission Date: November 25, 2014

PVP Submission Date: November 25, 2014

First Action Due Date: November 25, 2015

A. Introduction:

(Excerpts from the sponsor's submission are shown in quotes.)

Product information:

Fluad[®] (also referred to as aTIV, adjuvanted trivalent influenza vaccine), a Human Influenza Virus Type A (H1N1; H3N2) and B Hemagglutinin and Neuraminidase Vaccine, Purified, Inactivated (embryonated hen's eggs), is a trivalent seasonal influenza virus vaccine formulated to contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA each of influenza type A (H1N1), Influenza type A (H3N2) and influenza type B, inactivated with MF59 citrate adjuvant system (an oil-in-water emulsion, with a squalene internal oil phase and a citrate buffer external aqueous phase, stabilized by two nonionic surfactants, sorbitan trioleate and polysorbate 80; also referred to as "MF59.C.1" or "MF59" in the Biologics License Application and this review memo).

"The manufacturing process for the antigens of aTIV is essentially the same process as for Agriflu[™], the nonadjuvanted seasonal influenza vaccine equivalent to Agrippal that was approved in the US on 27 NOV 09, under STN 125297 for individuals 18 years of age and older." The adjuvant component, MF59, of Fluad[®] provides the emulsified properties of the vaccine. The MF59.C.1 is added then to the vaccine formulation. The adjuvant component of the vaccine has gone through a series of developmental advances including both modification of the MF59 adjuvant by changing from water buffer to citrate buffer and the stepwise removal of the preservative thimerosal from "full" to "trace" to "free".

Fluad[®], manufactured by Novartis Vaccines and Diagnostics (NVD), is formulated for active immunization of people aged 65 years and older against influenza disease caused by influenza virus subtypes A and B contained in the vaccine. The product is a thimerosal-free, with the MF59.C.1 buffer formulation, sterile suspension for injection in prefilled syringes. The clinical development of Fluad[®] is under BB-IND 14368/013.

Product regulatory history:

Fluad[®] was first licensed in Italy on May 15, 1997. It is currently licensed in 38 countries in Europe, South America, Asia, and Canada. The product was approved for the immunization of elderly individuals aged 65 years and older against influenza virus infection in most of the countries, except in the Philippines for ages 60 years and older and in South Africa for ages 12 years and older. (Note: Per NVD, the license in South Africa is currently dormant.)

This product is registered under different brand names by NVD, including Gripguard[®] in France and Chiromas[®] in Spain. Please note that Fluad[®], Gripguard[®], and Chiromas[®] may be used interchangeably throughout this review memo.

Objective of the review:

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed and to evaluate the Pharmacovigilance Plan (PVP) submitted by NVD for the Biologics License Application (BLA) of Fluad[®], an adjuvanted, formaldehyde inactivated, trivalent seasonal subunit (A/A/B hemagglutinin and neuraminidase; embryonated hen's eggs) influenza vaccine.

In this review, the term "aTIV" exclusively refers to MF59-adjuvanted trivalent seasonal influenza vaccine based on the Agriflu manufacturing platform. The term "TIV" refers to all non-adjuvanted trivalent influenza vaccines discussed. In addition, "elderly" indicate individuals at age 65 years or above if not otherwise specified.

B. Materials reviewed

Materials reviewed in support of this assessment include:

- a. 0000, 11/25/2014, STN 125510/0.0 (received on November 25, 2014)
 - a) Module 1.16, Risk Management Plan(RMP)
 - b) Module 2.7.4, Summary of Clinical Safety
 - c) Module 2.5, Clinical Overview
 - d) Module 5.3.5.1, Active Control without Placebo – study V70_27, A Phase 3, Randomized, Controlled, Observer-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity and the Consistency of Three Consecutive Lots of a MF59.C.1 Adjuvanted Trivalent Subunit Influenza Vaccine in Elderly Subjects Aged 65 Years and Older
 - i. Full Report, Clinical Study Report (CSR)
 - ii. Addendum 1 to Clinical Study Report
 - iii. Post-hoc Clinical Study Report
 - e) Module 5.3.5.3, Integrated Summary of Safety (ISS)
 - f) Module 5.3.6, Reports of Post-marketing Experience
 - i. Periodic Safety Update Report 35 (PSUR 35)
 - g) Module 5.4, Literature References
- b. 0014, 6/25/2015. STN 125510/0.14 (Amendment) (received on June 25, 2015)
 - a) Module 1.11.4, Information Amendment, Multiple Module Information Amendments
 - i. Attachment 1,
 - Product Quality Impact Assessment, DR169723, OOS Visible Particles – for Agrippal lot 126303 and subsequent investigation, Version 2, October 29, 2012
 - Product Quality Impact Assessment, DR169723, OOS Visible Particles – for Agrippal lot 126303 and subsequent investigation, Version 2, Addendum 1, November 3, 2012
 - ii. Attachment 2: Report of suspected adverse reactions with fatal outcome following Fluad vaccination, 5th Report (4th Update), December 12, 2014

- iii. Attachment 3: A Qualitative Review and Quantitative Analysis of Serious and Nonserious Adverse Events Reported for Fludac and Agrippal in the 2014-2015 Influenza Season, December 22, 2014
 - iv. Attachment 4: Overall Summary of Fludac product quality review as consequence of Serious Adverse Events notifications, Version 5, January 22, 2015
 - v. Attachment 5: PCIRN¹ Canadian National Vaccine Safety (CANVAS) Network 2014 Seasonal Influenza Safety Surveillance: Final Report
 - vi. Attachment 6: Report on “PROJECT SVEVAPLUS: EVALUATION OF THE EVENTS FOUND AFTER THE SEASONAL FLU VACCINATION IN ITALY, IN THE YEAR 2014/2015”, January 27, 2015,
- c. Input from CBER’s Clinical Reviewer
 - a) FDA briefing document of Fludac® for the Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting, September 15, 2015 (dated August 14, 2015, email from Dr. Sarah Browne)
 - b) Clinical reviewer’s presentation and mid-cycle reviewer report dated May 11, 2015, available at (b) (4)
- d. Input from CBER’s Clinical Statistical Reviewer
 - a) Statistical reviewer’s report, available at (b) (4)
- e. Medical Literature
 - a) Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, Boldori L, Caramaschi F, Gattinoni A, Malchiodi G, Rothman KJ. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. *Am J Epidemiol* 2012; 176:527-33.
 - b) Villa M, Black S, Groth N, Rothman KJ, Apolone G, Weiss NS, Aquino I, Boldori L, Caramaschi F, Gattinoni A, Malchiodi G, Crucitti A, Della Cioppa

¹ Public Health Agency/Canadian Institutes of Health Research Influenza Research Network

G, Scarpini E, Mavilio D, Mannino S. Safety of MF59-adjuvanted influenza vaccination in the elderly: results of a comparative study of MF59-adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy. *Am J Epidemiol* 2013; 178:1139-45.

- c) Van Buynder PG, Konrad S, Van Buynder JL, Brodtkina E, Krajcend M, Ramlera G, Bighama M. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine* 2013; 31:6122–6128.
- d) Novartis Suspends Distribution of Seasonal Flu Vaccines Agriflu and Fluad in Canada as a Precaution. Available at <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/15096a-eng.php>, retrieved on June 30, 2015.
- e) AGRIFLU and FLUAD – Health Canada Lifts the Suspension of Distribution of these Seasonal Flu Vaccines – For the Public. Available at <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/15825a-eng.php>, retrieved on June 30, 2015.
- f) AGRIFLU and FLUAD – Health Canada Lifts the Suspension of Distribution of these Seasonal Flu Vaccines – For Health Professionals. Available at <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/15577a-eng.php>, retrieved on June 30, 2015.
- g) Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y, Adjuvants and autoimmunity, *Lupus*. 2009 Nov;18(13):1217-25. Review.
- h) Shoenfeld Y, Agmon-Levin N, 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants, *J Autoimmun*. 2011 Feb;36(1):4-8. Review.
- i) Montagnani S, Tuccori M, Lombardo G, Testi A, Mantarro S, Ruggiero E, Blandizzi C, Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases, *Ann Pharmacother*. 2011 Jan;45(1): e8.
- j) Hawkes D, Benhamu J, Sidwell T, Miles R, Dunlop RA, Revisiting adverse reactions to vaccines: A critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA), *J Autoimmun*. 2015 May;59:77-84. Review.
- k) Pellegrino P, Clementi E, Radice S, On vaccine's adjuvants and autoimmunity: Current evidence and future perspectives, *Autoimmun Rev*. 2015 May 29. Review.

- l) Colafrancesco S, Perricone C, Priori R, Valesini G, Shoenfeld Y, Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), *J Autoimmun.* 2014 Jun;51:10-6. Review.
- m) Cerpa-Cruz S¹, Paredes-Casillas P, Landeros Navarro E, Bernard-Medina AG, Martínez-Bonilla G, Gutiérrez-Ureña S, Adverse events following immunization with vaccines containing adjuvants, *Immunol Res.* 2013 Jul;56(2-3):299-303.
- n) Tsai TF, MF59 adjuvanted seasonal and pandemic influenza vaccines, *Yakugaku Zasshi.* 2011;131(12):1733-41. Review.
- o) Tsai TF, Flud®-MF59®-Adjuvanted Influenza Vaccine in Older Adult, *Infect Chemother.* 2013 Jun;45(2):159-74. Review.
- p) Pellegrini M, Nicolay U, Lindert K, Groth N, Della Cioppa G, MF59-adjuvanted versus non-adjuvanted influenza vaccines: Integrated analysis from a large safety database, *Vaccine.* 2009 Nov 16;27(49):6959-65.
- q) European Union: Investigation into reports of serious adverse events following use of Flud, Other safety alerts, from the website of Drug Office, Department of Health, The Government of the Hong Kong Special Administrative Region. Available at http://www.drugoffice.gov.hk/eps/news/European_Union%3A_No_evidence_that_Flud_vaccine_caused_deaths_in_Italy/healthcare_providers/2014-12-04/en/24165.html, retrieved on June 30, 2015.
- r) European Union: Investigation into reports of serious adverse events following use of Flud, Medical recalls, from the website of Drug Office, Department of Health, The Government of the Hong Kong Special Administrative Region. Available at http://www.drugoffice.gov.hk/eps/news/European_Union%3A_Investigation_into_reports_of_serious_adverse_events_following_use_of_Flud/healthcare_providers/2014-11-29/en/24139.html, retrieved on June 30, 2015.

