DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Aventis Pasteur Incorporated
Attention: Luc Kuykens, M.D., M.P.H., D.T.M.
Vice President, Regulatory Affairs North America
Discovery Drive
Swiftwater, PA 18370-0187

Dear Dr. Kuykens:

We have completed the review of your submissions dated: July 26, September 13, 30, October 4, 5, 17, November 17, December 8, 2005; January 9, 16, February 24, April 21, 24, and 27, 2006, to your biologics license application (BLA) for Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus used to reconstitute Haemophilus b Conjugate Vaccine Combined (Pentacel™) for active immunization for the prevention of invasive *Haemophilus influenzae* type b disease, pertussis, diphtheria, tetanus and poliomyelitis caused by poliovirus Types 1, 2 and 3, submitted under section 351 of the Public Health Service Act.

We acknowledge receipt of your May 9, 2006, submission in response to information requested in the March 15, 2006, telephone conversation between CBER representatives and representatives of your office. You may refer to this submission as appropriate in response to pertinent items below.

The deficiencies are as follows:

The following items pertain to Study 494-01:

1. The Stage II study report, Table 5.3 (49401sii.pdf, page 83) provides information on completion of the 60-day follow-up post-dose 4 according to randomization. Because there were treatment errors in nearly 3% of subjects, please also provide this information according to actual treatment received at dose 4.

2. Please provide a summary table of withdrawals due to adverse events and protocol contraindications at any time during the study from dose 1 through the post-dose 4 follow-up period, for the Pentacel pooled lots and the Control group. For adverse events that led to withdrawal, please include withdrawals initiated by either the parent(s) or the investigator.

3. The Stage I study report, Table 5.2 and associated text (49401si.pdf, pages 85 and 87) indicate that four Pentacel subjects and two control subjects withdrew due to an adverse event. However, Table 5.1 (49401si.pdf, page 86) indicates that five Pentacel subjects and one control subject withdrew due to an adverse event. Please clarify and rectify this discrepancy.

4. Table 5.1 of the Stage I study report (49401si.pdf, page 86) indicates that Subject 2613 was withdrawn from the study because of hives within one day following the first dose of Pentacel. Please provide any additional available clinical data on this adverse event (e.g., associated symptoms, duration, treatment).

5. The Stage II study report, Table 5.2 (49401sii.pdf, page 81) indicates that subject 725 withdrew due to nephrotic syndrome. Footnote #3 also implies that the subject withdrew due to a seizure. Please clarify.

6. The Stage I study report (49401si.pdf, page 117) indicates that Subject 3141 experienced urticaria within 30 minutes following the third dose of Pentacel, but was not discontinued from the study.

   a. Please provide any additional clinical information on this event (e.g., associated symptoms, duration, treatment).

   b. Please summarize the post-dose 4 safety data for this subject.

7. In the analyses of solicited local and systemic adverse events, depending on dose number and event, approximately 10-15% of subjects in the ITT safety population who received the particular dose were excluded.

   a. Please provide an explanation for this rate of exclusion of subjects from these analyses.

   b. Please discuss the potential for biased estimates of adverse event rates that may result from this rate of exclusion.

8. For Stage I Tables 5.15, 5.16, 5.22, 5.23 and Stage II Tables 5.19 and 5.23, please indicate which routes of temperature measurement (rectal, axillary, oral, tympanic, not specified) were included in the analyses of fever.

9. In the non-inferiority analyses of fever rates (Pentacel vs. Control) (e.g., Stage I Table 5.16) and in the tables on the frequencies of solicited systemic adverse events within three days post-vaccination (e.g., Stage I Table 5.22), it appears that the numbers of subjects included in the analyses of fever are less than the total number of subjects with rectal and axillary temperatures (e.g., Stage I Table 9.29). Please explain this apparent inconsistency in the numbers of subjects included in the relevant analyses of fever, and provide corrected tables, if needed.

10. As described in Item 9 above, we have also noted inconsistencies in the numbers of subjects included in the Stage II analyses of fever (e.g., Stage II Tables 5.19, 5.23, and 9.24). Please explain the apparent inconsistencies, and provide corrected tables, if needed.

11. The case narrative for Subject 0008 indicates that the subject had a seizure associated with fever, as well as subsequent seizures not associated with fever (49401_addnl_safetyanalyses.pdf, page 12). Therefore, please clarify why the subject is classified as having only afebrile seizures in Table 1 (49401_addnl_safetyanalyses.pdf, page 7).

12. The case narrative for Subject 1958 indicates that the subject had a seizure associated with fever, as well as a subsequent seizure for which no additional clinical information was available (49401_addnl_safetyanalyses.pdf, page 14). Therefore, please clarify why the subject is classified as having only afebrile seizures in Table 1 (49401_addnl_safetyanalyses.pdf, page 7).

13. The adverse event in the case narrative for Subject 0066 is referred to as both a "possible febrile seizure" and a "febrile seizure" (49401_addnl_safetyanalyses.pdf, page 14). In Table 1 (49401_addnl_safetyanalyses.pdf, page 8), the event is listed as a febrile seizure. Please clarify whether this event should be classified as a febrile seizure or possible seizure.

14. For Subject 2501, case narratives for the event of seizures were provided in the Stage II study report (49401sii_b.pdf, page 6690) and in Amendment 1 (49401_addnl_safetyanalyses.pdf, page 15). Some of the clinical details for this serious adverse event differ in the two narratives (e.g., unspecified head injury vs. head hit by a swing; Stage II report indicates that following onset, there were seven episodes of seizures over the next

11 days; Amendment 1 implies there was only one occurrence of seizures). Please explain and resolve these differences.

15. The case narrative for Subject 3710 (49401_addnl_safetyanalyses.pdf, page 20) indicates that this subject experienced "infantile spasms (questionable seizure)" 26 days following dose 3 of Pentacel, and recovered without sequelae 16 days later. Please provide further details of the clinical course during the 16 days until resolution.

16. Subject 1230 developed a seizure disorder secondary to anoxia and ischemic encephalopathy, as a post-operative complication of cardiac surgery (49401si_d.pdf, page 12817). Subject 3449 discontinued due to migraine variant seizure activity (49401si.pdf, page 85). However, we note that these subjects were not included in the enumeration of seizures (e.g., 49401_addnl_safetyanalyses.pdf, pages 7-11).

    a. Since no criteria were specified for exclusion of certain types of seizures from the analyses, we recommend inclusion of all seizures regardless of underlying etiology and type in the calculations of seizure rates. CBER's evaluation of the data on seizures will take into account the clinical characteristics of the seizures. Therefore, please provide revised rates of seizures in response to Items 4 and 5 of CBER's July 5, 2005 FAX (49401_addnl_safetyanalyses.pdf), as needed, to include Subjects 1230, 3449, and any other subjects with seizures that may not have been included.

    b. Please revise Table 1 of 49401_addnl_safetyanalyses.pdf, as needed, to include all diagnoses of seizures.

    c. Please provide a case narrative for migraine variant seizure activity in Subject 3449.

17. Tables of serious adverse events submitted in Amendment 1 (e.g., Tables 9.13, 9.17, 9.18; 49401_addnl_safetyanalyses.pdf) indicate that one subject experienced sepsis within 7 days following dose 1 of Pentacel. However, based on the case narratives for serious adverse events included in Appendix 17 of the final study report, there appear to be no cases of sepsis

within 7 days following Pentacel. Please clarify and provide corrections.

18. The serious adverse event case narrative for Subject 1781 (49401si_d.pdf, page 12840) indicates that the results of blood and cerebrospinal fluid culture were pending at discharge. Please provide these results.

19. We note that there was one case of autism within three days following the fourth dose of Pentacel (49401_addnl_safetyanalyses.pdf, page 260). This event was not included in the tables of serious adverse events.

    a. The protocol-specified definition of serious adverse events included events that resulted in persistent or significant disability/incapacity. Please explain why autism was not classified as a serious adverse event.

    b. Please provide a summary of all adverse events that resulted in a persistent or significant disability/incapacity but were not classified as serious adverse events.

    c. Please provide a case narrative for the case of autism.

