Date: May 18, 2007

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: Post Licensure Safety Surveillance Study of Routine Use of Pentacel® Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined

Summary

Sanofi Pasteur Inc has submitted a protocol concept (code M5A11) for a descriptive, post-marketing safety surveillance study of routine use of Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (Pentacel®) [DTaP-IPV/Hib]. The study will be carried out in collaboration with the [redacted] under the direction of the [redacted] The objective of the study is to characterize the safety profile of Pentacel vaccine for identification of potential vaccine-related adverse events (AEs) not currently associated with Pentacel vaccine administration. The planned sample size will be at least 10,000 infants initiated on Pentacel vaccine, plus an unknown number of infants initiated on other DTaP vaccines, which 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. The study will continue by following through 6 months past their 4th dose (or until 24 months of age, whichever comes first), each child accrued to the study. Incidence rates and where applicable, rate ratios, of vaccine-related AE (e.g., non-elective hospitalizations and emergency room visits for all diagnoses combined and by ICD-9, CPT, or other relevant diagnostic or therapeutic codes) and pre-specified outcomes of interest from outpatient visits (e.g., specified neurological conditions, hypersensitivity reactions, and new-onset autoimmune disease) will be calculated for Pentacel and each or a combination of other DTaP vaccine groups. Vaccination history will be obtained through the [redacted] and vaccine-related AEs using [redacted] outpatient database (clinic and emergency room visits), [redacted] database, supplemental

database of non [redacted] hospitalizations among [redacted] members and state Mortality Tapes.

General Comment(s)

- Please note that post-marketing observational studies evaluate the safety 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 in safety profiles of Pentacel and other DTaP vaccines might be due to factors such as socio-demographic characteristics and differences in vaccine compositions (stand-alone vs combined) and concomitant vaccination (e.g., hepatitis B, pneumococcal, or rotavirus vaccines). Therefore, findings from these observational studies might not be appropriate to support comparison of product-specific AE rates among different types of vaccines from different manufacturers (e.g., Pentacel vs Pediarix) as proposed by Sanofi pasteur.

Question(s) to Sponsor

- Please clarify how the findings of the study will meet the study objective to characterize the safety profile of Pentacel vaccine for identification of potential vaccine-related AEs not currently associated with Pentacel vaccine administration.
- Please specify the post-vaccination time period for each of AEs to be evaluated.
- The study focuses on DTaP vaccination instead of the combined DTaP-IPV/Hib vaccination. Please provide the rationale for conducting a safety study with focus on the DTaP component and consider designing the study (e.g., cohort study with concurrent control) to evaluate the safety of Pentacel vaccine compared to that of separate, concomitantly administered, individual components (or its equivalents).
- Please provide the safety profile of Pentacel (or a plan to evaluate the safety profile of Pentacel) when simultaneously administered with other vaccines according to the Advisory Committee on Immunization Practices (ACIP)' US recommended immunization schedule for persons aged 0-6 years.
- In order to meet the study objective of characterizing safety profile not currently associated with Pentacel vaccination, please provide a summary describing the important identified risks, important potential risks, and important missing safety information associated with Pentacel vaccination.
- The size of the study population will be at least 10,000 infants initiated on Pentacel and unknown number of infants initiated on other DTaP vaccines. Since the study aims to describe the incidence rates (and where applicable compare rates between Pentacel and other DTaP vaccine groups) of a wide range of vaccine related AEs, which might be common (e.g., 1 to 100) or very rare (1 to 1,000,000), please justify the proposed sample size and provide the statistical power and hypothesized rate differences (e.g., RR < 2) for the studied AEs.

- Please provide a description of safety signal detection and evaluation. For identification, description, investigation and interpretation of safety signals (e.g., definition of safety signals, case report and case series, observational studies, and identification of potential safety risk), please refer to FDA's Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (accessible at http://www.fda.gov/Cder/guidance/6359OCC.htm).