C. Pharmacovigilance Plan Review

(Excerpts from the sponsor's submission or from the medical literature are shown in quotes.)

(C1) Clinical Safety Database

Influenza is one of the most frequent respiratory infections affecting both children and adults all over the world. The number of severe influenza cases in all age groups may reach 5 million during one influenza season worldwide.⁽⁵⁾ In the United States, seasonal influenza affects 5% to 20% of the population each year, resulting in 31.4 million outpatient visits, more than 3

million hospital days, and over \$87 billion total economic losses. Approximately half of the disease burden was contributed by elderly subjects at age 65 years or older.⁽¹⁻⁴⁾

Active immunization with seasonal influenza vaccines has been recognized as one of the most effective strategies for influenza prevention and symptom severity reduction for over five decades.

Influenza type A viruses are associated with epidemics and pandemics. Influenza type B viruses are related to annual epidemics. “Current inactivated seasonal influenza vaccines licensed in the US consist of trivalent (TIV²) or quadrivalent (QIV³) preparations that most commonly contain 15 µg of hemagglutinin (HA) for each of 2 influenza A subtypes (H1N1 and H3N2), as well as one influenza B strain (in TIV) or 1 each of 2 influenza B strains (in QIV) in formulations intended for use in adults.”

The protection level of a vaccine relies on the antigenic match between the most up-to-date vaccine strains and the circulating influenza strains of the same year. In addition, the efficacy of the current inactivated seasonal trivalent or quadrivalent influenza vaccines licensed in the US is affected by age and immune responsiveness of the population. “The decline of immune function in older people is considered as a hallmark of aging and has been clearly shown to affect the ability of this vulnerable population to resist influenza infection and to respond appropriately to vaccination.”

During vaccine development, adding an adjuvant is considered one of the effective approaches to formulate influenza vaccines with more consistent and broader coverage against all seasonal virus subtypes and variants to improve the homologous and heterologous immune responses, especially among the elderly recipients.

For the purpose of seasonal influenza prevention, a trivalent (H1N1, H3N2, and influenza B), inactivated seasonal influenza vaccine adjuvanted with MF59.C.1 (Fluad[®]) is developed by NVD for elderly individuals aged 65 years and older.

In the safety evaluation of Fluad[®], the following conditions were included in the study list of Adverse Events.

- a. Solicited Adverse Events (AEs)
 - a) Solicited local AEs:
 - a. Erythema (labeled as ‘redness’ on some case report forms [CRFs])
 - b. Induration (labeled as ‘hardness’ on some CRFs)
 - c. Swelling
 - d. Pain at injection site
 - e. Ecchymosis
 - f. Tenderness
 - b) Solicited systemic AEs
 - a. Chills

² TIV=Trivalent Influenza Vaccine

³ QIV=Quadrivalent Influenza Vaccine

- b. Myalgia
 - c. Arthralgia
 - d. Headache
 - e. Fatigue
 - f. Malaise
 - g. Nausea
 - h. Fever
 - i. Rash
 - j. Vomiting
 - k. Diarrhea
 - l. Sweating
- c) Other solicited AEs
 - a. Use of analgesic/antipyretic medication
 - b. Did the subject stay home due to a local or systemic AE
- b. Unsolicited Adverse Events or Treatment-Emergent Adverse Events (TEAEs), which “include all solicited AEs that were ongoing at day 4 or day 7 (depending on the study)”. (ISS Table 7)
 - a) Preferred Term (PT)
 - b) System Organ Class (SOC)
- c. Serious Adverse Events (SAEs) and other less frequently-occurring events
 - a) AEs leading to death
 - b) AEs leading to withdrawal
 - c) AEs leading to hospitalization
- d. Adverse events following immunization (AEFI)
- e. Adverse events of special interest (AESIs) defined as potential immune-mediated events

The safety of NVD’s Flud[®] was investigated through a phase III pivotal study, V70_27, under BB-IND⁴ 14368, and an integrated summary of safety (ISS) on 58 clinical studies conducted internationally between the 1992/1993 and 2013/2014 seasons.

(C1.1) Study V70_27

Study V70_27 was a phase III, randomized, controlled, observer-blind clinical study to evaluate the safety, immunogenicity, and clinical effectiveness of the current aTIV formulation (aTIV^{current}) among subjects aged 65 years and older during the 2010 to 2011 Northern Hemisphere influenza season. This study provided the “largest and most uniformly collected RCT⁵ dataset for assessing the reactogenicity of the aTIV formulation intended for US licensure.”

⁴ BB-IND=Biological Investigational New Drug

⁵ RCT=Randomized Clinical Trial

The safety objectives of study V70_27 were to describe 1) the safety and tolerability of aTIV compared to TIV in all subjects through day 8 following vaccination and all adverse events (AEs) and SAEs through day 22, and 2) “SAEs, new onset of chronic diseases, and AEs resulting in withdrawal from the study through day 366.”

A total of four vaccines, the Flud[®] (aTIV) lots A52P14H1, A52P15H1, A52P16H1, and Agriflu[®] (TIV) were evaluated in this pivotal study V70_27. Since the four vaccines contain identical antigen drug substance but are different in the MF59 adjuvant component, study V70_27 was able to evaluate the role of MF59 adjuvant on the safety and immunogenicity of aTIV as compared to TIV.

In this study, the 7104 study subjects from 38 international sites⁶ were stratified by age (65 to 75 years old vs 76 years and older) and randomized to one of the three Flud[®] lots or Agriflu[®] in a 1:1:1:3 ratio. Among them, there were 3545 (2545 between 65 and 75 years old and 1000 were older than 75 years) individuals received aTIV and 3537 received TIV. There were 11 subjects in each group who were randomized, but not vaccinated, thus excluded from the follow-up and analysis. Each vaccinated individual in study V70_27 received a single 0.5 mL dose of the assigned study vaccine administered intramuscularly (IM) and was followed at multiple time points for the next 12 month.

After vaccination, each study subject was checked at 30 minutes and 6 hours on day 1 and days 2 to 7 through dairy cards for solicited AEs. Information on TEAEs was collected from day 1 to day 21 after vaccination. “(A)ll local and systemic solicited AEs that persisted after day 7 were included in the category of at least possibly related TEAEs.” All the rest outcomes in the list of AEs above were recorded during the entire 12-month period following vaccination.

In this BLA, results of study V70_27 on the solicited local AEs regarding erythema, induration, and swelling were presented primarily in accordance with CBER Guidance “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”⁷, i.e., the presence of erythema, induration, and swelling in 30 minutes after vaccination was defined as ≥ 25 mm” (referred as “Type I analyses” in the BLA⁸).

Results of study V70_27 indicated that “5% of subjects in the aTIV group (N = 3515) and 4% of subjects in the TIV group (N = 3502) had solicited local AEs of pain, and 3% of subjects in each vaccine group had tenderness. All other solicited local AEs were reported by $\leq 1\%$ of subjects in both vaccine groups”. Compared to the TIV vaccinated subjects, having any solicited local AE was reported more in the aTIV group (32%) than the TIV group (17%) during the interval from 6 hours through 7 days postvaccination; injection site pain (25% vs 12%) and tenderness (21% vs 11%) occurred twice as likely in the aTIV vaccinated individuals. “Erythema, induration, and swelling were reported by $\leq 1\%$ of subjects in both groups during this interval.”

⁶ US (N=21), Philippines (N=11), Columbia (N=4), Panama (N=2).

⁷ Available at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm>, retrieved on April 17, 2015

⁸ Type II analyses defined as presence of erythema, induration, and swelling in 30 minutes after vaccination ≥ 1 mm

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After vaccination, each study subject was checked at 30 minutes and 6 hours on day 1 and days 2 to 7 through dairy cards for solicited AEs. Information on TEAEs was collected from day 1 to day 21 after vaccination. “(A)ll local and systemic solicited AEs that persisted after day 7 were included in the category of at least possibly related TEAEs.” All the rest outcomes in the list of AEs above were recorded during the entire 12-month period following vaccination.

In this BLA, results of study V70_27 on the solicited local AEs regarding erythema, induration, and swelling were presented primarily in accordance with CBER Guidance “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”⁷, i.e., the presence of erythema, induration, and swelling in 30 minutes after vaccination was defined as ≥ 25 mm” (referred as “Type I analyses” in the BLA⁸).

Results of study V70_27 indicated that “5% of subjects in the aTIV group (N = 3515) and 4% of subjects in the TIV group (N = 3502) had solicited local AEs of pain, and 3% of subjects in each vaccine group had tenderness. All other solicited local AEs were reported by $\leq 1\%$ of subjects in both vaccine groups”. Compared to the TIV vaccinated subjects, having any solicited local AE was reported more in the aTIV group (32%) than the TIV group (17%) during the interval from 6 hours through 7 days postvaccination; injection site pain (25% vs 12%) and tenderness (21% vs 11%) occurred twice as likely in the aTIV vaccinated individuals. “Erythema, induration, and swelling were reported by $\leq 1\%$ of subjects in both groups during this interval.”

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⁸ Type II analyses defined as presence of erythema, induration, and swelling in 30 minutes after vaccination ≥ 1 mm

“Less than 1% of subjects in each vaccine group reported local AEs that persisted past day 7, with the majority resolving by day 4.”