20. We note that there were two positive blood cultures in the HCPDT group and one positive blood culture in the Pentacel group within 30 days following any dose that were listed as unsolicited adverse events (49401_addnl_safetyanalyses.pdf, page 93). It appears that none of these events were listed as serious adverse events in Tables 9.11 and 9.17 (4949401_addnl_safetyanalyses.pdf, pages 59-61 and pages 70-71). For each of these events, please indicate the organism isolated. Also, please provide additional clinical information to justify the classification as non-serious. If the events should be classified as serious please make the necessary corrections to the relevant tables of serious adverse events.

21. The text of the Stage I study report (49401si.pdf, page 149) indicates that 39 Pentacel subjects and 18 control subjects experienced at least one serious adverse event within 60 days post-immunization. Table 9.51 (49401si.pdf, page 3206) indicates that 37 Pentacel subjects and 17 control subjects experienced at least one serious adverse

event within 60 days post-immunization. Please resolve this apparent discrepancy.

22. For the HCPDT and Pentacel groups (pooled lots for doses 1-3), please provide the incidence of any serious adverse event (number, percent and 95% confidence interval), per subject, that occurred:

    a. during the entire study period (post-dose 1 through end of the 60 day follow-up post-dose 4).

    b. within 60 days following any dose (doses 1-4).

    c. within 30 days following any dose (doses 1-4).

    d. within seven days following any dose (doses 1-4).

23. Please confirm whether the composition of control vaccine HCPDT as described in the Stage I and Stage II final study reports (49401si.pdf page 50 and 49401sii.pdf page 49) is correct with regard to [redacted] bovine serum, polymyxin B and neomycin.

24. As described in the protocol (49401si.pdf page 4557), the per-protocol immunogenicity (PPI) population includes subjects with no protocol violations but does include those with "protocol deviations" and other conditions, including protocol violations, if a sponsor waiver was obtained from the Medical Monitors.

    a. Please provide the number of subjects with protocol deviations included in the PPI populations for Stage I and II.

    b. Please identify how many subjects in the PPI population for each group had a protocol violation for which a sponsor waiver was obtained by the study site.

25. You have provided analyses of lot consistency and non-inferiority using the 2-sided 90% CI on the difference in seroresponse/seroprotection rates and the ratio of GMTs. Consistent with current CBER recommendations, please provide these analyses of equivalence and non-inferiority using 2-sided 95% CI. We acknowledge that these are post-hoc analyses not specified in the protocol.

26. The September 13, 2005, submission to this BLA includes data demonstrating that two subjects (2/42) with anti-tetanus levels of 0.082 IU/mL and 0.124 IU/mL as measured by ELISA did not have seroprotective levels ≥0.01 IU/mL as measured by [redacted] (red_00005321.pdf page 5). Therefore, we consider the analyses of lot-consistency and non-inferiority post-dose 3 using anti-tetanus level ≥ 0.1 IU/mL rather than ≥0.01 IU/mL to be more meaningful even though statistical criteria were not pre-specified. Please acknowledge.

27. According to the protocol, the first 478 subjects per group were to be bled for immunogenicity. The information provided (49401si.pdf page 87) indicates that 428-468 subjects per group received three doses of vaccine and were bled post dose 3.

    a. Please provide the number of subjects bled pre dose 1 and pre dose 4.

    b. The number of subjects excluded from the analyses of seroresponse/seroconversion represent up to 12% of the PPI population (for example, in Stage I analyses of seroresponders to pertactin in recipients of Pentacel lot 3, 325 subjects were evaluated, but PPI = 370). We understand that subjects may have been excluded from analysis due to lack of a pre-bleed sample or because of a hierarchical performance of serology testing.

        i. Please explain why none of the per-protocol analyses presented include the entire PPI population.

        ii. Please provide a summary of reasons for exclusions from the PPI analyses for each study group during Stage I and II.

28. The PPI Population used in Stage II analyses was defined "as all eligible subjects who received all 3 doses (regardless of treatment error) in Stage I and the correct randomized vaccine for dose 4..." Thus, subjects included in the PPI analyses may not have received the same vaccine for all four doses.

a. For each Stage II vaccine group please provide the number of subjects who did not receive the correct vaccine for any of the previous three doses.

b. For each per-protocol immunogenicity analysis presented in the 494-01 Stage II study report please provide the analysis for all eligible subjects who received the correct vaccine for all four doses, had all doses and blood draws within specified windows, and had a valid serology result for the relevant study antigen post dose 4.

29. As stated for Stage I Observational Objective #1 (Protocol version 13, Section 7.3.1.1), please compare the anti-hepatitis B GMTs and seroprotection rates from Study 494-01 with immune response data in the package inserts for RECOMBIVAX HB and COMVAX, and discuss the apparently lower responses observed in Study 494-01.

30. Please provide the percent of subjects with pre-dose 4 anti-tetanus levels ≥0.1 IU/mL and anti-diphtheria levels ≥0.1 IU/mL.

31. The study report for 494-01 Stage II (49401sii.pdf page 107) provides additional analyses of the response to PRP in those subjects with anti-PRP levels <0.15 ug/mL and <1.0 ug/mL post-dose 3. We note that among 46 subjects with an anti-PRP level <0.15 ug/mL one month post-dose 3, approximately 11% had an anti-PRP level ≥0.15 ug/mL (one subject ≥1.0 ug/mL) prior to administration of the fourth dose of ActHIB or Pentacel. Of subjects with an anti-PRP level <1.0 ug/mL post-dose 3, five had an anti-PRP level ≥1.0 ug/mL prior to administration of the fourth dose of Pentacel or ActHIB. Please discuss potential reasons for an increase in anti-PRP levels in some subjects between doses 3 and 4. In your response, please address the performance of the anti-PRP [redacted] (see also Item 140), and other potential contributing factors.

32. For subjects in the PPI populations who received all four doses of the same vaccine, please provide the post-dose 4 GMTs for each of the pertussis antigens stratified by the post-dose 3 pertactin level categorized as: <5, ≥5-<10, ≥10-≤20, >20 and <5-≤20 EU/mL.

The following items pertain to the Serology Bridge to Sweden 1:

33. To be consistent with CBER's current policy, please provide analyses of non-inferiority of GMTs using 2-sided 95% CIs. We acknowledge that these are post-hoc analyses not specified in the protocol.

34. You have provided (bridge.pdf page 49) a summary of the pertussis antibody seroresponse rates and GMTs following three doses of DAPTACEL in Sweden 1 and 4 doses of Pentacel in 494-01 relative to pre-dose 1 levels. Please provide the pre-dose 1 GMTs for subjects included in each of the pre-dose 1 categories.

The following items pertain to Study 494-03:

35. A routine audit of [redacted], conducted in January 2001, identified no problems. A "for cause" audit also was conducted because the [redacted] Principal Investigator reported potential non-conformances with Good Clinical Practices (GCP). This audit identified non-conformances related to subject rights, vaccine administration, proper documentation, and product accountability.

    a. Please provide a chronology, with dates, of the conduct of the study at [redacted] including the enrollment period, routine site visits as described in the protocol, routine audit(s), identification of potential non-conformances with Good Clinical Practices by the site principal investigator, and the "for cause" audit.

    b. Please provide the audit certificate and any other documentation from the "for cause" audit.

    c. Please discuss why the routine site visits and the routine audit did not identify the problems that were identified during the "for cause" audit.

    d. Please comment on any changes to the site audit program to enhance the ability to detect GCP deficiencies as a result of the additional audit of [redacted]

36. Appendix 15 contains line listings of demographic and safety data for subjects from Center 10 who were excluded

from the analyses. For Center 10 subjects, please provide the following items:

a. A summary table of subject disposition for Stages I and II, including the number of doses of Pentacel received, completion of follow-up, and reasons for not completing follow-up.

b. A summary analysis of demographic characteristics.

c. Analyses of solicited local and systemic adverse events within three days following each dose of Pentacel.

d. A listing of any seizure, possible seizure, HHE, or hypotonia following any dose of Pentacel.

