



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

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

From: Wei Hua, MD, PhD, MS, MHS
FDA/CBER/OBE/DE

To: Carmen M. Collazo-Custodio, PhD
FDA/CBER/OVRR/DVRPA/CMC3

Through: David Martin, MD, MPH
FDA/CBER/OBE

Subject: Pharmacovigilance Plan Review Amendment

Applicant: ID Biomedical Corporation of Quebec (dba GlaxoSmithKline
Biologicals)

Product: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted

Proposed Indication: Active immunization for the prevention of disease in persons 18
years of age and older at increased risk of exposure to the
influenza A virus H5N1 subtype contained in the vaccine.

Submission type: Original BLA (STN 125419)

Submission Date: February 22, 2012

PVP Submission Date: February 22, 2012

First Action Due Date: November 23, 2013

This is an Amendment to the Pharmacovigilance Plan (PVP) Review Memos completed by OBE/DE on March 22, 2013 and November 4, 2013, respectively.

A. Review of Swedish MPA 7-county Registry Study

On November 15, 2013, FDA received an English translation of a Swedish Registry study report entitled “A registry study with focus on neurological and immunorelated diseases after vaccination with Pandemrix” completed by the Swedish Medical Products Agency in collaboration with the Karolinska Institute and seven country councils/care regions. The report is published on the Swedish Medical Product Agency (MPA) website in March 2013 in Swedish. The English translation was commissioned by GSK and sent via email for FDA review in support of the GSK proposed language for the Package Insert (PI) Section 6.2: Narcolepsy.

On November 18, 2013, GSK notified FDA of the official publication of an updated report of the above study in English in the Journal of Internal Medicine. (*Ref: Persson et al. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med. 2013 Oct 17. doi: 10.1111/joim.12150.*) (<http://www.ncbi.nlm.nih.gov/pubmed/24134219>)

The OBE/DE reviewer reviewed both reports. The final review of the study was based on the official English language publication by Persson et al in the Journal of Internal Medicine (2013). The study evaluated a set of neurological and immune-related outcomes. This review is focused on narcolepsy.

Summary of Study

Study design: The study was a register-based cohort study covering approximately 5.8 million individuals (61% of the Swedish population) who lived in one of the seven Swedish regions as of January 1, 2009, excluding those who died, emigrated from Sweden, had inconsistent information on migration or moved out of the study area prior to the start of the study period.

Vaccinations with Pandemrix were carried out from 10/1/2009-3/1/2010. Population follow-up began on 10/1/2009 through one of the following pre-defined end points: the first date of a registered outcome, migration from the study region, death, and 12/31/2011, whichever occurred first. The study period spanned from 10/1/2009-12/31/2011 with a maximum follow-up of 27 months.

Data sources for exposure and outcome: Information on vaccination status was obtained from the vaccination registries in the seven regions. Information on outcomes was obtained from the nationwide registers, including the Population Registry (Statistics Sweden), the National Patient Register, the Prescribed Drug Register, the Cancer Registry, the Medical Birth Register and the National Cause of Death Register (National Board of Health and Welfare). The exposure and outcome data were linked by personal identification number that is given to every newborn in Sweden.

Identification of narcolepsy: Narcolepsy was identified through ICD-10 code G47.4 from hospitalizations and outpatient referrals from the Patient Register. To exclude prevalent cases, in addition to G47.4, prodromal diagnoses codes (G47.0-G47.3, G47.8, and G47.9) were also used to identify existing conditions prior to the start of the study.

Statistical analysis: Hazard ratios were calculated using Cox regression with individuals contributing unexposed person-time from the start of the study until the date of vaccination (if vaccinated) and exposed person-time thereafter. Potential confounding factors (e.g., age, gender, region, etc.) were considered in the model. Stratified analyses were conducted based on age at vaccination, time-point of vaccination (first 45 days of the vaccination program categorized as early and thereafter as late) and length of follow-up.

Results: Overall, an approximately 6.9 million exposed person-years and 6.0 million unexposed person-years were observed.

