

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

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From: Maria Said, MD, MHS
FDA/CBER/OBE/DE/AEB

To: Brenda Baldwin, PhD
FDA/CBER/OVRR/DVRPA/CMC3

Through: Deepa Arya, MD, MPH
FDA/CBER/OBE/DE/AEB

David Martin, MD, MPH
FDA/CBER/OBE/DE

Subject: Addendum to Pharmacovigilance Review Memorandum
(Yandong Qiang)

Applicant: Novartis Vaccines and Diagnostics, Inc.

Product: Influenza vaccine, surface antigen, inactivated, adjuvanted
with MF559.C.1 (Fluad®)

Proposed Indication: Active immunization of person 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

First Action Due Date: November 25, 2015

1. Introduction:

This memo serves as an addendum to the Office of Biostatistics and Epidemiology Pharmacovigilance Review Memorandum by Yandong Qiang, and contains updated information related to the BLA STN 125510 submission by Novartis Vaccines and Diagnostics, Inc (NVD) for Flud® (hereafter referred to as Flud or as aTIV, adjuvanted trivalent influenza vaccine). Since the date of the original memo, the following additional information is being considered:

- Reports of Postmarketing Experiences: Analysis of Flud Post-marketing Safety Data among Elderly Subjects (01 May 1997 – 29 April 2014)
- Periodic Safety Update Report (PSUR) 36, which provides information for the period May 1, 2014 to August 31, 2014
- PSUR 37, which provides information for the period September 1, 2014 to April 30, 2015
- NVD Risk Management Plan Version Number 3.0
- Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC), September 15, 2015

The purpose of this addendum is to provide additional information to identify potential safety issues that may need to be addressed through post-marketing safety surveillance or studies should the product be licensed.

2. Materials Reviewed

Materials reviewed in support of this assessment include:

- a. 0019, 8/24/2015, STN 125510
 - i. Module 5.3.6. Reports of Postmarketing Experiences: Analysis of Flud Post-marketing Safety Data among Elderly Subjects (01 May 1997 – 29 April 2014)
 - ii. Module 5.3.6 PSUR 36 (Reporting period 1 May 2014–31 August 2014)
 - iii. Module 5.3.6 PSUR 37 (Reporting Period 1 September 2014–30 April 2015)
- b. 0020 9/2/2015, STN 125510
 - i. Multiple Module Information Amendments – IR 21, 22, 24 (regarding FDA Information Request Dated 07 August 2015)
- c. 0021 9/10/2015 EU Risk Management Plan Version Number 3.0
- d. 0023 9/29/2015, STN 125510
 - i. Module 1.11.4 Multiple Module Information Amendment IR-27-IR-28 (Pharmacovigilance section)
- e. 0024 10/8/2015, STN 125510
 - i. Multiple Module Information Amendments – IR 27 IR 28 (Pharmacovigilance section)
- f. Transcript, 139th Meeting of the Vaccines and Related Biological Products Advisory Committee, September 15, 2015. Available at:
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm427602.htm>
- g. Pharmacovigilance Review Memorandum (Yandong Qiang)

3. Pharmacovigilance Plan Review

At the request of FDA, NVD submitted a new pharmacovigilance plan (EU Risk Management Plan (RMP) 3.0). The request was made to clarify the status of two active surveillance programs described in EU RMP 2.0: one using data from a Canadian annual active safety surveillance system, a part of the Public Health Agency/Canadian Institutes of Health Research Influenza Research Network (PCIRN), and the other following the protocol of the SVEVAPLUS project in the Lazio region of Italy. Both surveillance activities were being planned in accordance with the European Medicines Agency (EMA) “Interim Guidance on Enhanced Safety Surveillance for Seasonal Influenza Vaccines in the EU” (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165492.pdf) but had recruited very small numbers of participants during the 2014–2015 season.

EU RMP Version 3.0 no longer includes active surveillance occurring in Canada; while the surveillance will continue and is currently being funded for the period from 2014–2017, NVD does not have an agreement in place with PCIRN for the provision of a report of the 2015-2016 results. It also clarifies that the study in the Lazio region in Italy is “investigator initiated” and Novartis is not the sponsor for this activity.