“More subjects in the aTIV group (32%) than the TIV group (26%) also reported any solicited systemic AEs during the interval from 6 hours through 7 days postvaccination. The most commonly reported solicited systemic AEs included myalgia (15% aTIV vs 10% TIV), headache (13% vs 11%), and fatigue (13% vs 10%).” “In both vaccine groups, most of the solicited systemic AEs were reported as beginning within the first 3 days postvaccination. The majority of individual systemic AEs had an onset on day 2 for the aTIV group and on day 3 for the TIV group.” In addition, less than 1% of subjects in each vaccine group had individual systemic AEs that were ongoing on day 7.

The overall TEAEs observed in study V70_27 were the same in the aTIV and TIV groups (16%). “At the PT level, the most frequently reported TEAEs were nasopharyngitis (2% in both vaccine groups) and headache (1% aTIV group vs 2% in the TIV group). All other TEAEs were reported by < 1% of subjects in both vaccine groups.” At the System Organ Class level, similar percentages of AEs were observed in both groups (5% for the infections and infestations SOC; 3% for musculoskeletal and connective tissue disorders SOC in each vaccine group, and 2% in aTIV group vs 3% in TIV group for the general disorders and administration site conditions and respiratory, thoracic and mediastinal disorders SOCs). “For all other SOCs, ≤ 2% of subjects in each vaccine group reported TEAEs.”

In both vaccine groups, 7% of subjects claimed at least one SAE at any time during the period between day 1 and day 366 after vaccination. The most frequent SAEs reported at the SOC level were infections and infestations (n=66 in aTIV and n=68 in TIV) and cardiac disorders (n=64 in aTIV and n=54 in TIV), approximately 2% for each outcome and in each groups. At the PT level, pneumonia, cardiac failure congestive, chronic obstructive pulmonary disease, myocardial infarction, and osteoarthritis were the most frequent SAEs observed. Four SAEs were assessed by the investigator as possibly or probably related to study vaccine (n = 1 aTIV and n = 3 TIV); the related SAE in the aTIV subject was bronchitis that occurred within the first 22 days following vaccination and the related SAEs in the TIV group were Guillain-Barré syndrome (GBS), asthmatic crisis, and chronic obstructive pulmonary disease (COPD) (V70_27 CSR, Table 14.3.2.3).

“In the pivotal phase 3 Study V70_27, deaths due to TEAEs through day 366 were reported for 1.5% (n = 52) of subjects in the aTIV group and 1.3% (n = 46) of subjects in the TIV group. The most frequently reported causes of death in both vaccine groups were cardiac disease (0.5% in both groups), respiratory infections, particularly pneumonia (0.3% vs 0.2%), cerebrovascular accidents (0.2% in both groups), and neoplasms (0.2% in both groups).” (Study V70_27 CSR, Table 14.3.2.1).

Data from study V70_27 indicated that 6% of subjects in both aTIV and TIV groups reported a new onset of chronic disease NOCD. At the SOC level, the most frequent SOC reported was vascular disorders (n=50 aTIV and n=51 TIV), followed by metabolism and nutrition disorders (n=44 aTIV and n=33 TIV), musculoskeletal and connective tissue disorders (n=38 aTIV and n=27 TIV), and cardiac disorders (n=25 aTIV and n=31 TIV). The difference in

percentage for each of these NOCDs was $\leq 1\%$ in all cases (Study V70_27 CSR, Table 14.3.2.6). Details can be found on pages 148-149 of the Summary of Clinical Safety, pages 68-69 of the Clinical Overview, page 223 of the ISS, and in Study V70_27 CSR, Table 14.3.2.6.

According to the sponsor, “(o)verall, the percentages of subjects with TEAEs, SAEs, AEs leading to withdrawal, and AEs leading to death were similar between vaccine groups in Study V70_27 (Summary of Clinical Safety, Table 2.7.4.2.1.1.1.9-1).”

(C1.2) ISS

The major goals of ISS were to 1) “compare the safety profile of adjuvanted versus nonadjuvanted trivalent influenza vaccines”; 2) “summarize the safety experience with aTIV across as broad an elderly subject population as possible”.

A total of 58 clinical studies focused on the safety and immunogenicity of aTIV between 1992/1993 and 2013/2014 seasons were included in the ISS to build up the safety profile of aTIV among adults age 18 years and older. “Clinical studies included in this ISS were conducted using 4 different formulations of aTIV that differ only by MF59 buffer and thimerosal content: (1) a water-buffered formulation with thimerosal as a preservative (aTIV^{thio-w}) was administered to 11186 subjects (64% of aTIV-treated subjects); (2) a citrate-buffered formulation of aTIV containing a “full” amount of thimerosal (aTIV^{thio-c}) was administered to 1185 subjects (7%); (3) a “trace” thimerosal (aTIV^{trace-thio}) formulation was administered to 552 subjects (3%); and, (4) the current thimerosal-free, citrate-buffered formulation of aTIV (aTIV^{current}) was administered to 4557 subjects (26%).” “All subjects in the studies included in the integrated analysis received IM injections.”

The ISS summarized the data on subjects who received at least one study vaccination, through eight “pooled” analyses on 49 clinical studies and nine “unpooled” analyses using data from the rest nine clinical studies. In this BLA regarding US licensure approval of Fludax[®] for active immunization of persons aged 65 years and older, particular emphasis was given to elderly adults who were 65 years of age or older at the time of clinical study enrollment. For seven of eight pooled analyses, the primary focus of data pooling analyses was on populations aged 65 years and older. Although safety information from study V70_27 was presented separately, it was also included in four of the ISS pooled safety analyses to expand the safety knowledge of aTIV. Data across different pooling are also overlapped with each other. The number of clinical studies, age of population, total number of subjects by type of vaccine received, and proportion of subjects from study V70_27 for the ISS pooled and unpooled analyses were summarized in Table 1 of this OBE/DE review.

(C1.2.1) ISS pooled studies

(C1.2.1.1) First Dose Elderly (FDE) Pooling

“The FDE Pooling provides the largest integrated dataset in the Elderly Population. It includes data from subjects enrolled in controlled and uncontrolled studies, blinded and open-label studies and includes data from subjects who received doses of aTIV across several different

formulations over the years. Comparator vaccines in these studies included several nonadjuvanted TIVs as well as different formulations and preparations (single syringe versus single vial) of aTIV.” Among the 36 studies in FDE pooling, 21 were conducted in Italy. The rest 15 studies were conducted in the US, the Philippines, Germany, Lithuania, Belgium, Columbia, Panama, Poland, Australia, and The Netherlands, during a period of over 20 years. Approximately 30% (28% aTIV and 32% TIV) of the FDE pooling subjects were from the US and 47% of the aTIV vaccinees in FDE pooling participated in study V70_27 (Table 1).

Compared to the TIV group, the proportions of subjects who reported solicited AEs (45.1% vs 35.7%), solicited local AEs (31.4% vs 18.4%), and solicited systemic AEs (24.5% vs 22.4%) were higher in the aTIV group (ISS table 26). The difference was due to injection site pain (26.1% in aTIV vs 13.7% in TIV) and tenderness (22.2% in aTIV vs 12.2% in TIV). None of the differences for other AEs were more than 5%, indicating no clinically meaningful difference for other AEs in the FDE pooling data.

(C1.2.1.2) First Dose Randomized, Controlled Trial (FD-RCT) Pooling

The FD-RCT pooling, including elderly subjects from 15 phase 1b, 2 and 3 RCTs, was a subset of the FED pooling concentrated on RCTs only. This is the largest pooling of randomized, blinded, controlled trials. Study V70_27 contributed 62% of the aTIV subjects in the FD-RCT pooling.

“(A)ll studies in the FD-RCT Pooling collected solicited AEs for 4 to 7 days, TEAEs for 22 to 29 days, and SAEs for at least 22 days postvaccination”. Since all the solicited and TEAEs from the observer-blinded, randomized, well-controlled studies over the 20 years were included in the FD-RCT pooling and the reporting periods were relatively longer than that in the FDE pooling, the FD-RCT pooling provided the most robust data for many of the AE data presentations.

Results from the FD-RCT pooling indicated that the proportion of subjects with solicited AEs were higher in the aTIV (49.4%) vaccinees than in the TIV vaccinees (35.7%), attributing to both the solicited local AE (34.5% vs 18.4%) and the solicited systemic AE (27.5% vs 22.4%) (ISS tables 26 and 36). Injection site pain (28.3% vs 13.7%), tenderness (22.2% vs 12.2%), fatigue (13.4% vs 10.5%), myalgia (12.7% vs 7.9%), headache (11.3% vs 9.8%), and antipyretic/analgesic (10.9% vs 8.1%) were reported more frequently in the aTIV group than in the TIV group (ISS table 36). Results from the relative risk evaluation indicated a higher risk (i.e., RR, Lower confidence limit [LCL] >1) following vaccination with aTIV for myalgia (12.7% vs 7.9%, RR: 1.55 [95% CI: 1.38, 1.74]), chills (5.8% vs 4.0%; RR: 1.48 [95% CI: 1.25, 1.75]), fatigue (13.4% vs 10.5%; RR: 1.27 [95% CI: 1.13, 1.44]), and headache (11.3% vs 9.8%; RR: 1.16 [95% CI: 1.04, 1.30]).

For TEAEs, SAES, AESI, AEFI, and/or AEs leading to withdrawal, hospitalization, or death, differences in percentage of reporting between aTIV and TIV group were no more than 5%, indicating no clinically meaningful differences identified through the FD-RCT pooling (ISS tables 26 and 36). “No notable differences were observed in the duration of systemic events between vaccine groups” (ISS table 37).