37. For the safety population, please indicate the number of subjects who received hepatitis B vaccine on a 2, 4, 6 month schedule vs. a 0, 2, 6 month schedule.

38. In the analyses of solicited local and systemic adverse events, depending on dose number, event, and Stage II study group, approximately 5-20% of the ITT safety population who received the particular dose were excluded from the analyses.

a. Please provide an explanation for this rate of exclusion of subjects from these analyses.

b. Please discuss the potential for biased estimates of adverse event rates that may result from this rate of exclusions.

39. Two subjects reported an increase in limb circumference graded as severe (>40 mm) involving the Pentacel vaccinated arm (49403sii.pdf, page 203) post dose 4. Please provide the maximum increase in limb circumference reported by each of these subjects.

40. For the analyses of fever in Study 494-03 Stage I Table 5.9 and Stage II Table 5.20, please clarify which routes of temperature measurement were used.

41. For the analyses of fever in Stage I Table 5.9, it appears that the numbers of subjects included are less than the total number of subjects with rectal and axillary

temperature measurements (e.g., Stage I Table 9.20). Please explain this apparent inconsistency in the numbers of subjects included in the analyses of fever, and submit corrected tables, if necessary.

42. As described in Item 41 above, we have also noted inconsistencies in the numbers of subjects included in the analyses of fever in Stage II Tables 5.20 and 9.28. Please explain these apparent inconsistencies in the numbers of subjects included in the Stage II analyses of fever, and submit corrected tables, if needed.

43. Subject 0346 who presented with neurological symptoms eight days following Pentacel was diagnosed with "congenital encephalopathy." Please indicate whether a more specific diagnosis was eventually made, and provide any additional available clinical information that formed the basis for that diagnosis.

44. In the study report for Study 494-03 Stage I, the outcome for the event of truncal hypotonia in Subject 303 was "Event is continuing." Please provide any available updated information on the outcome of this event.

45. The final study report for Study 494-03 Stage I indicates that Subject 0473 died of possible SIDS 52 days following the first dose of Pentacel, that the case was under investigation, and that no additional information was available to the investigator. Please provide any additional information that may have become available for this case.

46. According to the serious adverse event case narrative for pneumonia, Subject 0352 presented with vomiting, diarrhea, and fever and was admitted to the hospital to rule out sepsis (49403si.pdf, Appendix 17). She had an unremarkable chest x-ray. In the case narrative there is no mention of respiratory symptoms or findings. Please explain the basis for the diagnosis of pneumonia.

47. We note that Subject 1213 presented with hydrocephalus and underwent ventriculoperitoneal shunt insertion within 14 days following the third dose of Pentacel (49403si.pdf, Appendix 17), and recovered with sequelae.

a. Please explain why this event was not included as a neurological event in Amendment 1, Tables 9.12, 9.15, and 9.17 (49403_addnl_safetyanalyses.pdf).

b. Please provide any available follow-up information on this subject's clinical course.

48. We note that two serious adverse events, mastoiditis 12 days post-vaccination (Subject 0112) and *E. coli* pyelonephritis 11 days post-vaccination (Subject 0497), were not included as serious bacterial infections in Tables 9.12 and 9.17 in Amendment 1 (49403_addnl_safetyanalyses.pdf). Please explain why these events were not considered serious bacterial infections. Please make any necessary corrections to the relevant tables.

49. We note that there was one case of pertussis reported within 60 days following the second dose of Pentacel (49403si.pdf, Table 9.27). Please provide any additional available information on this case of pertussis.

50. We note that there were two cases of "Sepsis NOS," one case of status asthmaticus, and one case of malignant histiocytosis within 60 days following Pentacel (49403si.pdf, Table 9.27 and 49403_addnl_safetyanalyses.pdf, Table 9.28) that were not considered serious adverse events (49403si.pdf, Table 9.40). Please provide any additional available information on these events and explain why they were not considered serious adverse events. If these events should be classified as serious adverse events, please provide corrected tables, as needed.

51. Please provide the incidence, per number of subjects, of any serious adverse event (number, percent and 95% confidence interval), for the four Stage II study groups pooled, that occurred:

a. During the entire study period (post-dose 1 Pentacel through end of the 60 day follow-up post-dose 4 Pentacel).

b. Within 60 days following any dose (doses 1-4) of Pentacel.

c. Within 30 days following any dose (doses 1-4) of Pentacel.

d. Within seven days following any dose (doses 1-4) of Pentacel.

52. The study reports for 494-03 Stage I and II acknowledge an inadvertent error in the protocol which permitted blood draws 21-48 days after administration of vaccines at 6 months and 15 months of age. The correct interval was 28-48 days. Please provide the number of subjects in the PPI populations for Stage I and II who provided blood samples 21-27 days after vaccination.

53. The response to hepatitis B vaccine when administered at 0, 2 and 6 months of age or at 2, 4 and 6 months of age appears lower than expected. Please discuss these results.

54. Please provide the number of subjects in each group bled prior to administration of vaccine at 15 months of age.

55. The expected seroresponse rate for mumps (by ELISA) was 98.4% (49403sii.pdf page 1244). The data presented indicate lower than expected mumps seroresponse rates in both study groups evaluated (i.e., by ELISA only: 71.4% in Stage II Group 2 and 69.4% in Stage II Group 4). When the definition of seroresponder was based on ELISA or neutralization assay the seroresponse rates increase (98.1% in Stage II Group 2 and 97.2% in Stage II Group 2) (49403sii.pdf page 665). Please discuss the lower than expected mumps seroresponse rates observed in Study 494-03, including potential factors that may have contributed to this finding.

56. Please clarify the appropriate criterion for mumps seroresponse based on ELISA: >500 IU/mL as specified in the protocol or ≥500 IU/mL as used in the analysis. If necessary, please provide revised analyses using the proper threshold for seroresponse.

57. Please clarify the appropriate criterion for measles seroresponse based on ELISA: >300 mIU/mL as specified in the protocol or ≥300 mIU/mL as used in the analysis. If needed, please provide revised analyses using the correct threshold for seroresponse.

The following items pertain to Study 5A9908:

58. Regarding the study population for Study 5A9908:

    a. Please describe how subjects were recruited for the study.

    b. Please provide information on the rate of participation among eligible subjects who were contacted to participate.

    c. If available, please provide information on reasons for non-participation.

    d. Please provide any available information to evaluate whether subjects who participated in Study 5A9908 are representative of all eligible subjects who received doses 1-3 of Pentacel.

59. The study report indicates that as a result of the clinical safety database audit, the number of solicited systemic reactions decreased due to solicited reactions having also been reported as unsolicited adverse events (5a9908.pdf, page 41). Please explain why the corrective action was to decrease correctly reported solicited events rather than to remove these events from unsolicited events.

60. One subject had urticaria of moderate severity within 30 minutes following receipt of Pentacel (5a9908.pdf, page 77). Please indicate any treatment administered and the duration of the event.

61. Eighteen subjects reported "severe" (>40 mm) increased limb circumference within 0-3 days following Pentacel (5a9908.pdf, Table 5.10).

    a. Please provide data to further quantitate the sizes of these reactions (e.g., >40-50, >50-60, >60-70, etc.).

    b. Please provide the range and median of these measurements.

62. Table 9.28 of 5a9908.pdf provides the frequency of fever each day after vaccination by temperature measurement route and severity. For the four study groups combined, please provide the frequency of fever during the period 0-3 days

post-vaccination, by temperature measurement route and by severity.

63. For the analyses of fever presented in Tables 5.8, 5.13, and 5.14 of 5a9908.pdf, please specify all routes of temperature measurement that were included.