For the 2015–2016 upcoming season, NVD plans to comply with the EMA guidance through enhanced passive safety surveillance rather than the two previously described active surveillance activities. The principle of the passive approach is to estimate, in a near-real time manner, the number of administered vaccines and to facilitate and estimate the number of spontaneously reported adverse events from the same population of vaccine recipients in a routine care setting. This surveillance activity aims to improve the capabilities to rapidly detect, evaluate and act on unexpected changes in reactogenicity or other adverse immune responses from one season to another. Vaccine exposure data will be obtained from the first 1000 recorded vaccinations at participating sites in Italy or from all vaccines administered by November 24 of the same season, whichever comes first. Vaccine recipients will be instructed to report adverse events occurring within 1 week of vaccination. They will be provided a call center number and a vaccination card with information on branch, batch number, and date of vaccine administration. Analysis will include reporting rates for adverse events based on the number of spontaneously reported adverse events per doses administered. Observed rates will be compared to expected rates, which will be defined prior to the start of surveillance. A final report will be made available.

4. Review of other safety information from the Managed Review process

- a. “Analysis of Fluad Post-marketing Safety Data among Elderly Subjects: 01 May 1997 – 29 April 2014”

A cumulative analysis of post-marketing adverse event data reported among elderly subjects (≥ 65 years of age) following vaccination with Fluad was conducted by NVD for the period of May 1, 1997 (the international birthdate) through April 29, 2014. Reports within the scope of the analysis were Fluad-confirmed spontaneous reports inclusive of those retrieved from the literature and those reported spontaneously from all sources. A total of 852 reports were included in the analysis, which consisted of a descriptive component and a comparative component. Of note, reports among elderly subjects comprised 60% of the total Fluad-confirmed spontaneous reports; many of the other reports pertained to medication error in which vaccine was given to adults < 65 years of age.

For the descriptive analysis, safety was evaluated in terms of demographics, the most frequently reported adverse events, reports with a fatal outcome, medication errors, adverse events of special interest (AESI), and select clinically important adverse events following immunization (AEFI). AESI refer to a set of clinical events or conditions of particular interest for adjuvanted vaccines, most commonly with a suspected immune-mediated mechanism. These include, but are not limited to neurological and neuro-inflammatory disorders, musculoskeletal disorders, gastrointestinal inflammatory disorders, rheumatologic conditions, metabolic disorders, vasculitides, connect tissue disorders, autoimmune-mediated conditions, severe immediate allergic reactions, and toxic skin reactions. AEFI refer to convulsions, febrile convulsions, anaphylaxis, and angioedema.

Over the 17-year period of review, most (30%) adverse event reports were received in 2008 and 2009, which was thought to be due in part to a relatively large number of non-serious reports from a single publication.

The most frequently reported non-serious adverse events were fever, injection site erythema and injection site swelling. Forty percent of cases contained at least one serious adverse event, most commonly dyspnea, followed by fever, and then Guillain- Barré syndrome (GBS). Five percent of spontaneous reports among the elderly were associated with a fatal outcome, with pulmonary edema (n=6) being the most commonly identified cause of death, when known. Among the 38 cases in which the onset latency between the date of vaccination and date of death was available, 19 described an onset latency of less than 7 days. The most common medication error was administration of the vaccine to subjects of inappropriate age (e.g., less than 65 years of age), with the majority of reports involving older adults between the ages of 55 years and 64 years. The most frequently reported AESI/AEFI were arthritis (0.08 per 100,000 doses sold), angioedema (0.07 per 100,000 doses sold), and demyelination (0.04 per 100,000 doses sold), the latter of which was largely reflective of reports of GBS.