(C1.2.1.3) First Dose Randomized, Controlled Trial with ≥ 180 Days Follow-up (RCT-180) Pooling

The RCT-180 included a total of 9448 elderly subjects from ten RCTs, in which the SAE observation period was between 180 and 366 days. Three quarters of the subjects in RCT-180 were from study V70_27 (Table 1). The ISS summarized the RCT-180 results on SAEs, death, and AESIs.

The proportions of SAEs (7.4% aTIV and 7.2% TIV), AEs leading to death (1.5% and 1.5%), or AESIs (1.1% and 1.0%) reported in both aTIV and TIV groups were similar in the RCT-180 Pooling (ISS Table 29).

(C1.2.1.4) RCT Extension (RCT-EXT) Pooling

The RCT-EXT pooling aimed to 1) evaluate AEs that occurred after the first aTIV vaccination for those subjects who were subsequently enrolled in an extension study; 2) compare the safety profile of aTIV to TIV within vaccination number for vaccinations 2 and 3 to evaluate whether there was any change in the safety profile with repeat aTIV vaccination in subsequent influenza seasons; and 3) compare the safety profile of aTIV after vaccination 2 and after vaccination 3 with the safety profile of aTIV after vaccination 1 to evaluate whether there was any change in the safety profile with repeat aTIV vaccination in subsequent influenza seasons. Data from 822 elderly subjects collected through seven revaccination studies were included in RCT-EXT pooling (Table 1).

Compared to the TIV group, higher percentages of solicited AEs (40.2% vs 31.8%), solicited local AEs (23.2% vs 12.1%), and solicited systemic AEs (13.8% vs 12.1%) were reported in the aTIV group after vaccination 1 (ISS table 28). The most apparent differences were in tenderness (56.4% in aTIV vs 25.7% in TIV) and injection site pain (19.5% in aTIV vs 7.3% in TIV) (ISS table 38).

Subsequent to vaccination 2, “solicited local AEs were reported for 31.7% of aTIV subjects and 23.3% of TIV subjects, with tenderness (28.2% aTIV and 11.4% TIV) and injection site pain (27.2% and 20.9%) the only AEs reported for $\geq 10\%$ of aTIV-vaccinated subjects for whom assessment of a(n) AE was planned” (ISS table 38). Solicited AEs were reported in 48.8% of the aTIV individuals and 45.8% of the TIV individuals. “(S)olicited systemic AE were reported for 17.3% of aTIV subjects and 14.2% of TIV subjects, with malaise (9.1% aTIV and 7.5% TIV) and headache (8.8% and 5.1%) reported for $\geq 5\%$ of aTIV-vaccinated subjects” (ISS table 38). TEAEs were reported less frequently in the aTIV group (32.3%) than in the TIV group (41.2%).

After vaccination 3 (n=150 aTIV and n=87 TIV), solicited local AEs were reported in a higher percentage of subjects in the aTIV subjects (29.3%) than in the TIV individuals (16.1%), “with injection site pain (28.0% aTIV and 16.1% TIV) the only AE reported for $\geq 10\%$ of aTIV-vaccinated subjects” (ISS table 38). “(S)olicited systemic AEs were reported for 12.0% of aTIV subjects and 8.0% of TIV subjects, with malaise (6.7% aTIV and 3.4% TIV) reported for $\geq 5\%$ of

aTIV-vaccinated subjects” (ISS table 38). “SAEs were reported infrequently after vaccination 3 and percentages were similar between vaccine groups” (ISS table 28).

The sponsor considers results of the RCT-EXT pooling may be affected by selection bias since “(o)nly subjects from the parent studies who chose to participate in an extension study were included. “If a subject withdrew due to an AE in the parent study and did not participate in the extension study, this subject was not included in the RCT-EXT Pooling”. Meanwhile, the small number of subjects after vaccination 3 limited scientifically meaningful inferences on safety conclusion from RCT-EXT pooling.

(C1.2.1.5) First Dose Citrate RCT (CIT-RCT) Pooling

The safety of the citrate-buffered formulation of aTIV was evaluated through the CIT-RCT pooling, using data from 8919 elderly individuals collected through studies between 1996 and 2011 (Table 1).

Similar to the FD-RCT and FDE poolings, “a higher percentage of subjects with solicited AEs (50.1% aTIV and 37.0% TIV) was observed in the aTIV group compared with the TIV group in the CIT-RCT Pooling, with a larger difference between vaccine groups observed for solicited local AEs (35.6% and 19.4%)”, mainly attributing to injection site pain (28.6% in aTIV vs 14.4% in TIV) and tenderness (21.8% in aTIV vs 12.1% in TIV). More solicited systemic AEs were also reported in aTIV group than in TIV group (30.3% and 24.3%). The most frequent solicited systemic AE was myalgia (14.0% vs 9.0%), followed by fatigue (13.4% vs 10.5%), and headache (12.5% vs 10.7%). “(T)he percentages of subjects in both vaccine groups who experienced solicited AEs, TEAEs, SAEs, AESIs, and AEs leading to withdrawal, hospitalization, or death were within 3% of the values observed in the FD-RCT Pooling” (ISS table 27).

(C1.2.1.6) Uncontrolled Studies (UNCON) Pooling

In order to evaluate the safety and immunogenicity of each influenza season’s aTIV formulation, data from 1005 aTIV-vaccinated elderly subjects from 17 small, open-label studies conducted outside the US between 1997 and 2013 were include in the UNCON pooling analysis (Table 1). Only SAEs, death, and AESIs were investigated in the UNCON pooling for ISS. “The SAE follow-up period for studies in the UNCON Pooling was shorter than for most of the RCTs.”

According to the sponsor, “(n)o SAE was considered related to study vaccine.” There was one report of AE leading to death and one serious AESI in the aTIV group (ISS Tables 30, 14.4.3.11.2).

(C1.2.1.7) Study V7P35 (V7P35) Pooling

Study V7P35 was a single-blinded post-marketing study conducted in Italy from 1997/1998 following the licensure of Flud[®] and compared aTIV^{thio-w} to Influvac (TIV) among

13761 elderly subjects⁹ (Table 1). Study participants were randomized to aTIV or TIV vaccine on a 2:1 ratio. After vaccination, each individual was followed through telephone “on day 7 to collect only AEs that had resulted in a physician visit” and every 30 days from day 30 to day 180 for SAEs. In the ISS V7P35 pooling (Table 1), data from study V7P35 were summarized separately per the request from the US Food and Drug Administration (FDA) because study V7P35 is a phase 4 study and the differences in safety data collection between study V7P35 and other pooled studies.

“Only SAEs, AEs leading to hospitalization or death, AESIs, and AEFIs in study V7P35 were summarized in V7P35 pooling.”

No clinically meaningful difference was identified for SAEs (8.2% aTIV vs 8.5% TIV), AEs leading to hospitalization (7.7% aTIV vs 8.2% TIV) or death (1.3% aTIV vs 1.0% TIV), AESIs (0.2% aTIV vs 0.3% TIV), or AEFIs (0.2% aTIV vs 0.2% TIV) (ISS table 31).

(C1.2.1.8) Younger Adult (YA) Pooling

The YA pooling provided a supportive safety summary of aTIV^{thio-w} formulation as compared to various TIV vaccines among 1296 subjects 18 to 64 years of age from eight studies (Table 1). “No integrated analyses of solicited AEs were conducted for the YA Pooling”. Only SAEs, death, AESIs, and AEFIs following the first vaccination were evaluated as a supplement to the safety profile of aTIV. No clinically meaningful difference was identified for SAEs, death, AESIs, or AEFIs (ISS table 32).

Data from YA pooling indicated that the between-group difference on percentage of individuals with SAEs (0.5% aTIV and 0.7% TIV), death (0% in both groups), AESI (0.4 aTIV vs 0.5 TIV), and AEFIs (0.4% in both groups) was similar (ISS table 32) in aTIV group as compared to the TIV group.

According to the sponsor, “the safety profile of aTIV was consistent across the key data poolings. Solicited local AEs and solicited systemic AEs were reported in a higher percentage of aTIV subjects than TIV subjects in the FD-RCT, FDE, CIT-RCT, and RCT-EXT Poolings (after all 3 vaccinations), as well as in the pivotal phase 3 Study V70_27. Unsolicited treatment emergent AEs were similar in both the aTIV and TIV groups across the FD-RCT, FDE, and CIT-RCT Poolings and in Study V70_27. The percentage of subjects with SAEs was similar between vaccine groups across the FD-RCT, FDE, CIT-RCT, RCT-180, and V7P35 Poolings and in Study V70_27. Few SAEs were reported in the UNCON and YA Poolings. TEAEs leading to withdrawal and/or death were infrequent and similar between vaccine groups across the poolings.”

(C1.2.2) ISS-Unpooled studies

⁹ Among the 13761 subjects, 39 individuals were younger than 65 years at the time of enrollment. However, their data were also included in the V7P35 pooling.

The nine unpooled studies (ISS table 89) include information from 2172 subjects vaccinated with aTIV and 348 subjects vaccinated with TIV. Among the nine studies, seven studies only enrolled subject between 18 to 64 years of age; “two studies enrolled younger and elderly subjects but categorized younger adults as 18 to 60 years of age and elderly as >60 years of age.” “The safety data from these studies were not pooled for one or more of the following reasons:

- aTIV was administered more than once in a primary series
- aTIV served as control vaccine for evaluation of an MF59 adjuvant containing pandemic influenza vaccine based on A/H5N1 strain (aH5N1 vaccine)
- aTIV was evaluated in younger adults with underlying chronic disease
- Study data were unavailable in electronic format”.

Data from the unpooled studies provided supplement safety information on deaths, SAEs, AESI, AEs leading to study withdrawal, and hospitalizations following aTIV vaccination.

