



Public Assessment Report

Name of the Product:

Tetraxim

suspension for injection in pre-filled syringe

**(diphtheria, tetanus, pertussis /acellular, component/
and inactivated poliomyelitis adsorbed vaccine)**

Procedure number: HU/H/0406/001/MRP

Marketing authorisation holder: Sanofi Pasteur SA

Date: 22 June 2016

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE
ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the concerned member states have granted the marketing authorisation of the Tetraxim suspension for injection in pre-filled syringe. The holder of the marketing authorisation is Sanofi Pasteur SA, France.

The active substances are in one dose (0.5 ml):

Diphtheria toxoid	not less than 30 IU
Tetanus toxoid.....	not less than 40 IU
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated) ¹	
Type 1 (Mahoney)	40 D antigen units ²
Type 2 (MEF-1)	8 D antigen units ²
Type 3 (Saukett)	32 D antigen units ²

Adsorbed on aluminium hydroxide, hydrated (0.3 mg Al³⁺).

¹Produced on Vero cells

²Or equivalent antigenic quantity determined by a suitable immunochemical method

The other ingredients are: Hanks medium without phenol red (complex mixture of amino acids including phenylalanine, mineral salts, vitamins and other substances such as glucose), formaldehyde, acetic acid or sodium hydroxide for pH adjustment, phenoxyethanol, ethanol anhydrous and water for injections.

The vaccine may contain traces of glutaraldehyde, neomycin, streptomycin and polymyxin B which are used during the manufacturing process.

What Tetraxim looks like and contents of the pack (not all pack sizes may be marketed):

- 0.5 ml of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (chlorobromobutyl, chlorobutyl or bromobutyl) with attached needle and needle shield (elastomer). Box of 1 and 10;
- 0.5 ml of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (chlorobromobutyl, chlorobutyl or bromobutyl) and tip cap (elastomer) with a separate needle. Box of 1;
- 0.5 ml of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (chlorobromobutyl, chlorobutyl or bromobutyl) and tip cap (elastomer) with two or twenty separate needles. Box of 1 and 10.

Tetraxim is a vaccine used to protect against infectious diseases. It is indicated to help protect children against diphtheria, tetanus, whooping cough (pertussis) and poliomyelitis, indicated in children from 2 months of age.

The use of this vaccine should be in accordance with the official recommendations.

What must be known before using Tetraxim

If the child

- is allergic to :
 - the active substances of Tetraxim or any of its other ingredients of Tetraxim,
 - any vaccine which protects against whooping cough,
 - glutaraldehyde, neomycin, streptomycin or polymyxin B, as these substances are used during the manufacturing process;
- experienced an allergic reaction after injection of a vaccine containing the same substances;
- suffers from evolving encephalopathy (cerebral lesions);
- has suffered from encephalopathy (cerebral lesions) within 7 days of a previous dose of a pertussis vaccine (acellular or whole cells pertussis);
- has a fever or an acute disease (the vaccination must be postponed)

Tetraxim must not be used.

Warnings and precautions

- This vaccine must not be injected by the intravascular route (the needle must not penetrate a blood vessel) nor by the intradermal route.
- If the child suffers from thrombocytopenia or clotting problems, there is a risk of bleeding during intramuscular administration.
- If the child already presented with febrile convulsions, not related to previous vaccine injection; in this case it is particularly important that temperature be monitored in the 48 hours following vaccination and that antipyretic treatment be regularly administered to help reduce fever, for 48 hours.
- If any of the following events are known to have occurred in temporal relation to receipt of vaccine, the decision to give further doses of pertussis containing vaccine should be carefully considered:
 - fever of 40°C or more within 48 hours not due to another identifiable cause,
 - collapse of shock-like state with hypotonic-hyporesponsive episode (drop in energy) within 48 hours of vaccination,
 - persistent, inconsolable crying lasting 3 hours or longer, occurring within 48 hours of vaccination,
 - convulsions with or without fever, occurring within 3 days of vaccination.
- If the child presented Guillain-Barre syndrome (abnormal sensitivity, paralysis) or brachial neuritis (paralysis, diffuse pain in the arm and shoulder) following receipt of a prior vaccine containing tetanus toxoid (vaccine against tetanus), the decision to give further vaccine containing tetanus toxoid should be evaluated by the doctor.
- If the child presented oedematous reactions (or swelling) occurring in the lower limbs after injection of a vaccine containing the *Haemophilus influenzae* type b valence, the two vaccines, diphtheria-tetanus-pertussis-poliomyelitis vaccine and the *Haemophilus influenzae* type b conjugate vaccine should be administered in two separate injection sites on two different days.
- If the child follows a treatment that suppresses her/his immune defences or if the child presents with immunodeficiency: in these cases the immune response to the vaccine

may be decreased. It is then recommended to wait until the end of the treatment or disease before vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.

Other medicines/vaccines and Tetraxim

This vaccine may be administered simultaneously with the MMR vaccine or with the Hepatitis B vaccine 0.5 µg/0.5 ml, but in two separate sites.

For primary vaccination and for the 1st booster dose, Tetraxim may be administered by reconstituting the Act-HIB (*Haemophilus influenzae* type b conjugate) vaccine or administered simultaneously with it in two separate injection sites.

