DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Sanofi Pasteur, BLA 125145,

Face to Face Meeting Date\Time: 18 May 2007, 1500, WOC 2 Conf Room

FDA/CBER Attendees:
Theresa Finn
Karen Farizo
Milan Blake
Edward Wolfgang
Paul Richman
Drusilla Burns
Sandra Menzies
Martha Lee
Tod Merkel
Martha Monser
Elizabeth Sutkowski
Lucia Lee
Norman Baylor

Sanofi Pasteur Attendees:
Gary Chikami
Luc Kuykens
Garvin Bixler
Fernando Noriega
John Riley
David J. Jemioco
Stephen Hildreth
Clotilde Thiariart
Eloi Kpamegan
Walter Woods
Yatika Kohli
Linda Young

Overview/ Purpose of the meeting
Following receipt of CBER's April 23, 2007, CR letter sanofi pasteur requested a Type A meeting to discuss whether the immunogenicity data presented in their pre-read materials (May 2, 2007, submission to the Pentacel BLA) would support their conclusions regarding the anti-PT response of Pentacel. Following review of the pre-read materials CBER faxed a response to sanofi May 17, 2007. Sanofi pasteur elected to meet with CBER to discuss what additional information was required to support the pertussis [redacted] and discuss alternative options for demonstrating the immunogenicity of the PT component of Pentacel.

The following comments were faxed May 17, 2007:

The following is our response to your discussion item: Based on the information provided in the CR responses and presented at the meeting, does CBER agree that the data for the PT antibody response provided in controlled trials and Sweden I serology bridge contained in the Pentacel BLA support the conclusions regarding the anti-PT response of Pentacel?

Based on our review of the information provided in the response to our CR letter, CBER does not agree that the data contained in the Pentacel BLA support the conclusions regarding the anti-PT response of Pentacel. Adequate information to demonstrate the validity of data generated by the assay currently used in the U.S.-facility or to allow direct comparisons between assays conducted in different laboratories at different times has not been provided. For example, we have not received complete information regarding the validation of the anti-PT [redacted] used in the U.S.-facility, we do not have adequate data to properly assess the purity of the PT [redacted], and we do not have adequate information concerning what effect fimbriae contamination of the PT [redacted] might have on the behavior of the reference used in the anti-PT [redacted] for both the Canadian and U.S. laboratories.

We recommend that you develop a comprehensive plan for assessment of immunogenicity of the pertussis toxoid components of Pentacel and ADACEL, based on non-inferiority relative to DAPTACEL using a validated anti-PT [redacted] in the U.S.-facility. It is our understanding that sera from the Sweden I Efficacy Trial that were used in serological bridging studies for Pentacel and ADACEL are no longer available.

With regard to Pentacel, it may be acceptable to evaluate the immunogenicity of the pertussis toxoid component of Pentacel based on re-assay of available Pentacel and DAPTACEL sera from Study P3T06 for anti-PT responses (GMCs and percent of subjects achieving a 4-fold rise). The acceptability of this approach will depend on the availability of a sufficient number of serum samples from Study P3T06 and the ability to demonstrate that available sera are representative of sera from the PPI and ITT populations. We recommend that you develop a plan to evaluate the representativeness of available sera from subjects immunized with Pentacel and DAPTACEL in Study P3T06, with regard to post-dose 3 and post-dose 4 responses to each of the pertussis antigens. We also recommend that you develop a protocol for re-evaluation of the anti-PT responses from Study P3T06. The protocol should include statistical power calculations based on available sera for assessment of non-inferiority of anti-PT GMC and seroresponse (4-fold rise) rates post-dose 3 and post-dose 4 for Pentacel relative to DAPTACEL.

The approach outlined above addresses only an evaluation of anti-PT responses following Pentacel relative to DAPTACEL to potentially support a claim of non-inferiority of Pentacel relative to DAPTACEL with regard to the immune response to PT. Any additional claims based on evaluation of pertussis immune responses (e.g., non-interference of concomitant Prevnar with responses to the pertussis component of Pentacel) would also require evaluation of anti-PT responses using a validated, specific assay.