Among the 59 cases (n=46 aTIV and n=13 TIV) reported with SAE, none of the elderly cases were assessed as vaccine related. Two younger cases in study V87P13 (one dystonia, and one bronchial hyperreactivity and pneumonia) were considered vaccine related. AEs leading to withdrawal were reported in studies V87P4 (n=4 aTIV) and V87P13 (n=4 aTIV) only. In both studies, the reports were in younger adults. No elderly participants reported an AE leading to withdrawal in all the nine unpooled studies. In study V87P4, there were two deaths in aTIV or TIV groups after the primary vaccination and two deaths in the period from the fourth week to six months following the second vaccination (Study V87P4). None of them was considered vaccine related according to the sponsor. No death cases were reported in the other eight unpooled studies. A brief summary of the unpooled studies is presented in Table 2 of this OBE/DE review.

(C1.2.3) Significant Adverse Events – pooled and unpooled studies.

(C1.2.3.1) Adverse Events of Special Interest

According to the sponsor, all AESIs in this BLA were identified and analyzed retrospectively because the AESIs were not prospectively defined or collected in any of the aTIV studies. In both the pooled and unpooled studies, the total numbers of elderly subjects exposed to aTIV and TIV were about 17000 and 10000, respectively. Among the younger subjects, 3003 were exposed to aTIV and 1000 were exposed to TIV. There were 73 AESIs identified in the aTIV group and 61 in the TIV group. “The most frequently reported AESI in elderly subjects was arthritis (n=18 aTIV and n=15 TIV), followed by rheumatoid arthritis (8 aTIV and 4 TIV) and hypothyroidism (6 aTIV and 11 TIV).” “Based on the verbatim terms, medical history, and/or baseline medications, some of these events appear to be pre-existing diseases.”

According to the FD-RCT pooled analysis, “(t)he 95% CIs for all RR point estimates for individual PTs and SOC crossed 1, indicating no increased risk for either vaccine group. The most frequently reported AESIs in the aTIV group were arthritis (n=15 and n=13; RR: 1.02 [95% CI: 0.49, 2.16]), rheumatoid arthritis (n=7 and n=3; RR: 2.25 [95% CI: 0.58, 8.73]), and hypothyroidism (n=4 and n=9; RR: 0.44 [95% CI: 0.13, 1.42]).” “(T)he percentage of subjects

reporting AESIs was comparable in the aTIV and TIV vaccine groups (0.9% both groups, n=52 aTIV and n=45 TIV; RR: 1.04 [95% CI: 0.70, 1.55])” (ISS Table 59). “(A) higher percentage of subjects in the aTIV group had onset of any AESI within 30 days of vaccination, as compared to the TIV group (n=23, 0.4% aTIV and n=10, 0.2% TIV)”. For AESIs occurred within 28 days following vaccination, “most events began between day 15 and 28 days postvaccination and were more frequently reported in the aTIV group as compared to the TIV group (n=10, 0.2% aTIV and n=5, 0.1% TIV)”, primarily attributing to musculoskeletal and connective tissue disorders. However, the results did not reveal clinically meaningful differences since none of the differences for other AEs were more than 5%.

The rest of AESIs in elderly not included in FD-RCT pooling were assessed by the investigator as not related to study vaccine. “The number of younger adults reporting AESIs by individual SOC or PT was comparable between vaccine groups, with the exception of enteritis, which occurred in fewer subjects in the aTIV group (n=1 aTIV and n=6 TIV).”

(C1.2.3.1) Adverse Events Following Immunization

The AEFI analysis, focusing on “hypersensitivity-type events (Anaphylactic Reaction and Angioedema) and seizures (Febrile Convulsion and Generalised Convulsive Seizures Following Immunisation), was also retrospective and it was a supplement for the AESI analysis.

The ISS AEFI analysis did not reveal new safety concerns.

(C1.2.4) Safety of Adjuvant

In order to address the safety concern regarding the adjuvant, “conditions associated with neurological and neuro-inflammatory disorders, musculoskeletal disorders, gastrointestinal inflammatory disorders, rheumatologic conditions, metabolic disorders, vasculitides, connective tissue disorders, autoimmune-mediated conditions, severe immediate allergic reactions, toxic skin reactions, narcolepsy, arthritis, rheumatologic diseases, and polymyalgia rheumatica were analyzed by searching the NVD Vaccine Safety database. Reporting proportion of these events among all AEs following aTIV was compared to that of the nonadjuvanted TIV through proportional reporting ratio method. According to the sponsor, “(a) signal of disproportionate reporting is considered detected if all the following conditions are met: a) PRR >2; b) Chi-squared, applying Yates correction >4; c) the number of individual cases safety reports (ICSRs) in each group >2.”

The results (ISS table 74) indicated “there was no quantitative evidence of disproportionality of AESIs/AEFIs in patients vaccinated with aTIV compared to those vaccinated with TIV. This suggests a similar risk profile for these events in patients who have received TIV, irrespective of MF59 adjuvant status. Thus, although aTIV has a substantially higher cumulative reporting rate relative to TIV, the data support that the excess was not attributable to a disproportionate number of reports of AESIs/AEFIs.”

Sponsor’s Summary of Clinical safety

“Overall, the safety profile of aTIV was consistent across the key data poolings. The primary difference noted in the aTIV safety profile as compared with TIV was in 2 local solicited events, pain and tenderness at the injection site.” “Unsolicited treatment-emergent AEs were similar in both the aTIV and TIV groups across the FD-RCT, FDE, and CIT-RCT Poolings and in Study V70_27. The percentage of subjects with SAEs was similar between vaccine groups across the FD-RCT, FDE, CIT-RCT, RCT-180, and V7P35 Poolings and in Study V70_27. Few SAEs were reported in the UNCON and YA Poolings. TEAEs leading to withdrawal and/or death were infrequent and similar between vaccine groups across the poolings.” In summary, “across all poolings and the pivotal phase 3 Study V70_27, aTIV was associated with a higher percentage of local and systemic AEs than TIV, particularly mild injection site pain and tenderness.”

“In summary, the safety of aTIV has been evaluated in 16 736 elderly subjects ≥ 65 years of age in an integrated safety analysis. Across a variety of poolings and subgroups, the data demonstrate that aTIV is safe and well tolerated in older adults, and that inclusion of the MF59 adjuvant in the formulation has minimal impact on safety beyond the known and anticipated risks associated generally with influenza vaccines in adults.”

(C.2) Safety concerns

No important safety issues were identified in the pivotal studies, the ISS report, and the PSUR 35 for Flud[®]. The “aTIV was associated with a higher percentage of local and systemic AEs than TIV, particularly mild injection site pain and tenderness”. Per the Sponsor, there was no evidence for “identified” or “potential” risks associated with the use of Flud[®] vaccine according to the available data since the clinical development of Flud[®].

(C.3) Pharmacovigilance Plan (PVP)

In the current BLA submission, NVD provided Version 2.0 of its European Union (EU) Risk Management Plan (RMP) as the PVP for Flud[®]'s US BLA. Please note that PVP and RMP may be used interchangeably throughout this review memo.

According to NVD, all pharmacovigilance activities proposed in the PVP followed the guidance of European Medicines Agency (EMA) and have been updated if there are new recommendations available or safety outcomes of concern. The major changes of the current RMP as compared to the previous versions were described on page 11 (section: Changes from previous Risk Management Plan [RMP] version) and presented in Table 13-8 of the RMP. The major change is that “(t)he company intends to attempt to implement an active safety surveillance in the Lazio region in Italy during the NH 2014-15 season to allow prospective follow-up of vaccine recipients for adverse events following Flud vaccination.” The objectives of the PVP are to support risk management strategies and ensure compliance with regulatory reporting requirements.

The proposed PVP includes three components: 1) passive surveillance, 2) active surveillance in Canada, and 3) feasibility assessment of an active surveillance study in Italy.

PASSIVE SURVEILLANCE

Since the licensure of Fluvad[®] in 1991, the product and the indication seeking for approval have been continuously studied in non-clinical, clinical, and post-marketing studies for safety concerns. However, safety concerns regarding outcomes that are rare or with long latency or the cumulative effects of multiple vaccine administrations may not be meaningfully evaluated through clinical studies due to limited statistical power or follow up time for study participants. According to the RMP, the following safety concerns are routinely monitored through PSUR to further characterize important identified risks, to determine if Fluvad[®] is causally related to a case on the list of important potential risks, or to identify the cause of vaccination failure.

- a. Important identified risks
 - Anaphylactic Reactions
 - Extensive Limb Swelling (ELS)
- b. Important potential risks
 - Convulsion
 - Neuritis
 - Encephalitis
 - Vasculitis
 - GBS
 - Demyelination
 - Bell's palsy
 - ITP
 - Haemolytic anaemia
 - Vaccination failure
- c. Other safety concerns
 - Medication error
 - Off-label use

ACTIVE SURVEILLANCE

Canadian Active Surveillance

In line with the EMA Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU (EMA/PRAC/222346/2014), NVD proposed to use data from the Canadian annual active safety surveillance system, a part of the Public Health Agency/Canadian Institutes of Health Research Influenza Research Network (PCIRN), to provide a report on safety of Fluvad, using 2014/15 as the pilot season.

PCIRN is “an electronic surveillance of the occurrence of adverse events following influenza vaccination” in Canada. It “aims to rapidly gather safety data from thousands of vaccinated individuals in order to provide data to the Canadian public health authorities before the core weeks of the annual influenza immunization campaign. The surveillance network has been in existence since 2009 and in 2012, the network was expanded to monitor the safety of influenza vaccine in children.”

In the PCIRN study, “adults of all ages and parents of children 6 months to 16 years are recruited by the PCIRN study staff in selected centres throughout Canada following routine vaccination with seasonal influenza vaccine.” “(O)ccurrence of any new health problem or the exacerbation of an existing condition that is severe enough to cause work or school absenteeism/prevent daily activities, or to require medical consultation” are collected through an electronic survey sent 8 days after vaccination. Patients or guardians with selected severe events including “vomiting and nausea, fever, persistent crying, rash, injection site reactions (e.g. pain, erythema, swelling) and events indicative of allergic and hypersensitivity reactions” are then contacted by telephone for more information. “The frequency of health events in vaccinated adults and children is then compared to the frequency of health events in an unimmunized group of adults and children just before the vaccination campaign (control group)” to evaluate the safety of aTIV.