In case the child should receive Tetraxim simultaneously with other vaccines than those already mentioned, the doctor must be consulted for more information.

The doctor should also be informed if the child is taking, have recently taken or might take any other medicines.

Tetraxim contains formaldehyde

During the manufacturing of Tetraxim formaldehyde is used as an excipient.

How to use Tetraxim

The usual recommended schedule includes primary vaccination, consisting of three injections at an interval of one or two months from the age of 2 months, followed by one booster vaccination within the second year of life.

The three doses of the vaccination course can be also administered at the age of 3, 5, and 12 months, in this case there is no need for a fourth dose during the second year of life.

For both schedules, a booster dose is recommended between 5 and 12 years of age.

The use of this vaccine should be in accordance with official recommendations.

Method of administration: for syringes without attached needles, the separate needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.

The product must be shaken before injection until a homogeneous whitish-turbid suspension is obtained.

It must be administered by the intramuscular route.

Administration should preferably be performed in the anterolateral side of the thigh (middle third) in infants and in the deltoid area in children aged between 5 and 13.

If more Tetraxim has been used than it should have been

Since the doctor administers Tetraxim to the child, overdose is not probable. If a parent thinks that the child received too much Tetraxim or the interval between two injections was too short, should discuss it with the doctor.

What to do if miss a dose of Tetraxim has been missed?

The doctor will decide when to administer the missing dose.

Possible side effects

Like all medicines, Tetraxim can cause side effects, although not everybody experiences them.

Serious allergic reactions

If any of these symptoms occur after leaving the place where the child received his/her injection, a doctor must be consulted immediately.

There is a possibility that very rarely (affects less than 1 user in 10000) serious allergic reactions occur after the administration of any vaccines. These can be the followings:

- difficulty in breathing,
- blueness of the tongue or lips,
- rash,
- swelling of the face or throat,
- low blood pressure causing dizziness or collapse.

When these signs or symptoms occur they usually develop quickly after the injection is given and while the child is still in the clinic or doctor's surgery.

Other side effects

If the child experiences any of the following side effects and it gets serious or if the parent notices any side effects not listed below, a doctor, nurse or pharmacist should be consulted.

- Very common reactions (may affect more than 1 user in 10) are:
 - vomiting,
 - loss of appetite (feeding disturbances),
 - somnolence (drowsiness),
 - headache,
 - nervousness (irritability),
 - abnormal crying,
 - myalgia (muscle pain),
 - redness at the injection site,
 - pain at the injection site,

- injection site swelling,
- fever of 38°C or more,
- malaise.
- Common reactions (may affect 1 to 10 users in 100) are:
 - diarrhoea,
 - insomnia (sleep disturbances),
 - induration at the injection site.
- Uncommon (may affect 1 to 10 users in 1,000) are:
 - prolonged inconsolable crying,
 - redness and swelling larger than 5 cm at the injection site,
 - fever of 39°C or more.
 - Rare reaction (may affect 1 to 10 users in 10,000) is: fever of 40°C or more.
- Reactions with not known frequency (these events have been very rarely reported; however exact incidence rates cannot be precisely calculated):
 - convulsion with or without fever,
 - syncope,
 - oedema (swelling) larger than 5 cm that may spread over the entire limb where the vaccine has been administered. This reaction occurs within 24-48 hours after vaccination and resolves spontaneously within 3-5 days. The risk appears to be dependent on the number of prior doses of acellular pertussis-containing vaccines, with a greater risk following the 4th and 5th doses,
 - rash, erythema and urticarial,
 - swelling of the glands in the neck, armpit or groin (lymphadenopathy).

Furthermore, oedematous reactions (swelling) affecting the lower lips have been reported when diphtheria, tetanus and pertussis containing vaccines were administered in combination with *Haemophilus influenzae* type b containing vaccines. These reactions are sometimes accompanied by fever, pain and crying. They are not accompanied by cardio-respiratory signs. These reactions recovered within 24 hours spontaneously without sequelae. This reaction may occur when Tetraxim and *Haemophilus influenzae* type b containing vaccine are administered concomitantly.

Potential side effects (i.e. they have not been reported directly with Tetraxim, but with other vaccines containing one or more of the antigenic constituents of Tetraxim) are the following:

- Guillain-Barre syndrome (abnormal sensitivity, paralysis) and brachial neuritis (paralysis, diffuse pain in the arm and shoulder) following administration of a vaccine containing tetanus toxoid;
- in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination;
- hypotonic-hyporesponsive episodes (hypotonic episodes, drop in energy, hyporesponsiveness, decreased mental awareness).

5. How to store Tetraxim

It must be stored in a refrigerator (2°C - 8°C). It must not be frozen.

Tetraxim should not be used if an abnormal colour or the presence of foreign particles is noticed.

This medicine must be kept out of the reach and sight of children

Scientific discussion

This module reflects the scientific discussion for the approval of Tetraxim suspension for injection in pre-filled syringe via Mutual Recognition Procedure. The procedure was finalised at 21 April 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This application concerns the approval via a Mutual Recognition Procedure of a diphtheria/acellular pertussis/tetanus/inactivated poliomyelitis (DTaP-IPV) vaccine, the Tetraxim/Tetravax suspension for injection in prefilled syringe. In this Public Assessment Report the name Tetraxim is used.

