Summary Basis for Regulatory Action

Date:	July 19, 2012
From:	Holly Wieland, RN, MPH Chair of the Review Committee
Through:	Paul Richman, PhD Branch Chief, CMC Branch 1
BLA/STN#:	125145/201
Applicant Name:	Sanofi Pasteur Limited
Date of Submission:	September 30, 2011
PDUFA Goal Date:	July 30, 2012
Proprietary Name:	Pentacel
Established Name:	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine
Application Type:	Efficacy Supplement

Reason for Submission: To revise the label to add a warning on apnea in very premature infants in Section 5 Warnings and Precautions, and to add the adverse event of anaphylaxis/anaphylactic reaction in Section 6.2 Data from Post-Marketing Experience.

Recommended Action:	Approval
Signatory Authorities Action:	
Offices Signatory Authority:	Wellington Sun, MD Director, Division of Vaccines and Related Products Applications/Office of Vaccines Research and Review/CBER/FDA

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

STN 125145/201	
Chair/Regulatory Project Manager	Holly Wieland, RN, MPH
Clinical Reviewer	Tina Khoie, MD, MPH
CMC Reviewer	Tina Roecklein, MS

1. Introduction

This efficacy supplement includes data that CBER requested to support the specific wording the sponsor proposed to use regarding apnea in very premature infants for inclusion in the Warnings and Precautions Section of the Highlights of Prescribing Information and the Full Prescribing Information for Pentacel. To fulfill this request, the sponsor reviewed medical literature on post-vaccination apnea in premature infants and conducted a review of cases of apnea in infants reported to the company and which occurred in premature infants after receipt of Pentacel. This was referred to as the Safety Analysis Report.

CBER reclassified the submission, which was originally submitted as a labeling prior approval supplement, as an efficacy supplement, because the supplement contained clinical data. However, the user fee was waived, because the data support the addition of new safety data in the label and were requested by CBER.

Other proposed labeling revisions include the addition of the term "anaphylaxis/anaphylactic reaction" in the postmarketing adverse reactions section of the package insert (section 6.2) and clarifying language in sections 2.2 (Administration) and 7.1 (Concomitant Administration with Other Vaccines). In addition, the sponsor addressed two CMC issues (see below).

2. Background

The sponsor is requesting FDA approval to make this change in order to globally implement consistent product/prescribing information for all the firm's pediatric vaccine products based on the requirement established for EU labeling of pediatric vaccines.

3. Chemistry, Manufacturing and Controls (CMC)

There were two proposed changes: one in Section 2.2 Administration and the second in Section 11 Description.

The first proposed change in Section 2.2 was submitted in response to a January 5, 2012, letter issued by CBER to all vaccine manufacturers to provide clear instructions

regarding vaccine withdrawal from the vial and method of administration. In addition, clear instructions on the inspection and handling of the vials during vaccine withdrawal were added.

The second proposed change was found in Paragraph 3 of the Description Section and lists other ingredients per 0.5 mL dose. The sponsor proposed to add 42.5 mg sucrose to this list. The Pentacel license cross-references the ActHIB license STN 103935. Sucrose is an excipient in ActHIB and is mentioned in the US package insert for ActHIB. Pentacel is a reconstituted vaccine containing ActHIB, and therefore, also contains sucrose as an excipient.

The CMC reviewer found both of these proposed revisions to be acceptable.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

Not applicable.

6. Clinical/ Statistical

It was concluded that the available data do not adequately address the need for respiratory monitoring for 48 to 72 hours post-vaccination. In addition, because the benefit of vaccination with Pentacel in preterm infants is not described in the package insert, it was not considered appropriate to include a statement that the benefit of vaccination is high in this group. The applicant was requested to revise the proposed language pertaining to apnea in premature infants due to the aforementioned conclusions.

It was concluded that sufficient data were provided to support the addition of the term “anaphylaxis/anaphylactic reaction” to the postmarketing section of the package insert.

7. Safety

Not applicable.

8. Advisory Committee Meeting

There were no issues in this supplement that required input from an Advisory Committee.

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

On July 13, 2012, the sponsor agreed to all the requested labeling revisions, including those comments that were sent to the sponsor on June 29, 2012. In summary, these labeling changes were as follows:

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION WARNINGS AND PRECAUTIONS** Section, the sponsor agreed to revise the proposed language regarding apnea in premature infants to be consistent with language that has been added to the labels for other vaccines recently (e.g., Infanrix®, Pediarix®, and Prevnar 13®), as advised by CBER. This revised language reads as follows:

   "Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination."

2. In the **FULL PRESCRIBING INFORMATION ADMINISTRATION** (Section 2.2):

   a. The sponsor agreed to remove the following proposed text from the label: "Prior to use, inspect the vial for evidence of leakage or a faulty seal." CBER explained that this proposed statement implies that there may be a problem with the manufacture of the vial or vial seal, and such language is not typically included in the package insert for a vaccine product.

   b. The sponsor agreed to add language similar to that in section 2.1 of the Adacel package insert regarding the need to use a separate sterile needle and syringe for each injection and language regarding changing needles.

   c. The sponsor agreed to add the language modifying the instructions for reconstitution of the ActHIB component with the DTaP-IPV component in Section 2.2, to read as follows: "The package contains a vial of the DTaP-IPV component and a vial of lyophilized ActHIB vaccine component. Gently swirl the vial now containing Pentacel vaccine gently until a cloudy, uniform, white to off-white (yellow tinge) suspension results.

3. In the **FULL PRESCRIBING INFORMATION WARNINGS AND PRECAUTIONS: APNEA IN PREMATURE INFANTS** (Section 5.7), the sponsor agreed to include the following statement:

   "Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination."

4. In the **FULL PRESCRIBING INFORMATION ADVERSE REACTIONS: DATA FROM POST-MARKETING EXPERIENCE** (Section 6.2), the sponsor added "anaphylaxis/anaphylactic reaction" as an event in the postmarketing section of the package insert with CBER's concurrence after review of representative case report forms for anaphylaxis/anaphylactic reaction events involving Pentacel and submitted in response to CBER's request for such.

5. In the **FULL PRESCRIBING INFORMATION DESCRIPTION** (Section 11), the sponsor added sucrose as an excipient.

11. Recommendations and Risk/ Benefit Assessment

Recommend: Approval of this supplement with the labeling revisions as stated.