Information from the previous seasons indicated that the overall response rate was approximately 70% for the PCIRN active surveillance. The demographics of the non-responders and the responders were compatible.

NVD proposed to work with PCIRN to have a report specifically for Flud[®] in line with the EU interim guideline. The following information is expected in the report

- Aggregated data of the events reported by the Flud[®] vaccine recipients in the online survey
- An aggregate of events reported by the control group
- A summary of events by age group
- A summary of the severe events that were followed-up

According to the RMP, NVD originally expects in the age group of above 65 years of age approximately 150 to 200 participants will be exposed to Flud[®] in the PCIRN during each season including the 2014/2015 season if there is 1) a similar survey participation; 2) about 25% of the total enrolled influenza vaccine exposed participants in the study; 3) 5% exposed to Flud, and that 4) Flud is only provided to subjects 65 years and older. However, information from the final report of the PCIRN 2014 seasonal influenza safety surveillance (STN125510/014, amendment, attachment 5) indicated “Flud was only given at 2 of our sites this year and the number who received it (n=51) and who completed the day 8 survey was very small (n=36) thus limiting the ability to detect signals in our sample.”

Italian Active Surveillance --- feasibility assessment

NVD proposed to consider a prospective active surveillance study in Italy that follow the similar principle of the PCIRN active surveillance, following the protocol of the SVEVAPLUS project, an Italian national project “aimed at the assessment of safety and efficacy in the field of influenza vaccines, whose protocol was written according to the new procedures for the execution of an active surveillance of adverse events following vaccination (*Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*, EMA/PRAC/222346/2014), adopted by the European Medicines Agency (EMA).” NVD is currently working with the regional public health agency for contract and ethical approval. The timeline for the Italian active surveillance is currently not available.

During the 2014/15 season, individuals were recruited between mid-October and the end of December by ASL (*Local Health Authority**) Roma A (ASL RM/A), one of the five health authorities in Rome and one of the 12 in the Lazio Region. “Subjects aged 65 years and older, who spontaneously attended the influenza center of ASL RM/A in Via Dina Galli for vaccination against influenza with the MF59-adjuvanted flu vaccine (Fluad) were eligible for enrollment.”

The study did not reveal safety signal. However, the results in the 2014/15 report were based on 95 elderly subjects enrolled.

OBE/DE Comments:

Both active surveillance studies for the safety of Fluad[®] are proposed by the NVD based on the EMA Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU (EMA/PRAC/222346/2014). Based on the information provided in the RMP received on November 25, 2014 (STN125510/0.0), and the Information received on June 25, 2015 (STN125510/0.14), OBE/DE reviewer has concerns that the sample size based on the current information may not be sufficiently large to identify safety concerns, especially for rare events.

An information request has been sent to NVD on August 7, 2015 regarding if NVD has alternative plans to detect potential signals if the ability of PCIRN or the Italian study for signal detection is limited by the number of vaccinees captured by the system. If NVD has plans, NVD is requested by the FDA to submit the requested information as an amendment to the BLA as soon as possible. NVD is recommended by the FDA to restate the comment and provide response in the same amendment.

D. Other safety related information from the submission

Clinical review memo

According to the clinical reviewer’s presentation/report during the mid-cycle meeting and the FDA briefing document for the Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC, scheduled for September 15, 2015) regarding Fluad[®], based on the data from study V70_27, “Fluad was associated with increased solicited local and systemic reactogenicity compared to Agriflu within the 7 day post-vaccination period (43% versus 33%, respectively), but rates of severe AEs were balanced across groups for both solicited local and systemic reactions and comprised $\leq 1\%$ of subjects across all categories. The percentage of unsolicited adverse events (AEs) through Day 21 postvaccination was 16% in both groups; 4% in Fluad versus 5% in Agriflu were considered by the investigator to be related. Four serious adverse events (SAEs) were assessed to be possibly or probably related to the study vaccination: 1 SAE (bronchitis, presented day 8) in the Fluad group and 3 SAEs (asthmatic crisis [presented day 13], chronic obstructive pulmonary disease [presented day 63], and Guillian-Barré syndrome [presented day 227]) in the Agriflu group. There were no deaths within 21 days of vaccine administration. Deaths occurring during the 1 year study duration were reported in similar proportions in both the Fluad and Agriflu groups: 1.5% and 1.3%, respectively. One

death was considered related to the study vaccination, a death attributed to Guillain-Barre Syndrome in a subject who received Agriflu.”

Additional data from 49 studies, conducted in adults ≥ 65 years of age between 1992 and 2013 (N=27,787) were submitted to provide evaluation on 4 different formulations of a MF59 adjuvanted product. The clinical reviewer considers information from these studies is supportive to enrich safety data, due to the small sample size and high variation in design (e.g., uncontrolled, open-label, non-randomized, and/or using comparators that were not licensed in the US). “Review of pooled safety analyses from these studies showed a similar safety profile to that observed in the above referenced pivotal trial V70_27 and did not reveal safety concerns.”

The OBE/DE reviewer agrees with the clinical reviewer’s safety assessment that the information provided did not reveal safety concerns.

Statistical review memo

As of August 14, 2015, the clinical statistics review memo is not available. According to the mid-cycle meeting report, information regarding statistical issues for safety evaluation is under review.

E. Postlicensure Safety Review

The postlicensure safety of NVD’s Flud[®] was investigated through a periodic safety update report (PSUR 35), covering the period between September 1 2013 and April 30, 2014, two non-NVD sponsored observational studies in Italy (study C70P1, a prospective cohort study, Villa M et al, 2013, Mannino S et al 2012) and Canada (study V70_49OBTP, a community based test-negative case-control study, Van Buynder PG et al, 2013), and an information amendment (STN 125510/0.14, Attachments 1 through 4) describing the temporary suspensions of Flud in Europe and Canada during the 2012/13 and 2014/15 influenza seasons.

(E1.1) Periodic Safety Update Report (PSUR 35)

Flud[®] was first licensed in Italy on May 15, 1997. It is currently licensed in 38 countries in Europe, South America, Asia, and Canada. The product was approved for the immunization of elderly individuals at 65 years of age or older against influenza virus infection in most of the countries, except in the Philippines for 60 years and older and in South Africa for 12 years and older (dormant though). Since the international birth date of Flud[®], there were a total of 35 PSURs, submitted approximately semi-annually, covering the period between May 15, 1997 and April 30, 2014.

PSUR 35 is the 35th PSUR of Flud[®], covering the period between September 1, 2013 and April 30, 2014. It was “compiled for regulatory authorities in the Periodic Benefit-Risk Evaluation Report (PBRER) format detailed in the International Conference on Harmonization E2C (ICH-E2C[R2]) guideline and the EU Good Pharmacovigilance Practice (GVP) guideline”. In this PSUR, safety information regarding 1) identified risks on anaphylaxis and extensive limb

swelling, 2) potential risks on neuritis, convulsions, encephalitis, vasculitis, GBS, demyelination disorder, Bell's palsy, ITP, hemolytic anemia, vaccination failure, and 3) other safety concerns including potential for medication errors and potential for off-label use were summarized. In addition to case reports, the worldwide safety data of Fludac[®] received by NVD and processed by Drug Safety and Epidemiology (DS&E) of Novartis Pharma during the 2013/14 influenza season were compared to the data from the previous three seasons combined (2010-11, 2011-12 & 2012-13), using proportional reporting ratio (PRR) for disproportionate reporting signal detection on adverse events of special interest.

By the end of April, 2014, the cumulative total number of subjects received Fludac[®] worldwide was estimated to be 7 747 740 (b) (4) doses of Fludac[®] were sold). Among them, 28 361 subject with Fludac[®] administration were from clinical trials and 17 708 subjects were 65 years or older. During the interval between September 1, 2013 and April 30, 2014 (i.e., period covered by PSUR 35), approximately 6 550 376 subjects were Fludac[®] vaccinated (based on one dose regimen). Among the 1991 reports received from both interventional and non-interventional solicited sources during the same period, 85 were Fludac[®]-confirmed spontaneous/literature reports, yielding a reporting rate of 1.29 per 100 000 subjects vaccinated for Fludac[®]-confirmed spontaneous/literature cases. Compared to the Fludac[®]-confirmed spontaneous/literature reporting rate during the period covered by PSUR 33 (September 1, 2012 to April 30, 2013), 3.43 per 100,000 subjects vaccinated, the reporting rate for Fludac[®]-confirmed spontaneous/literature cases in PSUR 35 decreased.

The numbers of reports received for each health outcome of interests are summarized in table 3 of this review.

According to PSUR 35, "A critical analysis of the efficacy and safety data revealed that the overall benefit-risk profile of Fludac[®] remains favorable" during the period covered by PSUR 35. For the safety concerns listed in table 16-1 of PSUR 35, information received for neuritis, convulsion, encephalitis, vasculitis, GBS, demyelination including neuromyelitis optica and multiple sclerosis, Bell's palsy, haemolytic disorders, immune thrombocytopenia, anaphylaxis, extensive limb swelling, vaccination failure, medication error, and off-label did not reveal any new safety concern during the period covered by PSUR 35.

(E1.2) Medical Literature: Observational Studies

(E1.2.1) Italian Study (Study C70P1, module 5, ISS section 7.3.1, Mannino et al 2012, Villa et al 2013)

"The Lombardia Influenza Vaccine Effectiveness (LIVE) study was an observational, noninterventional, prospective cohort study performed in the Italian local health authorities of Cremona, Mantova, Pavia, Lecco, and Bergamo during the 2006–2007, 2007–2008, and 2008–2009 influenza seasons to compare the effectiveness of the aTIV, Fludac[®], and a nonadjuvanted TIV, Agrippal". Information from the LIVE study also provided data to systematically assess the safety of the aTIV with respect to adverse events of special interest (AESIs) among elderly adults.