In comparative analysis, there were 852 reported cases for Fluad and 318 cases reported for Agrippal, a non-adjuvanted conventional trivalent sub-unit inactivated influenza vaccine. Sales adjusted adverse event (AE) reporting rates were 1.13 cases/100,000 doses for Fluad and 0.20 cases/100,000 doses for Agrippal. The higher rate among the Fluad group was attributed to the differences in the populations for which the vaccines are indicated, as Fluad is specifically indicated for the elderly and Agrippal is indicated for persons 6 month of age and older. Rates of AESI and AEFI among spontaneous reports in the elderly were compared between the two vaccines; no AESI/AEFI met signal criteria according to the proportional reporting ratio methodology used, and there was no evidence of quantitative disproportionality of AESI/AEFI among elderly subjects vaccinated with Fluad compared to those vaccinated with Agrippal.

b. PSUR 36

In PSUR 36, reports for health outcomes of interests were reported and are summarized in Table 1. Additional updates include that:

- The Core Data Sheet (CDS) was amended during the PSUR period (July 30, 2014) to add a new statement regarding anxiety-related reactions under “Warning and precautions for use” and two new AEs (syncope and presyncope) have been added under “Adverse reactions from post-marketing spontaneous reports.”
- The Marketing Authorization Holder (MAH) agreed to include data regarding co-administration of Prevenar 13 and trivalent inactivated influenza vaccine (TIV) in the Fluad Summary of Product Characteristics. The proposed wording is: “a higher frequency of some solicited systemic reactions has been reported in subjects vaccinated with trivalent inactivated influenza vaccine and pneumococcal vaccine compared with trivalent inactivated influenza vaccine alone.”
- Three Third-Party/Investigator-initiated studies (i.e. not sponsored by Novartis) were completed and for which clinical study reports became available during the reporting interval.
 - V70_38TP: A phase II study to evaluate the immunogenicity, safety, and tolerability of a seasonal influenza vaccine including H1N1 in immunocompromised adults who had undergone solid organ transplantation or bone marrow transplantation and in age-matched healthy volunteers. Of 14 SAEs experienced, none was thought to have a causal relationship to the study vaccine.
 - V111_16TP: A study in which subjects with chronic pulmonary disease, chronic heart disease and/or diabetes mellitus (chronic diseases) and age-matched healthy adults received adjuvanted vs. unadjuvanted vaccine. Only 12 subjects in the study received Fluad; none of the SAEs in the study were experienced by a Fluad recipient. Eight Fluad recipients reports treatment-emergent AEs. The investigators concluded that vaccination with Fluad was safe and tolerable.
 - V70_48TP: Ambulatory adults 65 years of age and older were enrolled to evaluate immunogenicity of four different vaccines (Fluad, Intradermal Intanza, Agriflu, or Vaxigrip) to evaluate the rates of local adverse events. The investigators concluded that the study vaccines did not differ in observed rates of general adverse effects, although Fluad caused injection site pain (most instances were rated mild), and Intanza caused a high rate of local reactions with redness

and swelling that were slow to resolve. No Suspected Unexpected Serious Adverse Reactions (SUSARs) were experienced in recipients of Flud.

c. PSUR 37

In PSUR 37, reports for health outcomes of interests were reported and are summarized in Table 2. Additional updates include that

- Changes to the reference safety information: The Reference Safety Information (RSI) was amended during the PSUR period to update the list of adverse events (AEs) observed from clinical trials. The frequency was changed from “common” to “very common” for: headache, myalgia, tenderness, pain at injection site and fatigue. The System Organ Class (SOC) “Gastrointestinal disorders” was added and includes the following AEs: nausea, diarrhea, vomiting, with a frequency of “common”. A new AE (rash) was added with the frequency of “uncommon”. The “Adverse reactions from post marketing spontaneous reports” was re-ordered within a SOC in order of decreasing morbidity or mortality (seriousness).
- During the period covered by this report, there was a temporary precautionary suspension of the distribution of two batches of Flud mandated by Italian Medicines Agency (AIFA) on November 27, 2014 and by the Department of Health (DOH) in Hong Kong on November 28, 2014 after serious adverse events (SAEs) including death were reported in temporal association with the vaccination. On December 3, 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that there was no evidence that Flud caused the serious events. On December 4, 2014, the DOH in Hong Kong lifted the precautionary suspension. Following further testing of the batches performed by the Italian Health Institute, which confirmed the safety of the vaccine, on December 24, 2015, AIFA also lifted the precautionary suspension.
- Study V70_52TP, a single center, investigator-initiated Phase IV, open-label study to evaluate the immunogenicity, safety, and tolerability of Flud administered alone or concomitantly with 23-valent pneumococcal polysaccharide vaccine (PPV23) in 216 Korean subjects ≥ 65 years of age was completed. In general, Flud + PPV23 co-administration elicited solicited local and systemic AEs at higher frequencies than did administration of Flud alone. No vaccine-related SAEs were reported.
- Pooled analyses from 23 randomized clinical trials (RCT) became available during the reporting period. The 23 RCTS shared a number of features: generally, each study compared Flud with a non-adjuvanted, commercially released, trivalent inactivated influenza vaccine (TIV) with an identical antigen composition and dose level specification; and, the study populations encompassed a broad range of elderly subjects in terms of underlying health status, and included subjects living at home, those living in community-based retirement centers, those living in nursing homes.