64. The case narrative for the febrile seizure in Subject 5170 (5a9908_addnl_safetyanalyses.pdf, pages 9-10) indicates that "there was no fever." Please explain why this event was classified as a febrile seizure rather than an afebrile seizure, and provide any necessary corrections.

65. We note that among reported serious adverse events, there were two cases of pyelonephritis (Subjects 7159 and 5107), one case of orbital cellulitis (Subject 2248), and one case of "bacterial infection" with jaw swelling (Subject 7156) that occurred within 60 days post-vaccination. Please explain why these events were not counted as "serious bacterial infections" (5a9908_addnl_safetyanalyses.pdf, Table 9.12 and Table 9.13). Please provide any necessary corrections to the relevant tables.

66. For Subject 7159, the case narrative for kidney infection, indicates that the subject developed fever 12 days post-immunization. There is no mention of any urinary tract signs, symptoms, or diagnostic studies. Please clarify the basis for the diagnosis "kidney infection."

The following items pertain to Study P3T06:

67. The DAPTACEL data from Study P3T06 are also currently under review in DAPTACEL Supplement 103666/5071. We acknowledge your May 10, 2006, responses to the complete response letter issued October 17, 2005. Our interpretation of the Pentacel data from study P3T06 will take into account the responses to items pertaining to the safety of DAPTACEL and the immunogenicity of the pertussis component conveyed in the DAPTACEL Supplement complete response letter. Please acknowledge.

68. In Table 5.1 "Summary of Subject Disposition in Stage I" (p3t06si.pdf, pages 79-80), under the heading "ITT Safety Population," there is a row labeled "Received All 3 doses of DAPTACEL or Pentacel." Subsequently, there is a separate subheading labeled "Received All 3 Doses of DAPTACEL or Pentacel." We note that for DAPTACEL Lot 3,

Pooled DAPTACEL, and Pentacel, the numbers in these two rows are different. Please explain these differences.

69. The Stage II study report indicates that one subject in DAPTACEL group 2 (Subject 0522) was discontinued for a contraindication. Please specify the contraindication that led to discontinuation.

70. There was one case of an allergic reaction and one case of urticaria within 30 minutes following DAPTACEL (p3t06si.pdf, page 108 and p3t06sii.pdf, pages 109-110). Please provide case narratives describing these events in further detail, including duration, associated symptoms, and any treatment administered. Please also specify if either of these events was considered a contraindication to receipt of subsequent doses of DAPTACEL or other vaccines. Please provide safety data following subsequent doses of vaccines, if administered.

71. In the analyses of solicited local and systemic adverse events following the fourth dose of study vaccines, approximately 10% of subjects in the ITT safety population were excluded.

    a. Please provide an explanation for this rate of exclusion of subjects from these analyses.

    b. Please discuss the potential for biased estimates of adverse event rates that may result from this rate of exclusion.

72. Please provide an analysis of the frequency of rash all over the body that occurred between 0-3 days after vaccination for the pooled DAPTACEL groups and the Pentacel group for doses 1-3, and by Stage II study group for dose 4.

73. For each dose of Pentacel, DAPTACEL, and other Control vaccines, for subjects who reported injection site redness, injection site swelling, or increased arm circumference graded as severe within three days following vaccination, please provide an ordered listing of the actual sizes measured. For doses 1-3 of DAPTACEL and other Control vaccines, please provide the data for the three study groups pooled. For dose 4 of DAPTACEL and ActHIB, please provide only the data for Stage II Group 1.

74. Stage I Tables 5.21 and 5.24 (p3t06si.pdf, pages 116 and 124, respectively) and Stage II Table 5.20 (p3t06sii.pdf page 117) provide information on routes of temperature measurement (axillary, rectal, oral, unspecified).

    a. Please indicate whether these tables include measurements obtained using a tympanic thermometer (e.g., tympanic thermometer on oral or rectal setting).

    b. Please revise the tables, as needed, to re-classify temperature measurements obtained using a tympanic thermometer as tympanic.

75. Please indicate which routes of temperature measurement (i.e., axillary, rectal, oral, tympanic, other, unspecified) were included in the analyses of fever presented in Stage I Tables 5.25-5.28, 9.17-9.19, 9.23, 9.24, and 9.25, and in Stage II Tables 5.21-5.24, 9.17-9.19, and 9.23.

76. We note that in Stage I Table 9.22 and Stage II Table 9.22, the combined denominators for axillary and rectal measurements exceed the denominators used in tables that present fever, irrespective of route of temperature measurement. For example, in Stage I Table 9.22, the combined denominator for axillary (N=684) and rectal (N=760) measurements within 0-3 days post-dose 1 DAPTACEL (pooled lots) is 1444. In contrast, in Stage I Table 5.25, the denominator used for the analyses of fever within 0-3 days post-dose 1 DAPTACEL (pooled lots) is 1390. For both Stage I and Stage II, please explain the apparent discrepancies in the denominators used for the analyses of fever, as noted above. Please provide any necessary corrections to the relevant tables.

77. Please provide a summary table of the frequencies of solicited local reactions, by severity (any, moderate or severe, and severe) at the Pentacel or DAPTACEL injection sites occurring within 0-3 days after each dose of study vaccines. For doses 1-3 of DAPTACEL, please provide the data for the pooled Stage I lots. For dose 4 of DAPTACEL, please provide the data only for Stage II Group 1. In the table, please provide the number and percent of subjects with each specified event (by severity), with 95% confidence intervals.

78. Please provide a summary table of the frequencies of solicited local reactions, by severity (any, moderate or severe, and severe) at the Pentacel or Control injection sites (highest severity of all control injection sites) occurring within 0-3 days after each dose of study vaccines. For doses 1-3 of Control vaccines, please provide the data for the pooled Stage I groups. For dose 4 of Control vaccines, please provide the data only for Stage II Group 1. In the table, please provide the number and percent of subjects with each specified event (by severity), with 95% confidence intervals.

79. Please provide a summary table of the frequencies of solicited systemic adverse events, by severity (any, moderate or severe, and severe) that occurred within 0-3 days following each dose of Pentacel or DAPTACEL. For doses 1-3 of DAPTACEL, please provide the data for the pooled Stage I lots. For dose 4 of DAPTACEL, please provide the data only for Stage II Group 1. Please include two separate analyses of fever, without any conversions: a) all measurements (i.e., any route specified or route not specified), and b) all rectal and axillary measurements. In the table, please provide the number and percent of subjects with each specified event (by severity), with 95% confidence intervals.

80. For each solicited local (Pentacel or DAPTACEL injection sites) and systemic adverse event, please provide summary analyses of subjects who had events that did not resolve by day 7 post-vaccination, including information on duration of the events. For subjects who received DAPTACEL, please provide dose 1-3 analyses for the Stage I lots pooled and dose 4 analyses for Stage II Group 1 only.

81. We note that in Stage II Table 5.27 "Subjects with seizure..." (p3t06sii.pdf, page 133), the study group listed for Subject 2416 is Group 3. In contrast, in Table 1 of Amendment 1 (p3t06addnl_safetyanalyses.pdf), the group listed for Subject 2416 is Group 4. Please indicate the correct study group, and specify which vaccines Subject 2416 received at each dose.

82. Please provide a summary table(s) with the number and percent of subjects (and 95% confidence intervals) with a) seizures (febrile and afebrile); b) febrile seizures; and c) afebrile seizures, for the pooled DAPTACEL lots and the Pentacel group for the following periods: 0-30 days

following any of doses 1-3 and 0-7 days following any of doses 1-3.

83. Please provide a summary table(s) with the rate per 1000 doses (and 95% confidence intervals) of a) seizures (febrile and afebrile); b) febrile seizures; and c) afebrile seizures, for the pooled DAPTACEL lots and the Pentacel group for the following periods: 0-30 days following any of doses 1-3 and 0-7 days following any of doses 1-3.