Included in the LIVE study were residents who 1) lived in the provinces of Cremona, Bergamo, Mantova, Lecco, and Pavia in the northern Italian region of Lombardy, 2) were aged 65 years and older, 3) sought influenza vaccination at local health authorities' district offices or participating general practitioners during each of the 2006/07, 2007/08, and 2008/09 influenza seasons, and 4) consented to participate the study. Excluded from the study were subjects who were 1) in the hospital, nursing homes, or rehabilitation centers in the 30 days preceding immunization, 2) receiving home care, 3) allergic to influenza vaccines, or 4) not able to confirm residency status by linkage with administrative databases.

Based on the lists of serious safety outcomes developed by the FDA, European Centre for Disease Control (ECDC), and the World Health Organization (WHO), the pre-specified safety outcomes of interest in this study were 1) incident Bell's palsy, encephalitis, vasculitis, GBS, acute transverse myelitis, demyelinating disease, optic neuritis, autoimmune hepatitis, immune thrombocytopenic purpura (ITP), in individuals who were not hospitalized for the same condition during the 3 months prior to the event identified; and 2) all events of anaphylaxis and convulsions. The biologically plausible window following vaccination was 0-2 days for anaphylaxis, 0-14 days for convulsion, 0-60 days for autoimmune hepatitis and Bell's palsy, and 0-42 days for the rest outcomes. Cases were identified using ICD-9 codes and chart validated by medical experts through pre-specified validation plan with pre-specified diagnosis criteria (Brighton Collaboration definitions or definitions developed by national specialty organizations if the Brighton Collaboration definitions were not available).

Information regarding basic demographics, smoking, conditions potentially affecting immune response, physical capabilities, household presence of children, and influenza vaccination in the previous year, was collected through a brief questionnaire before vaccinated with either aTIV or TIV based on the local, regional, and national influenza vaccination policy recommendations. Medical information was collected using record from databases on hospitalization, outpatient drug prescriptions, ambulance case, copayment of health-care costs.

During the 3 years between 2006 and 2009, there were 88 449 doses of aTIV and 82539 doses of TIV administered to 107 661 study participants. At baseline, subjects in the aTIV group appeared to be older (76.5 years in aTIV vs 74.9 years), with more functional limitation (48.4% vs 39.4% for daily activities and 50.1% vs 43.9% for climbing stairs), and more chronic disease conditions (Villa et al 2013, table 1). A total of 460 hospitalizations from 401 subjects were identified using the ICD-9 codes for potential AESIs during the 6-month window following vaccine, and among them, 58 hospitalizations from 56 individuals were in the predefined biologically plausible windows. After chart validation, there left 7 confirmed cases in the aTIV group (6 for convulsion and 1 for ITP) and 9 in the TIV group (4 for convulsion, 2 each for ITP and vasculitis, and 1 for Bell's palsy). Both the primary and secondary analysis found the risks of AESI were similar between the two groups. The study did not identify safety concerns regarding AESIs following aTIV.

(E1.2.2) Canadian Study (C70_49OBTP, Van Buynder PG, et al, 2013)

In order to investigate the effectiveness of aTIV and TIV, Van Buynder PG et al (2013) conducted a community based test negative case-control study in three health authorities located

in British Columbia, Canada during the 2011/12 influenza season. A total of 282 subjects who 1) were aged 65 years and older as of the influenza test date, 2) had influenza like symptoms (ILI), 3) were swabbed and tested for influenza within 7 days of commencement of ILI, and 4) had no immunodeficiency conditions, and 5) had complete medical information per study request, were enrolled into the study after patients' consent on participation.

A case was defined "if the respiratory sample was influenza positive" and a control was defined "if the test was negative and the diagnosis met a clinical case definition" of ILI. A participant was defined as vaccinated if he/she received influenza vaccination 14 days or more prior to the onset of symptoms. Otherwise, the participant was unvaccinated if the first dose of influenza vaccine was within 14 days before the symptom onset or if the person did not receive influenza vaccine.

Using telephone interview, participants' information on age, sex, hospitalization, residence in a long term care facility, immune-suppression, and coexisting medical conditions was documented. The diagnosis of ILI was confirmed through self-report or review of long term care records. Vaccine information regarding whether vaccinated, date and type of influenza vaccination was confirmed from the healthcare records.

The average age of the 282 study participants was 83.0 years with approximately half (n=132) of them aged 85 years and older. "The majority of participants were females (186, 66%), residents of long term care facilities (160, 57%), and reported at least one chronic disease (250, 89%). The most commonly reported chronic disease categories were cardiac (203, 72%) followed by neurological (110, 39%) and respiratory condition (85, 30%). One third of cases (30%) were hospitalized for their ILI symptoms." Among the 282 participants, 84 (30%) were confirmed as cases (12 for influenza B, 1 H1N1, and 71 H3N2). The number of subjects by vaccination status/type was 165, 62, and 55 for aTIV, TIV, and unvaccinated respectively.

According to the study investigator, aTIV "provided significantly improved protection against influenza in the elderly." (Van Buynder PG, et al, 2013)

This study focused on the effectiveness of aTIV among elderly population. The study design limited the information provided on aTIV safety. Since this study was conducted independent of the sponsor, there was no CSR provided.

(E1.3) Information Amendment (STN 125510/ 0.14, Attachments 1 through 4)

(E1.3.1) Temporary suspension/recall of Fluad/Agriflu/Agrippal in 2012

In October 2012, some batches of Fluad and Agriflu were temporarily suspended in Italy, France, Austria, Germany, Spain, Switzerland, and Canada due to clumping of protein aggregates observed in lot 126303 of Agrippal[®] (non-adjuvanted seasonal flu vaccine using the same manufacturing process as Fluad) produced in Italy. Because of this reason, two batches of Agrippal (126201A and 126102) were recalled in the United Kingdom on October 31, 2012. The EMA did not issue an investigation report. According to NVD's investigation report (Attachment 1), "(a)s the formation of protein aggregates is not unusual in the manufacture of biological

products, the identification of additional finished lots of Agrippal exhibiting visible protein aggregates should not be considered unexpected.” “The toxicological and clinical assessments conducted for this investigation identified no safety or efficacy concerns. No product technical complaints related to “protein aggregates” or “particles” have been reported for Agrippal and Fluad produced for the 2012/2013 season. Pharmacovigilance data for both the 2012/2013 season to date and the 2011/2012 season have been assessed and no safety signals identified.” Therefore, NVD concluded “we are confident that the Agrippal and Fluad lots manufactured as part of the 2012 / 2013 campaign are safe and effective and can continue to be made available worldwide, as licensed.” “(T)he incidence rate of visible protein aggregates in lot 126303 is anomalous and the batch remains on hold and will not be released.”

The suspensions were then lifted from the above-mentioned countries in October and November 2012.

(E1.3.2) Temporary suspension of Fluad in 2014

On November 27, 2014, Agenzia Italiana del Farmaco (AIFA) suspended the use of two Fluad lots (lots 143301 and 142701) as a precautionary measure due to serious adverse events and deaths observed in a short period of time.

According to the investigation of NVD with AIFA and the Pharmacovigilance Risk Assessment Committee, “the quality investigation of the batches confirmed that both batches met the established specifications and no relevant deviations were noted, and the assessment of the death cases received showed there was no evidence for a causal relationship between the reported fatal events and the administration of Fluad.”

Using different approaches¹⁰, NVD conducted observed/expected analyses to evaluate the relationship between Fluad and the serious adverse events including deaths observed as of December 10, 2014. The study revealed no evidence of an association between Fluad and death. Additional review on Agrippal did not identify evidence for unexpected increase of all-cause mortality following Agrippal. According to the overall quality review from NVD, the involved patches are compliant with internal procedures and with the Current Good Manufacturing Practice (cGMP) requirement.

Due to this temporary suspension of Fluad in Italy, the sponsor decided to hold all distribution of Fluad vaccine in Hong Kong as a precautionary measure, though the two affected batches of Fluad suspended by the AIFA were not exported to Hong Kong based on NVD. According to the health administration of Hong Kong, “(t)he Department of Health (DH) has not received any local adverse drug reaction reports related to Fluad vaccine.”

(E1.4) Medical literature on the safety of adjuvant

¹⁰ Four approaches were used for the outcome definition. 1) All cases within 24 hours following vaccination; 2) All cases within 7 days post vaccination, 3) All cases by cause of death, and 4) All cases of sudden cardiac death based on internal medical adjudication.

The OBE/DE reviewer conducted a Pubmed search for recent literatures concentrated on the safety of MF59. They are listed in Section B, items b, and g through p under medical literature.

Adjuvants have been used in the process of vaccine development and production to enhance the immunogenicity to a vaccine without introducing specific antigenic effect in itself. However, in addition to the beneficial role of adjuvants in vaccination, events including diseases with autoimmune nature following adjuvanted vaccine were occasionally reported in immunization practice (Israeli E., et al., 2009, Pellegrini M., et al., 2009, Montagnani S., et al., 2011, Tsai T., 2011, Shoenfeld Y. & Agmon-Levin N. 2011, Cerpa-Cruz S, et al., 2013, Tsai T., 2013, Colafrancesco S., et al., 2014, Hawkes D., et al., 2015). Although studies focused on the safety profile of MF59 as an adjuvant did not reveal evidence for an increased risk of autoimmune diseases following MF59 as compared to the background (Tsai T., 2011, Pellegrini M., et al., 2009, Tsai T., 2013), OBE/DE reviewer considers the safety of MF59 merits further investigation because of the biological plausibility (Israeli E., et al., 2009, Hawkes D., et al., 2015, Pellegrino P., et al., 2015) and the temporal relationship in the cases reported between the adjuvant and the potential AEs.

