Public Assessment Report

Decentralised Procedure

Pediacel
Suspension for injection in pre-filled syringe

Procedure No: UK/H/2388/01/DC

UK Licence No: PL 06745/0128

Sanofi Pasteur MSD Limited
On 5th November 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, The Netherlands and the United Kingdom agreed to grant a Marketing Authorisation to Sanofi Pasteur MSD Ltd for the medicinal product Pediacel suspension for injection in pre-filled syringe (PL 06745/0128; UK/H/2388/01/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 3rd December 2010. This medicine is subject to restricted medical prescription and is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis (whooping cough), poliomyelitis and invasive Haemophilus influenzae type b disease in infants and children from the age of 6 weeks up to the fourth birthday. Pediacel should be used in accordance with applicable official recommendations.

PediaCel was originally approved as a single-dose vial presentation (PL 06745/0120) indicated for the primary immunisation series in infancy which may be commenced from 2 months of age according to applicable official recommendations. This application concerns Pediacel in a new presentation, suspension for injection in a pre-filled syringe (PL 06745/0128), which has the same indication as that of the single-dose vial, but a lower age at which immunisation can be commenced, i.e. from 6 weeks of age has been approved.

The primary vaccination series consists of 2 or 3 doses of 0.5 ml and may be commenced from 6 weeks of age according to applicable official recommendations. There should be an interval of at least one month between doses. After primary series vaccination with either 2 doses (e.g., 3, 5 months) or 3 doses (e.g., 2, 3, 4 months) of Pediacel, a booster dose should be given at least 6 months after the last priming dose in accordance with applicable official recommendations. Pediacel should be administered intramuscularly. The recommended injection sites are the anterolateral aspect of the thigh or the deltoid region of the upper arm if there is adequate muscle mass, according to local clinical practice recommendations. The anterolateral aspect of the thigh is the preferred site for infants under one year of age.

No new or unexpected safety risks arose from this application and it was therefore judged that the benefits of using Pediacel suspension for injection in pre-filled syringe outweigh the risks; hence a Marketing Authorisation has been granted.
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<td>P35</td>
</tr>
</tbody>
</table>
# Module 1

## Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Names</strong></th>
<th>Pediacel suspension for injection in pre-filled syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types of Application</strong></td>
<td>Known active substance, Article 8(3)</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Diphtheria, tetanus, pertussis [acellular, component], poliomyelitis [inactivated] and haemophilus type b conjugate vaccine [adsorbed]</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Suspension for injection in pre-filled syringe</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>Each 0.5 mL dose contains:</td>
</tr>
<tr>
<td></td>
<td><strong>Diphtheria Toxoid</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Tetanus Toxoid</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Acellular Pertussis Antigens</strong></td>
</tr>
<tr>
<td></td>
<td>Pertussis Toxoid (PT)</td>
</tr>
<tr>
<td></td>
<td>Filamentous Haemagglutinin (FHA)</td>
</tr>
<tr>
<td></td>
<td>Pertactin (PRN)</td>
</tr>
<tr>
<td></td>
<td>Fimbriae Types 2 and 3 (FIM)</td>
</tr>
<tr>
<td></td>
<td><strong>Poliovirus (Inactivated)</strong>*</td>
</tr>
<tr>
<td></td>
<td>Type 1 (Mahoney)</td>
</tr>
<tr>
<td></td>
<td>Type 2 (MEF-1)</td>
</tr>
<tr>
<td></td>
<td>Type 3 (Saukett)</td>
</tr>
<tr>
<td></td>
<td><strong>Haemophilus influenzae Type b Polysaccharide</strong></td>
</tr>
<tr>
<td></td>
<td>(Polyribosylribitol Phosphate)</td>
</tr>
<tr>
<td></td>
<td>Conjugated to Tetanus Toxoid (PRP-T)</td>
</tr>
<tr>
<td></td>
<td>Adsorbed on aluminium phosphate</td>
</tr>
<tr>
<td>*</td>
<td>Produced in Vero cells.</td>
</tr>
<tr>
<td>†</td>
<td>Or equivalent antigenic quantity determined by a suitable immunochemical method.</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Sanofi Pasteur MSD Limited</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and The Netherlands</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/2388/01/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 05 November 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
PEDIACEL®, suspension for injection in pre-filled syringe
Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated)
and Haemophilus type b conjugate vaccine (adsorbed)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 0.5 mL dose contains:
Diphtheria Toxoid not less than 30 IU
Tetanus Toxoid not less than 40 IU
Acellular Pertussis Antigens
  Pertussis Toxoid (PT) 20 micrograms
  Filamentous Haemagglutinin (FHA) 20 micrograms
  Pertactin (PRN) 3 micrograms
  Fimbriae Types 2 and 3 (FIM) 5 micrograms
Poliovirus (Inactivated)*
  Type 1 (Mahoney) 40 D antigen units†
  Type 2 (MEF-1) 8 D antigen units†
  Type 3 (Saukett) 32 D antigen units†
Haemophilus influenzae Type b Polysaccharide
  (Polyribosylribitol Phosphate) 10 micrograms
  Conjugated to Tetanus Toxoid (PRP-T) 20 micrograms
Adsorbed on aluminium phosphate 1.5 mg
  (0.33 mg aluminium)

* Produced in Vero cells.
† or equivalent antigenic quantity determined by a suitable immunochemical method.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Suspension for injection in pre-filled syringe
PEDIACEL is a uniform, cloudy, white to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
PEDIACEL is indicated for primary and booster vaccination against diphtheria,
tetanus, pertussis, poliomyelitis and invasive Haemophilus influenzae type b
disease in infants and children from the age of 6 weeks up to the fourth birthday.
PEDIACEL should be used in accordance with applicable official
recommendations.

4.2 Posology and method of administration
Posology
Primary Vaccination
The primary vaccination series consists of 2 or 3 doses of 0.5 mL and may be commenced from 6 weeks of age according to applicable official recommendations. There should be an interval of at least one month between doses.

**Booster Vaccination**
After primary series vaccination with either 2 doses (e.g., 3, 5 months) or 3 doses (e.g., 2, 3, 4 months) of PEDIACEL, a booster dose should be given at least 6 months after the last priming dose in accordance with applicable official recommendations.

PEDIACEL can be considered for the booster if the composition is in accordance with the applicable official recommendations.

Based on safety and immunogenicity data from clinical studies, PEDIACEL should preferably be given to children who received the same vaccine in infancy. However, PEDIACEL may be given as a booster to children who received other diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b (Hib) with or without hepatitis B vaccines in their primary series.

**Method of Administration**
PEDIACEL should be administered intramuscularly. The recommended injection sites are the anterolateral aspect of the thigh or the deltoid region of the upper arm if there is adequate muscle mass, according to local clinical practice recommendations. The anterolateral aspect of the thigh is the preferred site for infants under one year of age.

Do not administer PEDIACEL by intravascular injection; ensure that the needle does not penetrate a blood vessel. Do not administer subcutaneously.

### 4.3 CONTRAINDICATIONS
- PEDIACEL should not be administered to children with known hypersensitivity
  - to diphtheria, tetanus, pertussis, polio or Hib vaccines
  - to any other component of the vaccine (see Section 6.1)
  - to any residual substances carried over from manufacture (neomycin, streptomycin, polymyxin B, glutaraldehyde, formaldehyde and bovine serum albumin), which may be present in undetectable trace amounts.
- PEDIACEL is contraindicated if the infant has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria, tetanus, polio and Hib vaccines.
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to children with such conditions until a treatment regimen has been established and the condition has stabilized.
- As with other vaccines, administration of PEDIACEL should be postponed in children suffering from acute severe febrile illness. The presence of a minor infection (e.g., mild upper respiratory infection) is not a contraindication.
4.4 Special warnings and precautions for use

Applicable official recommendations for childhood immunizations should be consulted before administering this vaccine to children in or after the second year of life since the exact combination of antigens may not be considered appropriate and/or necessary after completion of the primary vaccination series.

Prior to Immunization

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of the vaccine.

If any of the following events have occurred after administration of a pertussis-containing vaccine, the decision to administer PEDIACEL should be based on careful consideration of potential benefits and possible risks.