The active ingredients and excipients used in Tetraxim are well-known. The same active ingredients are used in the preparation of other licensed vaccines (e.g. Tetravac/Tetraxim (D,T,aP,IPV) and Pentavac/Pentaxim (D,T,aP, IPV,Hib) in Europe and in international markets.

Sanofi Pasteur DTaP-IPV was first licensed on 30 January 1998 in Sweden. This authorisation was extended on 3 August via a Mutual Recognition Procedure (with Sweden as the Reference Member State, RMS) involving the following countries as the Concerned Member States (CMSs): Austria, Belgium, Denmark, Finland, Greece, Iceland, Ireland, Italy, Luxembourg, Portugal and United Kingdom. These marketing authorisations were renewed in 2002.

This product has also been authorised for marketing in France, Germany, Norway, Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Romania and Hungary via national procedures.

Tetraxim suspension for injection in prefilled syringe was authorised for marketing on 22 April 2004 in Hungary via national procedure then renewed for unlimited period in 2008. Tetraxim has been used in HU within the frame of National Immunization Schedule since 2011 for the immunization of 6 years old children, and will be used for at least three more years.

With Hungary as the RMS in this Mutual Recognition Procedure, Sanofi Pasteur has applied for marketing authorisations for Tetravax in Croatia, Czech Republic, Cyprus, Poland and Slovakia.

This vaccine is indicated in the joint prevention of diphtheria, tetanus, pertussis and poliomyelitis:

- for primary vaccination in infants from the age of 2 months,
- for booster vaccination, one year after primary vaccination during the second year of life,
- for booster vaccination between 5 and 12 years of age, according to official recommendations.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

Tetraxim is a liquid vaccine for intramuscular administration which combines aluminium hydroxide as adjuvant and four Drug Substances as follows:

- purified Diphtheria Toxoid (PDT),
- purified Tetanus Toxoid (PTT),
- 2-component acellular pertussis (Adsorbed Purified Pertussis Toxoid (PTxd) and Adsorbed Purified FHA),
- inactivated Vero Trivalent Poliovaccine Bulk (serotypes 1, 2 and 3).

The vaccine is a whitish-turbid sterile suspension presented in a pre-filled syringe (with or without needle) containing a single dose of 0.5 ml.

Tetraxim vaccine complies with the European Pharmacopoeia (Ph. Eur.) and the recommendations of the World Health Organization (WHO).

II.2 Drug substances

II.2.1 Purified Diphtheria Toxoid (PDT)

The Purified Diphtheria Toxoid is prepared according to its Ph. Eur. monograph.

Diphtheria Toxoid is manufactured through the fermentation of *Corynebacterium diphtheriae*, the toxin being harvested and then detoxified by formaldehyde. The resulting Crude Diphtheria Toxoid is further purified through a selective precipitation by ammonium sulphate leading to the PDT.

The production of the PDT drug substance is based on a well-documented seed lot system. The manufacturing process is well defined and controlled by in-process controls.

Process validation studies have been conducted to demonstrate the control of the fermentation, detoxification and purification processes through the conformity of the process parameters, as well as the reproducibility of these processes through the conformity of the quality control tests (as in-process control/release tests) and additional characterization tests. Validation studies demonstrated that the manufacturing process is reproducible and under control.

The physicochemical properties of PDT were characterized by Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE) and mass spectrometry.

Since the production of PDT involves the use of culture media containing material of animal origin (bovine/ovine), the possibility of carry-over of animal proteins into the

active ingredients (vaccine components) and hence into the final product was considered, during the initial development of the product, as recommended by WHO. All the purified toxoid batches tested were negative for bovine albumin antisera.

The tests and specifications for the control of the PDT drug substance are in compliance with the bulk purified toxoid part of the Ph. Eur. monograph *Diphtheria vaccine (adsorbed)*, and the WHO Technical Report Series (TRS) No. 800 Annex 2 *Requirements for diphtheria, tetanus, pertussis and combined vaccines (adsorbed)*. The PDT complies with the requirements for sterility, absence of toxin, irreversibility of toxoid and antigenic purity.

The results of stability studies support the claimed shelf-life when stored in polypropylene flasks.

II.2.2 Purified Tetanus Toxoid (PTT)

The Purified Tetanus Toxoid is prepared according to its European Pharmacopoeia (Ph. Eur.) monograph.

PTT is a detoxified protein obtained from the *Clostridium tetani* Harvard 49205 strain.

The fermentation of *Clostridium tetani* leads to a toxin which is harvested then detoxified by formaldehyde. The resulting Crude Tetanus Toxoid is further purified through a selective precipitation by ammonium sulphate leading to the PTT.

The production of the PTT drug substance is based on a documented seed lot system. The in-process controls applied are considered appropriate for the production process.

Each production step of the manufacturing process has been validated. The validation studies were carried out by evaluating the production parameters, in-process controls and quality control tests and additional characterization studies.