84. Please provide any additional available data on the event of hypotonia following DAPTACEL in Subject 0293 (p3t06si.pdf, page 141).

85. In Amendment 1, you have provided analyses of serious adverse events of interest occurring within 30 days following each dose of study vaccines (p3t06_addnl_safetyanalyses.pdf, Tables 9.13 through 9.16). Please provide similar analyses of serious adverse events of interest occurring within 30 days following any of doses 1-3 of Pentacel or DAPTACEL (pooled lots). For the category "asthma and related diagnoses," please include all cases of bronchiolitis, whether or not there was laboratory evidence of RSV infection.

86. Please provide a table of serious adverse events classified by MedDRA system organ class and preferred terms that occurred within 30 days following any of doses 1-3 of Pentacel or DAPTACEL (pooled Stage I lots), including numbers of subjects, percentages, and 95% confidence intervals.

87. Please provide a table of serious adverse events classified by MedDRA system organ class and preferred terms that occurred within 30 days following dose 4 of Pentacel or DAPTACEL (Stage II Group 1 only), including numbers of subjects, percentages, and 95% confidence intervals.

88. According to Stage II Table 5.28, 19 subjects included in Stage II Group 4 (Pentacel) experienced serious adverse event(s) prior to dose 4. However, in the serious adverse event case narratives included in Appendix 17, these subjects are categorized in DAPTACEL Group 3. Please clarify the correct study group for these subjects.

89. At the time the study report for Stage II P3T06 was prepared, the autopsy report for Subject 0493 was pending. This subject died eight days following the fourth dose of Pentacel, presumably due to suffocation. If available, please provide information from the autopsy report for this subject.

90. According to the case narrative for Subject 1814 (p3t06si_c.pdf, page 13152), the subject developed bloody stools and respiratory distress ten days post-vaccination and was admitted to the hospital. The subject tested positive for RSV and was treated with oxygen and "breathing treatments." In your summary table of serious adverse events (p3t06si.pdf, pages 144-150) and presumably in Stage I Tables 9.45, 9.46, 9.49, 9.50, the only serious adverse event listed for this subject is "bloody diarrhea." Please explain why respiratory distress and RSV were not considered serious adverse events in this subject, and revise tables of serious adverse events, if needed.

91. According to the case narrative for Subject 1891 (p3t06si_c.pdf page 13156), blood and sputum cultures obtained during the subject's first hospitalization grew *H. influenzae*. Please indicate the results of *H. influenzae* typing for these cultures, if available.

92. According to the case narrative for Subject 0919 (p3t06si_c.pdf, page 13173), the subject was admitted to the hospital following symptoms of infectious gastroenteritis. A WBC count showed neutropenia with an absolute neutrophil count of 295. Although the neutropenia was thought to be due to viral suppression, please explain why neutropenia was not listed as a serious adverse event for this subject in the summary table of serious adverse events (p3t06si.pdf, pages 144-150). Please revise the summary table and any other serious adverse event tables if needed.

93. According to the case narrative for Subject 0761 (p3t06sii_c.pdf, page 8497), following two days of fever and fussiness, the subject was admitted to the hospital for dehydration. Blood and urine cultures were positive for *E. coli*. In your summary table of serious adverse events (p3t06sii.pdf, pages 135-142), the only serious adverse event listed for this subject is "dehydration." Please explain why *E. coli* bacteremia was not considered a serious

adverse event and revise any tables of serious adverse events, if needed.

94. According to the case narrative for Subject 2111 (p3t06sii_c.pdf, page 8527), following a febrile episode, the subject was hospitalized due to a rash accompanying ataxia. She was found to have neutropenia, with measured absolute neutrophil counts between 0 and 200, and was treated with granulocyte colony stimulating factor. In your summary table of serious adverse events (p3t06sii.pdf, pages 135-142), the only serious adverse event listed for this subject is "viral infection." Please explain why neutropenia was not considered a serious adverse event and revise any tables of serious adverse events, if needed.

95. In your tables of unsolicited adverse events (p3t06si.pdf, Table 9.33, and p3t06sii.pdf, Table 9.33), there are three cases of orbital cellulitis, none of which were reported as serious adverse events. As the treatment for orbital cellulitis typically involves hospitalization with intravenous antibiotics and close monitoring for visual compromise, please explain why each of these cases of orbital cellulitis was not considered a serious adverse event, and revise any tables of serious adverse events, if needed.

96. In Stage I Table 9.33 on unsolicited adverse events that occurred within 60 days post-vaccination, there was one case of drowning, one case of hydrocephalus, and one case of blood culture positive. None of these events were included as serious adverse events within 60 days post-vaccination in Stage I Table 9.46. Please explain why these apparently serious adverse events were not classified as serious, and revise tables of serious adverse events, if needed.

97. Stage I Table 9.33 (p3t06si.pdf) indicates that there were two cases of pertussis reported within 60 days following the first dose of DAPTACEL. A case narrative was provided for one case of pertussis that was considered a serious adverse event. Please provide any additional available clinical information for the other case of pertussis that was not considered a serious adverse event.

98. One subject had petechiae within three days following DAPTACEL (p3t06si.pdf, Table 9.30). Please provide any additional information available on this event, including

more specific information on temporal relationship to vaccination, results of any diagnostic studies, etiology, treatment, and outcome.

99. The final safety follow-up on or after Day 180 following the fourth dose of Pentacel or DAPTACEL was conducted to inquire about serious adverse events, chronic events, or events of possible autoimmune origin that may have occurred since the previous contact (Day 60 post-dose 4). Please provide an analysis of chronic events and events of possible autoimmune origin that were captured through the final safety follow-up.

100. You have provided a tabulation and narrative description of subject disposition in Stage I and II of Study P3T06. For subjects in Stage I (DAPTACEL pooled and Pentacel) and II (Group 1 and 4) of Study P3T06 please provide the number of subjects per group who provided a blood sample pre-dose 1 and pre-dose 4 of DAPTACEL or Pentacel.

101. Please provide exploratory analyses of non-inferiority of three doses of DAPTACEL (pooled lots) as compared to Pentacel with regard to anti-tetanus levels ≥0.1 IU/mL post-dose 3.

102. The study report for P3T06 Stage I contains analyses of the pertussis immune response data based upon pre-vaccination antibody levels (see p3t06si.pdf, pages 3350 and 3354).

    a. Please explain how these antibody levels were chosen.

    b. Page 3354 presents the post-dose 3 response to pertussis antigens based on pre-dose 1 antibody levels. Please provide the post-dose 4 antibody response (% of subjects with a four-fold rise and GMT) based on the pre-dose 1 levels.

103. Table 9.79 presents the results of an observational analysis of diphtheria and tetanus responses based on pre-dose 4 levels (p3t06sii.pdf, page 956). Please clarify if subjects with pre-dose 4 anti-diphtheria and anti-tetanus levels <0.1 IU/mL were assessed for post-dose 4 levels >0.4 IU/mL or ≥0.4 IU/mL.

104. You have presented (Table 9.81, p3t06sii.pdf, pages 958-960) a summary of post-dose 4 GMT response to each pertussis antigen based on post-dose 3 anti-pertactin

levels < 5 EU/mL, ≥5-<10 EU/mL, ≥10-≤20 EU/mL and >20 EU/mL. Please present the data in this table according to the following post-dose 3 anti-pertactin levels: <5 - ≤20 EU/mL and >20 EU/mL.

105. In P3T06 Stage II non-inferiority was not demonstrated for the GMT response to pertactin following four doses of Pentacel as compared to four doses of DAPTACEL. To address how subjects with a low response to pertactin post-dose 4 respond to the other pertussis antigens please provide analyses of the post-dose 4 response to PT, FHA and fimbriae stratified by post-dose 4 anti-pertactin levels ≤20 EU/mL and >20 EU/mL.