- Temperature of $\geq 40^\circ C$ within 48 hours, not attributable to another identifiable cause
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours
- Persistent crying lasting $\geq 3$ hours within 48 hours
- Convulsions with or without fever within 3 days.

If Guillain-Barré syndrome or brachial neuritis has occurred following receipt of prior vaccine containing tetanus toxoid, the decision to give any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

A history of febrile convulsions, a family history of convulsions or Sudden infant death syndrome (SIDS) do not constitute a contraindication for the use of PEDIACEL. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunization series to very premature infants (born $\leq 28$ weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Immunocompromised children (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. HIV infection is not considered as a contraindication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Administration Precautions

As for all injectable products, the vaccine should be administered with caution to children with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular injection.

Other Considerations
As with any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1).

Vaccines that contain Hib antigen do not provide protection against infections caused by other types of *Haemophilus influenzae* or against meningitis of other origin.

Granuloma or sterile abscess at the injection site has been reported with vaccines containing aluminum.

Since the Hib capsular polysaccharide antigen is excreted in the urine, a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

### 4.5 Interaction with other medicinal products and other forms of interaction

#### Concomitant Vaccine Administration

PEDIACEL may be administered at the same time as, but as a separate injection to, any of the following monovalent or combination vaccines: hepatitis B, 7-valent pneumococcal conjugate, measles, mumps and rubella (MMR), varicella or meningococcal group C conjugate vaccines. Injections should be made into separate sites and, preferably, into separate limbs.

**Meningococcal Group C Conjugate Vaccines**

In a controlled clinical study PEDIACEL was administered concomitantly with two different meningococcal group C conjugate vaccines (a meningococcal group C CRM197 conjugate and a meningococcal group C tetanus toxoid conjugate vaccine) at 2, 3 and 4 months of age. Although seroprotection rates were high in both groups (>88.0% anti-PRP ≥0.15 micrograms/mL), antibody responses to the Hib component of PEDIACEL (PRP conjugated to tetanus toxoid) were lower when co-administered with a meningococcal group C CRM197 conjugate vaccine than with a meningococcal group C tetanus toxoid conjugate vaccine. PEDIACEL did not affect the proportions of infants with meningococcal group C serum bactericidal antibody (SBA) titres of at least 1:8 (measured with rabbit complement) when co-administered with either a CRM197 conjugate or a tetanus toxoid conjugate vaccine. (See Section 5.1.)

**Vaccine/Drug Interactions**

Immunosuppressive treatments may interfere with the development of the expected immune response. (See Section 4.4.)

### 4.6 Pregnancy and lactation

Not applicable. This vaccine is not intended for administration to women of child-bearing age.

### 4.7 Effects on ability to drive and use machines

Not relevant.

### 4.8 Undesirable effects

**Data from Clinical Trials**

The data from 11 clinical trials conducted in several countries and using various immunization schedules were pooled. In these studies, PEDIACEL was
administered in a primary series (N = 1487) and as a booster dose (N = 1632). The adverse reactions occurring after vaccination are summarized below. Adverse reactions are ranked under headings of frequency using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very Rare (<1/10,000), including individual cases

Metabolism and Nutrition Disorders
Very common: Appetite loss

Psychiatric Disorders
Very common: Irritability, Abnormal crying

Nervous System Disorders
Uncommon: Convulsion (with or without fever)

Gastrointestinal Disorders
Very common: Vomiting
Common: Diarrhoea

General Disorders and Administration Site Conditions
Very common: Decreased activity, injection site tenderness, injection site erythema, pyrexia (≥38°C), injection site swelling
Common: Injection site bleeding, injection site bruising
Uncommon: Extensive limb swelling (from the injection site beyond one or both joints)

Data from Post-Marketing Experience
Based on spontaneous reporting, the following adverse events have been reported following commercial use of PEDIACEL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Therefore, the frequency category ‘Not Known’ is assigned to these adverse events.

Immune System Disorders
Hypersensitivity, anaphylactic reaction (such as urticaria, angioedema).

Nervous System Disorders
High-pitched crying, hypotonic hypoactive episode (infant appears pale, hypotonic (limp) and unresponsive). To date, this condition has not been associated with any permanent sequelae. Somnolence.

Vascular Disorders
Pallor

Skin and Subcutaneous Tissue Disorders
Rash.

Musculoskeletal, Connective Tissue and Bone Disorders
Pain in vaccinated limb.

**General Disorders and Administration Site Conditions**

Pyrexia (>40.5°C), injection site mass, asthenia, and listlessness.

Edematous reactions affecting one or both lower limbs have occurred following vaccination with *H. influenzae* type b containing vaccines. When this reaction occurs, it does so mainly after primary injections and is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolved spontaneously without sequelae within 24 hours.

**Additional Information on Special Populations**

Apnoea in very premature infants (≤28 weeks of gestation). (See section 4.4.)

4.9 **Overdose**

Non-applicable.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Bacterial and viral vaccines combined, diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus, ATC code J07CA06.

**Immunogenicity**

In a randomized, single-blind, controlled multi-centre clinical trial, the immunogenicity of PEDIACEL was compared to another DTaP-IPV+Hib vaccine when administered to infants using the three-dose primary immunization schedule of 2, 3 and 4 months with a booster dose given at 12-18 months. Antibody responses one month after completion of the three-dose primary series and one month after the booster dose of PEDIACEL are summarized below.

**Table 1: Immune Responses**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Criteria</th>
<th>PEDIACEL Post-dose 3</th>
<th>PEDIACEL Post-dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N = 248</td>
<td>N = 220</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>≥0.01 IU/mL</td>
<td>99.2%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>≥0.1 IU/mL</td>
<td>39.3%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>≥0.01 IU/mL</td>
<td>100.0%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>≥0.1 IU/mL</td>
<td>99.2%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Pertussis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis Toxoid</td>
<td>seroresponse*</td>
<td>98.7%</td>
<td>96.7%</td>
</tr>
<tr>
<td>Filamentous Haemagglutinin</td>
<td>seroresponse†</td>
<td>93.2%</td>
<td>83.2%</td>
</tr>
<tr>
<td>Pertactin</td>
<td>seroresponse*</td>
<td>87.5%</td>
<td>86.9%</td>
</tr>
<tr>
<td>Fimbriae Types 2 and 3</td>
<td>seroresponse*</td>
<td>95.8%</td>
<td>95.7%</td>
</tr>
<tr>
<td>Polio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>≥1:8 Dilution</td>
<td>100.0%</td>
<td>99.5%</td>
</tr>
<tr>
<td>Type 2</td>
<td>≥1:8 Dilution</td>
<td>99.2%</td>
<td>99.5%</td>
</tr>
<tr>
<td>Type 3</td>
<td>≥1:8 Dilution</td>
<td>99.6%</td>
<td>99.5%</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>≥0.15 micrograms/mL</td>
<td>91.0%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>≥1.0 micrograms/mL</td>
<td>63.3%</td>
<td>99.1%</td>
</tr>
</tbody>
</table>
In a controlled clinical trial, the immunogenicity of booster vaccination with PEDIACEL was compared to a hexavalent DTaP-IPV-Hib-Hepatitis B vaccine given at 11 to 18 months of age in toddlers who had been primed with 3 doses of DTaP-IPV-Hib-Hepatitis B vaccine. 100% of participants receiving PEDIACEL achieved seroprotective levels for diphtheria and tetanus (≥0.1 IU/mL), PRP (≥1.0 micrograms/mL) and all three types of polio (≥1:8 dilution). The booster response rates for pertussis antigens PT, FHA, PRN and FIM were 90.4%, 86.7%, 95.9% and 26.4%. This was the first dose containing FIM for these participants.

In a randomized, double-blind, controlled clinical trial, the immunogenicity of PEDIACEL was compared to another DTaP-IPV+Hib vaccine when administered to infants using the two-dose primary immunization schedule of 3 and 5 months followed by a booster dose at 12 months. Antibody responses one month after completion of the three-dose series are summarized below.

