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From: Soju Chang, MD, MPH
Medical Officer, Vaccine Safety Branch, Division of Epidemiology

To: Theresa Finn, PhD
Chair, Pentacel® BLA Review Committee

Through: Robert Ball, MD, MPH, ScM
Chief, Vaccine Safety Branch

M. Miles Braun, MD, MPH
Director, Division of Epidemiology

Re: Surveillance for Rates of Pertussis Disease Among Persons Aged 0-4 Years Receiving Pentacel® or Other Pertussis Vaccines

Summary

Sanofi pasteur has submitted a protocol concept (code M5A16) for a post-marketing surveillance study to determine the rates of pertussis disease among persons aged 0-4 years receiving Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (Pentacel®) [DTaP-IPV/Hib] or other pertussis vaccine. Sanofi Pasteur is proposing to conduct a cohort study among children aged < 5 years in Wisconsin receiving 4 doses of Pentacel or 4 doses of any other pertussis vaccines (all doses were a single brand) for 5 full calendar years following launch of Pentacel and nested case-control studies for confirmed endemic pertussis cases and outbreak pertussis cases. The objectives of the study are to determine the rates, relative risk (RR) and odds ratio (OR) of confirmed pertussis disease. For the cohort study, a 2-sided 90% confidence interval for the RR of Pentacel versus control will be calculated and if the upper bound of that interval is less than 2 then Pentacel will be declared to be non-inferior to control. Same statistical approach will be applied to the nested case control studies for OR. Control vaccines include Sanofi Pesteur's stand-alone DTaP (Daptacel and Tripedia) and reconstituted DTaP-Hib (TriHIBit) vaccines and GlaxoSmithKline's stand-alone DTaP (Infanrix) and combined DTaP, inactivated polio and hepatitis B (Pediarix) vaccines. Data on vaccination history and confirmed pertussis disease cases will be obtained from the Wisconsin Immunization Registry and Wisconsin Division of Public Health, respectively. In 2006, the population of Wisconsin included approximately 68,000 children in each birth cohort <5 years of age. The number of reported pertussis cases in Wisconsin children aged <5 years were, respectively, 48, 209, and 930 for calendar years 2006, 2005, and the outbreak year 2004. Sample size and statistical power calculations were based on overall age-specific pertussis rates during 2004-2006, projection of Pentacel market share, magnitude of measures of association (RR=1.5 to RR=3.0; OR=1.5 to OR=3.0), and projected pertussis cases and Wisconsin population aged 0 to 4 years during 2008-2012.

General Comment(s)

- Please note that the evaluation for the immunogenicity of one of Pentacel pertussis antigens failed to reach the non-inferiority criteria during the pre-licensure clinical trials. Although post-marketing observational studies evaluate the effectiveness of a drug or a vaccine in a real-life setting, these studies have several limitations including non-randomization of the study population and uncontrolled exposure and outcome assessment. Also, these types of study are subject to confounding, effect modification, and other bias, which may make the results of observational studies more difficult to interpret than the results of clinical trials. Observed differences for the pertussis rates among Pentacel and other pertussis vaccine recipients might be due to factors (e.g., socio-demographic characteristics, health care access, geographical location, pertussis disease detection and reporting, etc) other than the vaccine effect. Such confounding factors could have been minimized by prospective, randomized and controlled clinical trials. Therefore, findings from these observational studies might not be adequate to support comparative statements (e.g., the rate of Pertussis disease among Pentacel recipients is non-inferior to the rate of Pertussis disease among other pertussis vaccine recipients) among different pertussis vaccines by brand names as proposed by Sanofi pasteur.
- Please note that a representative of Sanofi Pasteur is listed as one of the lead investigators in this post-marketing pertussis surveillance study, which can represent a conflict of interest because the study might be conducted under undue influences of the sponsor.
- Please note that the proposed study population of Wisconsin children aged < 5 years might not reflect the US population for the same age group and the reported pertussis disease rates for Wisconsin might significantly differ from the national ones.
- The proposed study sample size consists of approximately 68,000 children in each birth cohort <5 years of age. However, the number and percentage of these children enrolled in the Wisconsin Immunization Registry was not provided. Although it is stated in the concept protocol that other suitable sources will also be used to determine the vaccination information of study population, it is unclear how the numbers of exposed (e.g., Pentacel recipients) and unexposed (e.g., other pertussis vaccine recipients) persons are determined in the cohort study. In addition, it is not stated whether the compliance of healthcare providers in adhering to the Wisconsin Division of Public Health guideline for pertussis case management including reporting of cases is consistent across the Pentacel and other pertussis vaccine groups.
- Please note that there is a big discrepancy in the numbers of pertussis cases and pertussis disease rates reported during the period 2004-2006. It is unclear how "outbreak" year in 2004 was defined and the difference in reporting between the two "non-outbreak" years 2005 and 2006 is still significant. The overall age specific pertussis disease rate during this three-year period might not reflect the

background pertussis disease rate in Wisconsin, which might be inappropriate to be used in determining the statistical power of the cohort study.

- Please note that the matching criteria based on age and vaccination completeness in the nested "endemic case control study" might be inadequate and can't account for other relevant confounding factors (e.g., geographical location) for pertussis disease.

Question(s) to Sponsor

- As stated in the protocol concept "for 50% Pentacel market share, the projected power with a non-inferiority boundary of 2 is 93.46% and 98.32% in years 4 and 5. For market shares other than 50%, the power decreases but is still maintained at or above 80% at years 4 and 5". Please consider designing the study to evaluate the rates of pertussis disease in a timely manner (e.g., recruiting additional study sites).
- Please clarify whether data from the Wisconsin disease surveillance system can be linked to the Wisconsin immunization registry.
- Please justify (e.g., based on benefit risk of Pentacel vaccine) the selection of magnitude of less than 2 for the RR and OR, respectively, in the cohort and case control studies. A magnitude of the measures of association in the range between 1 and 2 conveys that the Pentacel recipient group still is more at risk for pertussis disease than the other pertussis vaccine recipient group.
- Please provide the rationale for evaluating the rates of confirmed pertussis cases instead of reported pertussis cases, which include both probable and confirmed pertussis cases.
- In addition to other factors, statistical power calculations for the cohort and case control studies are dependent on the different projections of Pentacel market share (i.e., 25%, 50% and 75%). It is possible that Pentacel market share might not reach the minimum projection of 25% and the study might not have adequate power (80% or greater) to detect the "noninferiority boundary of two". Please provide an alternative plan to address such possibility.