106. The immune responses to RECOMBIVAX HB (seroprotective levels and GMTs) observed in Study P3T06 appear to be lower than that observed with previous clinical experience with RECOMBIVAX HB or COMVAX, and reported in the package inserts for these vaccines. The immune responses to RECOMBIVAX HB (seroprotective levels and GMTs) also appear to be lower than that observed in Pentacel Studies 494-01 and 494-03. Please discuss the lower than anticipated immune responses to RECOMBIVAX HB in Study P3T06 in the context of available data on the previous clinical experience with this vaccine as well as with COMVAX.

The following items pertain to studies 494-01, 494-03, 5A9908 and P3T06:

107. In the telecon of July 15, 2005, between CBER and representatives from your firm, we had recommended that for the presentation of data on unsolicited and serious adverse events of interest, cases of bronchiolitis for which laboratory testing for RSV was positive be counted separately from those in which laboratory testing for RSV was negative or not available. However, subsequently, based on our review of case narratives for serious adverse events in the pivotal studies of Pentacel, it appears that classification of cases of bronchiolitis by RSV positivity may not be reliable, as terms used for these adverse events may not necessarily reflect available diagnostic information. Therefore, for Studies 494-01, 494-03, P3T06 and 5A9908, for the responses to items 7a-d of the July 5, 2005, FAX, please provide revised calculations of serious adverse events in the category "asthma and related diagnoses" to include all occurrences of asthma, wheezing,

bronchiolitis, RSV and related diagnoses, irrespective of whether there was laboratory evidence for RSV infection.

108. Please indicate whether any subjects reported swelling of the entire injected thigh or upper arm following Pentacel or Control vaccines. If so, please summarize the data on associated local and systemic adverse events, and provide information on time of onset, duration, treatment, and outcome.

109. The study reports contain a summary of subject demographics for the safety population. Please provide this information for the PPI population for each of the pivotal studies.

110. Please provide exploratory analyses of the response to PRP-T (seroprotective rate ≥0.15 ug/mL, ≥1.0 ug/mL and GMT) and the 95% CIs, following three doses of ActHIB or Pentacel by race/ethnicity per study group for the PPI and ITT immunogenicity populations for studies 494-01, 494-03 and P3T06.

The following items pertain to Study M5A08:

111. Please clarify whether subjects who participated in Study M5A08 had received three previous doses of Pentacel.

112. Under "Events of Particular Interest" (m5a08.pdf, page 35), for 4 of 6 subjects with low blood count or low platelet count, additional clinical information and/or Subject numbers that can be linked to case narratives were provided. For the other two subjects who had low blood count or low platelet count, please specify the diagnoses and provide any available clinical information.

113. The study report for Study M5A08 indicates that life-threatening episodes were reported for 33 subjects in the Primary Analysis Population. Three of these episodes were considered possibly or probably related to Pentacel administration (febrile seizure, atypical Kawasaki disease, and allergic reaction). Please provide a tabular summary, categorized by System Organ Class/Preferred Term/Literal Term for all life-threatening episodes regardless of the investigator's assessment of relationship to vaccination.

The following items pertain to the historical non-IND studies of Pentacel:

114. For historical studies PERTB9402, PERTB9501, PERTB9502, PERTB9505, PERTB9506, and PERTB9601, Table 2.5 in iss.pdf indicates that serious adverse events were monitored through 60 days after each vaccination. However, the synopses and protocols either do not appear to indicate the duration of monitoring for serious adverse events or indicate that monitoring was for 30 days following the last dose of study vaccines. Please clarify the monitoring period for serious adverse events in these studies and indicate where this information is provided in the protocols.

115. For historical study PNF35299, we have noted multiple inconsistencies regarding administered vaccines noted in the serious adverse event case narratives (pnf35.pdf, pages 17-58) and in Listing 2 (pnf35.pdf, pages 395-403). For example, the case narrative for subject 002-00298 indicates that 7 days following pneumococcal conjugate vaccine, Pentacel and OPV, the subject experienced afebrile seizures. However, Listing 2 indicates that the subject experienced afebrile seizures 7 days following Pentacel and OPV. As another example, the case narrative for subject 001-00166 indicates that the subject developed gastroenteritis 20 days following pneumococcal conjugate vaccine, Pentacel, and OPV, but Listing 2 indicates that the subject had not received Pentacel.

    a. Please submit corrected versions of the serious adverse event case narratives and Listing 2 of serious adverse events for Study PNF35299.

    b. Please provide an analysis of all serious adverse events (classified by body system/literal term/preferred term) that occurred within 30 days following:

        i. Any dose of Pentacel administered concomitantly with pneumococcal conjugate vaccine.

        ii. Any dose of Pentacel administered without concomitant pneumococcal conjugate vaccine.

116. In Study 5A9703, there was one death due to SIDS 40-44 days following the second dose of Pentacel in a 23-week old

infant. Please indicate whether there were any deaths reported following Pentacel in any of the other historical studies listed in iss.pdf Table 2.5.

The following items pertain to post-marketing reports of adverse events:

117. In Section 5.3.9.1 Spontaneous Reports of Adverse Events, we have noted several apparent inconsistencies in the numbers of post-marketing reports of seizures, HHEs and deaths reported during the period 5/1/97 through 3/1/05. Table 5.24 indicates that there were 15 reports of convulsions, 8 reports of HHEs, and 5 non-SIDS deaths. In contrast, the text indicates that during the period of review, there were 11 medically confirmed and 5 consumer reports of convulsions (Section 5.3.9.1.1), 9 medically confirmed and 2 consumer reports of HHE (Section 5.3.9.1.2), and 7 cases with fatal outcome including 3 SIDS, one sudden death, one death subsequent to *H. influenzae* pneumonia and meningitis, and 2 with unknown cause (Section 5.3.9.1.4). Furthermore, Section 5.3.9.1.4.3 indicates that there are 5 cases of other unexplained deaths following Pentacel reported during the period under review.

    a. During the reporting period 5/1/97 through 3/1/05, please clarify the total number (medically confirmed, consumer reports, literature reports) of cases of the following, reported after Pentacel:

        (i) Seizures (including cases coded as convulsions or other seizure like diagnoses),

        (ii) HHEs (including cases coded as hypotonia that met the criteria for HHE provided in Section 5.3.9.1.2), and

        (iii) Deaths.

    b. For each death, please provide the cause of death, if known, and a summary of the available clinical and autopsy information.

118. For Table 5.24 of iss.pdf, please clarify whether the five cases of "Death" includes the three cases of SIDS.

119. For Table 5.24 of iss.pdf, please clarify whether the eight cases of HHE listed includes the two hypotonic events that met the criteria for HHE.

120. For Table 5.24 of iss.pdf, please further describe the three cases of "Decreased level of consciousness," and indicate whether there is overlap of these cases with either the eight cases of HHE or the three cases of encephalopathy.

121. Please provide any report forms and additional clinical documentation (e.g. regarding diagnostic studies and outcome) for the three cases of encephalopathy following Pentacel that were identified post-marketing.

122. In reference #15 cited in iss.pdf, we note that there were three cases of encephalopathy within 7 days of Pentacel vaccination identified by IMPACT in 1998. Two of these cases were thought to be due to influenza A infection and one case was attributed to a probable gastrointestinal infection.

    a. Please verify whether the two cases of encephalopathy attributed to influenza A infection are the same as those described in iss.pdf Section 5.3.9.1.

    b. The third case of encephalopathy within 7 days following Pentacel in 1998 that was identified by IMPACT and described in Reference #15 does not appear to be included as a case of encephalopathy in the post-marketing reports (spontaneous reports and literature data) received from 5/1/97-3/1/05 summarized in Section 5.3.9.1 of iss.pdf. Please explain why this case of encephalopathy was not captured by the pharmacovigilance activities for Pentacel.

123. Please clarify the number of doses of Pentacel that the 5-month old infant who died of *H. influenzae* meningitis and pneumonia had received (iss.pdf, page 142).

124. Please provide more specific clinical information on the four cases of "Therapeutic response decreased" listed in Table 5.24 of iss.pdf.