### Table 2: Immune Response

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Criteria</th>
<th>PEDIACEL Post-dose 3 N = 325</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>≥0.01 IU/mL</td>
<td>98.2%</td>
</tr>
<tr>
<td></td>
<td>≥0.1 IU/mL</td>
<td>95.1%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>≥0.01 IU/mL</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>≥0.1 IU/mL</td>
<td>100.0%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>seroresponse*</td>
<td>98.5%</td>
</tr>
<tr>
<td>Pertussis Toxoid</td>
<td>seroresponse†</td>
<td>99.1%</td>
</tr>
<tr>
<td>Filamentous Haemagglutinin</td>
<td>seroresponse*</td>
<td>96.9%</td>
</tr>
<tr>
<td>Pertactin</td>
<td>seroresponse*</td>
<td>96.3%</td>
</tr>
<tr>
<td>Fimbriae Types 2 and 3</td>
<td>seroresponse*</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>≥1:8 Dilution</td>
<td>99.4%</td>
</tr>
<tr>
<td>Type 1</td>
<td>≥1:8 Dilution</td>
<td>99.7%</td>
</tr>
<tr>
<td>Type 2</td>
<td>≥1:8 Dilution</td>
<td>98.8%</td>
</tr>
<tr>
<td>Type 3</td>
<td>≥1:8 Dilution</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>≥0.15 micrograms/mL</td>
<td>99.1%</td>
</tr>
<tr>
<td>PRP</td>
<td>≥1.0 micrograms/mL</td>
<td>93.2%</td>
</tr>
</tbody>
</table>

* Post-dose 3 ≥4 EU/mL if pre-dose 1 <4 EU/mL or post-dose 3 ≥ pre-dose 1 if pre-dose 1 ≥ 4 EU/mL.
† Post-dose 3 ≥3 EU/mL if pre-dose 1 <3 EU/mL or post-dose 3 ≥ pre-dose 1 if pre-dose 1 ≥ 3 EU/mL.

### Pertussis Efficacy

In a clinical trial in Sweden (Sweden I Efficacy Trial), the pertussis components in PEDIACEL (i.e., PT, FHA, PRN and FIM) have been shown to prevent pertussis in infants with a protective efficacy of 85.2% using the WHO case definition (≥21

* Post-dose 3 ≥ 4 EU/mL if pre-dose 1 <4 EU/mL or post-dose 3 ≥ pre-dose 1 if pre-dose 1 ≥ 4 EU/mL.
† Post-dose 3 ≥ 3 EU/mL if pre-dose 1 <3 EU/mL or post-dose 3 ≥ pre-dose 1 if pre-dose 1 ≥ 3 EU/mL.
consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiological link to a confirmed case). In the same study, the protective efficacy against mild disease (≥1 day of paroxysmal cough with culture or serologic confirmation) was 77.9%. In a controlled clinical trial in Sweden (Sweden II Trial), a DTaP vaccine with the same formulation of pertussis antigens as PEDIACEL demonstrated protection against pertussis with any cough.

5.2 Pharmacokinetic properties
No pharmacokinetic studies have been performed.

5.3 Preclinical safety data
Limited pre-clinical testing of PEDIACEL and closely related products revealed no unexpected findings and no target organ toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Phenoxyethanol
Polysorbate 80
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, PEDIACEL must not be mixed with other medicinal products.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store in a refrigerator (2°C–8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container
0.5 mL of suspension in pre-filled syringe (type I glass) with a plunger stopper (halobutyl elastomer), without attached needle, with a tip-cap (halobutyl elastomer) - pack size of 1, 10 or 20.

0.5 mL of suspension in pre-filled syringe (type I glass) with a plunger stopper (halobutyl elastomer), without attached needle, with a tip-cap (halobutyl elastomer) and 2 separate needles - pack size of 1 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling
Instructions for use
The vaccine should be used as supplied; no dilution or reconstitution is necessary.

Inspect for extraneous particulate matter and/or discolouration before use. If these conditions exist, the product should not be administered.
Shake the pre-filled syringe well to uniformly distribute the suspension before administering the vaccine. The normal appearance of the vaccine is a uniform, cloudy, white to off-white suspension, which may sediment during storage.

The needle should be pushed firmly on to the end of the pre-filled syringe and rotated through 90 degrees.

Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Marketing Authorisation Holder – UK:
Sanofi Pasteur MSD Limited
Mallards Reach, Bridge Avenue
Maidenhead, Berkshire
SL6 1QP

8 MARKETING AUTHORISATION NUMBER(S)
PL 06745/0128

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/12/2010

10 DATE OF REVISION OF THE TEXT
03/12/2010
Module 3

Please note that the Patient Information leaflet below is the version for the product that would be marketed in the UK only. The indications listed therein may differ in other member states.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
Based on the review of the data on the quality, safety and efficacy, the MHRA granted Sanofi Pasteur MSD Limited a Marketing Authorisation for the medicinal product Pediacel suspension for injection in pre-filled syringe (PL 06745/0128; UK/H/2388/01/DC) on 3rd December 2010. The product is a prescription-only medicine.

This is an abridged complex decentralised outgoing application for Pediacel suspension for injection in pre-filled syringe, submitted under Article 8.3 of 2001/83 EC, as amended. Pediacel was originally approved as a single-dose vial presentation (PL 06745/0120) on 16th October 2002 indicated for the primary immunisation series in infancy which may be commenced from 2 months of age according to applicable official recommendations. This application concerns Pediacel in a new presentation, suspension for injection in a pre-filled syringe (PL 06745/0128), which has the same indication as that of the single-dose vial, but a lower age at which immunisation can be commenced, i.e. from 6 weeks of age has been approved.

Pediacel suspension for injection in pre-filled syringe is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and invasive Haemophilus influenzae type b disease in infants and children from the age of 6 weeks up to the fourth birthday. Pediacel should be used in accordance with applicable official recommendations.

Tetanus is an acute infection caused by Clostridium tetani, which colonise as a non-pathogenic organism in the gut of humans and animals. The organism is also found in soil contaminated by faeces and may survive in soil for years as infectious spores. Thus, tetanus is not considered an eradicable disease. Tetanus can be prevented through immunisation with vaccine composed of tetanus toxoid, usually adsorbed to an aluminium salt adjuvant. A serum titre of $\geq 0.01$ IU/mL of tetanus antitoxin antibodies when measured by a neutralisation assay has generally been viewed as protective.

Diphtheria is an acute infection caused by the bacteria Corynebacterium diphtheriae. The organism is generally transmitted to susceptible persons by respiratory droplets from active cases or carriers. The only reservoir for C. diphtheriae is man. Transmission is by direct contact with secretions or discharges from an infected individual. Individuals are contagious as long as bacteria are observed in the secretions, a period which may last up to 4 weeks after infection. Transmission may also occur with infected fomites. Toxigenic strains of diphtheria bacilli (pharynx, skin, and ear) are still detected each year in carriers sometimes associated with mild clinical symptoms. Asymptomatic carriage of C. diphtheriae is far more common than clinical diphtheria. Although occasional cases of mild clinical diphtheria do occur in apparently fully immunised persons, antibodies stimulated by immunisation is believed to persist at protective levels for 10 years or more. The WHO recommends that in order to achieve sufficient herd immunity against diphtheria, the proportion of the population with serologic evidence of immunity should be 90% in children and 75% in adults. Recent serologic surveys in many European countries have documented levels of immunity in adults that are significantly lower than those recommended by WHO, and have led to suggestions for introduction or enhancement of programs of booster immunisation of adolescents and adults.

Pertussis, also called whooping cough, is a highly communicable respiratory disease caused by the gram-negative bacterium Bordetella pertussis. Pertussis is transmitted by
respiratory droplets or direct contact with secretions from the respiratory tract of an infected person. It has a high rate of contagion, with secondary attack rates among non-immune household contacts as high as 90%. Analysis of the epidemiology of pertussis indicates that *B. pertussis* continues to circulate even in populations where high vaccine coverage of infants and children is achieved. Adults serve as the reservoir for infections in very young infants, too young to have completed the primary series of immunisation, in whom pertussis may be severe and life-threatening. It has been difficult to identify serologic correlates of protection. Two studies have suggested that serologic correlates of protection against pertussis may exist and that high anti-PRN combined with high anti-PT and/or high anti-FIM correlates with high protection (89.1% efficacy).

