Department of Health and Human Services
Center for Biologics Evaluation and Research
Division of Bacterial, Parasitic and Allergenic Products (DBAP)

Date: April 7, 2006

From: Tod J. Merkel, DBPAP

Subject: BLA 125145

To: Theresa Finn, DVRPA

Through: Drusilla Burns, Chief, LRSP/DBPAP
Richard Walker, Director, DBPAP

General Information:

BLA Title:	Tetanus, Diphtheria, and Pertussis Toxoids, Adsorbed for Adolescent and Adult Use.
Sponsor:	Sanofi- Pasteur, Inc.

Executive Summary (Pertussis Component CMC):
PENTACEL™ is a combination of *Haemophilus b* Conjugate Vaccine reconstituted with Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed and Poliovirus Vaccine Inactivated. The Component Pertussis Vaccine is produced by combining the individual adsorbed antigens: pertussis toxoid (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN) and Fimbriae types 1 and 2 (FIM). The adsorbed antigens used for the formulation of PENTACEL™ are the same antigens used for the formulation of the U.S. licensed vaccines DAPTACEL™ and ADACEL™.

I reviewed the manufacture of the adsorbed pertussis antigens including the seed banking, fermentation, purification and adsorption of the antigens to produce adsorbed bulk antigens. I found the manufacturing processes including the in process controls, lot consistency and stability to be satisfactory.

I reviewed the formulation of the HCPDT-IPV focusing, in my review, on the pertussis component. I found the formulation, in process controls, lot consistency and stability to be satisfactory. One of the consistency lots (Lot #C0154B) failed one of the [redacted] pertussis potency specifications for pertactin. The pertussis potency test is a mouse immunogenicity test. There are [redacted] specifications: [redacted] Lot #C0154B met the PRN release specification for [redacted]
The release specifications for the pertussis mouse immunogenicity test were not in place at the time the consistency lots were produced. Lot #C0154B was subsequently used in a clinical trial to demonstrate consistency (clinical study 494-01) and shown to be not inferior to the other two lots included in the trial. Some stability trials were still in progress at the time this submission was prepared. Updated study reports should be requested.

I have reviewed the immunogenicity data for the pertussis component antigens. Because there are no universally accepted correlates of immunity for pertussis antigens, the efficacy of PENTACEL is inferred from the comparison of PENTACEL immunogenicity to the immunogenicity of the U.S.-licensed vaccine DAPTACEL. DAPTACEL and PENTACEL are produced from the identical antigens produced by the same manufacturing process in the same facility. The efficacy of DAPTACEL was directly demonstrated in the Sweden I efficacy trial. The immunogenicity of PENTACEL was compared to that of DAPTACEL in U.S. kids in study P3T06 and to the immunogenicity of DAPTACEL in Swedish kids using a sub-set of sera from the Sweden I efficacy trial in studies P3T06 and 494-01. Because PENTACEL would be co-administered with PREVNAR if licensed, the impact of co-administration of PREVNAR on the immunogenicity of PENTACEL was evaluated in clinical trial M5A07. A summary of the immunogenicity results from those trials is itemized below.