Characterization of the Tetanus Protein was conducted at different steps of its production (Crude Tetanus Toxoid and Purified Tetanus Toxoid) by the following physico-chemical characterization tests: Differential Scanning Calorimetry (DSC) and SDS PAGE.

Since the production of PTT Toxoid involves the use of culture media containing material of animal origin (bovine/ovine), the possibility of carry-over of animal proteins into the active ingredients (vaccine components) and hence into the final product was considered, during the initial development of the product, as recommended by WHO in the TRS 800.

None of the toxoid batches (development lots) contained detectable levels of blood substance or bovine albumin.

The specifications for the PTT are in compliance with the bulk purified toxoid part of the Ph. Eur. monograph 0452 *Tetanus vaccine (adsorbed)*, and with WHO TRS 800 Part 2 (*Tetanus Toxoid*). The tests performed on each batch of PTT are sterility, the absence of remaining Tetanus Toxin, the irreversibility of the toxoid and the antigenic purity of the Purified Tetanus Toxoid.

The results of stability studies support the claimed shelf-life when stored in polypropylene or glass flasks.

II.2.3 2-Component Acellular Pertussis (FHA-PTxd)

The 2-component acellular pertussis correspond to individually prepared and purified antigenic components of *Bordetella pertussis*: pertussis toxoid (PTxd) and filamentous haemagglutinin (FHA) adsorbed on aluminium hydroxide.

The pertussis antigens are manufactured according to its Ph. Eur. monograph.

The production of the 2-Component Acellular Pertussis drug substance is based on a seed lot system. The origin and history of the *B. pertussis* strain is known.

Pertussis antigens are produced from *Bordetella pertussis* strain No. 1591, grown in fermentor under aerobic conditions. The fermentation culture is harvested and filtered. The supernatant (containing PT and FHA) is then concentrated by ultrafiltration. Both pertussis antigens are obtained from the same fermentation process and are separately processed by adsorption chromatography and affinity chromatography steps. The pertussis toxin is precipitated using ammonium sulphate and the native purified toxin is detoxified using glutaraldehyde (GTA) as detoxifying agent. The native purified FHA is precipitated using ammonium sulphate as well, but the purified FHA, devoid of toxic activities, is used in its native form.

Both antigens (purified Pertussis Toxoid in solution and purified FHA in solution) are then adsorbed separately onto aluminium hydroxide.

The manufacturing process is well defined and controlled by in-process controls.

The results of the validation studies demonstrate that the manufacturing process is reproducible and under control.

The acellular pertussis components were characterized by their physicochemical properties (electrophoretic profile, mass spectrometry, DSC) and their immunogenic properties (test in vivo in mice, intranasal challenge in mice).

Results of investigations show that all possible impurities were eliminated at the end of the process.

The tests and specifications for the control of the 2-Component Acellular Pertussis drug substance (adsorbed Pertussis toxoid and adsorbed FHA) are in compliance with monograph Ph. Eur. on *Acellular component Pertussis* and WHO TRS 878. Beside PTxd or FHA identification, sterility, pH, and aluminium content are tested.

Stability studies results for the adsorbed Pertussis toxoid and adsorbed FHA support the claimed storage time in glass containers.

II.2.4 Inactivated Vero Trivalent Poliovaccine Bulk

The Inactivated Vero Trivalent Poliovaccine Bulk consists of an aqueous suspension of inactivated poliovirus of types 1, 2 and 3 which are antigenically distinct:

Type 1: Mahoney;

Type 2: MEF-1;

Type 3: Saukett.

The poliovirus antigens are manufactured according to the Ph. Eur. 0214 monograph.

The virus replicates inside the Vero cells and is then harvested in a single harvest by decanting the supernatant from the bioreactor. Each monovalent is manufactured separately, *i.e.* only one type is inoculated into a tank of Vero cell substrate at any one time.

After settling, the harvest is clarified, concentrated and purified by chromatography. The resultant volume of concentrated purified viral suspension undergoes inactivation with formaldehyde. The viral inactivation takes place in two stages; the inactivation stage is confirmed by control test results.

The production of the concentrated trivalent is achieved by blending quantities of each of the three monovalents in proportions calculated to obtain the required D-antigen content in the drug substance.

The production of the Inactivated Vero Trivalent Poliovaccine Bulk drug substance is based on a seed lot system. The history, generation and control of the poliovirus seed lots as well as Vero cell banks are well documented and comply with Ph. Eur. and WHO requirements.

The manufacturing process of monovalent batches of type 1, 2 and 3 and the Inactivated Vero Trivalent Poliovaccine Bulk is validated, reproducible and under control.

Results of in-process and quality control tests indicate that the production process is adequate.

The studies on potential impurities confirm that level of impurities is under control by purification steps.

Quality control profile of the drug substance (concentrated trivalent) takes into account the requirements of the Ph. Eur. Monograph No. 0214 *Poliomyelitis vaccine (inactivated)* and the recommendations of the WHO TRS No. 910 (2002) Annex 2 *Recommendations for the production and control of poliomyelitis vaccine (inactivated)*” as well as internal practices. Sterility, residual formaldehyde content, bovine serum albumin content, D-antigen content, bacterial endotoxin content and pH are tested.