The following items pertain to the integrated summary of safety:

125. Based on your responses to the July 5, 2005, FAX and to items in this letter, please provide a revised integrated summary of safety, incorporating necessary changes.

126. In iss.pdf Tables 5.17, 5.18, and 5.19 and associated text, you have provided summaries of non-febrile seizures, febrile seizures, and "other possible neurological events," respectively, reported after Pentacel or Control vaccines for the pivotal Pentacel studies. Please provide revised tables of non-febrile seizures, febrile seizures, and "other possible neurological events," as well as tables of possible seizures, containing information on vaccine (Pentacel or Control), study, subject #, literal term, days since last dose, last dose and outcome. In these tables please order the data primarily by vaccine (Pentacel then Control), followed by days since last dose. For the control please order by days since last dose, irrespective of whether the control was HCPDT or DAPTACEL. In these tables, please incorporate any necessary revisions based on your responses to the July 5, 2005, FAX as well as your responses to the items in this letter.

127. In iss.pdf Tables 5.22 and 5.23, you have provided summary tables of serious adverse events occurring in at least two subjects within 60 days post-vaccination for doses 1-3 and dose 4, respectively. Please provide similar tables of serious adverse events occurring in at least two subjects within 30 days post-vaccination for doses 1-3 and dose 4.

128. In iss.pdf Tables 9.73 and 9.74, you have provided summary tables of serious adverse events by subjects and events occurring within seven days after vaccination for doses 1-3 and dose 4, respectively. Please provide similar tables of serious adverse events, by subjects, using the adverse event categories of interest outlined in our July 5, 2005, FAX. In the category "asthma and related diagnoses," please include all occurrences of asthma, wheezing, bronchiolitis, RSV, and related diagnoses, irrespective of whether there was evidence for RSV infection.

129. In iss.pdf Tables 9.78 and 9.79, you have provided summary tables of serious adverse events by subjects and events occurring within thirty days after vaccination for doses

1-3 and dose 4, respectively. Please provide similar tables of serious adverse events, by subjects, using the adverse event categories of interest outlined in our July 5, 2005, FAX. In the category "asthma and related diagnoses", please include all occurrences of asthma, wheezing, bronchiolitis, RSV, and related diagnoses, irrespective of whether there was evidence for RSV infection.

130. In iss.pdf Table 5.15, you have provided a summary table that includes rates of seizures, febrile seizures, and possible neurological events occurring within 60 days after vaccination across the four pivotal studies. Based on the responses to our July 5, 2005, FAX in which you classified each seizure episode as febrile, afebrile, or possible, as well as the responses to items about seizures in this letter, please provide a revised summary table of rates of non-febrile seizures, febrile seizures, and possible seizures for each study and across studies for doses 1-3 and dose 4, for the periods 0-30 days and 0-7 days post-vaccination.

131. In iss.pdf Table 5.3, you have provided a list of adverse events that led to withdrawal in subjects whose withdrawal was categorized as due to an adverse event. Please provide a summary table of all adverse events that led to study withdrawal, categorized by types of events (e.g., using System Organ Class). Please include all withdrawals due to adverse events, including withdrawals due to adverse events that are contraindications to subsequent doses and voluntary withdrawals due to adverse events.

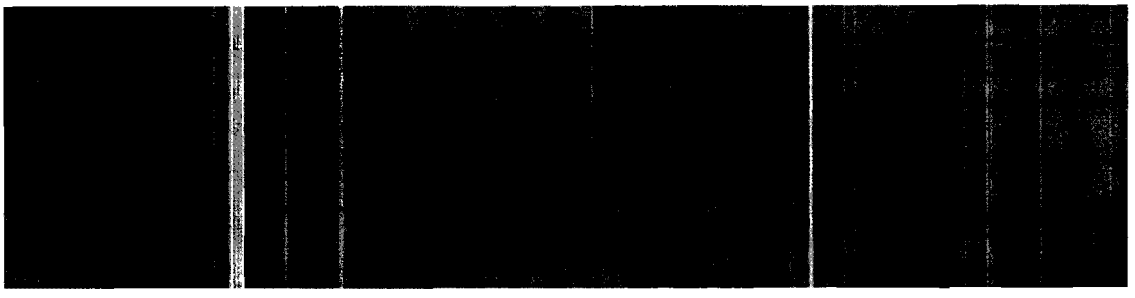
132. Except for the duration of follow-up for serious adverse events (60 or 180 days after the last dose of study vaccines), safety monitoring procedures were essentially the same across the pivotal studies. However, as noted in the Integrated Summary of Safety (iss.pdf page 114), the rate of serious adverse events, within 60 days post-vaccination, was lower in Study 494-01 than in the other pivotal studies of Pentacel. Please discuss any differences between studies that may have contributed to differences in rates of reported serious adverse events.

133. Please provide a summary, across pivotal studies of Pentacel, of all cases of pertussis (confirmed or suspected) and invasive disease due to *H. influenzae*

type b, including number of previous doses of Pentacel or Control vaccines received.

The following items pertain to serological assays:

Rubella [redacted]

134. 

Measles and Mumps [redacted]

135. Please specify the passage number of the [redacted] challenge virus in the measles [redacted] SOP. Please modify the SOP to include this information.

136. Please specify the passage range of the [redacted] used in the measles and mumps [redacted] Please modify the SOP to include this information.

VZV FAMA Assay:

137. Please specify the passage range of the [redacted] used in this assay. Please modify the SOP to include this information

138. Please specify the VZV titer used to infect [redacted] in this assay. Please modify the SOP to include this information

Polio Neutralization Assay:

139. You have provided the methodology for your [redacted] for assessment of antibody response to the polio virus serotypes (methval.pdf pg 210).

    a. Please compare your assay to that recommended by the World Health Organization (WHO) (WHO, Manual for the virological investigation of polio. WHO/EPI/GEN97.01, 1997). Please discuss your modifications to this

assay and the potential impact of each of these on the measurement of titer to each of the serotypes.

b. Please clarify whether back titration is performed when each assay is performed.

c. The acceptable range for your in-house reference serum [redacted] is higher than that recommended by WHO. Please discuss the impact of this on the titers measured in your assays.

PRP [redacted]

140. In the section (serology.pdf) describing the PRP assay methodology and validation, you have provided data on the low control samples to support the performance of the assay. However, the submitted data indicate that a majority of clinical samples have concentrations below the low control. Specifically, the post-dose 3 PRP antibody reverse cumulative distribution curve (RCDC) submitted in the 494-01 Stage I study report (49401si.pdf page 3404) shows that approximately 60% of Pentacel subjects had anti-PRP values below 5.02 ug/mL, the GMT of the assay low control, 104-B017, used in Building [redacted]. Similarly, the RCDC included in the P3T06 Stage I study report (p3t06si.pdf page 3388) indicates that approximately 70% of Pentacel and DAPTACEL subjects had antibody levels below 5.30 ug/mL, the GMT of the low control, 104-B017, as used in Building [redacted] Additionally, in the AvP-US Transfer Validation Report, C001285, only one of the test samples had reported concentration between the lower limit of quantitation [redacted] Therefore, the PRP assay methodology and validation information that you submitted provides limited information to support the acceptable performance of the assay in Buildings [redacted] in the range that appears most relevant for the clinical samples under evaluation. Please provide additional evidence to support the acceptable precision, accuracy, and stability of the assay in the range between [redacted]

The following items pertain to CMC and Establishment Information:

141. The consistency lots of DTaP-IPV used in 494-01 Stage I, C0094A, C0154B, and C0155A, were formulated at [redacted]

[redacted] scale respectively. Please clarify the scale of formulation of commercial lots of DTaP-IPV.

142. The BLA summary (summary.pdf page 19) contains a table identifying the lot number of concentrates used to formulate lots of DTaP-IPV for Study 494-01 stage I.

    a. Please indicate which DTaP-IPV lot was administered to each group (1, 2 and 3) in the lot consistency study.

    b. Please provide the PRP-T final bulk administered to each study group (1, 2, and 3).