- For both P3T06 and 494-01, the post dose 3 GMTs for PT, FHA and FIM were as high or higher for the PENTACEL groups as they were for the control group. The GMTs for PRN were only slightly lower in the PENTACEL group relative to the DAPTACEL group in P3T06 and were the same as the HCPDT group in 494-01. The percent of individuals with a four-fold rise in antibody to each of the four antigens was the same in the PENTACEL and control groups in both studies.
- For both P3T06 and 494-01, the post dose 4 GMTs for PT, FHA and FIM were as high or higher for the PENTACEL groups as they were for the control groups. The GMTs for PRN were significantly lower in the PENTACEL group relative to the DAPTACEL group in P3T06 and lower than the HCPDT group in 494-01. The percent of individuals with a four-fold rise in antibody to each of the four antigens was the same in the PENTACEL groups and the control groups in both studies. Therefore, this data indicates that PENTACEL elicits stronger responses to PT and FHA than DAPTACEL although it should be pointed out that these studies were not designed to demonstrate superiority. This data also indicates that following the 4^{th} dose, PENTACEL elicits a weaker response to PRN than DAPTACEL.
- For the P3T06 bridge to the Sweden I efficacy study the GMTs for PT, FHA and FIM were higher in the PENTACEL group (post-dose 4) than in the CPDT group (post-dose 3). The GMTs for PRN were slightly lower in the PENTACEL group (post-dose 4) than in CPDT group (post-dose 3) but non-inferiority was met. The percent responders (4-fold rise) for PT, FHA and FIM was higher in the PENTACEL group (post-dose 4) than in CPDT group (post-dose 3) but the percent responders (4-fold rise) for PRN was lower in the PENTACEL group (post-dose 4) than in the CPDT group (post-dose 3). Non-inferiority was not met.
- For the 494-01 bridge to the Sweden I efficacy study the GMTs for PT, FHA and FIM were higher in the PENTACEL group (post-dose 4) than in the CPDT group (post-dose 3). The GMTs for PRN were slightly lower in the PENTACEL group (post-dose 4) than in CPDT group (post-dose 3) but non-inferiority was met. The percent responders (4-fold rise) for PT, FHA and FIM was higher in the PENTACEL group (post-dose 4) than in CPDT group (post-dose 3) but the percent responders (4-fold rise) for PRN was lower in the PENTACEL group (post-dose 4) than in the CPDT group (post-dose 3). Non-inferiority was not met.

- In study M5A07 the antibody response elicited to the Pertussis component antigens was compared when Prevnar was given concurrently with PENTACEL vs. when the Prevnar and PENTACEL vaccinations were staggered. There were no significant differences in the antibody responses to any of the pertussis component antigens between these two groups.

Table 1. Immunogenicity comparisons from study P3T06. Comparisons that failed to meet non-inferiority criteria are highlighted.

	U.S. Standard of Care				Bridge to Sweden I			
	GMTs[1]		% Responders[1]		GMTs[2]		% Responders[2]	
	DAPTACEL	PENTACEL	DAPTACEL	PENTACEL	DAPTACEL	PENTACEL	DAPTACEL	PENTACEL
PT	168.48	174.03	97.1	97.4	87.50	174.0	86.3	97.4
FHA	64.02	107.94	79.3	88.4	40.70	107.9	68.8	88.4
FIM	513.54	553.39	91.6	93.5	339.31	553.4	86.3	93.5
PRN	186.07	93.59	98.3	92.7	111.26	93.6	98.8	92.7

1 Post-dose 4 PENTACEL compared to post-dose 4 DAPTACEL in U.S. kids.
2 Post-dose 4 PENTACEL in U.S. kids compared to post-dose 3 DAPTACEL in Swedish kids (Sweden I)

Table 2. Immunogenicity comparisons from study 494-01. Comparisons that failed to meet non-inferiority criteria are highlighted.

	Bridge to Sweden I			
	GMTs[1]		% Responders[1]	
	DAPTACEL	PENTACEL	DAPTACEL	PENTACEL
PT	87.50	195.10	86.3	94.9
FHA	40.70	129.85	68.8	91.7
FIM	339.31	506.57	86.3	91.5
PRN	111.26	90.82	98.8	89.2

1 Post-dose 4 PENTACEL in U.S. kids compared to post-dose 3 DAPTACEL in Swedish kids (Sweden I)

Conclusions:

I believe that taken together these data support the efficacy of the pertussis component of PENTACEL. Although one has to recognize that PENTACEL elicits a lower antibody response to the pertactin component than that elicited by DAPTACEL, I believe that this lower antibody response is not likely to result in significantly lower efficacy. In reaching this conclusion, I have considered the following.

- Although we use immunogenicity to infer efficacy, there is no internationally recognized correlate of immunity for any pertussis antigen.
- DAPTACEL was highly efficacious in the Sweden I efficacy trial with an estimated efficacy of 84.9%. It is unlikely that the lower PRN response will significantly affect

that efficacy and it almost certainly will not reduce the efficacy to a level below that accepted for other currently licensed Pertussis vaccines.