Stability studies support the claimed shelf-life of the poliomyelitis concentrated trivalent stored in a stainless steel container or in glass bottles.

II.3 Medicinal product

The Tetraxim vaccine is a suspension for injection to be administered by the intramuscular route.

It is a combined DTaP-IPV vaccine which consists of the following antigens: purified diphtheria toxoid (D), purified tetanus toxoid (T), *Bordetella pertussis* antigens: pertussis toxoid and filamentous haemagglutinin (aP) and inactivated poliovirus Type 1, 2 and 3 (IPV). Aluminium hydroxide is added as adsorbent.

The composition of the medicinal product is as follows:

Drug substances	
Component	Quantity per dose (0.5 ml)
Diphtheria toxoid	Minimum 30 IU*
Tetanus toxoid	Minimum 40 IU*
<i>Bordetella pertussis</i> antigens	
- Pertussis toxoid	25 µg
- Filamentous haemagglutinin	25 µg
Poliovirus (inactivated)**:	
- Type 1 (Mahoney)	40 DU***
- Type 2 (MEF-1)	8 DU***
- Type 3 (Saukett)	32 DU***
Excipients	
Component	Function
Aluminium hydroxide, hydrated, for adsorption	Adjuvant
Phenoxyethanol – Ethanol (50 % v/v solution)	Preservative

Drug substances	
Component	Quantity per dose (0.5 ml)
Formaldehyde solution	Preservative
Medium 199 Hanks 10xC without phenol red [§]	Diluent
Water for injections	Diluent

*As lower confidence limit (p = 0.95)

**Produced on Vero cells

***Or equivalent antigenic quantity determined by a suitable immunochemical method

[§]complex mixture of amino acids (including ca. 7.5 µg/dose phenylalanine), mineral salts, vitamins and other substances (such as glucose)

NaOH or acetic acid can be used for pH adjustment. These components are only present in trace amounts.

The vaccine may also contain traces of:

- glutaraldehyde used during production of the purified adsorbed Pertussis Toxoid;
- neomycin, streptomycin and polymixin B, used during production of the inactivated poliomyelitis trivalent concentrate vaccine.

The vaccine is presented in single-dose (Type I) glass syringes (with or without needle).

Tetraxim is a tetravalent adjuvanted combined vaccine. A study was performed to demonstrate the stability of the different antigens when they are mixed together in the DTaP-IPV vaccine. This study is based on the immunogenicity results comparison between monovalent vaccines and combined vaccines.

The formulation of Tetraxim vaccine has been developed from the experience gained by Sanofi Pasteur with the whole cell Pertussis combined vaccine: DTwP-IPV.

The antigen concentrations of Tetraxim are similar to those usually used in other Sanofi Pasteur paediatric vaccines.

Aluminium-based compounds, and more specifically aluminium hydroxide, are the most commonly used adjuvants with human vaccines. Based on immunogenicity results of a study the aluminium content has been set at 0.3 mg aluminium/0.5 mL dose. This value is below 1.25 mg Al/dose (as required by the Ph. Eur. monograph 1934).

Formaldehyde associated with 2-phenoxyethanol is used as a preservative in the final formulation of the Tetraxim vaccine. It allows the blending of all antigens without deleterious interferences.

The use of preservatives in this single dose vaccine is explained by the fact that the Tetraxim vaccine has been initially formulated with the aim to have a single Final Bulk Product used for

two presentations: a single dose pre-filled syringe presentation and a multidose vial presentation; and the clinical development has been carried out with this common formulation.

Preparation of the Final Bulk Product (FBP) comprises blending of the five drug substances with the excipients to achieve a homogeneous blend prior to filling into primary containers. The manufacture of the FBP and the filling of the sterile FBP into the container-closure system are aseptic processes. Moreover, the microbial quality is ensured by sterilization of the Final Bulk Product components.

Appropriate controls are in place to monitor the critical steps of manufacturing process.

The manufacturing process is well described with details of each step.

Based on the validation data presented it can be concluded that the manufacturing process of Tetraxim vaccine is reproducible and leads to obtain consistently a product meeting its pre-determined specifications and quality attributes. The equivalence of the product manufactured at the two manufacturing sites is demonstrated.

Tests and specifications for the non-pharmacopoeia excipient Medium Hanks without phenol red are described. All the other excipients used in the manufacture of Tetraxim vaccine are tested according to Ph. Eur. monographs.

No new excipients are used for the formulation of Tetraxim vaccine.

For the control of the finished product, tests can be performed either on the final bulk or on the final container. The vaccine is tested according to Pharmacopoeia methods where applicable. Methods developed in house are validated.

The specifications of the drug substance of Tetraxim vaccine takes into account the requirements laid down in Ph. Eur. Monograph No.1934 *Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed)* and Ph. Eur. Monograph No.0153 *Vaccines for human use*, current edition, and the recommendations of WHO TRS No. 800 Annex 2 (1990) *Requirements for diphtheria, tetanus, pertussis and combined vaccines (adsorbed)*, WHO TRS No. 878 Annex 2 (1998) *Guidelines for the production and control of the acellular pertussis component of monovalent or combined vaccines* and WHO TRS No. 910 Annex 2 (2002) *Recommendations for the production and control of poliomyelitis vaccine (inactivated)*, as well as internal practices.

