DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Sanofi Pasteur, BLA 125145
Teleconference Date\Time: 11 September 2007, 10.30

FDA/CBER participants:
Theresa Finn
Edward Wolfgang
Bob Ball
Soju Chang
Martha Lee
Karen Farizo
Norman Baylor
Flo Houn
Paul Richman

Sanofi participants:
Gary Chikami
Luc Kykens
Fotula Fegaras
Yatika Kohli
Michael Decker
David Greenberg
Fernando Noriega
Walter Woods

Background/ Purpose of the meeting
Sanofi pasteur have proposed post-licensure surveillance for cases of invasive Hib disease by the Active Bacterial Core (ABC) Surveillance program to evaluate effectiveness of the Hib component of Pentacel. CBER's August 20, 2007 letter to sanofi pasteur stated that the proposed surveillance project (M5A15) to evaluate the potential for an increased incidence of invasive Hib disease among children who received Pentacel was inadequate because of the magnitude of detectable risk and the relatively long period of surveillance required. CBER requested that sanofi pasteur address the potential for an increase in cases of invasive Hib disease over time if the immune response to the Hib component of Pentacel is diminished relative to separately administered ActHIB, as observed in Study 494-01.

In response to this letter sanofi submitted a pre-read and a revised Concept Document for their Hib surveillance project (Study M5A15, August 31, 2007, submission to the Pentacel BLA). A telecon was scheduled for September 11, 2007.

Summary August 31, 2007, submission: The revised surveillance document corrects an error in the power calculations. The revised power table shows the study has approximately 80% power to detect a 7-fold increase in the incidence of invasive Hib disease among Pentacel vaccinees after 6

years, assuming Pentacel has a 50% market share of Hib vaccines (previous version of table showed the study had 80% power to detect a 9 fold increase).

The statistical section of the synopsis presents Poisson estimation of the number of cases of invasive Hib disease observed in the Pentacel group needed to exceed the upper 95% confidence limit for the number of expected cases. The meeting pre-read also presents this table and notes that although it "would take 3 or more years to accurately characterize the relative risks, if there were an increase..." an increased relative risk of 4 or less might be detected earlier. Sanofi propose that if breakthrough cases of invasive Hib disease in the Pentacel group exceed the expected number (by margins shown in the table of Poisson distribution) this will trigger a meeting between FDA, CDC and sanofi to "identify additional analyses, surveillance activities or other actions or interventions that ought to be considered or undertaken."

The pre-read narrative which accompanies the revised surveillance document states that M5A15 is the best available option to evaluate effectiveness of the Hib component of Pentacel. Sanofi note that the ABC system is the largest Hib surveillance system in the world. They further note that CDC does not have the funding to expand the geographic area of the ABC system and cannot accept private funds for this purpose. Sanofi also state that the Alaskan public health authorities have declined a request to meet to discuss Pentacel and have reiterated that they did not wish to change the Alaskan vaccination program.

September 11, 2007 telecon discussion with sanofi:

CBER noted that if the pre-licensure data had clearly demonstrated non-inferiority of Pentacel compared to ActHIB the concept of using the ABC surveillance system to estimate the relative risk of invasive Hib disease following Pentacel relative to other Hib vaccines may be an acceptable post-licensure surveillance study. Due to inconsistent data on anti-PRP responses from the Pentacel pivotal studies and the limitations of post-marketing surveillance to evaluate effectiveness of Pentacel against invasive Hib disease, CBER continues to have concerns about the potential for an increase in cases of invasive Hib disease over time that may be associated with the use of Pentacel if the immune response to the Hib component is diminished relative to separately administered ActHIB. CBER asked sanofi to consider a pre-licensure study to evaluate the anti-PRP immune response following three doses of Pentacel relative to separately administered ActHIB. CBER proposed a study in which several (e.g. 5) consecutively manufactured lots of ActHIB would be used. Within each lot, subjects would be randomized to receive Pentacel or separately administered ActHIB. The proportion of subjects with anti-PRP levels $\geq$1.0 ug/mL and anti-PRP GMCs one month following three doses of Pentacel compared to separately administered ActHIB would be assessed as co-primary non-inferiority analyses. CBER recommended a stratified data analysis for non-inferiority for each endpoint by considering each "lot" as a stratum. CBER said they would fax sanofi an outline of the study including a reference for the stratified analysis. (Study proposal faxed, see attached).