With regard to ADACEL, it may be acceptable to evaluate the immune response to the pertussis toxoid component of ADACEL by comparing anti-PT immune responses in adolescents and adults vaccinated with ADACEL for whom sera are available for re-assay, relative to subjects who received DAPTACEL in Study P3T06. As described above for Pentacel, the acceptability of this approach will depend on the availability of a sufficient number of sera for re-assay and the ability

to demonstrate that the available sera are representative of sera from the PPI and ITT populations. Please submit a proposal for this evaluation to the ADACEL IND.

Prior to re-assay of sera to evaluate the immune response to the pertussis toxoid components of Pentacel and ADACEL, we recommend that you submit protocols for our review and comment. In addition, since you currently do not have a validated anti-PT [redacted] we recommend that you submit assay validation data for our review and comment prior to re-assay of the sera.

The following items were discussed during the May 18, 2007 meeting.

The following items pertaining to the PT [redacted]
Purification of PT [redacted] in the U.S. and Canadian laboratories: sanofi explained that the [redacted] used in the U.S. laboratory was more extensively purified than that used in the Canadian assay.
CBER requested additional information on methods and calculations for assessment of purity of PT [redacted] in the Canadian and U.S. laboratories.
CBER suggested spiking experiments to assess the sensitivity and specificity of methods to detect and accurately measure fimbriae contamination of the PT [redacted]
Alternate sourcing of PT [redacted] was briefly mentioned. Sanofi said that this may cause uncertainties with respect to supply.
CBER requested sanofi provide control charts for assays performed in the U.S. and Canada using [redacted]
CBER requested sanofi revise the acceptance criteria for comparison of the new PT [redacted] to previous [redacted] detailed in SOP SWI J003789 as follows: [redacted]
CBER requested sanofi identify the [redacted] reference used in the U.S. and Canadian laboratories and provide data to address whether the reference was affected when different [redacted] were used.

The following items pertaining to assessment of non-inferiority of response to the PT component of Pentacel relative to DAPTACEL:
Sanofi said a sample size of 130 paired sera was required for analyses of non-inferiority of Pentacel relative to DAPTACEL. Sanofi indicated that sufficient sera from subjects administered Pentacel in Study P3T06 were not available since these had been used to generate the data in the pre-read materials. Sanofi proposed using sera from subjects administered DAPTACEL in Study P3T06 and comparing to anti-PT response of subjects administered Pentacel in Study 494-01. Sanofi proposed evaluating non-inferiority of fold-rise and GMC using 90% CI.

CBER expressed concern regarding the use of sera from two studies noting that assessment of non-inferiority should be evaluated using sera from subjects vaccinated in a randomized, controlled study. Exceptions to this – such as comparisons to historical data generated in clinical end-point efficacy studies had been discussed publicly. CBER requested that the non-inferiority analyses be based on 95% CIs (sanofi will discuss this internally).

Sanofi stated that the magnitude of the anti-fimbriae response affected the ability to measure anti-PT levels using the various [redacted] Sanofi indicated that post dose three values were not affected by [redacted]. CBER noted that the reference used may affect [redacted] values reported. CBER suggested that since the availability of sera from Study P3T06 was limited the number of pre-vaccination samples it may be possible to use the pre-vaccination [redacted] values

measured in the Canadian laboratory if it can be demonstrated that these values were unaffected by [redacted] or reference. CBER stated they would send a CR letter to sanofi requesting [redacted] information and a plan to assess immunogenicity of the PT component of Pentacel. CBER requested that sanofi not assay any additional sera until their assay and proposal had been reviewed by CBER and all comments addressed.

The following item pertains to ADACEL:
CBER confirmed that, as stated in the fax from CBER, sanofi should submit a plan for assessment of the immunogenicity of the PT component of ADACEL to the ADACEL IND.

Action Items:
CBER will compile comments pertaining to the Pentacel file and send a CR letter to sanofi.