**Poliomyelitis** is an acute communicable disease caused by poliovirus types 1, 2 and 3, transmitted through person-to-person contact. In the pre-vaccine era, it was estimated that 1 out of 200 susceptible children infected by poliovirus developed the paralytic form of the disease.

An effective inactivated poliovirus vaccine (IPV), comprising all three serotypes, was licensed after large-scale field trials in 1955. Extensive use of this vaccine (Salk vaccine) decreased poliomyelitis incidence in many industrialised countries and interrupted wild poliovirus transmission in four northern European countries (Finland, Iceland, The Netherlands, and Sweden). For poliomyelitis, poliovirus neutralising antibody titres \( \geq 1:8 \) dil were considered indicative of protection against all 3 poliovirus strains.

**Haemophilus influenzae type b** may colonise the respiratory tract and occasionally cause invasive disease (including meningitis, epiglottitis, pneumonia and osteomyelitis). Before the advent of conjugated Hib vaccines almost all Hib disease occurred in children aged < 4 years with naturally-acquired immunity protecting older children and adults. Hib vaccines are now included in routine childhood vaccination programmes in more than 90 countries in all regions of the world. As a consequence, invasive Hib disease has been practically eliminated in many industrialised countries, and its incidence has been dramatically reduced in some parts of the developing world.

In general, a 2-dose or 3-dose primary series is given at the same time as the primary series of diphtheria–tetanus–pertussis (DTP). The first dose may be given to infants as young as 6 weeks of age, and further doses may be given at 4–8 week intervals along with DTP. Experience has shown that a booster should be given during the second year of life to maintain protection through the period of risk.

A PRP antibody concentration of >0.15 \( \mu g/ml \) is considered to be a serological marker for short-term protection; concentrations >1.0 \( \mu g/ml \) 1 month after the completion of primary immunisation are considered to be markers of long-term protective immunity against invasive Hib disease.

**About the product**

Pediace is a pentavalent paediatric combination vaccine containing a 5 component acellular pertussis vaccine, diphtheria toxoid, tetanus toxoid, a *Haemophilus influenzae* type b conjugate vaccine and an inactivated poliomyelitis vaccine. This combination vaccine is manufactured by Sanofi Pasteur SA in France.

Pediace (DTaP5-IPV-Hib) is indicated for the active immunisation of infants against diphtheria, tetanus, pertussis, poliomyelitis, and invasive infections caused by *Haemophilus influenzae* type b. The primary vaccination series consists of 2 or 3 doses
of 0.5 ml and may be commenced from 6 weeks of age according to applicable official recommendations. There should be an interval of at least one month between doses. After primary series vaccination with either 2 doses (e.g., 3, 5 months) or 3 doses (e.g., 2, 3, 4 months) of Pediaceal, a booster dose should be given at least 6 months after the last priming dose in accordance with applicable official recommendations.

The UK licence for Pediaceal was granted on the 16 October 2002, and Pediaceal was introduced into the UK’s national vaccination programme for the primary immunisation of infants on the 27 September 2004. Subsequent to the licensure of Pediaceal in the UK, the Dutch and Portuguese health authorities expressed an interest in the product. Mutual Recognition Procedure, with UK as Reference Member State, was therefore conducted in 2005 to licence Pediaceal in The Netherlands and Portugal (UK/H/0775/001). The MRP was successfully completed on 23 September 2005. As of September 2008, more than 15 million doses of Pediaceal have been distributed worldwide.

In a meeting between the MHRA, Sanofi Pasteur MSD and Sanofi Pasteur on 02 November 2006, the MHRA agreed that an application for a pre-filled syringe (PFS) presentation of Pediaceal could be submitted and reviewed according to the Decentralised Procedure (DCP) in the current member states where Pediaceal is approved and additional EU countries.

**General comments on the submitted dossier**

In general the submitted dossier is acceptable. Non-clinical data are not overly extensive as the abundance of clinical study data is considered more relevant for the procedure.

**General comments on compliance with GMP, GLP, GCP and agreed ethical principles.**

**GMP**
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations and GMP certificates issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates and manufacturing authorisations.

**GLP**
All nonclinical safety studies were conducted in compliance with Good Laboratory Practice (GLP).

**GCP**
All 22 clinical studies included in this submission were conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. The company provided an assurance in relevant clinical study report documentation that all studies were conducted in accordance with applicable national and local requirements regarding Ethical Committee Review, informed consent, and other statutes or regulations pertinent
to the protection of the rights and welfare of human subjects participating in biomedical research.

**Pharmacovigilance system**

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**

A risk management plan has been submitted in line with the EU template. There is extensive experience with this vaccine which has been summarised in the safety specification. The important identified risks are convulsions, hypotonic hyporesponsive episode (HHE) and extensive limb swelling (ELS), with potential risks listed as anaphylactic shock and apnoea. A specific warning concerning the risk of apnoea in very premature infants after immunisation with all paediatric vaccines was issued in 2007 and was approved for Pediacel SmPC in the EU in June 2008. Regular (six monthly) evaluation of the incidence of apnoea using the UK THIN database is proposed during the first 2 years after approval of the PFS in the EU.

The risk management plan is satisfactory.

**Pharmacovigilance Plan**

Pharmacovigilance plan fulfils the requirements.

**Risk Minimisation Plan**

Routine pharmacovigilance and risk minimisation are proposed for all risks.

**Environmental Risk Assessment**

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).
## ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Pediacel suspension for injection in pre-filled syringe |
| Name(s) of the active substance(s) (INN) | Diphtheria, tetanus, pertussis [acellular, component], poliomyelitis [inactivated] and haemophilus type b conjugate vaccine [adsorbed] |
| Pharmacotherapeutic classification (ATC code) | Diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenzae* vaccines(J07CA06) |
| Pharmaceutical form and strength(s) | Suspension for injection in pre-filled syringe |
| Reference numbers for the Decentralised Procedure | UK/H/2388/01/DC |
| Reference Member State (RMS) | United Kingdom |
| Member States concerned | Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and The Netherlands |
| Marketing Authorisation Number(s) | PL 06745/0128 |
| Name and address of the authorisation holder | Sanofi Pasteur MSD Limited, Mallard’s Reach, Bridge Avenue, Maidenhead, Berkshire, SL6 1QP, UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

Drug substance
HCPDT-IPV-PRP-T Vaccine, (Pediacel) contains the following drug substances; diphtheria toxoid adsorbed, tetanus toxoid adsorbed, five component acellular pertussis adsorbed, inactivated trivalent poliomyelitis vaccine and *Haemophilus influenzae* type b conjugate to tetanus protein (PRP-T).

The history and origins of bacterial and viral strains used to establish the seed lot system are well documented. The establishment of the Vero cell bank is fully documented. All the antigens are produced in compliance with the relevant Ph. Eur. monographs. The manufacturing processes are well established and are adequately described in the dossier. The critical manufacturing steps have been identified and appropriate in-process controls applied. Satisfactory validation studies have been completed and batch analyses provided.

After adsorption the DTP antigens are not accessible for some relevant quality control tests, therefore, tests are performed on the pre-adsorbed Diphtheria and Tetanus antigens. Tests are also performed on the separately adsorbed antigens which form the drug substances.

Quality control tests are also performed on the pre-adsorbed component Pertussis antigens and the IPV monovalent bulks. Each intermediate in the manufacture of *Haemophilus* polysaccharide conjugated concentrated bulk is tested and the final concentrated bulk complies with Ph. Eur.

The control tests and specifications applied to the drug substances are appropriate and meet the requirements of the relevant Ph. Eur. monograph. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

Stability studies have been performed with the drug substances and intermediates. No significant changes in any parameters were observed. The shelf-lives assigned for the drug substances and respective intermediates are considered justified.

Drug Product
Other ingredients consist of pharmaceutical excipients, namely aluminium phosphate, phenoxyethanol, polysorbate 80 and water for injections.

All excipients used comply with their respective European Pharmacopoeia monograph.