Data for safety and tolerability of Flud in the elderly population comprised 14,958 elderly subjects who received a first dose of Flud in 16 RCTS. Thus, pooled safety data for Flud summarized pertain to those from (a) pooled data for all elderly subjects who participated in RCTs of all Flud formulations (FD-RCT pooling); and (b) pooled data for elderly subjects who received two or three vaccinations over several influenza seasons in the extension (revaccination) studies (RCT-EXT pooling).

- FD-RCT Pooled Analysis: The FD-RCT pooling included 5,754 and 5,198 elderly subjects who received Flud versus TIV, respectively. Flud was associated with more local and systemic solicited AEs than TIV. Within the seven-day post-vaccination period, a higher percentage of subjects in the Flud group than in the TIV group reported any solicited AEs (49.4% Flud vs 35.7% TIV). The percentage of subjects reporting solicited systemic AEs was also higher in the Flud group than in the TIV group (27.5% vs 22.4%, respectively); the most common events were fatigue (13.4% Flud vs 10.5%), myalgia (12.7% vs 7.9%), and headache (11.3% vs 9.8%). Within the seven day follow-up period for solicited AEs, the use of analgesics/antipyretics was higher in the Flud group compared with the TIV group (10.9% Flud and 8.1% TIV). The majority of local and systemic AEs were mild in severity. Severe local AEs were infrequent

(32/1,972=1.6% Flud and 17/949=1.8% TIV). The most frequent severe local AE in both groups was pain at the injection site (0.4% vs 0.2%). Severe systemic AEs were reported for 1.9% Flud vs 1.8% TIV subjects, with all individual systemic severe AEs reported for < 1% of subjects in either vaccine group.

The SAE analyses include data from 51 subjects (26 Flud and 25 TIV) for whom hospitalizations and deaths were reported. The most frequent SAEs (PTs) reported at any time post-vaccination were pneumonia (0.7% Flud vs 0.8% TIV), congestive cardiac failure (0.3% vs 0.5%), and myocardial infarction (0.2% vs 0.3%). The overall number and percentage of subjects with fatal events was similar between vaccine groups (n=78 Flud [1.4%] vs n=81 TIV [1.6%]).

- **RCT-EXT Pooled Analysis:** The RCT-EXT pooled analysis included 492 Flud and 330 TIV subjects who received vaccinations 1 and 2, and 150 Flud and 87 TIV subjects who received vaccination 3. Similar to the FD-RCT Pooling, solicited local AEs were reported in higher percentages of subjects in the Flud group than the TIV group following each of the three vaccinations over consecutive influenza seasons. Solicited systemic AEs were reported in a similar percent of subjects (within 4.0%) in the Flud and TIV groups following all three vaccinations. The percentage of subjects reporting severe local AEs following vaccination 2 (1.4% Flud and 0.3% TIV) was the same as the percentage reported after vaccination 1 for both vaccine groups and was mostly attributable to severe injection site pain (0.6% and 0.3%) or erythema (0.6% and 0.3%). Severe systemic AEs following vaccination 2 were reported for two Flud subjects (0.4%) with severe fever and one TIV subject (0.3%) with severe malaise and nausea. Following vaccination 3, the only severe local AE reported was one Flud subject (0.7%) with severe injection site pain. Severe systemic AEs were reported for two Flud subjects (1.3%), of which one had severe headache (0.7%) and one had severe fever (0.7%).