- DAPTACEL and PENTACEL contain four different pertussis antigens. The response to each of these antigens independently contributes to protection. As long as an individual has a good response to most of those antigens, that individual is likely to be protected. The responses to PT, FHA and FIM elicited by PENTACEL is as high or higher than that elicited by DAPTACEL and the percentage of individuals that had good responses to PT, FHA and FIM was higher for PENTACEL than DAPTACEL. Finally, although the peak titers of antibody to PRN were lower in the PENTACEL groups relative to the DAPTACEL groups post-dose 4, the percentage of individuals that had significant rises in titers (relative to pre-dose 1) was not lower for the PENTACEL groups.
- The differences in antibody responses to PRN observed between the PENTACEL groups and the control groups did are not observed until post-dose 4. Therefore, even if the reduced response to PRN results in reduced efficacy, we have some assurance that individuals are protected as well by PENTACEL as by DAPTACEL during the most vulnerable period of their lives.
- The Canadian experience is unique and compelling. It is unique in that since its approval and introduction in Canada in 1998, it has been the only pertussis vaccine in use in that country. Therefore we have the benefit of observing the outcome of the "real-world" and exclusive use of this vaccine in a neighboring country. Since the vaccine's introduction in 1998, the incidence of pertussis has decreased and remained low for nine years. Like the United States, reported pertussis cases in Canada peak every 3-5 years. It is notable that since the last peak in the years 1997-1998, there has not been another peak in reported pertussis cases. Clearly PENTACEL has been effective in controlling pertussis in the Canadian population and there is no reason to believe it would not perform equally well in the U.S. population.

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CMC (Pertussis Component)

BACKGROUND

PENTACEL™ is the product combination of *Haemophilus b* Conjugate Vaccine (Tetanus Protein-Conjugate) reconstituted with Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed and Poliovirus Vaccine Inactivated. HCPDT-IPV Vaccine is manufactured at Aventis Pasteur Limited and PRP-T Vaccine is manufactured at Aventis Pasteur SA. PRP-T Vaccine (filled and freeze-dried) is received at Aventis Pasteur Limited where it is labeled and co-packaged with labeled HCPDT-IPV Vaccine.

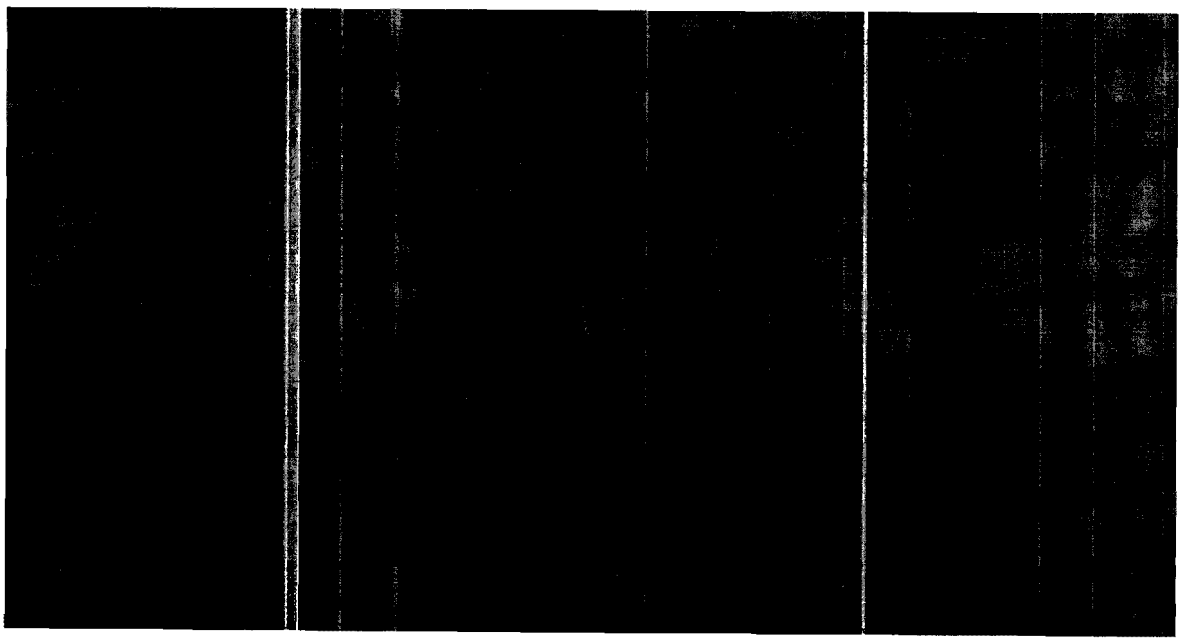
HCPDT-IPV Vaccine is a sterile uniform cloudy, white to off-white (yellow tinge) suspension, filled into glass vials, labeled and packaged. HCPDT-IPV Vaccine is formulated using the same antigens (Component Pertussis antigens PT, FHA, PRN and FIM, Diphtheria Toxoid, Tetanus Toxoid and Poliovirus Vaccine Inactivated) that are present in other US-licensed combination vaccines, including CPDT Vaccine Adsorbed (DAPTACEL®), DT Vaccine Adsorbed, Td Adsorbed and POLIOVAX®. The Pertussis component antigens used for the formulation of HCPDT-IPV are the same components as those used for the manufacture of CPDT Vaccine Adsorbed (DAPTACEL®).