There are no excipients of human origin. The raw material of animal origin used in the manufacture of HCPDT-IPV-PRP-T vaccine is polysorbate 80. None of the excipients are sourced from genetically modified organisms.

Formulation development
HCPDT-IPV-PRP-T Vaccine (Pediacel) has been used in the UK since October 2004. This is a complex vaccine containing a number of bacterial and viral antigens. The formulation development has been adequately justified.
Manufacture
The validation data and the in-process controls applied at the various stages of manufacture indicate that the process is under control. The tests and release specifications applied to the intermediate products and the final vaccine are in line with the requirements of the Ph. Eur.

Finished product specification
Product specifications cover appropriate parameters for this product as laid down in the relevant Ph. Eur. monographs or developed by the applicant. Validations of the analytical methods not mentioned in the Ph. Eur. have been presented. Batch analyses have been provided. The batch analysis results show that the finished products meet the specifications proposed.

Container Closure System
The drug product is licensed for marketing in Type I glass pre-filled syringes of volume 0.5 ml, with a plunger stopper (halobutyl elastomer) without attached needle, with a tip-cap (halobutyl elastomer), - pack size of 1, 10 or 20. The syringes contain 0.5ml of suspension of Pediacel.

The drug product is also licensed for marketing in Type I glass pre-filled syringes of volume 0.5 ml, with a plunger stopper (halobutyl elastomer) without attached needle, with a tip-cap (halobutyl elastomer) and 2 separate needles, - pack size of 1 or 10. The syringes contain 0.5ml of suspension of Pediacel.

Stability
Real-time stability data for the Finished Vaccine in the pre-filled syringe intended for marketing support a storage claim of at least 36 months at 2°C to 8°C and the supporting data for the finished vaccine in other containers demonstrate stability for 48 months. However, it is recommended that the shelf life of Pediacel in the pre-filled syringe should be restricted to 36 months until further real-time stability data are available.

Quality Overall Summary
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved SmPC, patient information leaflet (PIL), and labelling are satisfactory. Mock-ups of the labelling and PIL have been provided.

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PIL), and labelling are satisfactory. Mock-ups of the PILs and labelling have been provided. The PIL user testing report has been evaluated and is accepted.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion
All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of the proposed product, Pediacel suspension for injection in pre-filled syringe, from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Pharmacology
Potency and immunogenicity tests were conducted in different animal models to evaluate the ability of the Pediacel to produce antibodies to the individual component antigens in vivo. All pharmacology tests were applied to three batches. The results support the intended indication by demonstrating that Pediacel (or the representative vaccine) induces appropriate immunological responses to each of the antigens in the animal models tested.

Pharmacokinetics
No pharmacokinetic evaluation was conducted which is in accordance with the EMEA “Note for guidance on preclinical pharmacological and toxicological testing of vaccines” CPMP/SWP/465/95 and the WHO guidelines on nonclinical evaluation of vaccines.

Toxicology
No specific toxicology studies were conducted with Pediacel, however, information from toxicology studies conducted on each of the antigens present in Pediacel has been presented in support of this application.

In general, the findings in the acute, repeated-dose and local tolerance toxicity studies were largely limited to local reactions at the site of injection following administration of all antigens. These findings were also present in some controls, suggesting that the adjuvant was contributory.

Lymph node enlargement and/or minor effects on some haematological/clinical chemistry parameters following repeated-administration of the antigens are not unexpected with high doses of injected antigens. Such findings are not likely to be relevant to clinical use involving much lower doses (on a ml/kg basis) and less frequent dosing.

The lack of genotoxicity, carcinogenicity and reproductive and developmental toxicity studies and the absence of an environmental risk assessment are acceptable.

Conclusion
In conclusion, the limited preclinical data on Pediacel and on products containing some of the components of Pediacel, suggest that systemic toxic effects are unlikely but that local reactions may occur when using the clinical route (im injection). Extensive clinical safety data is available which supports these conclusions and appropriate comments on such reactions are provided in SPC Sections 4.4 and 4.8.

The wording of the SPC is considered to be acceptable from a non-clinical perspective.

Overall, the non-clinical data provided by the applicant are considered to support the grant of a marketing authorisation.

III.3 CLINICAL ASPECTS

Indications
Pediace is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and invasive Haemophilus influenzae type b disease in infants and children from the age of 6 weeks up to the fourth birthday. Pediace should be used in accordance with applicable official recommendations.
Posology and method of administration

Primary Vaccination
The primary vaccination series consists of 2 or 3 doses of 0.5 mL and may be commenced from 6 weeks of age according to applicable official recommendations. There should be an interval of at least one month between doses.

Booster Vaccination
After primary series vaccination with either 2 doses (e.g., 3, 5 months) or 3 doses (e.g., 2, 3, 4 months) of Pediacel, a booster dose should be given at least 6 months after the last priming dose in accordance with applicable official recommendations.

Full details concerning the posology are provided in the SmPC. The posology is satisfactory.

Clinical Studies
Complete reports of 22 studies (31 clinical study reports) are presented in the application.

These 31 study reports cover approximately 17 years of clinical trials with Pediacel and include a variety of immunisation schedules, various countries/populations, differing comparison groups, and varied co-administration of concomitant vaccinations. Over time, adverse event definitions, safety data collection tools and coding methods have changed, and laboratory methods for serological determinations have evolved. Therefore the company provided a serological report explaining various concordance issues between assays conducted in different locations. In addition, an integrated safety analysis of all pivotal and supportive studies was included.

The efficacy (and, therefore, immunogenicity data from most of the studies) of Pediacel was assessed from 18 clinical studies (26 study reports) of the total 22 studies (31 study reports) included in Module 5 of this CTD. The 4 clinical studies (5 study reports) that did not generate immunogenicity data were specifically designed to assess safety only (Studies PB9506, PB9603 (primary series and booster), PB9505 and Phase IIC France) and did not collect sera for immunogenicity assessment. The studies with immunogenicity/efficacy endpoints were conducted over a period of 17 years and were performed in different countries. The data represent most commonly used vaccination schedules, a variety of combination vaccine comparison groups, different immunisation backgrounds for booster studies, and commonly co-administered childhood vaccines.

The 18 clinical studies (26 study reports) were categorised into the 3 main groups (pivotal Pediacel studies, supportive Pediacel studies and supportive non-Pediacel studies), and were further subdivided into primary series and booster dose schedules.

The pivotal Pediacel study group included 7 active-controlled studies (12 study reports):
- A5115 (2-dose primary and 3rd dose booster);
- A5116 (primary series and 4th dose booster);
- A5119 (4th dose booster on a hexavalent primary series background);
- PB9502 (primary series and 4th dose booster);
- PB9602 (primary series and 4th dose booster);
- PB9402 (4th dose booster on a whole-cell pertussis combination background), and;
- U01-A51-I-302 (Parts I, II and III).
The supportive Pediacel study group included 4 active-controlled studies (6 study reports):

- A5I06/A5I09 (primary series and 4th dose booster);
- HE9810/A5I07 (primary series and 4th dose booster);
- HE9811 (primary series), and;
- HE9812 (primary series).

The supportive non-Pediacel study group included 7 studies (8 study reports):

- Sweden I (primary series);
- Sweden II (2-dose and 3-dose primary and 3rd dose booster);
- PB9601 (primary series);
- PB9501 (4th dose booster on a whole-cell pertussis combination background), and;
- 494-03 (primary series and 4th dose booster).

Over the 17 year clinical trial history of Pediacel, the nomenclature for the vaccines included in the clinical trial data has changed, including the registration of trade names. While assessment of the safety and efficacy of PRP, diphtheria, tetanus, and IPV types 1, 2 and 3 antigens was generally established by the early 1990s (including serological correlates of clinical protection), evidence for the efficacy of the purified acellular pertussis antigens compared with the whole-cell pertussis vaccines was established by 2 landmark clinical trials conducted in the early and mid-1990s, Sweden I and Sweden II.