The percentage of subjects with SAEs after vaccination 2 was comparable between vaccine groups (9.6% Flud and 9.4% TIV) and was higher in both vaccine groups after vaccination 2 when compared with vaccination 1 (3.5% Flud and 2.7% TIV). All individual SAEs were reported in ≤5 subjects in either vaccine group after each vaccination. Few subjects in either vaccine group had SAEs following vaccination 3 (3.3% [n=5] and 4.6% [n=4]). The only serious event reported in >1 subject in either vaccine group in the RCT-EXT Pooling after vaccination 1 was cataract, occurring in four Flud vaccinated subjects (0.8%) and one TIV vaccinated subject (0.3%).

AEs resulting in death were reported only following vaccination 2. A higher percentage of subjects in the Flud group, compared with the TIV group, had AEs resulting in death (3.5% Flud (n=17) and 1.8% TIV (n=6); however, this difference was not statistically significant (RR: 1.68 [95% CI: 0.66, 4.26]). The difference noted between vaccine groups was primarily due to cardiac disease treatment-emergent adverse events (TEAE) commencing within 31 to 180 days following vaccination 2 (n = 14 [2.9%] Flud and n = 4 [1.2%] TIV). The most frequently reported SOC resulting in death following vaccination 2 was Cardiac disorders (2.6% Flud and 1.5% TIV), and the most frequently reported conditions that resulted in death included congestive cardiac failure (n = 5 [1.0%] Flud and n = 4 [1.2%] TIV), cardiac arrest (n = 3 [0.6%] Flud and n = 1 [0.3%] TIV), and cardiac failure (n = 3 [0.6%] Flud and 0 TIV).

- An evaluation of “AEs of Special Interest” (AESI) focused on rare but clinically important AEs of possible immune-mediated etiology. The evaluation of AESI was retrospective, since the events were neither prospectively defined nor collected in any of the Flud studies. The FD-RCT Pooling enabled relative risk estimates with 95% CIs to be calculated for the AESI events using a Poisson Regression Model including terms for duration of follow-up. The percentage of elderly subjects reporting AESIs was comparable in the Flud and TIV vaccine groups (0.9% both groups, n=52 Flud and n=45 TIV; RR: 1.04 [95% CI: 0.70, 1.55]). The most frequently reported AESIs in the Flud 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]). The percentage of subjects with AESIs graded as moderate or severe was also

comparable between groups (n=24 [0.5%] both groups) and most of these were events of arthritis or rheumatoid arthritis. Based on the verbatim terms, medical history, and/or baseline medications included in the database, many of these AESIs were likely to have been pre-existing conditions. A higher percentage of subjects in the Fluad group had onset of any AESI within 30 days of vaccination, as compared to the TIV group (n=23, 0.4% Fluad and n=10, 0.2% TIV), while the percentage of subjects reporting AESIs was similar between vaccine groups for the periods 31 to 180 days post-vaccination (n=20, 0.4% and n=23, 0.5%) and >180 days postvaccination (n=10, 0.2% and n=14, 0.3%). The events with an earlier onset (i.e., within 30 days post-vaccination) that occurred in more than one Fluad subject were arthritis, rheumatoid arthritis, myositis, and radiculitis.