F. Integrated risk assessment

Except injection site pain and tenderness, no important safety issues were identified in the pivotal studies, the ISS reports, or the postmarketing studies. Subjects with clinically severe underlying medical conditions, and immunocompromised individuals were excluded from the pre-licensure clinical studies and the Italian observational study. Safety data among individuals with underlying medical conditions and immunocompromised was not systematically summarized in the PSURs. Therefore, safety profile on these populations is not available.

The OBE/DE reviewer agrees with the sponsor that the “the interpretation and medical assessment of these data is limited by (1) imprecise AE diagnoses based on verbatim terms, PTs, and other available data; (2) the existing background rate of many autoimmune/inflammatory diseases in the elderly population; and (3) few standardized definitions for clinically important AESIs” and AEFIs since both AESIs and AEFIs were defined and collected retrospectively. In addition, the AE definitions and follow up time varies across the 58 studies included in the ISS (ISS tables 6 and 7), making the safety outcomes cannot be assessed consistently and the inference of data complicated. Since the primary focus of the ISS is on the safety of aTIV in individuals vaccinated with the first dose of aTIV, information on aTIV safety following the second and third dose was limited to make meaningful scientific inference due to small size of sample, selection bias, and, restricted comparability due to potential confounders that were not considered in the randomization conducted at the first dose of aTIV administration. The safety profile of aTIV following the second and third dose of aTIV needs to be further studied.

No evidence for safety concerns was identified during the two temporary suspensions based on NVDs investigations. The relationship between Flud and serious adverse reactions including death should be continuously monitored.

Literature information concentrating on the relationship between adjuvants and potential AEs is controversial. Though studies revealed no evidence for an increased risk of AEs following MF59, the OBE/DE reviewer considers further investigation and continuous monitoring of AEs especially diseases with autoimmune nature are needed because of the biological plausibility and the temporal relationship between adjuvants and the potential AEs.

Regarding active surveillance, NVD proposed two active surveillance studies using surveillance systems in Canada and Italy, respectively. Based on the current data, the ability of those systems to capture sufficient vaccinated individuals to identify potential safety signals, especially for rare events, is highly concerned. Pending NVD's response to OBE/DE's Information Request dated 7 Aug 2015, alternative active surveillance approaches might be proposed by NVD.

G. Recommendations

OBE/DE agrees with the RMP/PVP (version 2.0, Section C.3) and pharmacovigilance actions (Appendix II) proposed by the Sponsor.

Per NVD, the RMP/PVP will be implemented globally by NVD. NVD will work with the local regulatory authorities/agencies, including EMA's CHMP, FDA, and CDC, to monitor, analyze, and report available pharmacovigilance data.

The following actions are recommended by the OBE/DE reviewers for post-licensure safety surveillance activities.

1. Routine passive surveillance in accordance with 21 CFR 600.80
In order to support risk management strategies and to ensure compliance with regulatory reporting requirements, routine (standard) pharmacovigilance activities shall be performed for the Flud[®].
2. Expedited reports to the Vaccine Adverse Event Reporting System (VAERS) for the following conditions as previously communicated (Guillain-Barré Syndrome, ITP, Neuritis, Encephalomyelitis, Vasculitis, Demyelination, Bell's palsy) as described in 21 CFR§600.80.(c).(1).(i).
3. Active surveillance
In the PVP, NVD proposed to conduct prospective active surveillance in Canada and Italy using national/local surveillance systems. However, based on the current data, the OBE/DE reviewer has concerns that the proposed systems may not have the ability to capture a sufficiently large vaccinated population to identify potential safety signals, especially for rare events. Pending NVD's response to FDA Information Request dated August 7, 2015, alternative approaches might be proposed.

References

1. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. MMWR Morb Mortal Wkly Rep 2010; 59(33): 1057-62
2. Interim adjusted estimates of seasonal influenza vaccine effectiveness - United States, February 2013. MMWR Morb Mortal Wkly Rep 2013; 62(7): 119-23
3. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices--United States, 2013-2014. MMWR Recomm Rep 2013; 62(RR-07): 1-43
4. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine 2007; 25(27): 5086-96
5. World Health Organization. Influenza (Seasonal), Fact sheet N211. 2014.

Table 1: Overview of ISS Poolings

Study type	Study label (Abbreviation)	Pooling Number	# Clinical studies included	Age of study subjects	# Subjects by type of vaccine (subtype)			Proportion from study V70_27 (table 12 of ISS)
					aTIV (water buffered %, current formulation %, other citrate-buffered %)	TIV	Total	
Pooled Studies	First Dose Elderly (FDE)	1	36	>=65 years	7532 (1412, 4557, 1563)	5198	12730	56%
	First Dose RCT (FD-RCT)	2	15	>=65 years	5754 (1210, 3592, 952)	5198	10952	53%
	First Dose RCT with >=180 days follow up (RCT-180)	3	10	>=65 years	4758 (786, 3545, 427)	4690	9448	75%
	RCT-Extension (RCT-EXT)	4	7	>=65 years	492 (405, 0, 87)	330	822	0%
	First Dose Citrate RCT (CIT-RCT)	5	7	>=65 years	4544 (0, 3592, 952)	4375	8919	79%
	Uncontrolled Studies (UNCON)	6	17	>=65 years	1005(109, 667, 229)	0	1005	0%
	Study V7P35 (V7P35)	7	1	>=65 years*	9204 (9204, 0, 0)	4557	13761	0%
	Younger Adults (YA)	8	8	<65 years	744 (570, 0, 174)	552	1296	0%

* 39 subjects were younger than 65 years.

Table 2. Overview of Unpooled Studies

Study label	Age of subject	Health condition of subjects	Reasons for not included in the pooling	Vaccination	# subjects		SAEs		AE Leading to hospitalization*	AE leading to withdrawal
					aTIV	TIV	aTIV	TIV	aTIV	aTIV
V7P39	18-64	chronic disease	major confounder due to comorbidities	1st	58	55	1	2	1	0
V70P3	18-64	chronic disease	major confounder due to comorbidities	1st	180	179	2	2	2	0
V70P4	18-64	chronic disease	major confounder due to comorbidities	1st	52	0	0	0	N/A	0
V7P1	18-65	healthy	major confounder due to comorbidities	1st	24	6	0	0	N/A	0
V7P18 X1	18-65	healthy	revaccination	2nd	104	96	3	3	3	0
V87P4	≥18	healthy	pandemic regimen, comparator vaccine also contained MF59 adjuvant	2nd	971	0	27	N/A	N/A	4
V87P13	≥18	healthy	pandemic regimen, comparator vaccine also contained MF59 adjuvant	3rd	735	0	15	N/A	N/A	4
V95P1	18-40	healthy	phase I study, aTIV was administered only in small control groups (N=12)	1st	12	12	0	0	N/A	0
V104P1	18-40	healthy	phase I study, aTIV was administered only in small control groups (N=36)	1st	36	0	0	0	N/A	0

*All SAEs in aTIV group from these studies were hospitalized.

Table 3. Overview of Health Outcomes of Interest described in PSURs

Health outcomes of Interest	PSUR 35 (period between September 1, 2013 and April 30, 2014)				All time from May 15, 1997 to April 30, 2014				Reporting rate of spontaneous and literature cases per 100, 000 vaccinated	New signal
	Number of spontaneous* reports (INN)		Reporting rate of Flud [®] -confirmed cases per 100,000 subjects vaccinated		Total number of reports (INN)					
	Total	Flud [®] - confirmed	PSUR 35	Reference period **	All	Literature	Spontaneous	Clinical/PMS		
Neuritis	7 (7)	0	0	0	29 (19)	3 (3)	26 (16)	0	0.013	No
Convulsions***	42 (40)	2	0.03	0	115 (73)	9 (9)	75 (64)	31(0)	0.015	No
Encephalitis	16 (15)	1	0.02	0.04	50 (41)	25 (25)	25 (16)	0	0.012	No
Vasculitis	10 (10)	0	N/A	N/A	97 (79)	44 (43)	47 (36)	6 (0)	0.016	No
GBS	52 (51)	1	0.02	0.15	173 (133)	37 (37)	136 (96)	0	0.053	No
Demyelination disorder****	71 (70)	1	0.02	0.15	237 (189)	67 (66)	169 (122)	1 (1)	0.063	No
Bell's palsy	16(16)	0	N/A	N/A	56 (44)	12 (12)	42 (32)	2 (0)	0.013	No
ITP	9 (8)	1	0.02	0.07	62 (47)	7 (7)	54 (40)	1 (0)	0.018	No
Haemolytic disorders	3 (3)	0	N/A	N/A	12 (5)	5 (3)	6 (2)	1 (0)	0.008	No
Vaccination failure	17 (17)	0	N/A	N/A	128 (87)	50 (50)	67 (36)	11 (1)	0.041	No
Anaphylaxis	79 (78)	1	0.02	0.04	217 (144)	6 (6)	169 (135)	42 (3)	0.045	No
Extensive Limb Swelling	229 (228)	1	0.02	0.34	504 (346)	11 (11)	493 (334)	3 (1)	0.21	No
Potentials for medication errors	49 (44)	5	0.08	0.34	240 (144)	25 (24)	212 (120)	3 (0)	0.125	No
Potential off-label use	44		0.24	0.467	537				0.467	No

* “spontaneous” for the period between September 1, 2013 and April 30, 2014 includes spontaneous report and literature cases

**Reference period=PSUR 33 or previous 8-month review period

***Background incidence is 29-29 per 100,000 per year for convulsions.

****The same individual as the GBS case

PMS= post-marketing surveillance, INN=International Non-proprietary Name