In Sweden I, using the 5-component acellular pertussis combination vaccine, Daptacel (containing PT, FHA, FIM and PRN), a protective efficacy of 85% against typical pertussis (defined as ≥21 consecutive days of paroxysmal cough and laboratory or culture-confirmed B. pertussis) and 78% for mild pertussis (defined as ≥1 day of paroxysmal cough and laboratory confirmed pertussis) was achieved. Daptacel contains a lower antigen content for PT and FHA than Pediacel, but contains the same amounts of FIM and PRN antigens.

Clinical development

In the clinical development of Pediacel, the HCPDT vaccine (investigated in Sweden II) was combined with a liquid-based PRP-T and vero IPV to provide a fully liquid pentavalent combination vaccine which contains a 5-component acellular pertussis vaccine. Three Phase I and Phase II studies investigating Pediacel were conducted in Canada between 1995 and 1998; these studies (PB402, PB9502 and PB9602) have been included as pivotal Pediacel studies. Based on these studies and the supportive efficacy results from the Sweden efficacy trials (Sweden I and Sweden II), Pediacel was licensed in Canada in 2000.

From 1999 through 2002, several clinical trials were conducted to support MAAs in Taiwan (primary series Study A5I06 and booster Study A5I09), the Philippines (primary series Study HE9810 and booster Study A5I07), Mexico (Study HE9811) and Brazil (Study HE9812). These studies have been grouped as Pediacel supportive studies. Licensure of Pediacel in Europe was obtained in the UK in 2002 with clinical data from the Pediacel trials conducted in Canada, the efficacy data from Sweden I and Sweden II as well as from several other trials that investigated vaccines with the same or similar composition as contained in Pediacel (i.e., Pentacel, CPDT-IPV//PRP-T, QUADRACEL and ACT-HIB, CPDT-IPV-PRP-T) and which are referred to as supportive Non-Pediacel trials (i.e., Studies PB9501, PB9506, PB9601, PB9603, PB9503 and PB9504). To support the UK vaccination schedule of 2, 3 and 4 months, Study U01-A5I-302 was conducted (in the UK), and was initiated in 2001 to provide safety and immunogenicity.
data with coadministration of 2 different meningococcal C conjugate (MCC) vaccines (Part I), and antibody persistence data gathered at 12-13 months of age (Part II), and 3.5 to 4.5 years of age (Part III). This study was included as a Pediacel pivotal study.

Following a decision in 2005 to seek licensure of Pediacel in countries throughout Europe, additional Pivotal Pediacel studies were conducted, and were designed to address vaccination schedules most frequently used in countries in Europe, as well as to augment the safety and immunogenicity database following co-administration of Pediacel with other childhood vaccines. Studies A5I15 (3, 5 and 12 month schedule, conducted in Sweden and Finland), A5I16 (2, 3, and 4 month schedule co-administered with a 7-valent pneumococcal conjugate vaccine, Prevenar, in France and Poland), and A5I19 (booster dose on a hexavalent acellular pertussis combination vaccine background in Germany) were conducted from 2006 to 2008.

Lastly, data to support co-administration of Pediacel with measles, mumps, rubella (MMR) and varicella vaccines was obtained from the supportive Non-Pediacel study, Study 494-03 Stage II, in which Pentacel was administered. Given the similarity in vaccine formulation with Pentacel, as well as the similarity in the safety and immunogenicity profiles of these two vaccines, the Pentacel data were considered as supportive of Pediacel. Immunogenicity and safety data from Study 494-03 Stage I were also included to support Pediacel co-administration claims for hepatitis B and pneumococcal vaccines in the primary series as outlined below.

In total, 1,657 subjects received at least 1 dose of Pediacel during the primary series (from 1,659 subjects randomised to the Pediacel groups), of which 1,262 were subjects from the pivotal Pediacel studies. A total of 1,632 subjects received a 3rd or 4th booster dose of Pediacel, of which 1,508 subjects were from the pivotal Pediacel studies.

Based on the integrated safety analysis 697 subjects were administered at least 1 dose of an Infanrix-based combination vaccine, 797 subjects a whole-cell pertussis combination vaccine and 4,135 subjects a 5-component acellular pertussis combination vaccine, for the primary series. For the booster, 815 subjects were vaccinated with an Infanrix-based combination vaccine, 383 subjects with a whole-cell pertussis combination vaccine, and 3,667 subjects with a 5-component acellular pertussis combination vaccines. In addition, in 2 studies that could not be integrated into the safety database (Studies Sweden I and Phase IIC France), 2,102 subjects were vaccinated with a whole-cell pertussis combination vaccine and 3,170 subjects were vaccinated during the primary series with at least 1 dose of a 5-component acellular pertussis combination vaccine (Daptacel or HCPDT).

**Clinical efficacy**

The pivotal study A5I16 demonstrated that Pediacel induces a robust immune response when given at 2, 3 and 4-months of age with Prevenar that was comparable to that of Infanrix-IPV+Hib. In Study A5I15 administration at 3, 5 and 12 months also demonstrated satisfactory immune responses with no differences compared to Infanrix-IPV+Hib that were thought to be of clinical significance. Administration at 2, 4 and 6 months was assessed in PB9502 and PB9602. PB9502 demonstrated lot-to-lot consistency and Pediacel elicited comparable immune responses to the standard of care vaccine in use in Canada at the time.

U01-A5I-302 study conducted in UK was completed before the UK introduced routine Hib and MenC boosting at age 12-13 months and also before Prevenar was added to the primary series (with important implications for anti-D titres). Administration at 2, 3, 4
months picked up a negative effect of DTaP on anti-PRP responses which persisted up to age 3.5 to 4.5 years. At the last sampling time there also appeared to be an advantage with regard to antibody avidity in the original DTwP group. The data from the study (as well as primary series data from A5I15 and A5I16 studies) support the need for a Hib booster dose in the second year of life to maintain anti-PRP levels during the risk period for invasive Hib disease. This study was one of the first to indicate that interactions between different MenC conjugates are complex and may be affected by co-administration of DTwP or DTaP. However, at age 3.5 to 4.5 years there was no appreciable advantage for the initial wP group compared to the aP group, regardless of the type of MenC conjugate that had been administered. In addition the data clearly supported the need for a booster dose in the second year of life.

Booster response data from A5I15 (12 months), A5I19 (11-18 months), PB9502 and PB9602 indicated that Pediacel provides a robust immune response for all antigens when administered as a booster dose after priming with DTaP or DTwP vaccines.

Supportive immunogenicity data come from A5I06, HE9810, HE9811 and HE9812 for the primary series; A5I09 and A5I07 for the booster. The most important conclusions from these studies that the aP combination vaccines had similar or higher seroprotection rates and ≥4-fold rise response rates for PRP, diphtheria, tetanus, and all 3 polio types compared to wP vaccines. Some differences in GMTs were observed but are unlikely to be clinically relevant given the high seroprotection rates.

With no serological correlate of protection established for pertussis, the estimation of the likely efficacy of Pediacel in preventing pertussis is based on comparisons with immune responses observed in subsets enrolled into the Swedish efficacy studies in which the same 5-component pertussis antigen complex was used.

494-03 showed that the immune responses to all antigens were satisfactory when Pentacel was administered alone or co-administered with Prevenar, MMRII and VARIVAX. Since Pentacel is similar in composition to Pediacel, these data support the use Pediacel as a booster vaccination for children in the second year of life and also support co-administration with the vaccines tested in this study. Other data in the dossier support co-administration with rHBsAg vaccines.

Antibody persistence between the primary series and booster dose was examined in several studies and include comparative datasets. The data indicate that antibody persistence after priming with Pediacel is not likely to put children at a disadvantage compared to priming with other vaccines containing a similar array of antigens.

In conclusion, there has been a comprehensive documentation of the immunogenicity of Pediacel and the data do not raise any concerns.

**Concomitant use studies**

Concomitant use of Pediacel with MMR (494-03), Varivax (494-03), Prevenar (A5I16, A5I19, 494-03), MenC (U01-A5I-302), and Hepatitis B vaccine (A5I19, A5I06, HE9810, HE9811, HE9812, 494-03) was studied in several pivotal and supportive (Pediace and non-Pediace) studies with no evidence of clinically relevant interference on the immunogenicity of any of the antigens contained in Pediacel or the concomitantly used vaccine. U01-A5I-302 study was one of the first to indicate that interactions between different MenC conjugates are complex and may be affected by co-administration of DTwP or DTaP. However, at age 3.5 to 4.5 years there was no appreciable advantage for the initial wP group compared to the aP group, regardless of the type of MenC conjugate.
conjugate that had been administered. In addition the data clearly supported the need for a DTaP booster dose in the second year of life.