- AEs Following Immunization (AEFIs): A second retrospective analysis of 4 clinically important AES following immunization (anaphylactic reaction, angioedema, febrile convulsion, and generalized convulsive seizures following immunization) was done. The cumulative total number of subjects across all pooled and un-pooled studies was approximately 17,000 elderly subjects in the Fluad group and approximately 10,000 elderly subjects in the TIV group. A total of 38 elderly Fluad and 24 elderly TIV subjects were identified across the pooled and un-pooled studies based on the four AEFI search terms. In the FD-RCT Pooling, AEFIs were reported by 0.3% of 5754 Fluad subjects and 0.2% of 5,198 TIV subjects.
- h. Death/sudden cardiovascular death in Italy: As discussed in Pharmacovigilance Review Memorandum Amendment (Yandong Qiang), an increase in the reporting of deaths from Italy resulted in the suspension of two Fluad lots. According to PSUR 37, these events were evaluated with six analyses and included both qualitative and quantitative analyses into all serious (fatal and non-fatal) and non-serious adverse events reported from September 1, 2014 to December 15, 2014. The final report concluded that the signal was not a risk, and the signal was closed. From December 15, 2014 until the end of the season, April 30, 2015, enhanced signaling activities were performed, and no new signals were identified.
- Hyperglycemia/new onset diabetes mellitus (DM): In December 2014, monthly disproportionality signaling in (b) (4) detected a signal for disproportionate reporting (SDR) for the Standardised MedDRA Query (SMQ) hyperglycemia/new onset diabetes mellitus (EB05=1.68; threshold for a signal is 1.5). The (b) (4) global safety database was searched for all Fluad confirmed post-marketing and literature reports using the SMQ (narrow) hyperglycaemia/new onset DM as of February 18, 2014 and was repeated as of April 30, 2015. The February 2014 search yielded 15 cases cumulatively. Each case underwent medical case review and a causality assessment. Based on a qualitative review of the post-marketing cases and a review of the Fluad integrated clinical trial safety database, the sponsor identified no evidence of a causal association between Fluad and hyperglycemia and determined that hyperglycemia and DM would continue to be monitored by routine pharmacovigilance activities.
- Decreased appetite: In February 2015, monthly disproportionality signaling in (b) (4) showed a new SDR of decreased appetite (cumulative proportional reporting rate (PRR) 2.51). A cumulative search of the (b) (4) safety database was performed and yielded 26 cases. Based on review, the signal of decreased appetite was considered as a possible potential risk of Fluad in adults. However, because the event was mild and transient and usually associated with other flu-like symptoms (such as fever, malaise, nausea), which are listed in the Core Data Sheet, no changes were made to the RMP. Decreased appetite will continue to be monitored by routine pharmacovigilance activities.
- An increase in the reporting rate of off-label use (use in subjects' age <65 years of age) from the previous eight-month reporting interval was observed (1.17 per 100,000 subjects vaccinated compared to 0.26 per 100,000 subjects vaccinated.).
- d. 139th Meeting of the Vaccines and Related Biological Products Advisory Committee, September 15, 2015

The meeting was convened so that the committee could discuss and make recommendations on the safety and immunogenicity of Fluad, a seasonal trivalent influenza vaccine, surface antigen, inactivated, adjuvanted with

MF59, manufactured by NVD and submitted as a BLA under the accelerated approval regulation, which requires a surrogate marker that is reasonably likely to predict clinical benefit, as well as demonstration of safety. A confirmatory efficacy trial is also required of Novartis to verify and describe the clinical benefits.

Both effectiveness and safety data were reviewed by Novartis and FDA, respectively. The safety data, as summarized by FDA, is as follows:

- The pivotal Phase 3 trial, V70_27 demonstrated increased mild and moderate local reactogenicity seen after Flud administration. Flud demonstrated increased systemic reactogenicity overall, but only slight differences for any given parameter. There were no imbalances in severe, local or systemic reactogenicity. There were no imbalances in unsolicited AEs, and there were no imbalances in deaths, SAEs, withdrawals due to AEs or new onset chronic disease.
- Pooled safety analyses, which included 49 studies conducted over 16 years, were small, highly varied, and conducted outside the United States. There were no imbalances in unsolicited AEs, deaths, SAEs, AEs leading to study withdrawal or AEs of special interest. Observed imbalance in deaths was noted at year 2 upon the analysis of five revaccination studies (17 out of 492 subjects in the Flud group and 6 out of 330 in the non-adjuvanted vaccine group), but this was in a small number of subjects with a lack of similar trends in first-vaccination studies, and with lack of observed deaths in year 3 revaccination studies.
- No new safety signals were identified from post-marketing surveillance. A review of an investigation of reports related to the temporary suspension of Flud in Italy in 2014 as the result of four death reports in elderly people post-vaccination found no causal link between Flud and the deaths, and the suspension was lifted with no regulatory action.