Active Components	Quantity/dose in Formulated Product
Component Pertussis	
Pertussis Toxoid	20 µg
Filamentous Haemagglutinin	20 µg
Fimbriae Types 2 and 3	5 µg
Pertactin	3 µg
Diphtheria Toxoid	15 Lf
Tetanus Toxoid	5 Lf
Poliovirus Inactivated	
Poliovirus Inactivated Type 1 (Mahoney)	40 D-antigen units
Poliovirus Inactivated Type 2 (M.E.F.1)	8 D-anitgen units
Poliovirus Inactivated Type 3 (Saukett)	32 D-antigen units
Inactive Substances	**Concentration in Formulated Product**
2-Phenoxyethanol	0.6% [redacted] v/v
Aluminum Phosphate (aluminum)	1.5 mg/dose (0.33 mg/dose)
Tween 80	[redacted]
Bovine Serum Albumin	≤ 50 ng/dose
Polymyxin B Sulphate	< 4 pg/dose
Neomycin	< 4 pg/dose
Formaldehyde	≤ 0.001% w/w
Glutraldehyde	< 100 ppb

One of the Pertussis components in HCPDT-IPV Vaccine, Pertussis Toxin (PTx), is detoxified with glutaraldehyde. Chemical treatment of FHA with formaldehyde is undertaken to detoxify potential residual PTx. Formaldehyde (rather than glutaraldehyde) is used for detoxification of residual PTx in FHA because it was determined that treatment of FHA with glutaraldehyde resulted in [redacted] Formaldehyde is also

used to detoxify Diphtheria and Tetanus Toxins and to inactivate Purified Poliovirus Monovalent Concentrates. Each of the Component Pertussis antigens as well as Diphtheria Toxoid and Tetanus Toxoid are adsorbed individually with aluminum phosphate and stored [redacted] Two-phenoxyethanol is used in all licensed Component Pertussis Vaccine formulations to allow for flexibility in use of components in the different component Pertussis-containing vaccines produced by the manufacturer. Two phenoxyethanol was selected as the preservative as it was shown to meet preservative efficacy criteria (USP XXI) during the early combination product development. Recently [redacted] At this time, Sonofi Pasteur is classifying 2- phenoxyethanol as an excipient. The adsorbed concentrates of PT, FHA, FIM, PRN, Diphtheria Toxoid and Tetanus Toxoid are blended together into an HCPDT Intermediate Vaccine. The HCPDT Intermediate Vaccine is blended with Poliovirus Vaccine Inactivated Trivalent Concentrate to formulate HCPDT-IPV. Vaccine Final Bulk Product. The Final Bulk Product also contains aluminum phosphate, 2-phenoxyethanol and Tween 80. The HCPDT-IPV Vaccine Final Bulk Product is filled in the final container and they are co-packaged with Haemophilus b Conjugate Vaccine (Tetanus Protein Conjugate) (PRP-T).

The five-component acellular Pertussis based vaccine combinations (CPDT Vaccine and HCPDT) were first licensed in Canada in December 1996. Since then these combination vaccines have been licensed in many countries around the world. Pentacel™ was licensed in Canada in May 1997 and has been exclusively used in Canada for infant immunization since that time. A similar acellular Component Pertussis vaccine, DAPTACEL® was licensed in the United States in May 2002. Pentacel™ differs from DAPTACEL® in that it has a higher content of the Component Pertussis PT and FHA antigens and contains Poliovirus antigens Types 1, 2 and 3. HCPDT-IPV Vaccine is used to reconstitute PRP-T Vaccine at the time of use. The quantities of Diphtheria Toxoid, Tetanus Toxoid, PRN and FIM are the same.



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