**Lot to lot consistency studies**
Lot to lot consistence was proven in the PB9502 study, which demonstrated lot-to-lot consistency and Pediacel elicited comparable immune responses to the standard of care vaccine in use in Canada at the time. All antibody responses were non-inferior to the immune responses elicited in the various comparator groups.

**Persistence of antibodies**
In the 5 primary series/booster study combinations presented for antibody persistence, immunogenicity data were summarised for the following primary series vaccination schedules: 6, 10 and 14 weeks of age (Study HE9810), 2, 3 and 4 months of age (Study U01-A5I-302 Part I), and 2, 4 and 6 months of age (Studies PB9502, PB9602, A5I06).

Antibody persistence serology data were available from different studies for subjects aged 12-13 months (Study U01-A5I-302 Part II) and aged 18-19 months (Studies PB9502, PB9602, A5I09, A5I07) following completion of the primary series, and for subjects 3.5 to 4.5 years of age following completion of a 3-dose primary series followed by a Hib booster dose at 12-13 months (Study U01-A5I-302 Part III). Antibody levels generally declined from post-primary series levels but remained above prevaccination levels in the second year of life. An exception was for FHA and PRN antibodies in Study HE9810 using the 6, 10 and 14 week schedule, for which antibody levels had declined to near pre-vaccination levels prior to the 4th dose booster. For this study, a booster dose was administered (as planned in the booster part of the Study A5I07) at 18-19 months of age, which resulted in a robust immune response to all antigens. In Study U01-A5I-302, a 3-dose primary series was administered at 2, 3 and 4 months of age (Part I of this study, followed by antibody persistence assessed during the second year of life at age 12-13 months (Part II of this study) at which time a Hib booster dose was administered. Antibody persistence was assessed again in Part III of this study at 3.5 to 4.5 years of age and the immune response had declined further and the need for a pre-school booster vaccination to sustain high rates of immunity (as planned in this study) was suggested and evidenced by the robust immune response following the booster dose (of Repevax). In all studies, data for comparator vaccines within each study showed similar results.

Thus, the antibody persistence data indicate that Pediacel administered in a variety of primary series schedules provides a lasting immune response and was assessed up to 3 to 4 years following the primary series. A booster dose in the second year of life can be considered in order to sustain high levels of immunity for all antigens into later childhood.

**Clinical safety**
The pooled safety database for Pediacel included 1657 infants but clinical data from supportive studies and 5-component aP combinations (Pentacel) are also pertinent to the assessment of the vaccine safety. Therefore excluding data with Infanrix and the total safety database will consist of 4135 infants, what is considerably in excess of 3000 subjects as per CHMP guideline requirement for licensing of new vaccines.

The safety of the Pediacel and the reactogenicity profile was evaluated on the day of the vaccination and for the next 0-3 and/or 0-7 days for solicited and at various time points over maximal 6 months for unsolicited Adverse Events.
Overall, the safety of Pediacel was similar to comparable to other DTaP-IPV vaccines regardless of the previous vaccination status, previous vaccines used or concomitant use of MenC, Prevenar, Hepatitis B, MMR and Varivax vaccines. Of the injection site reactions, “any” tenderness was the most frequently reported solicited reaction, followed by “any” redness and “any” swelling, after most doses of the primary series, after any dose of the primary series and after the booster dose. For each solicited injection site reaction (“any”), the incidence rates following each dose of the primary series did not tend to increase with subsequent doses. For the booster dose, incidence rates of each solicited injection site reaction tended to be higher than after each dose of the primary series, and were similar or lower to rates after any dose of the primary series. The rates of “severe” injection site reactions were low after each dose of the primary series (≤3.1% (for Tenderness after Dose 1)) and the booster dose (≤6.5% (for Redness)), indicating that Pediacel was well tolerated.

Therefore Pediacel has a similar safety profile for local solicited adverse events when compared to the Infanrix and 5-Component Acellular Pertussis vaccines, and is less reactogenic than the wP combination vaccines.

For the solicited systemic reactions, “Any” Fussiness was consistently the most frequently reported reaction after each dose of the primary series, after any dose of the primary series and after the booster dose. After any dose of the primary series, the incidence of “Any” Fussiness was followed in decreasing order by Abnormal Crying, Less Active, Eating Less, Fever and Vomiting (“Any” for each reaction). For each solicited systemic reaction, the incidence rates of “Any” reaction following each dose of the primary series did not tend to increase with subsequent doses.

After the booster dose, the rank order of incidence rates for “Any” reaction was generally similar to the primary series, although Fever became the second most frequent reaction (i.e., “Any” Fussiness, Fever, Abnormal Crying, Less Active, Eating Less and Vomiting). With the exception of “Any” Fever and “Any” Eating Less, for which incidence rates tended to be higher after the booster dose than after each dose of the primary series, the incidence rates of the remaining solicited systemic reactions tended to be similar to each dose of the primary series, and were lower than rates after any dose of the primary series. The rates of “Severe” solicited systemic reactions were low after each dose of the primary series (≤3.6% (for Fussiness after Dose 1)) and the booster dose (≤2.7% (for Fever)), indicating that Pediacel was well tolerated.

When compared to the Infanrix Combination and 5-Component Acellular Pertussis Combination vaccine groups, Pediacel had a similar safety profile for solicited systemic reactions, and was generally less reactogenic than the wP combination vaccine group.

The incidence of related non-serious unsolicited ARs in the Pediacel group (combined and pivotal) was similar to the Infanrix and wP groups and was higher than in 5-Component aP group. Most ARs reported in ≥1% of subjects were injection site reactions.

For Pediacel, 3 AEs were identified as other significant AEs:

- Extensive limb swelling (ELS);
- Hypotonic-hyporesponsive episode (HHE);
- Seizures/convulsions.
All three identified types of significant AEs are well recognised with other aP vaccines. Overall there were few reported other significant AEs. Within 7 days after vaccination, there were no reports of ELS after any dose of the primary series, and after the booster dose the incidence of ELS was low in all groups with only 2 subjects having confirmed ELS in the Pediacel group and 1 subject in the Infanrix group. It is recognised, however, that ELS was systematically collected as a solicited reaction only from study A5I19 and the booster part of study A5I16. With respect to HHE, no cases of HHE were reported for the Pediacel, Infanrix or 5-Component aP groups. Only 1 subject in the wP group reported a HHE within 7 days after any dose of the primary series, and there were no reports of HHE within 7 days after the booster dose. The incidence of seizures/convulsions was also low in all groups and in all studies. In conclusion, these significant AEs are not solely attributed to Pediacel but also recognised with other pertussis containing vaccines. It is impossible to make any associations of the occurrence of such events with primary series, boosters or co-administration with other vaccines.

The incidence rates after any dose of the primary series for all SAEs for Pediacel (combined and pivotal) were similar to those for the Infanrix, wP and 5-Component aP groups. The rates per 1000 doses were similar to those for the Infanrix and 5-Component aP groups and were slightly higher for the Pediacel groups than the wP group. Across all groups, the most frequently reported SOC at any time after any dose of the primary series was Infections and Infestations, with bronchiolitis being the most frequently reported PT. Overall, and consistent with the findings of the non-serious unsolicited AEs, the SAEs were typical health concerns representative of the infant and toddler population included in the clinical trials that could lead to hospitalisation. In the Pediacel group, related SAEs were reported in 4 (0.3%) of 1487 subjects at any time after the primary series (1 per 1000 doses). Related SAEs were febrile convulsion, syncope vasovagal, crying and petechiae. Three of the 4 SAEs were identified as related to Pediacel; Petechiae were considered possibly related to the co-administered MenC vaccine, and not to the Pediacel vaccine.