143. For each lot of ActHIB used in pivotal studies, either administered as Pentacel or control vaccine, please provide a tabular summary showing bulk lot number, final lot number, and date the lot was manufactured. Please specify which study group received each lot. Also, please provide a timeline of significant ActHIB manufacturing changes (such as: new master seed, working seed, revised release testing methods, revised release specifications, facility/equipment changes) and which changes apply to these lots.

144. In Section 4.17.1 of specsanalyticalmeth.pdf, you have requested an exemption from the general safety test (21 CFR 610.11). In order to evaluate this request, please provide results of the general safety test performed on lots of the DTaP-IPV component to date.

145. The Containment and Cross Contamination document, Section 2.1.1.3.10.1 states that "cleaning validation for the [redacted] (for FHA) was not completed due to manufacturing constraints, and this validation will be completed during [redacted] the results will remain on file at Aventis Pasteur Limited." Please submit a copy of the completed cleaning validation for the [redacted] to this BLA.

146. The Executed Batch Production Record (BPR-300-FP-06-02 Bulk Lot C0154B) for the Filling Work Record states that [redacted] vials are required for sterility testing. However, the record does not identify when during the filling process the vials were removed for testing. Please provide this information and amend the master production record accordingly (21 CFR 211.186).

147. A short summary of the validation of the [redacted] test of closure integrity was provided in Item 4: CMC HCPDT-IPV Container Closure System Section 6.3.1.2.

    a. After the test, the vials are inspected in a [redacted]. In the validation report provided (PV01-033-PRO Table 2, page 9 of 12), the [redacted] source is listed as a piece of equipment and the Calibration/Certification due date is listed as N/A. Please explain how the [redacted] and indicate the range of [redacted] output optimal for visual inspection.

    b. Please provide a copy of SS01-023-REP and the corresponding protocol.

    c. Please provide a copy of PV-01-012-REP and the corresponding protocol.

    d. Please provide a copy of SOP 15QC-040.

    e. Please describe how personnel are trained and qualified to perform this test.

148. In the Biological Substance, IPV, Specifications and Analytical Methods Section (specsanalyticalmeth.pdf page 28), selectivity (specificity) of the [redacted]

Please provide data to demonstrate [redacted]

149. Please provide updated reports for the following prospective stability studies:

    a. Prospective Stability Study W-202500/202510/202520/202530/2001295-025 (CMC: [redacted] Page 37).

    b. Prospective Stability Study W-20138295-054-04 (CMC: [redacted] Page 7).

    c. Prospective Stability Study W2013048-092-03 (CMC: HCPDT-IPV Stability: Page 1, Table 1).

d. Prospective Stability Study B007227/[redacted] 013-05 (CMC: [redacted] Stability: Page 8).

e. Prospective Stability Study W-2013048-021-02 CMC: HCPDT-IPV Stability: Page 28).

f. Prospective Stability Study W2013048-065-03 (CMC: HCPDT-IPV Stability: Page 34).

g. Prospective Stability Study W-2013048-067-03 (CMC: HCPDT-IPV Stability: Page 38).

The following comments (150-156) were conveyed in the teleconference of March 15, 2006. We acknowledge your response to some of these items submitted May 9, 2006.

150. In SOP 18MI-001 (Version Number 5.0) "Mouse Immunogenicity," you propose to immunize mice, for the DTaP-IPV pertussis potency test, with [redacted] of vaccine. This dose is equivalent to the dose used for DAPTACEL. However, the DTaP-IPV component of Pentacel is formulated to contain, per human dose, twice as much inactivated pertussis toxin (PT) and four times as much filamentous hemagglutinin (FHA) as DAPTACEL. The test dose selected should be located in the linear region of the curve relating dose-antibody response for all antigens; therefore, it may not be feasible to use a single test dose for all pertussis antigens. Please provide data to support the test dose of DTaP-IPV that you propose.

151. You propose, in Section 4.14.5 of "HCPDT-IPV Specifications and Analytical Methods," to retain the [redacted] acceptance criteria for the minimal number of mice that should respond to PT and FHA in the potency test of the pertussis component of DTaP-IPV [redacted]. According to your "Statistical Analysis of Responder Mice and Geometric Mean Unitage (GMU) for the Component Pertussis Mouse Immunogenicity Test for the HCPDT-IPV Vaccine (December 2004), Version Number 1.0," the proportion of responders to [redacted] of vaccine is consistently [redacted].

a. If the suitability of the [redacted] test dose is confirmed, please revise the acceptance criteria for the number of responder mice to PT and FHA to accurately reflect the data.

b. If the test dose is revised, please provide data to support the proposed acceptance criteria for the number of responders to these antigens at the new test dose.

152. DAPTACEL supplements 103666/5036, describing modifications to the [redacted] assays for all pertussis antigens and 103666/5041, describing modifications to the potency assay for the pertactin pertussis component, were approved June 28, 2005. Please explain your plans to extend the changes approved for DAPTACEL testing described in these supplements to the testing of the [redacted]

153. Please explain actions to be taken when "alert limits" documented in Section 2 of "Component Pertussis Specifications and Analytical Methods" are reached.

154. Regarding the [redacted] Test, summarized in section 4.10 of "HCPDT-IPV Specifications and Analytical Methods":

[redacted]

155. You have proposed the [redacted]
Please explain the rationale for [redacted] limits for detoxified PT and the other pertussis antigens.

156. Section 1.5 "Shipping, Labeling and Copackaging of ActHib for Pentacel," submitted on February 24, 2006, indicates that the expiry date of copackaged DTaP-IPV and ActHIB components of Pentacel will be based on the shortest expiry date of the two components. Please clarify whether, for the purpose of dating period, the date of manufacture of each component is based on potency testing or final bulk formulation.

Additional comments:

157. Section 3 of "HCPDT-IPV//PRP-T Vaccine Summary" does not indicate a permissible period between reconstitution of PRP-T with DTaP-IPV and administration of Pentacel. Please indicate the maximal period that PRP-T can remain reconstituted with DTaP-IPV before administration. Please provide stability data or other relevant information to support this period. This information should be included in the package insert.

158. Six cases of encephalopathy following Pentacel were described in the BLA (three identified through spontaneous post-marketing reports and one each in studies M5A08, 494-01, and 494-03). For each of these cases, when possible, please provide:

    a. Information on race/ethnicity,

    b. The lot number of DTaP-IPV and ActHIB administered, and,

    c. The results of [redacted] testing of the pertussis toxin component and the calculation of [redacted]

159. Table 6.1 in "hib_epidemiology.pdf" provides age-specific incidence rates for invasive pneumococcal and Hib diseases and pertussis in children in Alberta, Canada.

    a. Please provide an estimate of the size of the annual birth cohort in Alberta, Canada during the period covered in the table.

    b. If available, please provide the incidence rates of pertussis for infants <6 months and for infants 6-11 months, separately, for each of the six years included in the table.

160. Please submit a revised version of Table 2.1 in compilation_hib_responses.pdf to include the number of subjects evaluated for response to PRP-T in each of the studies listed.

161. You have submitted a copy of ActHIB supplement 103935/5062. Please also submit to the Pentacel BLA, for cross reference, your February 17, 2006, response to CBER's November 16, 2006, complete response letter.

162. You have provided the results of an analysis of post-dose 3 immunogenicity data from study P3T07. Please provide a time line for completion of the Stage II study report.

163. Please address the requirements of the Pediatric Research Equity Act.

164. Pending our review of your responses to this letter and further discussion, we may request post-marketing safety and/or immunogenicity studies and reserve comment on these until such discussions have occurred. Please acknowledge.

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,

Karen L. Goldenthal, M.D.
Director
Division of Vaccines
and Related Products Applications
Office of Vaccines
Research and Review
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DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

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Date: May 26, 2006 Time: 14:25

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