The Committee voted in the affirmative that the available data was adequate to support the safety of Flud when administered to adults 65 years of age and older (10 yes, two no, and one abstention). There was some concern noted, however, about the data regarding deaths with the second dose in the revaccination studies, although the fact that this data came from studies that were small, inadequately uncontrolled, with multiple confounders in an elderly population was noted. Suggestions included post-marketing surveillance focused on second-dosing adverse events and extension of the confirmatory efficacy trial to two-years, so as to capture data after repeat vaccination.

6. Integrated Risk Assessment

The additional safety data as provided in this amendment does not alter the integrated risk assessment as described in Qiang, Pharmacovigilance Review Memorandum. In brief, clinical studies do not demonstrate important safety issues other than increased reactogenicity with Flud, with no imbalance in severe reactogenicity noted. Post-marketing surveillance has not identified any clear serious safety concern. Given the use of an adjuvant, MF59, and the potential biologic plausibility between adjuvants and AEs, especially autoimmune diseases, particular attention to this subject will be given.

7. Recommendations

- a. Routine passive surveillance in accordance with 21 CFR 600.80.
 - i. The Risk Management Plan 3.0 identifies potential (convulsion, neuritis, encephalitis, vasculitis, Guillain-Barré Syndrome (GBS), demyelination, Bell's palsy, Immune thrombocytopenia (ITP) haemolytic anaemia, and vaccination failure) and identified (anaphylaxis and extensive limb swelling (ELS)) risks for which it will continue to provide ongoing data.
 - ii. In addition, the results of enhanced passive surveillance as required by the EMA to assess reactogenicity, which will be conducted in Italy, will be followed by the FDA.
 - iii. NVD will continue to include a section in Periodic Safety Reports discussing any spontaneous reports or AEs from other sources from a list of specified AESI and AEFI conditions.. The conditions will be the same as those evaluated in PSUR 37. AESIs will include neuro-inflammatory disorders (myelitis, radiculitis, radiculitis brachial and narcolepsy), rheumatological disorders (musculoskeletal autoimmune disorders including rheumatoid arthritis, inflammatory bowel disease (ischemic colitis), thyroid disorders (hypo and hyperthyroidism), inflammatory skin

disorders (Raynaud's phenomenon, skin autoimmune disorders and severe cutaneous adverse reactions), autoimmune hematologic disorders, and vasculitis.

- b. Expedited reporting (i.e., report to FDA as a 15-day report regardless of seriousness or expectedness) for the following conditions: GBS, ITP, neuritis, encephalomyelitis, vasculitis, demyelination and Bell's palsy
- c. An updated Risk Management Plan that includes cumulative information from previous Risk Management Plans on the investigator-initiated active surveillance in Italy

Table 1 - PSUR 36 Summary of Reports for Health Outcomes of Interests

Health outcomes of Interest	PSUR 36 Spontaneous* reports (INN) Total 5/1/14-8/31/14	PSUR 36 Spontaneous* reports (INN) Fluad® - confirmed 5/1/14-8/31/14	PSUR 36 Reporting rate of Fluad® - confirmed cases per 100,000 subjects vaccinated 5/1/14-8/31/14	Reference period ** Reporting rate of Fluad® - confirmed cases per 100,000 subjects vaccinated	All reports (INN) 5/15/97 – 8/31/14	Literature reports (INN) 5/15/97 – 8/31/14	Spontaneous reports (INN) 5/15/97 – 8/31/14	Clinical/PMS*** reports (INN) 5/15/97 – 8/31/14	Reporting rate of spontaneous and literature cases per 100,000 vaccinated 5/15/97 – 8/31/14	New signal
Neuritis	0	0	0	0	29 (19)	3 (3)	26 (16)	0	0.013	No
Convulsions	6 (6)	0	0	0	117 (75)	9 (9)	77 (66)	31(0)	0.014	No
Encephalitis	2 (2)	0	0	0	51 (42)	26 (26)	25 (16)	0	0.012	No
Vasculitis	1 (0)	1	0.25	0	98 (79)	44 (43)	48 (36)	6 (0)	0.017	No
GBS	8 (8)	0	0	0	177 (137)	38 (38)	139 (99)	0	0.053	No
Demyelination disorder	12 (12)	0	0	0	244 (196)	70 (69)	173 (126)	1 (1)	0.063	No
Bell's palsy	2 (2)	0	0	0	58 (46)	12 (12)	44 (34)	2 (0)	0.013	No
ITP	1 (1)	0	0	0.82	62 (47)	7 (7)	54 (40)	1 (0)	0.018	No
Haemolytic disorders	1 (1)	0	0	0	12 (5)	5 (3)	6 (2)	1 (0)	0.008	No
Vaccination failure	7 (7)	0	0	0	134 (93)	50 (50)	72 (41)	12 (2)	0.041	No
Anaphylaxis	11 (10)	1	0.02	0	223 (149)	7 (7)	173 (138)	43 (4)	0.046	No
Extensive Limb Swelling	24 (22)	2	0.50	0	516 (353)	12 (12)	500 (339)	4(2)	0.211	No
Potentials for medication errors	12 (11)	1	0.25	0	252 (155)	27 (26)	222 (129)	3 (0)	0.126	No
Potential off-label use	127 (126)	1	0.25	2.46	2779 (2078)				0.470	No

