DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Our STN: BL 125145/0

JUN - 8 2007

Sanofi Pasteur Inc.
Attention: Gary K. Chikami, M.D.
Associate Vice President, Regulatory Affairs, North America
Discovery Drive
Swiftwater, PA 18370-0187

Dear Dr. Chikami:

We have completed the review of your submissions to date to your biologics license application (BLA) for Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (Pentacel™) for active immunization for the prevention of diphtheria, tetanus, pertussis, poliomyelitis and invasive *Haemophilus influenzae* type b disease, submitted under section 351 of the Public Health Service Act.

The deficiencies, some of which were conveyed in our May 17, 2007, fax and during the May 18, 2007, meeting between CBER representatives and representatives of your office are as follows:

1. Based on discussions during the meeting it is our understanding that you intend to support a claim of non-inferiority of Pentacel relative to DAPTACEL with regard to the immune response to PT, on analyses of [redacted] data generated in your U.S.-facility [redacted]. The following items pertain to the validation of the anti-PT [redacted]:

   a. The May 2, 2007, response to our CR letter contained a copy of a partial response to a February 23, 2007, IR letter regarding IND [redacted]. This letter requested additional information regarding the transfer of the pertussis [redacted]s from the Canadian laboratory to the U.S. location. Please submit responses to items 1, 2, and 5 of this IR letter to the Pentacel BLA.

   b. Please provide control charts that include data for assays performed at both the U.S. and Canadian laboratories using [redacted]. Please identify the high control serum used for each assay.

c. The following items pertain to Table 4, "OD Results for Experiments examining the FIM reactivity in PT Antigen Lot [redacted] using [redacted]," (May 2, 2007, cr_response.pdf page p. 128):

i. During the meeting of May 18th, you indicated that Table 4 contained decimal place errors. Please provide a corrected copy of the table and the raw data that were used to determine the values listed in the table.

ii. Please provide the reactivity of PT [redacted] with the fimbriae [redacted]. Please present this information in tabular form together with reactivity data (generated in the same assay) of lots of newly purified PT [redacted], available historical lots of PT [redacted] (in particular lots [redacted], any potential candidate PT [redacted], available purified antigen from alternate sources and appropriate positive and negative controls. Please provide the raw data used to generate the tabular summary.

d. The following comments pertain to Table 4 (May 2, 2007, cr_response.pdf p. 9).

i. Please provide detailed descriptions of the test methods and all calculations used to determine [redacted]

ii. Please provide experimental evidence demonstrating the accuracy of the percent fimbriae contamination of the PT [redacted] listed in this table. Such data may be the results of experiments spiking a PT preparation with no demonstrable fimbriae contamination (e.g. determined with [redacted] with appropriate, known amounts of fimbriae and then measuring the fimbriae content in the PT preparation using your normal methodology.

e. Please provide evidence to support your hypothesis that fimbriae contamination of the [redacted] is the only factor contributing to the increase in PT antibody levels observed when post-dose 4 sera or sera from adults/adolescents are assayed using PT [redacted] as compared to lot [redacted]

f. The acceptance criteria applied to PT [redacted] used in your Canadian [redacted] and U.S. [redacted] laboratories are listed in Table 5 (May 2, 2007, cr_response.pdf p. 9).

i. Please revise the acceptance criteria, stated in SOP SWI J003789, for comparison of the new [redacted] to the previous [redacted] as follows: At least [redacted] samples should be evaluated and greater than or equal to [redacted] of the results must be within [redacted] of the calculated results with the previous [redacted].

ii. Please describe the procedure used at [redacted] for evaluation and release of a new [redacted]. Please provide the acceptance criteria for a new [redacted]

g. Certain conclusions presented in your submission of May 2, 2007, are based on comparisons of anti-PT responses measured in assays that utilized different lots of PT [redacted]. For example, your conclusion that post-dose 3 GMCs are relatively insensitive to [redacted] and your conclusion that the anti-PT response following Pentacel administered in Study P3T06 (assayed in the U.S. laboratory) is non-inferior to the anti-PT response following DAPTACEL administered in Sweden I (assayed in the Canadian laboratory) both rely on direct comparisons between assays that utilize different lots of PT [redacted]. Because [redacted] of a test sample is reported relative to the reference, the performance of the reference(s) with the different lots of [redacted] must be taken into account when evaluating these data. Please provide the lot(s) of reference used and detailed information on the performance of the references used in both the U.S.

and Canadian laboratories with the [redacted]. In your response please ensure that data are included addressing how the references perform with the different [redacted] relative to a control serum that does not contain detectable anti-fimbriae antibodies.

2. Based on discussions during the meeting, we are assuming that immunogenicity analyses using anti-PT [redacted] data generated in your U.S.-facility will be necessary to support a non-inferiority claim of Pentacel relative to DAPTACEL. Thus, we recommend that you develop and provide a comprehensive plan for assessment of immunogenicity of the PT component of Pentacel using a validated assay in your U.S.-facility. In our fax of May 17, 2007 we proposed an evaluation of the immunogenicity of the PT component of Pentacel based on re-assay of available Pentacel and DAPTACEL sera from Study P3T06. The acceptability of this approach depends on the availability of sufficient sera for re-assay and the ability to demonstrate that the available sera are representative of sera from the PPI and ITT populations. Your plan should include statistical power calculations based on available sera for assessment of non-inferiority of anti-PT responses following three and four doses of Pentacel and DAPTACEL (GMC and percent of subjects achieving a 4-fold rise). If sufficient sera from P3T06 are not available and you propose to use sera from subjects immunized with Pentacel and DAPTACEL in different studies please discuss. Please provide a justification for use of such sera to conduct a serological bridge in lieu of conducting a randomized, controlled study to compare the immune response following Pentacel and DAPTACEL.

3. Following our concurrence with your anti-PT [redacted] validation package (Item 1) and review and agreement with your plan for assessment of immunogencity of the PT component of Pentacel relative to DAPTACEL (Item 2) please provide the anti-PT immunogenicity data following three and four doses of Pentacel and DAPTACEL, including the results of non-inferiority analyses.

4. If you view the anti-PT [redacted] data generated in your Canadian laboratory and included in the BLA as adequate for the evaluation of Pentacel relative to DAPTACEL, and you do not concur that it is necessary to re-assay sera for anti-

PT in your US laboratory, please provide your rationale and supporting assay information and data.

We reserve comment on the proposed labeling until the application is otherwise acceptable.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Regulatory Project Manager, LCDR Edward Wolfgang, at (301) 827-3070.

Sincerely yours,

Paul Richman

Paul Richman, Ph.D.
Acting Director
Division of Vaccines
and Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research