Test methods on the Final Bulk Product comprise test for free formaldehyde content, 2-phenoxyethanol content, osmolality, bacterial and fungal sterility, diphtheria activity, tetanus activity, pertussis immunogenicity in mice, D-antigen content and histamine-sensitising activity.

Test and methods on the Filled Product comprise appearance, extractable volume, pH, aluminium content, diphtheria and tetanus identifications, pertussis identification (FHA, pertussis toxoid), poliomyelitis identification, bacterial endotoxins as well as bacterial and fungal sterility.

The potential product- and process-related impurities present in the Finished Product originate from the manufacturing process of the four drug substances and are described in corresponding sections of each drug substance.

Tetraxim is a liquid combined vaccine presented in single-dose syringes (with or without needle). The container for the Tetraxim vaccine, a type I glass syringe, is indicated for the injectable preparations, according to the Ph. Eur. The glass containers avoid possible container-content interactions. Moreover, this container is compatible with steam sterilization and easy to sterilize.

In order to have more flexibility in routine production, it was proposed alternative container closure system: three alternative plunger-stoppers (latex free bromochlorobutyl, chlorobutyl or bromobutyl) and two alternative tip caps (latex free bromochlorobutyl or synthetic isoprene-bromobutyl).

Results of physicochemical and biological tests demonstrate the equivalence of the alternative plunger-stoppers and tip caps. Results of stability studies demonstrate that the alternative plunger-stoppers and tip caps do not have any impact on product quality.

On the basis of the stability results obtained in long-term conditions, a shelf-life of 36 months can be claimed for the Tetraxim vaccine in single dose presentation stored at $+5^{\circ}\text{C}\pm 3^{\circ}\text{C}$.

All utilities that could impact on product quality fulfil compendial specifications when applicable. The production and distribution systems are designed according to Good Manufacturing Practice (GMP) requirements.

Adventitious Agents Safety Evaluation

Appropriate measures during manufacture of the individual antigens as well as in process and quality control tests ensure safety from a bacterial and fungal standpoint. In case of IPV, mycoplasma test is performed on the Master Cell Bank (MCB).

All materials of ruminant origin used in the production are compliant with Ph. Eur. 1483 and 5.2.8 regarding the risk of transmitting animal spongiform encephalopathy. For applicable materials, Certificates of Suitability (CEP) of European Directorate for the Quality of Medicine (EDQM) are provided.

Potential viral contamination is controlled by selection of raw materials, manufacturing conditions, and appropriate control tests. The safety of Tetraxim with respect of Adventitious Agents has been demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Tetraxim vaccine is a well-established product. The manufacturing process has been adequately described and validated, appropriate in-process and quality controls applied. The studies performed demonstrated that all the processes are reproducible and under control. The results of

tests carried out indicate satisfactory consistency and uniformity of product quality characteristics. Specifications are justified in detail and are in accordance with the Ph. Eur. and WHO requirements. The shelf-lives assigned for the drug substances and the drug product are considered justified. The vaccine is prepared according to Good Manufacturing Practices rules.

The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

All studies were conducted in compliance with Good Laboratory Practice, except for the investigative local tolerance study conducted in rabbits by the intramuscular route of administration (comparison of different batches of Tetraxim).

In accordance with European Medicines Agency (EMA) *Note for guidance on preclinical pharmacological toxicological testing of vaccines* (CPMP/SWP/465/95), carcinogenicity studies were not considered necessary as the exposure to the vaccine is short term.

III.2 Pharmacology

In consideration of

- the extensively documented pharmacodynamic profile of Tetraxim in humans,
- the nature of the *in vivo* potency release tests for Tetraxim, which rely on the ability of the vaccine to generate immune responses in animals and
- the non-clinical pharmacology profiles of the individual antigens that make-up this vaccine have been well documented in studies with a number of other combined vaccines

no purposely-designed pharmacology studies were conducted with the product. Instead, the non-clinical pharmacodynamics of the Tetraxim vaccine, i.e. the immunogenicity of each active substance, was documented from release and characterization tests, carried out in suitable animal models for each antigen as per Ph. Eur. requirements. All antigens were shown to be immunogenic and met the acceptance criterion.

III.3 Pharmacokinetics

In accordance with the EMA *Note for guidance on preclinical pharmacological and toxicological testing of vaccines* CPMP/SWP/465/95 pharmacokinetic studies that assess serum or tissue concentrations of vaccine components were not performed for this vaccine.

III.4 Toxicology

The non-clinical safety of Tetraxim was evaluated in a local tolerance study in rabbits. Also, toxicity data have been obtained with D.T.Pacel2.IPV//A vaccine, which consists of the reconstitution of ActHIB (lyophilisate) with Tetraxim vaccine (fully liquid) and are considered supportive of the safety assessment of Tetraxim; the studies included single dose toxicity studies in mice and rats, a repeat dose toxicity study in rats, a local tolerance study in rabbits and a hypersensitivity test in guinea pigs. In addition to toxicity data with the vaccine itself, preclinical studies were conducted with Lymphocytosis Promoting Factor (LPF) and LPF-Filamentous Hemagglutinin (FHA) acellular Pertussis vaccines, which contains 1 and 2 antigens present in

Tetraxim, respectively. The toxicity data obtained with D.T.Pacel2.IPV//A, LPF and/or FHA are considered supportive for the nonclinical safety assessment of Tetraxim.