1. Positive control - Vaccination reactions
 - a. Vaccination reactions were evaluated as a positive control comparing exposed and unexposed cohorts. An approximately 20-fold risk increase was identified within weeks immediately after vaccination in the exposed cohort, suggesting the study's ability of capturing a symptom-based diagnosis reporting from a hospital.
2. Outcome of interest – Narcolepsy (Table 1)
 - a. An increased risk of narcolepsy was reported in children/adolescents ≤ 20 years of age (HR=2.92, 95% CI: 1.78-4.79), corresponding to 4 additional cases per 100,000 vaccinated individuals per year.
 - b. An increased risk of narcolepsy was reported in adults 21-30 years of age (HR=2.18, 95% CI: 1.00-4.75). No estimation of attributable risk was provided.
 - c. No increased risk was reported in other adult age groups.

Table 1. Narcolepsy risk estimates by age groups

Age group	Number of cases	Hazard Ratio (95% CI)
≤ 20 years	126	2.92 (1.78-4.79)
21-30 years	23	2.18 (1.00-4.75)
31-40 years	18	1.53 (0.68-3.44)
>40 years	40	1.06 (0.64-1.76)

OBE/DE Reviewer's Comments

The Swedish 7-county registry study reported an increased risk of narcolepsy in children/adolescents ≤ 20 years of age and in adults 21-30 years of age. The major limitations of the study and the corresponding impact on risk estimation are discussed below:

1. Cases were identified through ICD-10 code and were not chart confirmed. As a result, non-cases could be possibly misclassified as cases. The positive predictive value of G47.4 for this data is unknown. Assuming there was no appreciable difference in the positive predictive value between vaccinated and unvaccinated cohorts, this misclassification could be considered non-differential across exposed/unexposed groups. In the meantime, due to an increased media attention on narcolepsy following Pandemrix as the data suggested, both sensitivity and positive predictive value of G47.4 could be influenced especially for the vaccinated cohort. In either case, depending on the actual number of cases misclassified, the bias in risk estimation due to misclassification could be in either direction.
2. Narcolepsy onset was not assessed in this study. Narcolepsy is a disorder with a relatively insidious onset. Lack of accurate assessment of narcolepsy symptom onset is seriously concerned due to the potential for misclassification of exposure (e.g., before vs. after vaccination, risk vs. control period) and/or disease status (e.g., undiagnosed case considered as a non-case). However, because the cohort design takes into account the cumulative population person-time at risk, the potential bias due to the delay in diagnosis in this study is considered less severe relative to other studies employing self-controlled designs in which cumulative person-time at risk is not reflected in the conditional likelihood function.
3. Lack of adequate adjustment for confounding factors, including natural H1N1 influenza infection, seasonality and other potential risk factors, could also lead to biased risk estimation either away from the null or towards the null.

OBE/DE Assessment

Given the major limitations of the study, OBE/DE considers the results reported in the Swedish MPA 7-county registry study are inconclusive. However, OBE/DE agrees to include these crude risk estimates in the PI Section 6.2: Narcolepsy, to reflect the actual data in the literature.

Review of the Swedish MPA 7-county registry study report does not change OBE/DE's Integrated Risk Assessment for Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, or safety assessment of narcolepsy, as stated in the Primary OBE/DE Review Memo (Stamped by Dr. Yandong Qiang on March 22, 2013) and the Memo Amendment (Stamped by Dr. Yandong Qiang on November 4, 2013). Based on the current information available to the OBE/DE reviewer, no additional safety issues have been identified that may need to be addressed through postmarketing safety surveillance or studies.

B. Review of Amendments Regarding Narcolepsy Labeling

The OBE/DE reviewer has reviewed the following Amendments (32, 41, 43, 45, and 48) regarding Narcolepsy labeling submitted by GSK in response to the FDA comments. OBE/DE agrees with the narcolepsy labeling language proposed by GSK in Amendment 48.

- STN 125419/0.32
- STN 125419/0.41
- STN 125419/0.43
- STN 125419/0.45
- STN 125419/0.48

C. Review of Amendments Regarding Pregnancy Registry

The OBE/DE reviewer has reviewed the following Amendments (42 and 46) regarding Pregnancy Registry submitted by GSK in response to the FDA comments. OBE/DE agrees with GSK's statement in Amendment 46 regarding agreement upon establishing a Pregnancy Registry as a Postmarketing Commitment (PMC).

- STN 125419/0.42
- STN 125419/0.46