***"Spontaneous" includes spontaneous reports and literature cases

** Reference period=PSUR 34

*** Postmarketing Surveillance

Table 2 – PSUR 37 Summary of Reports for Health Outcomes of Interests

Health outcomes of Interest	PSUR 37 Spontaneous* reports (INN) Total 5/1/14-8/31/14	PSUR 37 Spontaneous* reports (INN) Fluad® - confirmed 5/1/14-8/31/14	PSUR 37 Reporting rate of Fluad® - confirmed cases per 100,000 subjects vaccinated 5/1/14-8/31/14	Reference period ** Reporting rate of Fluad® - confirmed cases per 100,000 subjects vaccinated	All reports (INN) 5/15/97 – 8/31/14	Literature reports (INN) 5/15/97 – 8/31/14	Spontaneous reports (INN) 5/15/97 – 8/31/14	Clinical/PMS*** reports (INN) 5/15/97 – 8/31/14	Reporting rate of spontaneous and literature cases per 100,000 vaccinated 5/15/97 – 8/31/14	New signal
Neuritis	1 (1)	0	0	0	30 (20)	3 (3)	27 (17)	0	0.0123	No
Convulsions	20 (19)	1	0.02	0.03	137 (94)	10 (10)	96 (84)	31(0)	0.0136	No
Encephalitis	10 (7)	3	0.06	0.02	61 (49)	27 (27)	34 (122)	0	0.0148	No
Vasculitis	5 (4)	1	0.02	0	103 (83)	44 (43)	53 (40)	6 (0)	0.0173	No
GBS	20 (17)	3	0.06	0.02	197 (154)	40 (40)	157 (114)	0	0.053	No
Demyelination disorder	30 (27)	3	0.06	0.02	274(223)	74 (73)	197 (147)	3 (3)	0.0629	No
Bell's palsy	14 (14)	0	0	0	72 (60)	12 (12)	58 (48)	2 (0)	0.0123	No
ITP	1 (1)	0	0	0.02	63 (48)	7 (7)	55 (41)	1 (0)	0.0173	No
Haemolytic disorders	0 (0)	0	0	0	12 (5)	5 (3)	6 (2)	1 (0)	0.0074	No
Vaccination failure	14 (12)	2	0.04	0	148 (105)	53 (53)	83 (50)	12 (2)	0.0407	No
Anaphylaxis	58 (54)	4	0.07	0.02	282(204)	7 (7)	231 (192)	44 (5)	0.0481	No
Extensive Limb Swelling	161 (159)	2	0.04	0.02	594 (443)	11 (11)	580 (430)	3 (2)	0.1849	No
Potentials for medication errors	65 (54)	11	0.21	0.08	324 (211)	27 (26)	294 (185)	3 (0)	0.1381	No
Potential off-label use	1059 (996)	63	1.17	0.26	3842 (3074)				0.5190	No, but increase noted

**"Spontaneous" includes spontaneous reports and literature cases

** Reference period=PSUR 35

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