Sanofi noted that while they may have been receptive to such a study design a few years ago but at this stage of development they are less so.

Dr. Decker stated that the BLA data do not support that Pentacel "underperforms the standard of care." He further stated that in the study in which Pentacel did not demonstrate non-inferiority (Study 494-01) the comparator group received an unlicensed DTaP (HCPDT) administered with POLIOVAX and ActHIB. Moreover, published data suggest that the response to the Hib

component of Pentacel is similar to that of ActHIB. Furthermore, data from a [redacted] The circumpolar surveillance data show Pentacel is superior as compared to the Merck product. The proposed post-marketing surveillance would use the ABC system which includes approximately 1/9th the US population. Under the proposal as few as 3 excess cases among children who received Pentacel would be detected. Dr. Decker stated that sanofi had an ongoing clinical trial, M5A10, which includes a group of children who received Pentacel and another group administered ActHIB separately. Although subjects will be administered four doses of study vaccines all subjects have received three doses. These clinical data can be submitted to CBER.

Dr. Kykens stated that while the response to ActHIB has been variable the response to the Hib component of Pentacel has been consistent in clinical studies. He asked whether CBER had any concern regarding the performance of ActHIB. CBER explained that based on the clinical data in the BLA the response to ActHIB is variable. The proposed study is designed to evaluate whether the response to Hib among subjects administered Pentacel formulated with several lots of ActHIB was comparable to that of subjects administered the same several lots of ActHIB separately.

Sanofi again stated that post-dose 3 results from study, M5A10, may provide additional data. Dr. Noriega noted that the post-dose 3 data from M5A10 had been "locked". Data could be provided to CBER within a few weeks.

Sanofi explained that recruitment into the study CBER proposed would be difficult since the control group would not receive a combination product. In addition, once the study was completed it would take several months to prepare a study report and submit to CBER. CBER clarified that since the objective of the proposed study was an evaluation of the response to PRP-T post-dose 3 the control group could receive a standard of care regimen – such as Pediarix administered with ActHIB. CBER also stated that it was not necessary to evaluate immune response to any antigen other than Hib. Pre-bleeds and post-dose 4 bleeds for immunogenicity were not necessary. Subjects administered Pentacel should however, receive a fourth dose to complete the pertussis primary series. Preliminary sample size estimates conducted by CBER statisticians indicated that approximately 160 evaluable subjects/lot were required for non-inferiority analyses of the Hib endpoints proposed.

Sanofi asked whether CBER would accept the M5A10 data pre-licensure and they would conduct the study CBER proposed as a post-licensure commitment. CBER agreed to consider this request.

Action Items:
Sanofi will provide CBER with timelines for providing the M5A10 post-dose 3 immunogenicity data.
Sanofi will provide estimated time lines for conducting the study CBER proposed.
CBER will fax a more detailed description of the proposed study design together with a reference for the stratified analysis (faxed – Sept. 11, 2007)

CBER September 11, 2007 fax to sanofi pasteur:
In follow-up to the conversation this morning between sanofi pasteur and OVRR representatives the following is a summary of our suggested study design:

We recommend that several (e.g., at least 5) consecutively manufactured lots of ActHIB be used in this study, both for the ActHIB control group and for formulation of Pentacel. Within each lot, subjects would be randomized to receive Pentacel or separately administered ActHIB. We recommend co-primary non-inferiority analyses of the proportion of subjects with anti-PRP levels $\geq$1.0 ug/mL and anti-PRP GMCs one month following three doses of Pentacel compared to separately administered ActHIB. Since the study will only evaluate the post-dose 3 response to the PRP-T component those subjects randomized to receive ActHIB separately may be administered a licensed combination vaccine to reduce the number of vaccinations. In addition, we do not consider it necessary to obtain a pre-vaccination blood sample. We recommend that you apply stratified data analysis for non-inferiority for each endpoint by considering each "lot" as a stratum [Miettinen O. and Nurminen, M. (1985) Comparative analysis of two rates. Statistics in Medicine, Vol 4, 213-226]. Study subjects should reflect the race/ethnicity distribution of the U.S. population. Subjects who receive Pentacel (and Daptacel if used) should be administered a fourth dose at 15-18 months of age.