Overall, the incidence of SAEs related to Pediacel was low and similar to the other vaccine groups. Convulsions, whether febrile or not and abnormal crying are ARs identified in the current Summary of Product Characteristics (SmPC) for Pediacel vial and are proposed in the SmPC for the PFS presentation for Pediacel.

Across all studies, there was one reported, non-related death in the pivotal Pediacel group. In Study PB9502 (primary series), a 13-month-old female was diagnosed with idiopathic primary pulmonary hypertension 6 months following Dose 3 of Pediacel. The condition was not treatable and the subject died approximately 1 month after diagnosis. Idiopathic primary pulmonary hypertension was considered not related to the study vaccine. There were no reported deaths in any of the other paediatric combination vaccine groups.

Product information:

Summary of Product Characteristics (SmPC)
The approved SmPC is acceptable.

Product Information Leaflet (PIL)
The approved PIL is in line with the approved SmPC, and is satisfactory.

Labelling
The labelling is satisfactory.
Clinical Overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Post marketing experience

Pediacel was first registered on 8 December 2000 but was not distributed until 2004. It is currently licensed in 18 countries and distributed in 14 countries, including 3 countries in the EU. Pediacel was launched in the UK in September 2004, in The Netherlands in January 2006 and in Canada in October 2007. Between December 2000 and May 2008, approximately 13,000,000 doses of Pediacel were distributed worldwide.

The cumulative safety data collected from 8 December 2000 to 7 June 2008, that represent post-marketing spontaneous reports, reports received through health authorities and literature data. Details of post-marketing data were presented in one 2-year PSUR (PSUR_315_1), one 1-year PSUR (PSUR_315_2), nine 6-month PSURs (PSUR_315_3 to PSUR_315_11) and a bridging report covering the 7-year and 6-month period from 8 December 2000 to 7 June 2008. In addition, one 6-month PSUR (PSUR_12, covering the period from 8 June to 7 December 2008) issued beyond the data-lock time point of this post-marketing analysis was included in 2.7.4 of the CTD.

During this period, 1314 new medically-confirmed case reports following Pediacel administration were received by the manufacturer: 1305 from health care professionals and health authorities, and 9 reported cases from clinical trials. In total, these reported cases involved 3667 AEs. Out of the 1314 cases reported, 470 (36%) were serious.

The company provided a detailed analysis of adverse events of special interests, which are currently covered by current SmPC (HHE, ELS, seizure/convulsions) and described all adverse events with potential or theoretical link to the vaccination with Pediacel or other co-administered vaccines (anaphylactic shock, apnoea, encephalopathy and breakthrough of *H. influenzae* cases given the theoretical possibility of interference between Pediacel and Meningococcal C vaccine). Although no specific risk was associated with Pediacel, the following events were reviewed: SIDS and other fatal cases; Vaccine failure; and Misuse. Detailed analysis of all reviewed cases was provided in the Clinical AR. In summary, the number of cases and the nature of events do not allow to conclude a causality of SIDS with Pediacel. However all mentioned above identified, potential and theoretical risks are currently listed in RMP and continuously monitored by MHRA, Health Protection Agency (UK), MBE and National Institute for Public Health and Environment in The Netherlands (RIVM) and the company.

Based on the post-marketing data presented up it is concluded that:

- Pediacel is safe and well tolerated for the primary series and booster dose vaccination, with the most frequently reported AEs already included in the SmPC for Pediacel (vial presentation) and proposed for the PFS presentation.

- No changes to the safety profile of Pediacel were identified based on the analysis of postmarketing data:

- AEs of Special Interest include ELS, HHE and seizures/convulsions. These events (including convulsion, whether febrile or not) are listed in the current vial SmPC, are proposed for the Pediacel PFS presentation and are included as Identified Risks in the proposed RMP.
• Other Events of Interest included anaphylactic shock, apnoea, invasive infections to *H. influenzae* type b or *N. meningitidis* serogroup C, and encephalopathy. These events are included as Potential Risks in the proposed RMP.

• Pediacel was not associated with a risk of SIDS or other fatal cases, or vaccine failure.

• The overall reactogenicity profile of Pediacel indicates that Pediacel is a well-tolerated vaccine with a safety profile that is satisfactory for licensure.

Routine surveillance is considered acceptable for monitoring the risk of convulsions, HHE, anaphylactic shock, SIDS, encephalopathy and possibly for increased infection with Hib and Men C, although the company may need to liaise with HPA and other EU surveillance authorities for the latter.

**Periodic Safety Update Report (PSUR)**

The applicant has not requested a different PSUR cycle upon approval. The PSUR submission scheme will follow Volume 9A of The Rules Governing Medicinal Products in the European Union starting with 6-monthly PSUR. The company will provide analyses every six months examining the incidence of apnoea following administration of Pediacel. These analyses will be included in the PSURs beginning in June 2010. It should be noted that there is a lag time between when the EMR (electronic medical records) database (THIN) is updated, and when the analyses will be performed. For example, the June 2010 PSUR will include exposure from October 2004 (i.e., when Pediacel was firmly established as the primary DTP series in infants in the UK), through January 2010. Similarly, the subsequent PSUR in December 2010 will extend the analysis period through June 2010. The PSUR in June 2011 will include data up until January or early February 2011. The final analysis (PSUR December 2011) will cover exposure up to October 2011. The RMS considers that the proposal for PSUR submission is acceptable.

**BENEFIT RISK ASSESSMENT**

The drug substances present in Pediacel, includes the following constituents: Diphtheria Toxoid, Tetanus Toxoid, Inactivated Polio and the 5-Component Pertussis antigens.

The quality of the drug substances is adequate, as demonstrated by the data provided by the applicant. Regarding the drug product the quality is adequate, as well.

Nonclinical pharmacological and toxicological data from early stage of product development were included and appeared to be supportive.

From clinical perspective, Pediacel is expected to contribute to an increase in vaccination compliance by saving healthcare professionals time when administering the vaccine, and through the elimination of administration errors related to the need for reconstitution that is required for other Hib-containing pentavalent vaccines currently available in Europe. The administration of Pediacel is also compatible with the many country-specific immunisation recommendations across Europe, and will help in attaining and sustaining high vaccination coverage, improved compliance and provide protection at the earliest possible age. In addition, the availability of Pediacel will augment current
vaccine supply options in countries across Europe by making available another vaccine and/or manufacturer.

An extensive clinical development program was carried out in different parts of the world and consisted of over 22 clinical studies. These studies cover approximately 17 years of clinical trials with Pediacel and include a variety of immunisation schedules, various countries/populations, differing comparison groups, and varied co-administration of concomitant vaccinations. Over time, adverse event definitions, safety data collection tools and coding methods have changed, and laboratory methods for serological determinations have evolved. However presented integrated analyses of pivotal and supportive studies support a robust immunogenicity characteristics and favourable safety profile of Pediacel.

Pediacel has shown in various studies pre- as well as post licensure that it induces sufficient immune response to all antigens included and is non-inferior to other vaccines used for primary and booster series. Additionally, concomitant use with MenC, Pneumococcal, MMR, Varicella, and Hepatitis B vaccines has been shown without any signs of immune or safety interference.

Overall, Pediacel is generally well-tolerated. This is also shown by the fact, that no significant safety signal was found in the course of clinical studies and also during the 7 years of post-marketing surveillance with approximately 13 million vaccine doses distributed worldwide.

All issues raised by RMS and CMS are considered broadly resolved.

The benefit-risk-balance is positive and the marketing authorisation should be granted.

**Conclusion**
The grant of a marketing authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pediacel suspension for injection in pre-filled syringe are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No pharmacokinetic evaluation or specific toxicology studies were submitted in support of this application and none are required. The pharmacology studies provided support the intended indication by demonstrating that Pediacel induces appropriate immunological responses to each of the antigens in the animal models tested.

EFFICACY AND SAFETY
The immunogenicity of Pediacel has been comprehensively documented and the data are satisfactory.

The safety profile of Pediacel is well known and no new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are acceptable.

BENEFIT-RISK ASSESSMENT
No new non-clinical or clinical safety concerns have been identified. Sufficient clinical experience with Pediacel suspension for injection in pre-filled syringe is considered to have demonstrated the therapeutic value of the new presentation. The benefit-risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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