The subcutaneous administration of the LPF and LPF-FHA vaccines to rats once every 2 weeks for 8 weeks did not result in systemic toxicity. Vaccine-related effects consisted of local inflammatory reactions at the injections sites (less severe than those observed with the cellular Pertussis vaccine), clinical pathology changes considered secondary to the inflammatory response and effects on the lymphoid organs considered related to the immune response.

III.5 Ecotoxicology/environmental risk assessment

At the time of the national authorisation of Tetraxim vaccine the environmental risk assessment was not required.

Because of the nature and use of this vaccine this mutual recognition procedure authorisations will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There has been a large amount of safety data generated in both clinical and non-clinical studies, with vaccines containing one or more of the D, T, aP, IPV antigens.

The pharmacology studies of Tetraxim consisted of potency assays and immunogenicity studies in different animal models to show the vaccine's ability to induce protection against challenge or to produce antibodies to individual antigen components of the vaccine. All these antigens met the acceptance criterion for each analysis of the potency or immunogenicity. Based on the results from all nonclinical studies, the vaccine was shown to be immunogenic.

Single and multiple subcutan or intramuscular administration of Tetraxim vaccine was well tolerated in animal models and consisted mainly of local reactions and haematological and histopathological changes that are expected in the context of a response to the administration of a vaccine. No specific risk is anticipated and the data from the non-clinical safety studies showed that the vaccine was well tolerated with expected injections site reactions. Non-clinical safety data are consistent with the clinical safety data. Local injection-site reactions were observed in any clinical studies and reported with market use.

There are no specific concerns identified with Tetraxim. The local reactogenicity is one of limited medical significance, and is observed with a variety of like vaccines.

IV. CLINICAL ASPECTS

IV.1 Introduction

During the course of its clinical development program, and since its initial marketing authorisation, approximately 4,000 subjects received Tetraxim in Sanofi Pasteur or Sanofi Pasteur-MSD sponsored clinical trials.

Subjects received this vaccine either as a primary series vaccine with three doses administered during their first year of life followed by a first booster dose administered during their second year of life, or received this vaccine as a late booster administered at pre-school age in children aged 4 to 7 years, or in adolescents aged 8 to 13 years having experienced different primary series vaccination histories.

As it has been about 17 years since DTaP-IPV (Tetraxim) was first introduced on the market, the total number of subjects exposed to commercially available product far exceeds the number of subjects exposed during the clinical trials introduced in this application. Nevertheless, the original file which supported the first marketing authorisations of DTaP-IPV is provided in this application as a source of specific information (all the efficacy and safety data submitted in the historical file which supported the initial authorisation of DTaP-IPV). It should be noted that clinical data on the pentavalent DTaP-IPV/Hib combination vaccine have been included in this document because they were considered supporting the safety of DTaP-IPV as well.

The clinical trials were performed in accordance with GCP as claimed by the applicant.

It should be noted that, as for other vaccines of this class, the pharmacological profile of Tetraxim is represented by its immunogenicity profile and, similar to many inactivated vaccines its efficacy is inferred from immunogenicity data. In the field of diphtheria, tetanus and poliomyelitis vaccines, the well-accepted serological correlates of protection are a level of circulating serum toxin or virus neutralizing antibodies above different thresholds. These correlates of protection are used by all Regulatory Agencies when reviewing applications. For acellular pertussis-containing vaccines, there is an active debate since decades on the relative merit of the different population of antibodies induced by the different acellular pertussis-containing vaccines evaluated in the field, and no consensus has been achieved for determining clear serological correlate of protection. This reinforces the value of interventional clinical end point efficacy trials or observational field effectiveness evaluations of vaccines.

IV.2 Pharmacokinetics

Due to the nature of the product, its composition (amounts of active substances in the intramuscularly administered dose) and its mode of action, information relative to the pharmacokinetic profile (absorption, distribution, metabolism and excretion) of the components following administration have not been compiled.

IV.3 Pharmacodynamics

The *Reports of Human Pharmacodynamic Studies* section has not been populated which is acceptable.

IV.4 Clinical efficacy

Immunogenicity studies have shown that all infants (100%) vaccinated with three doses of vaccine from 2 months of age developed a seroprotective antibody titre (> 0.01 IU/ml) to both diphtheria and tetanus antigens.

As for pertussis, one to two months after the third dose of the primary vaccination, more than 87% of infants achieved a four-fold increase in pertussis Filamentous Hemagglutinin antibody titres.

Following primary vaccination, at least 99.5% of children had seroprotective antibody titres to poliomyelitis virus types 1, 2 and 3 (≥ 5 as expressed by reciprocal of dilution in seroneutralisation) and were considered as protected against poliomyelitis.

After the first booster dose (16-18 months), all the toddlers developed protective antibodies against diphtheria (> 0.1 IU/ml), tetanus (> 0.1 IU/ml) and 87.5% against poliomyelitis viruses (≥ 5 as expressed by reciprocal of dilution in seroneutralisation).

The seroconversion rate in pertussis antibodies (titres higher than four-fold the pre-vaccinal titres) is 92.6% for PT and 89.7% for FHA.

After booster vaccination between 5 to 13 years of age, all children developed protective antibody titres against tetanus (> 0.1 IU/ml) and poliomyelitis viruses. Protective antibody titres against diphtheria (> 0.1 IU/ml) were achieved in at least 99.6% of them. Seroconversion rates in pertussis antibodies (titres higher than four-fold the pre-vaccinal titres) are from 89.1% to 98% for PT and from 78.7% to 91% for FHA.

Combining IPV and DTaP vaccines does not adversely impact the serological response to any antigen components, which is similar to that observed following administration of the two vaccines separately.

This vaccine may be associated or combined with the *Haemophilus influenzae* type b conjugate vaccine (Act-HIB).

Tetraxim can be administered simultaneously with MMR vaccine during the second year of life, without affecting the immunogenicity of the two vaccines.

IV.5 Clinical safety

A consolidated discussion approach has deliberately been chosen to discuss the safety data collected from some of the clinical trials submitted in this application as an illustrative purpose exclusively.

In three clinical studies, over 2800 infants were vaccinated with Tetraxim, administered simultaneously with Act-Hib at one or two injection sites.

Over 8400 doses were administered as a primary series and the most frequently reported reactions included: irritability (20.2%), local reactions at the injection site such as redness >2 cm (9%) and induration >2 cm (12%). These signs and symptoms usually occur within 48 hours following the vaccination and may continue for 48-72 hours. They resolve spontaneously without requiring specific treatment. After the primary series, the frequencies of injection-site reactions tend to increase with the booster dose. Tetraxim safety profile does not differ significantly between different age groups however some adverse events such as myalgia, malaise and headache are specific to children ≥ 2 years of age.

Tetraxim new clinical trials are submitted and evaluated in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. Three Public Assessment Reports are published on the CMDh website with the following conclusion: „No SmPC and package leaflet changes are proposed as a result of this study.”

Complete reviews and analysis of the post-marketing safety information available with Tetraxim have been performed in the successive periodic safety reports that have been prepared over the years and in the Risk Management Plan. These documents represent an updated summary and analysis of all safety information collected over the years with Tetraxim, including a discussion on all the identified risks with this vaccine.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

<i>Summary of safety concerns</i>	
Important identified risks	<ul style="list-style-type: none">• Anaphylactic reactions.• Convulsions.• Syncope.

<i>Summary of safety concerns</i>	
Important potential risks	<ul style="list-style-type: none"> • Guillain-Barre syndrome. • Brachial neuritis. • Encephalopathy/encephalitis.
Missing information	<ul style="list-style-type: none"> • Subjects with history of severe prematurity. • Immuno-compromised individuals. • Patients with other relevant co-morbidities.

Summary of safety concerns as proposed by the holder of the marketing authorisation: due to a comment by a CMS Sanofi Pasteur made a commitment to include “apnoea in very premature infants” and “hypotonic-hypo-responsive episode” as important potential risks into the Risk Management Plan. This modification will be made by a Type I.B.C.I. 11.z variation after the end of this mutual recognition procedure.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Tetraxim vaccine. No additional activities are proposed.

Risk Minimisation Measures: routine risk minimisation measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Tetraxim vaccine. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

With regard to the submission of Periodic Safety Update Reports (PSUR), the marketing authorisation holder should take the following into account:

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the Data Lock Points and frequency of submission of the next PSUR.

IV.7 Discussion on the clinical aspects

The pharmacological profile is presented by its immunological profile, which is acceptable for the vaccine of this class. The immunogenicity of each component of Tetraxim is satisfactory, after both a primary series and booster doses. Tetraxim is generally well-tolerated and has an acceptable safety profile. In clinical trials when compared with any of the vaccines with whole cell pertussis component, the incidence of systemic reactions were distinctly lower with Tetraxim. Post-marketing surveillance experience: distribution of more than 28 million doses during 17 years. Safety is monitored and evaluated regularly. All related adverse events are well-known from long-standing safety profile of Tetraxim and listed in the approved SmPC.

There is no objection against authorisation of Tetraxim from clinical points of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

This application concerns the approval via a Mutual Recognition Procedure of a diphtheria/acellular pertussis/tetanus/inactivated poliomyelitis (DTaP-IPV) vaccine, the Tetraxim suspension for injection in prefilled syringe. The applicant and the holder of marketing authorisation is Sanofi Pasteur SA.

The active ingredients and excipients used in Tetraxim are well-known. The same active ingredients are used in the preparation of other licensed vaccines in Europe and in international markets.

This vaccine is indicated in the joint prevention of diphtheria, tetanus, pertussis and poliomyelitis:

- for primary vaccination in infants from the age of 2 months,
- for booster vaccination, one year after primary vaccination during the second year of life,
- for booster vaccination between 5 and 12 years of age, according to official recommendations.

The successful clinical trials conducted by the applicant at the time of the first national authorisations have been supported by a vast post-marketing experience.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Tetraxim suspension for injection in prefilled syringe.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached