

PUBLIC ASSESSMENT REPORT
FOR
PREVNAR 13

Common Name: ... Pneumococcal 13-valent Conjugate Vaccine
(Diphtheria CRM₁₉₇ Protein)

Application No. 2 C 90002/53 (NB)

Assessment Report as adopted by the TFDA with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant **...Pfizer (Thailand) Limited ...** submitted on ...2 February 2010... an application for Marketing Authorization to the Thailand Food and Drug Administration (TFDA). At the time of submission and validation, **PREVNAR 13** was designated as medicinal product in the following indication: For... Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age.

The legal basis for this application refers to: **Drug Act 2510 B.E.**

The application submitted was a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Licensing status:

The product was licensed in ...EU...(country) at the time of submission of the application.

TFDA Product Team Leader: (PTL)

Ms. Prapassorn Thanaphollert

TFDA External Experts

- Quality:

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1.2 Steps taken for the assessment of the product

- The application was received by the TFDA on ...02 February 2010.....
- The procedure started on ...08 February 2010.....
- TFDA considered the consolidated list of questions, identifying “major objections” and/or “other concerns” may be adopted. These were sent to the applicant together with the TFDA recommendation and scientific discussion on ...19 May 2010, 11, 16 and 31 Aug 2010
- Final draft of English SPC, labeling and package leaflet was sent by applicant to the TFDA PTL on ...14 Jul 2010.....
- TFDA adopted the decision on marketing authorization on24 Nov 2010.....

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Streptococcus pneumoniae is a gram-positive encapsulated diplococcus and a major cause of mortality and morbidity worldwide with the highest incidence in infants under 2 years of age and in the elderly over 60 years of age. *S. pneumoniae* has been estimated to cause ~16 million deaths every year, including up to one million in children below 5 years of age. The highest morbidity and mortality rates have been reported from developing countries. The spectrum of disease encompasses invasive pneumococcal disease (IPD), such as sepsis and meningitis, lower respiratory infections, such as bacterial pneumonia and upper respiratory infections, such as acute otitis media (AOM). The relative incidences of the various disease entities are estimated to be that for 1 case of IPD there are 100 cases of pneumonia and 1000 cases of otitis media. Extrapolation of data on hospitalizations due to IPD from England and Wales (Melegaro, 2006) (prior to introduction of 7-valent Prevnar to the EU paediatric population <5 years of age indicate that there would be 6500 IPD (meningitis and sepsis) cases and 61,000 pneumonia cases (50% hospitalized) annually.

Acute otitis media is most prevalent in early childhood, with the peak attack-rate occurring from 6 to 18 months of age and with ~60% of children having had at least one episode of AOM by 1 year of age. A study from England and Wales (Melegaro 2004) estimated that 270,000 AOM cases would occur annually in children <5 years of age, which would correspond to 2.1 million AOM cases in the EU. Bacteria are isolated in ~70% of middle ear fluid samples from children with otitis media; with *S. pneumoniae* and *H. influenzae* being the most commonly identified pathogens.

Despite the availability of antibiotic therapies the mortality of pneumococcal disease remains high. The continuing emergence of penicillin-resistant and multidrug-resistant pneumococcal strains is an increasing global threat posing serious therapeutic challenges. Although the resistance patterns vary between countries, the predominance of certain serotypes (i.e. 6A/B, 9V, 14, 19A/F, and 23F) among the resistant organisms is shared. Another important aspect of *S. pneumoniae* epidemiology is the nasopharyngeal (NP) carriage of the pathogen occurring in virtually all children at some time. The relationship between the acquisition of carriage of individual serotypes and their likelihood of causing IPD is not known. However, NP carriage plays an important role in the transmission of pneumococcal strains and in particular, of antibiotic-resistant strains.

There are 91 distinct pneumococcal serotypes, which can be grouped by immunological relatedness into 46 serogroups. However, only 10 to 15 serotypes cause the vast majority of invasive disease worldwide. Serotypes differ in invasiveness with types 1 and 5 frequently mentioned among those with the highest invasive potential. The global epidemiology of pneumococcal serotypes and their role in disease differ between continents. The prevalence of individual serotypes may also vary regionally, between different age groups and over time. Serotype 14 and serogroup 6 predominate worldwide, serotypes 1 and 5 being more common in the developing world, whereas serogroup 18 is

more common in the industrialised countries. The epidemiology in Europe differs from that in the US; before the introduction of Prevnar (7-valent pneumococcal conjugate vaccine), the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) targeted by the vaccine were responsible for almost 90% of cases of IPD in young children in the US and for more than 60% of cases in Europe.

Vaccine impact on invasive pneumococcal disease

Since 2000, when universal mass vaccination with Prevnar was implemented in the US, the number of IPD cases among children aged below 5 years has fallen substantially, in 2001 the incidence of IPD in children less than 5 years of age had declined by 56% and in 2004 by 76%, with a 96% decline in IPD caused by vaccine serotypes. A significant decline in IPD caused by penicillin-resistant strains has also been seen. In addition, substantial decreases in IPD in other, non-immunized age groups have been documented, and the number of cases prevented through this indirect (herd) protection is approximately double that attributed to direct protection alone. However, over subsequent years an increase has been observed for IPD caused by the vaccine-related serotype 19A, and to a lesser extent for IPD caused by some other non-vaccine serotypes (serotypes 3, 15, 22F, 33F and 35). It is so far a relatively small number of cases compared to the overall decline in IPD. Such serotype replacement with 19A has also been observed in the EU (Spain, France), but not in some other countries with universal childhood vaccination, i.e. Australia and Canada. The reason for the rises in serotype 19A is not fully clear and may, in addition to the introduction of Prevnar, be related to antibiotic pressure or emergence of new clones. The experience gained indicates that close long-term monitoring of pneumococcal disease is essential during widespread use of pneumococcal vaccines. Generalised immunisation programmes with Prevnar have been implemented in EU countries in recent years and effectiveness data against IPD are becoming available.

In view of the considerable public health impact of successful vaccines against pneumococcal disease, the WHO has stated that the development of safe, effective vaccines that offer broad protection against pneumococcal disease should be a high priority. There is an unmet medical need for extended valency vaccines beyond the 7 serotypes in Prevnar designed to better cover the global pneumococcal serotype distribution. Of note is that the presence of serotypes 1 and 5 is considered critical by WHO and GAVI, given their important contribution to the burden of disease in developing countries. Therefore, a 10-valent pneumococcal conjugate vaccine has been developed that recently gained a positive CHMP opinion in the EU. The 13 serotypes in the 13-valent pneumococcal conjugate vaccine (7 Prevnar types + 6 additional serotypes (1, 3, 5, 7F, 6A, 7F, 19A)) would further expand coverage and would in Europe cover 80% or more of IPD cases in children less than 5 years of age, as documented by surveillance studies performed before the introduction of 7-valent Prevnar.

Licensure criteria for pneumococcal conjugate vaccines

Over the past years, regulatory agencies and experts in the field have reflected upon the serological criteria for the evaluation and licensure of new pneumococcal conjugate vaccines. It was agreed to follow the same pathway as used for licensure of Hib and MenC conjugate vaccines, and after the demonstration of a high level of invasive pneumococcal disease efficacy in Northern California with Prevnar, to licence future new pneumococcal conjugate vaccines for IPD purely on the basis of immunological data in comparison with the licensed vaccine. A consensus recommendation on criteria for licensure of new pneumococcal conjugate vaccines against IPD was reached at the WHO Expert Committee meeting in 2003 (WHO 2005, Jodar 2004, Lee 2003). The WHO has issued a technical report series (TRS 927, annex 2) with recommendations for the evaluation of new pneumococcal conjugate vaccines that reflect these principles.

The following criteria are recommended for use as the primary end-point for demonstration of non-inferiority against a registered vaccine:

- IgG antibody concentration, as measured by ELISA, in sera collected 4 weeks after a three-dose primary series is considered to be the optimal primary end-point and main licensing parameter.
- A single threshold or reference antibody concentration is recommended for use for all pneumococcal serotypes. A reference antibody concentration of 0.35 µg/ml, that has been determined through a pooled analysis of data from the efficacy trials with invasive disease end-points that have been completed to date, is recommended. This threshold does not necessarily predict protection in an individual subject.
- The reference value is defined on the basis of data obtained using ELISA without pre-adsorption with serotype 22F. Antibody concentrations determined using an alternative method will need to be bridged to this method to derive an equivalent threshold concentration. It is recommended that the assay used be calibrated against a reference assay.
- Direct clinical comparison of the registered (established) vaccine with the new one is the preferred method for evaluating new vaccine formulations.
- The percentage of responders (those in whom post-immunization antibody concentration is above the threshold) should be used as the criterion to determine non-inferiority.
- For the serotypes present in a registered vaccine, the percentage of responders to each serotype in the new formulation or combination should be compared with the percentage of responders to the same serotype in the registered vaccine in the same population.
- Non-inferiority to antibody response for each of the serotypes in the registered vaccine is desirable, but not an absolute requirement. Registration of products in which one or more serotypes do not meet non-inferiority criteria would have to be decided on an individual basis.

- Serotypes not contained in a registered formulation may be evaluated for non-inferiority to the aggregate response to the serotypes in the registered vaccine. Failure of one or more new serotypes to meet this criterion may be considered on an individual basis.

Additional criteria that must be met to support registration:

- In addition to showing non-inferiority with respect to the primary end-point, additional data to demonstrate the functional capacity of the antibody and induction of immunological memory in a subset of the sera are required for registration.

Functional antibodies

- Opsonophagocytic activity (OPA) as measured by opsonophagocytic assay after a three-dose priming series is required to demonstrate the functionality of antibodies.
- The method used to demonstrate OPA should be comparable to the reference assay.

Immunological memory

- Evidence of memory should be demonstrated. One possible method is to administer a booster dose of pneumococcal polysaccharide vaccine and to compare concentrations between age-matched unprimed and primed individuals; data from non-concurrent controls may be sufficient for the purposes of comparison.
- A full dose of polysaccharide vaccine should be used at this stage because the use of a reduced dose of the polysaccharide vaccine as a booster has not been sufficiently tested.
- Avidity of antibodies is also a useful marker for immunological memory.

In follow-up of WHO 2003 meeting, a WHO workshop took place in January 2007 with the objective to formulate a plan for the standardisation of the pneumococcal OPA assay (WHO 2007).

Product development rationale

The Applicant has developed the 13-valent pneumococcal conjugate vaccine (Pevnar 13), as a successor to the currently registered vaccine, Pevnar, for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease (IPD), pneumonia, and acute otitis media (AOM), caused by the 13 pneumococcal serotypes contained in the vaccine. Pevnar is a 7-valent vaccine that contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. In addition to these serotypes, Pevnar 13 contains serotypes 1, 3, 5, 6A, 7F, and 19A. As in Pevnar, each of the polysaccharides is covalently conjugated to the diphtheria toxoid cross-reactive material₁₉₇ (CRM₁₉₇) protein, which acts as an immunologic carrier.

Rationale for the 6 additional serotypes in the 13-valent vaccine

Serotypes 1 and 5 are encountered more frequently in the developing world. In Europe, serotype 1 causes around 6% of childhood IPD, but the majority of infections occur in children after the 2nd year of life. Recent data from the UK, after the introduction of Prevnar, have shown that serotype 1 is responsible for 14.6% of IPD cases in children <5 years. Serotype 1 has been associated with complicated pneumonia, such as parapneumonic empyema (PPE). IPD cases by serotype 5 are unusual in Europe, but recent reports from Spain underscore the increasing importance with 5% of IPD in children <5 years caused by this serotype in 2007. An increase in the proportion of serotype 5 isolates from 0.2% to 4.2% of IPD cases has also been recently reported from England and Wales (2007 to 2008), predominately due to an outbreak.

Serotype 3 IPD in young EU children is less common; the mean proportion of all cases is 2.5%. The frequency of type 3 IPD from recent years, as documented in countries that have introduced Prevnar, is 6.5% in Germany and 5.9% in the UK in the age group <5 years. Invasive infections by serotype 3 are more commonly seen in older children and have shown an association with severe pneumonia.

Serotype 6A is an important serotype in Europe responsible for a mean proportion of 4.9% of IPD cases and has also been shown to be associated with diminished antibiotic susceptibility. The highest proportion of cases is reported from Germany (mean 9.8% of cases, peaking to 14% in 2006 to 2007). Due to cross-reactivity with 6B, Prevnar have been shown to significantly reduce the incidence of 6AIPD in vaccinated children in the US, but less so with regard to 6A NP carriage. Despite high vaccination rates in the US no reduction of 6A-specific IPD cases in adults through herd immunity as was seen with each of the 7 serotypes in the vaccine.

Serotype 7F is responsible for a substantial IPD burden in Europe and the mean proportion of paediatric IPD is 5.5%. In the UK, an increase in the numbers of cases since 2006 has been observed, with 7F accounting for 12.5 % of all IPD cases in 2007-08. In a recent publication from Germany (Rückinger, 2009) 7F was found to account for a higher risk of severe IPD and fatal outcome than other serotypes.

Serotype 19A is responsible for a significant proportion of IPD in Europe, with the highest rates reported in Belgium (9.6%), France (16%) and Spain (21%) in children below 5 years. Prevnar does not provide protection against 19A, instead an increase in IPD due to this serotype has been reported in the US after the introduction of Prevnar, which has also been reported from some EU countries. Of concern, the prevalence of IPD due to penicillin-resistant and often multiply antibiotic resistant 19A isolates increased from 6.7% to 35% in the US. In addition to ineffectiveness of Prevnar against 19A, antibiotic resistance, clonal expansion and emergence, and capsular switching may have each contributed to the genetic diversity of 19A and to its emergence as the predominant invasive pneumococcal serotype in the United States.

2.2 Quality aspects

Introduction

Prevnar 13, the Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein) vaccine, is a 13-valent, inactivated vaccine, which belongs to the pharmacotherapeutic group of ...pneumococcus, purified polysaccharide antigen conjugated... vaccines (ATC CODE J07AL02).

Manufacture of the Product

The 13 conjugates are added to a mixture of Succinate/Sodium chloride buffer and polysorbate 80 and then sterile filtered. The solution is then mixed with Aluminium phosphate suspension and stirred. The adsorbed vaccine is then filled in prefilled syringes. The manufacture of 5.5 mM succinate, 0.85% NaCl buffer, pH 5.8 (succinate/saline buffer) and 1% polysorbate 80 in succinate/saline buffer includes routine monitoring of established operating parameters, and in-process control testing.

The formulation of Pevnar 13 bulk vaccine includes routine monitoring of established operating parameters, and in-process control testing. The controls performed during formulation and filling is acceptably described.

Three process validation runs were performed at the commercial scale to validate the formulation and filling process for Pevnar 13 bulk vaccine into the syringes. These results validate the formulation process, demonstrating that the process produced Pevnar 13 that meets its pre-determined quality attributes.

All three batches met the pre-determined acceptance criteria and release specifications for aluminum, antigenicity, appearance, endotoxin, pH, polysorbate 80, protein (total and bound), sterility and extractable volume. All tests met acceptance criteria.

A thorough validation program has been performed and shows that the process is well under control.

Active Substance

Each dose (... 0.5 ... ml) contains.

Active Substances

Nominal Composition

| | |
|--|--------|
| Pneumococcal polysaccharide serotype 1 ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 3 ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 4 ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 5 ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 6A ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 6B ¹ | 4.4 µg |

| | |
|---|--------|
| Pneumococcal polysaccharide serotype 7F ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 9V ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 14 ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 18C ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 19A ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 19F ¹ | 2.2 µg |
| Pneumococcal polysaccharide serotype 23F ¹ | 2.2 µg |

¹Conjugated to CRM₁₉₇ carrier protein and adsorbed on aluminium phosphate (0.125 mg aluminium).

Manufacturers

| Manufacturing Facility | Operations |
|---|--|
| Wyeth Pharmaceuticals Inc. 1 Burt Road Andover, MA 01810 USA | - Manufacture of pneumococcal polysaccharides - Quality control testing including release and stability testing of pneumococcal polysaccharides |
| Baxter Pharmaceutical Solutions LLC 927 South Curry Pike Bloomington IN USA | Contract Manufacturer: - 13vPnC vaccine formulation and syringe filling - Quality control testing of Drug Product syringes ·Microbiological: sterility ·Microbiological: non-sterility ·Chemical/Physical |
| BioReliance Corp. 14920 Broschart Road Rockville, MD 20850 USA | Contract Testing Laboratory: - Sterility Testing of pneumococcal polysaccharides |
| Wyeth Medica Ireland Grange Castle Business Park Clondalkin, Dublin 22 IRELAND | - Release testing of Drug Product syringes ·Biological |
| Wyeth Pharmaceuticals New Lane Havant, Hampshire UNITED KINGDOM | - Final labeling and packaging of Drug Product syringes - Batch Release by Qualified Person in the EEA (European Economic Area) |

| Manufacturing Facility | Operations |
|--|--|
| Molecular Epidemiology 15300 Bothell Way NE Lake Forest Park, WA 98155 USA | Contract Testing Laboratory: - Alternate Laboratory for Sterility Testing |
| Wyeth Pharmaceuticals Division of Wyeth Holdings Corporation 401 North Middletown Road, Pearl River, NY USA | - Manufacture of pneumococcal polysaccharides - Quality control testing including release and stability testing of pneumococcal polysaccharides - ALPO4 manufacture - 13vPnC vaccine formulation and syringe filling (<i>This operation is not applied to the supply for Thailand market</i>) - Quality control testing of ALPO4 and Drug Product syringes including stability testing |
| Wyeth Pharmaceuticals Inc. 4300 Oak Park Sanford, NC 27330 USA | - Cell bank storage - Quality control testing including release and stability testing of pneumococcal cell banks - Alternate site for performing anthrone and residual protein testing of pneumococcal polysaccharides |
| Spectral Data Services, Inc. 818 Pioneer St. Champaign, IL 61820 USA | NMR Testing of pneumococcal polysaccharides |

I. DRUG SUBSTANCE(S)

1. General Information, Starting Materials and Raw Materials

1. **Streptococcus pneumoniae Serotype 1**: ATCC no. 6301

Chemical Name(s): Serotype 1 Polysaccharide consists of a trisaccharide repeating subunit of -3-(2-acetamido-4-amino-2,4,6-trideoxy-D-galactopyranosyl-1- α)-4-(D-galacturonopyranosyl-1- α)-3-(D-galacturonopyranosyl-1- α) residues. The galacturonopyranosyl residues are partially O-acetylated. Each mole of the saccharide repeat unit carries a non-stoichiometric amount of O-acetyl groups per repeating unit.

Appearance: Clear to slightly turbid, colorless to pale yellow liquid
Molecular weight: as determined by SEC-MALLS is 500–625 kDa

2. **Streptococcus pneumoniae Serotype 3:** Streptococcus pneumoniae Serotype 3 was obtained from Dr. Robert Austrian (University of Pennsylvania, Philadelphia)

Chemical Name(s): Serotype 3 Polysaccharide consists of a disaccharide repeating subunit of -4-(D-glucopyranosyl-1-β)-3-(D-glucuronopyranosyl-1-β) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 1500-2050 kDa

3. **Streptococcus pneumoniae Serotype 4:** Serotype 4 was obtained from Dr. Gerald Schiffman (State University of New York, Brooklyn, NY)

Chemical Name(s): Serotype 4 Polysaccharide consists of a repeating subunit of -3-(D-2-acetamido-2-deoxy-D-mannopyranosyl-1-β)-3-(L-2-acetamido-2-deoxy-D-fucopyranosyl-1-α)-3-(D-2-acetamido-2-deoxy-D-galactopyranosyl-1-α)-4-(D-2,3-S-pyruvyl-galactopyranosyl-1-α) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 475–825 kDa

4. **Streptococcus pneumoniae Serotype 5:** Serotype 5 was obtained from Dr. Gerald Schiffman of State University of New York in Brooklyn, New York

Chemical Name(s): Serotype 5 Polysaccharide consists of a penta-saccharide repeating subunit of -4-(D-glucopyranosyl-1-β)-4-[L-2-acetamido-2-deoxy-3-(2-acetamido-2,6-dideoxy-L-talopyranosyl-1-α-2-D-glucuronopyranosyl-1-β)-fucopyranosyl-1-α]-3-(D-2-acetamido-2,6-dideoxy-D-xylo-hexopyranos-4-ulosyl-1-β) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 250–350 kDa

5. **Streptococcus pneumoniae Serotype 6A:** Serotype 6A was obtained from Dr. Gerald Schiffman of State University of New York in Brooklyn, New York

Chemical Name(s): Serotype 6A Polysaccharide consists of a repeating subunit of -2-(D-galactopyranosyl-1-α)-3-(D-glucopyranosyl-1-α)-3-(L-rhamnopyranosyl-1-α)-3-(D-ribitol-1-phosphate) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 475–650kDa

6. **Streptococcus pneumoniae Serotype 6B:** Serotype 6A was obtained from Dr. Gerald Schiffman of State University of New York in Brooklyn, New York

Chemical Name(s): Serotype 6B Polysaccharide consists of a repeating subunit of -2-(D-galactopyranosyl-1-α)-3-(D-glucopyranosyl-1-α)-3-(L-rhamnopyranosyl-1-α)-4-(D-ribitol-5-phosphate) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 850 – 1250 kDa

7. **Streptococcus pneumoniae Serotype 7F:** Serotype 7F was obtained from the Wyeth Pearl River vial "7F-T-F2-83," which was the source to create the Serotype 7F cell lineage

Chemical Name(s): Serotype 7F Polysaccharide consists of a branched repeating subunit of -6-[D-2-(galactopyranosyl-1-β)-galactopyranosyl-1-α]-3-(L-2-O-acetyl-rhamnopyranosyl-1-β)-4-(D-glucopyranosyl-1-β)-3-[D-2-acetamido-2-deoxy-4-(2-acetamido-2-deoxyglucopyranosyl-1-α)-2-(L-rhamnopyranosyl-1-β)-galactopyranosyl-1-β] residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 850–1050 kDa

8. **Streptococcus pneumoniae Serotype 9V:** Serotype 9V was obtained from Dr. Gerald Schiffman (State University of New York, Brooklyn, NY)

Chemical Name(s): Serotype 9V Polysaccharide consists of a repeating subunit of -4-(D-glucuronopyranosyl-1- α)-3-(D-galactopyranosyl-1- α)-3-(D-2-acetamido-2-deoxy-mannopyranosyl-1- β)-4-(D-glucopyranosyl-1- β)-4-(D-glucopyranosyl-1- β) residues.

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 900–1200 kDa

9. **Streptococcus pneumoniae Serotype 14:** ATCC no. 6314

Chemical Name(s): Serotype Serotype 14 polysaccharide consists of a repeating subunit of -4-(D-glucopyranosyl-1- β)-6-[D-2-acetamido-2-deoxy-4-(D-galactopyranosyl-1- β)-glucopyranosyl-1- β]-3-(D-galactopyranosyl-1- β) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 725–1100 kDa

10. **Streptococcus pneumoniae Serotype 18C:** Serotype 18C was obtained from Dr. Gerald Schiffman (State University of New York, Brooklyn, NY)

Chemical Name(s): Serotype 18C Polysaccharide consists of a repeating subunit of -4-(D-glucopyranosyl-1- β)-4-[(2-glucopyranosyl-1- α -3-glycerophospho)-D-galactopyranosyl-1- β]-4-(D-glucopyranosyl-1- α)-3-(L-rhamnopyranosyl-1- α) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 675–925 kDa

11. **Streptococcus pneumoniae Serotype 19A:** Serotype 19A was obtained from Dr. Gerald Schiffman (State University of New York, Brooklyn, NY)

Chemical Name(s): Serotype 19A Polysaccharide consists of a repeating subunit of -4-(D-2-acetamido-2-deoxy-D-mannopyranosyl-1- β)-4-(D-glucopyranosyl-1- α)-3-(L-rhamnopyranosyl-1- α -phosphate) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 575–750 kDa

12. **Streptococcus pneumoniae Serotype 19F:** Serotype 19F was obtained from Dr. Gerald Schiffman (State University of New York, Brooklyn, NY)

Chemical Name(s): Serotype 19F Polysaccharide consists of a repeating subunit of -4-(D-2-acetamido-2-deoxy-D-mannopyranosyl-1- β)-4-(D-glucopyranosyl-1- α)-2-(L-rhamnopyranosyl-1- α -phosphate) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 625–825 kDa

13. **Streptococcus pneumoniae Serotype 23F:** Serotype 23F was obtained from Dr. Gerald Schiffman (State University of New York, Brooklyn, NY)

Chemical Name(s): Serotype 23F Polysaccharide consists of a repeating subunit of -4-(D-glucopyranosyl-1- β)-4-[D-2-(L-rhamnopyranosyl-1- α)-3-(glycerophospho)-galactopyranosyl-1- β]-4-(L-rhamnopyranosyl-1- β) residues

Appearance: Clear to slightly turbid, colorless to pale yellow liquid

Molecular weight: as determined by SEC-MALLS is 1100–1450 kDa.

| Properties | |
|-----------------------------|---|
| Appearance | CRM ₁₉₇ exists as a clear, colorless to slightly yellow solution (liquid frozen CRM197) or as a dry, white to off-white, granular to fibrous (lyophilized CRM197). |
| Apparent Size | The approximate molecular weight of the CRM ₁₉₇ protein is 58.4 kDa |
| Molecular Charge (pI) | The pI value has been determined to be 5.6. |
| Protein Structural Analysis | <p data-bbox="267 506 462 541">Primary Structure</p> <p data-bbox="267 562 386 621">Secondary Structure</p> <p data-bbox="267 659 487 718">Tertiary/Quaternary Structure</p> |
| Biological Activity | Detection of CRM ₁₉₇ toxicity is reported by measuring the enzymatic activity of Diphtheria toxin in a purified CRM ₁₉₇ preparation. |

Amino Acid Analysis and N-terminal Sequencing confirmed that the primary amino acid composition and sequence matches the theoretical composition/sequence.

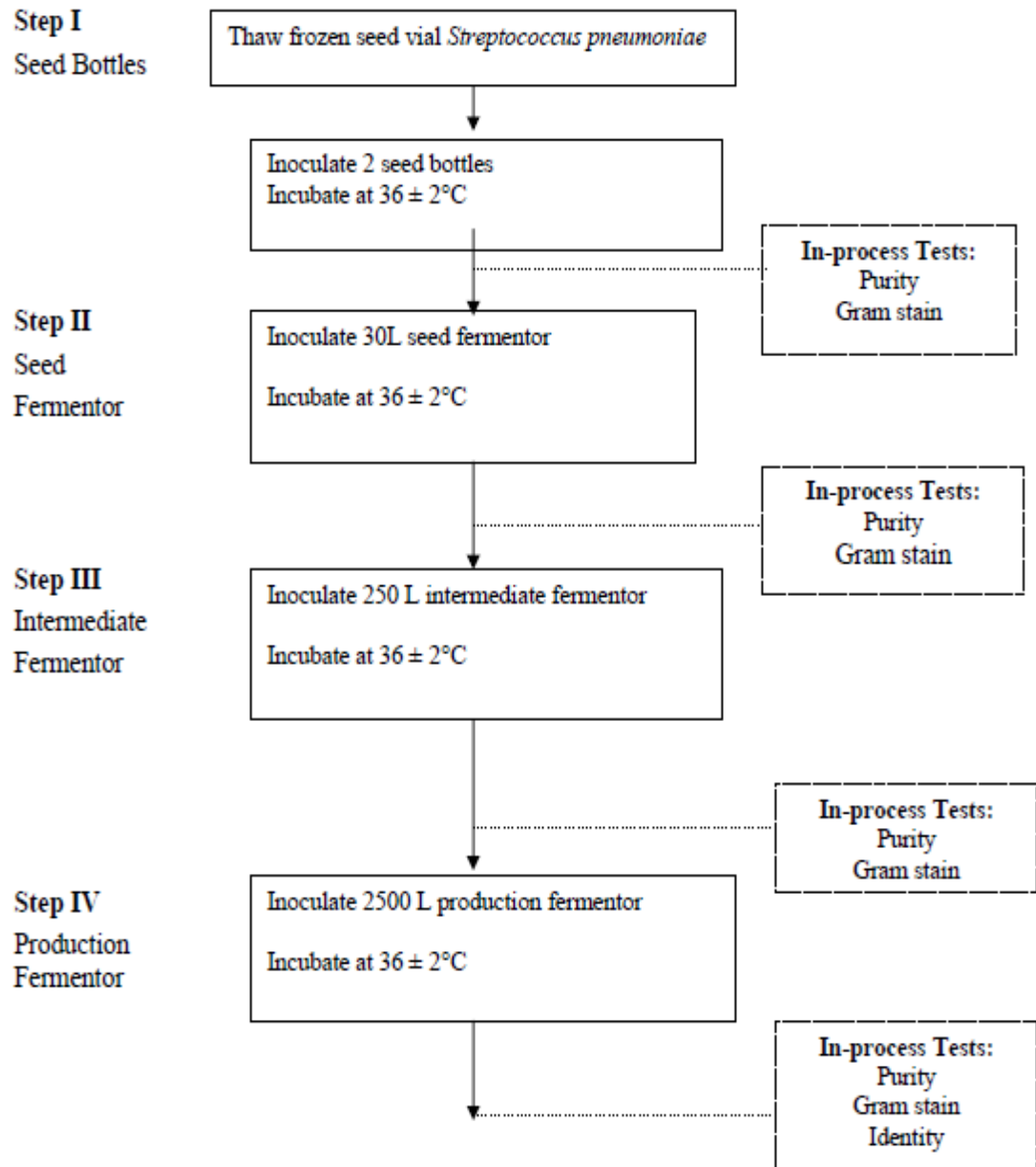
The Circular Dichroism spectrum exhibits negative bands in the far-UV region typical of secondary structures rich in α -helices and β -structures.

Binding to the Human Heparin-Binding Growth Factor Receptor and Differential Scanning Calorimetry established the tertiary structure
Gel Electrophoresis (SDS-PAGE and native gels) and SEC-MALLS were used to generate information on the quaternary structure

2.

Manufacturing Process of the Drug Substance(s)

Figure 1-1: Production Scheme for Pneumococcal Polysaccharide Fermentation and Harvesting



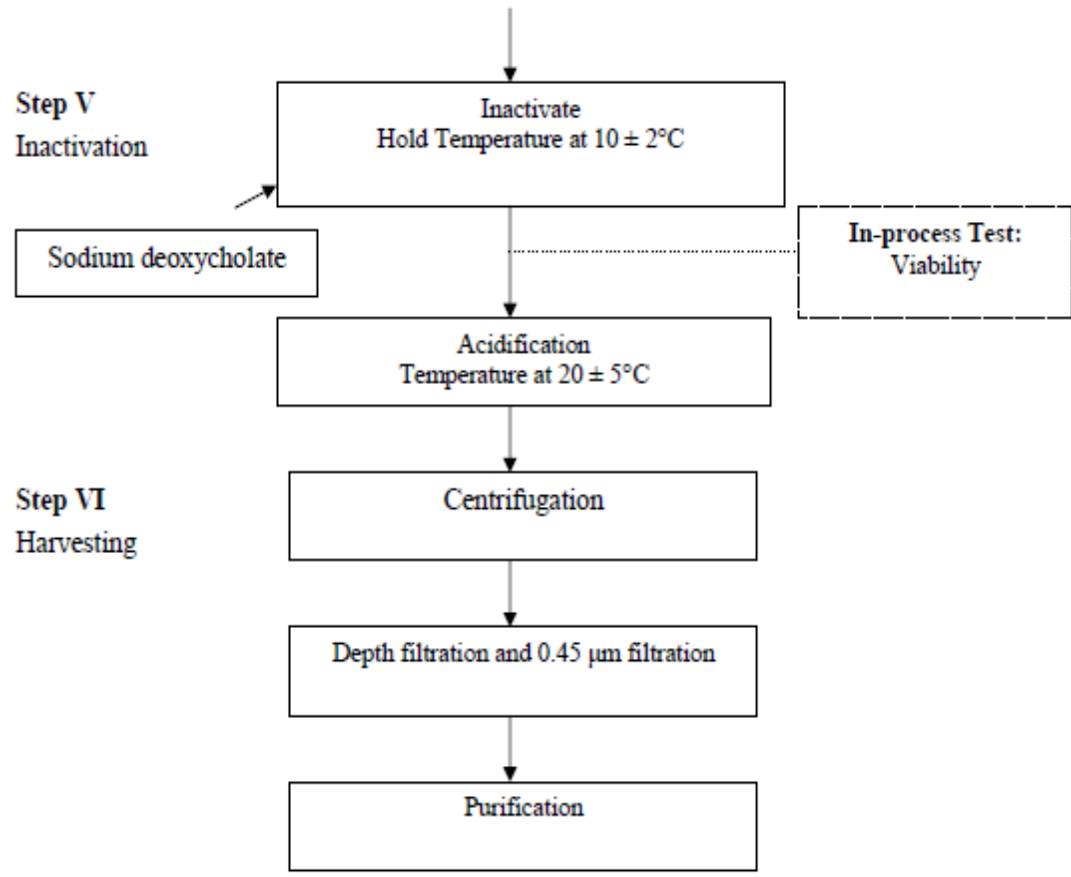
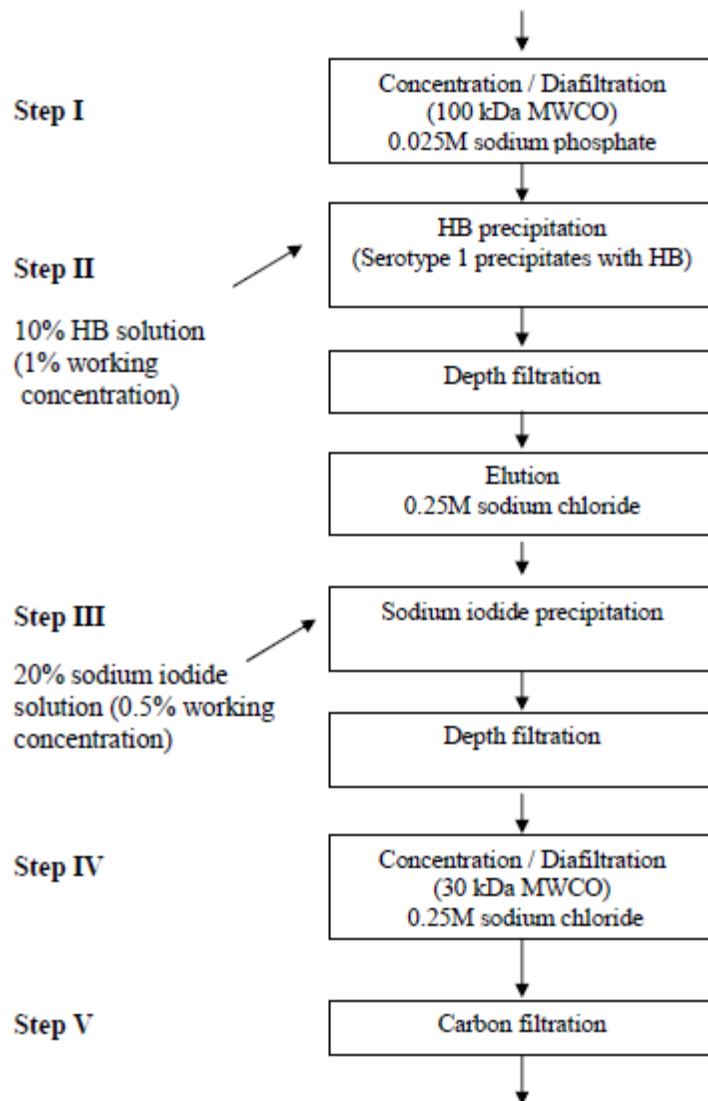


Figure 1-2 : Polysaccharide Purification Process Flow Diagram



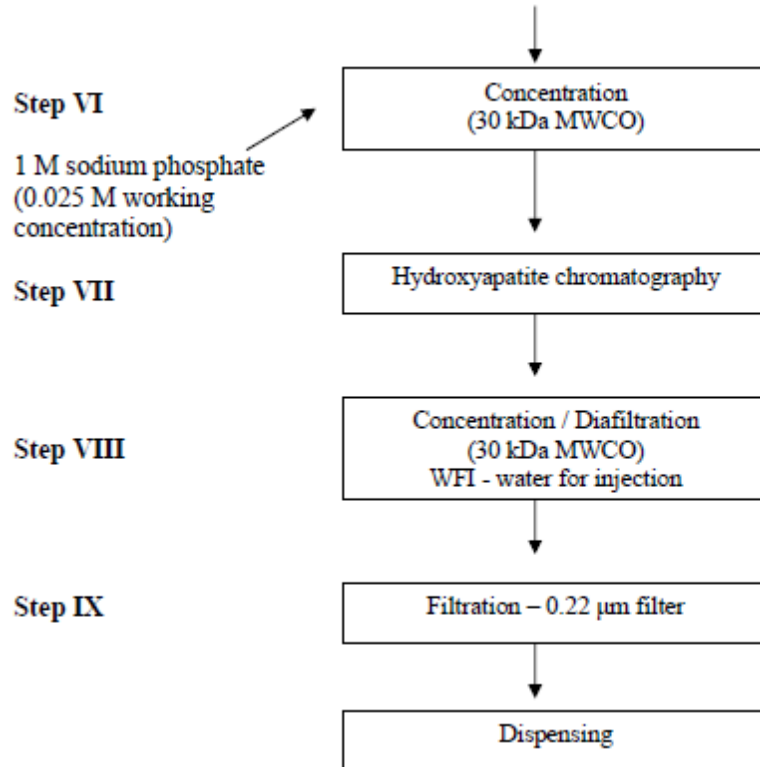


Figure 1-3 : Production Scheme for Plasmid Diphtheria CRM₁₉₇ Carrier Protein (CRM₁₉₇)
Fermentation and Harvesting

Step I
Primary Flask

One tertiary cell bank vial of *Corynebacterium diphtheriae* C7 (β197)/pPX3520 thaw at room temperature

Inoculate 2 flasks (CY medium)
Incubate at 32 ± 2 °C for 6 - 10 hours under agitation

In-process Tests:
Selective plating
Gram stain

Step II
Aspriator Bottle

Inoculate bottles (target 2) containing CY medium
Incubate at 32 ± 2 °C for 10 - 18 hours under agitation

In-process Tests:
Selective plating
Gram stain

Step III
Seed Fermentor

Pool 1 - 2 bottles of culture: inoculate 150 L fermentor containing CY medium
Incubate at 32 ± 2 °C for 4 - 10 hours

In-process Tests:
Selective plating
Gram stain

Step IV
Production Fermentor

Inoculate 1500 L production fermentor containing CY medium
Incubate at 32 ± 2 °C for 18 - 24 hours

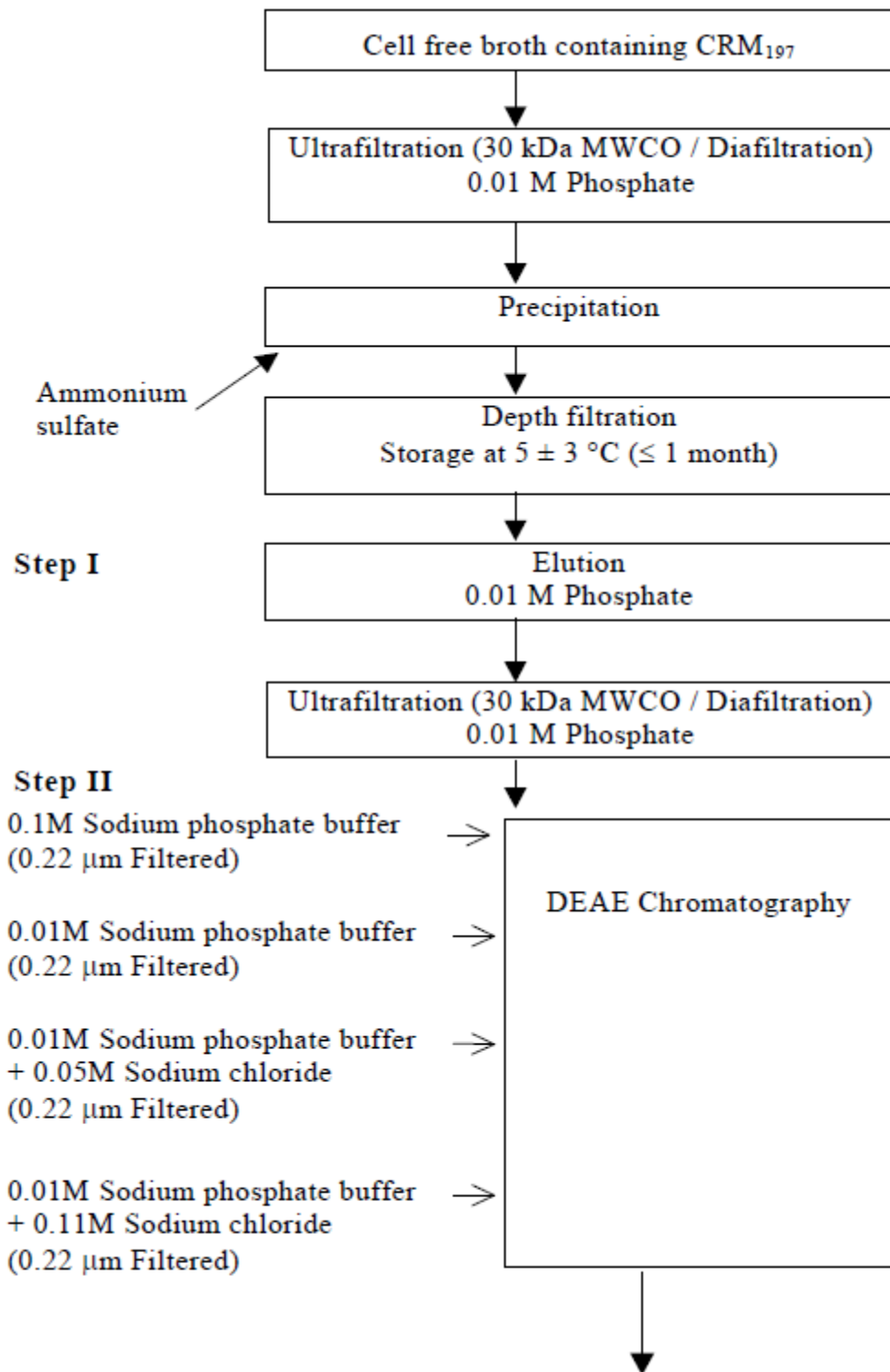
In-process Tests:
Selective plating
Gram stain
Latex agglutination test

Step V
Primary Flask

Transfer to harvest tank; separation of cells from broth by tangential filtration
Filtering of permeate through 0.22 μm filter

Purification

Figure 1-4 : CRM₁₉₇ Purification Process Flow Diagram



Step III

Concentration by Ultrafiltration (10 kDa MWCO)

In-process Test: Total protein

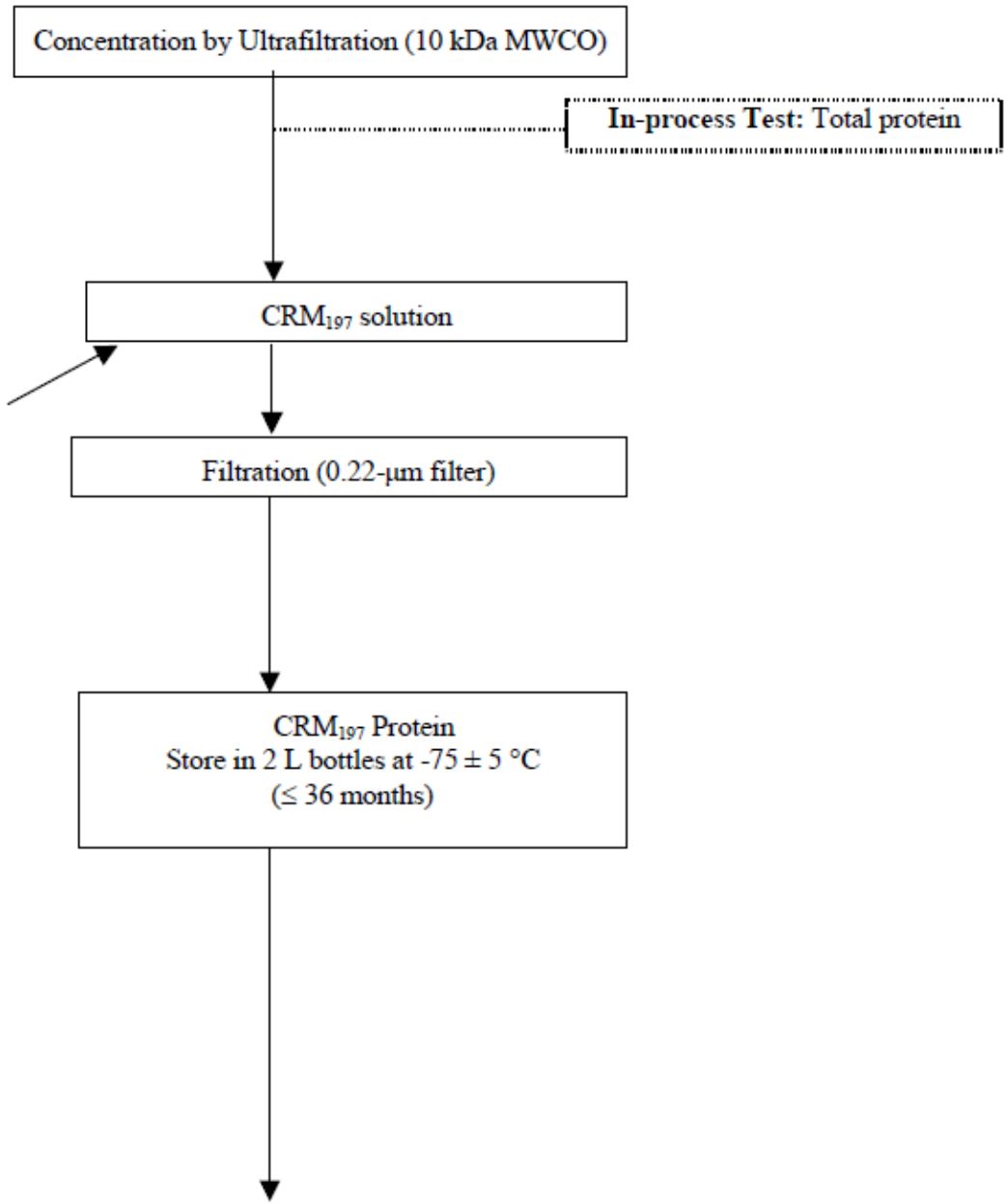
Step IV

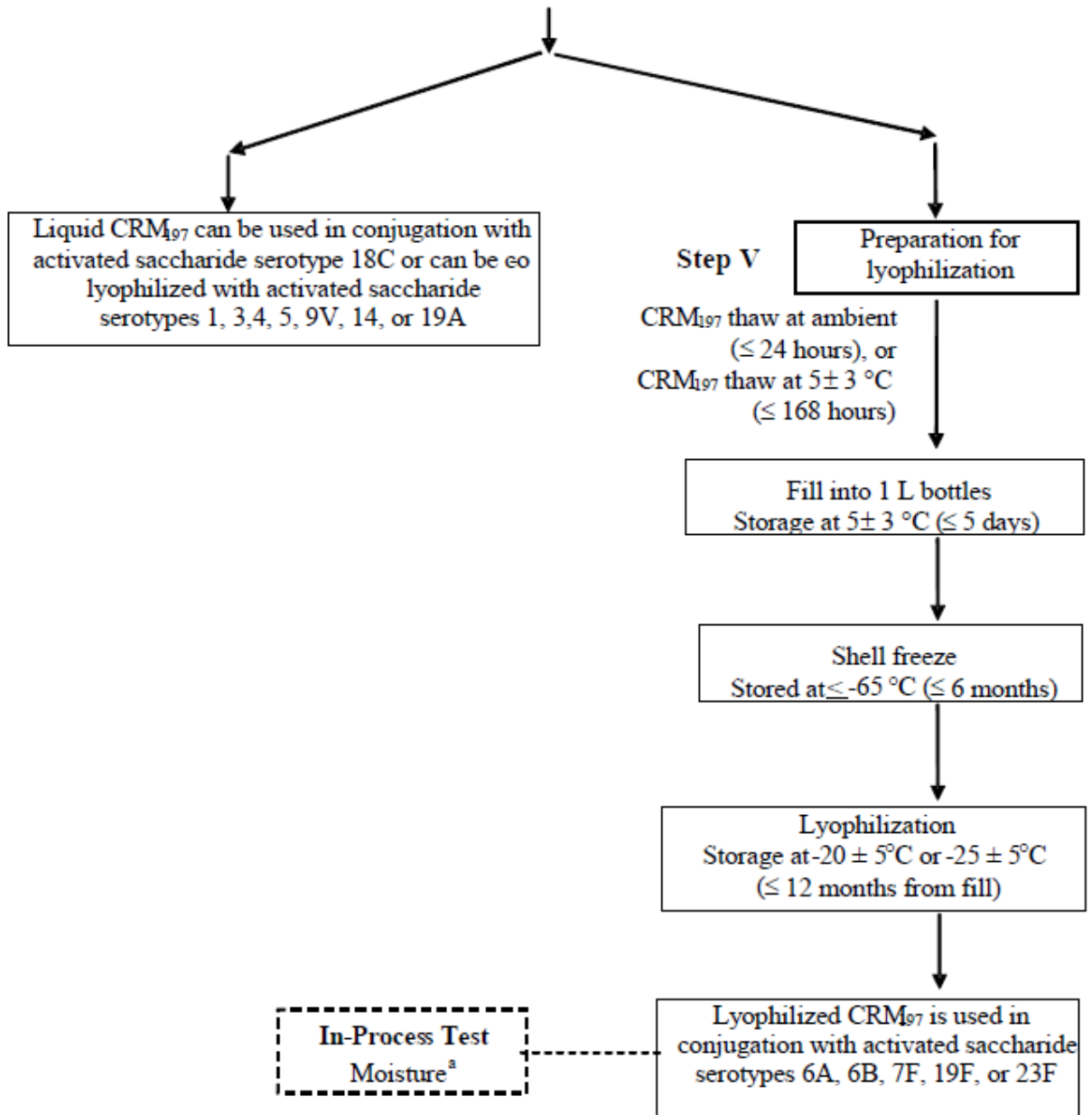
CRM₁₉₇ solution

Sucrose

Filtration (0.22- μ m filter)

CRM₁₉₇ Protein
Store in 2 L bottles at -75 ± 5 °C
(≤ 36 months)





a. This test is performed just prior to the start of the Conjugation process.

Note: Temperatures noted in Figure 1-1 refer to cooling system settings or cold room environment.

Activated saccharide: the details of each serotype are different but it could be summarized as followed: *Pneumococcal polysacchride Hydrolysis Oxidation Diafiltration Filtration Activate with CRM Dispensing Lyophilization*
 No information about the capacity of each steps.

3 Characterization of the Drug Substance(s)

As described in *1. General Information, Starting Materials and Raw Materials*

4 Quality Control of the Drug Substance(s)

Release and Stability Tests and Justification of Specification for Pneumococcal Saccharide-CRM₁₉₇ Conjugate

| Attribute | Method | Type specification Release | | | | | | | | | | | | |
|---|-------------------------------------|---|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | | 1 | 3 | 4 | 5 | 6A | 6B | 7F | 9V | 14 | 18C | 19A | 19F | 23F |
| Appearance | Visual Determination | Clear to moderately turbid and colorless to pale yellow | | | | | | | | | | | | |
| Endotoxin | LAL Kinetic | <0.75 EU/ μ g saccharide | | | | | | | | | | | | |
| Free Protein | HPLC | \leq 1% total Protein (w/w) | | | | | | | | | | | | |
| Free Saccharide (w/w) | Uronic acid | \leq 40% | \leq 25% | \leq 36% | \leq 42% | \leq 26% | \leq 20% | \leq 20% | \leq 35% | \leq 35% | \leq 20% | \leq 30% | \leq 20% | \leq 18% |
| Identity (Saccharide/CRM ₁₉₇) | Slot Blot | Positive for Serotype | | | | | | | | | | | | |
| Molecular Size % Saccharide \leq 0.3 Kd (CL-4B) | Size Exclusion Chromatography | \geq 50% | \geq 45% | \geq 40% | \geq 55% | \geq 60% | \geq 35% | \geq 65% | \geq 40% | \geq 50% | \geq 40% | \geq 50% | \geq 50% | \geq 35% |
| pH | pH electrode | 5.5 – 6.5 | | | | | | | | | | | | |
| Protein Concentration | Lowry | Calculation μ g/mL | | | | | | | | | | | | |
| Residual Cyanide pg/ μ g saccharide | Instrumental Cyanide Analyzer | \leq 1200 | \leq 700 | \leq 500 | \leq 600 | \leq 200 | \leq 200 | \leq 250 | \leq 925 | \leq 200 | \leq 200 | \leq 200 | \leq 250 | \leq 200 |
| Saccharide Concentration | Uronic Acid | \geq 350 μ g/mL | | | | | | | | | | | | |
| Saccharide to Protein Ratio | Calculation | 0.6 – 2.0 | 0.4 – 1.5 | 1.0 – 1.9 | 1.3 – 2.5 | 0.7 – 1.6 | 0.4 – 0.8 | 0.7 – 1.5 | 1.2 – 2.2 | 1.4 – 2.6 | 0.7 – 1.5 | 0.4 – 0.9 | 0.5 – 1.0 | 0.4 – 1.0 |
| % Soluble Protein | Lowry | 80 – 120% | | | | | | | | | | | | |
| Sterility | Membrane Filtration | Meets the requirements of the test, no growth observed | | | | | | | | | | | | |

| Attribute | Method | Type specification Stability | | | | | | | | | | | | |
|---|-------------------------------------|---|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | | 1 | 3 | 4 | 5 | 6A | 6B | 7F | 9V | 14 | 18C | 19A | 19F | 23F |
| Appearance | Visual Determination | Clear to moderately turbid and colorless to pale yellow | | | | | | | | | | | | |
| Endotoxin | LAL Kinetic | <0.75 EU/ μ g saccharide | | | | | | | | | | | | |
| Free Protein | HPLC | \leq 1% total Protein (w/w) | | | | | | | | | | | | |
| Free Saccharide (w/w) | Uronic acid | \leq 40% | \leq 25% | \leq 36% | \leq 42% | \leq 26% | \leq 20% | \leq 20% | \leq 35% | \leq 35% | \leq 20% | \leq 30% | \leq 20% | \leq 18% |
| Identity (Saccharide/CRM ₁₉₇) | Slot Blot | Positive for Serotype | | | | | | | | | | | | |
| Molecular Size % Saccharide \leq 0.3 Kd (CL-4B) | Size Exclusion Chromatography | \geq 50% | \geq 45% | \geq 40% | \geq 55% | \geq 60% | \geq 35% | \geq 65% | \geq 40% | \geq 50% | \geq 40% | \geq 50% | \geq 50% | \geq 35% |
| pH | pH electrode | 5.5 – 6.5 | | | | | | | | | | | | |
| Protein Concentration | Lowry | Calculation μ g/mL | | | | | | | | | | | | |
| Residual Cyanide pg/ μ g saccharide | Instrumental Cyanide Analyzer | \leq 1200 | \leq 700 | \leq 500 | \leq 600 | \leq 200 | \leq 200 | \leq 250 | \leq 925 | \leq 200 | \leq 200 | \leq 200 | \leq 250 | \leq 200 |
| Saccharide Concentration | Uronic Acid | \geq 350 μ g/mL | | | | | | | | | | | | |
| Saccharide to Protein Ratio | Calculation | 0.6 – 2.0 | 0.4 – 1.5 | 1.0 – 1.9 | 1.3 – 2.5 | 0.7 – 1.6 | 0.4 – 0.8 | 0.7 – 1.5 | 1.2 – 2.2 | 1.4 – 2.6 | 0.7 – 1.5 | 0.4 – 0.9 | 0.5 – 1.0 | 0.4 – 1.0 |
| % Soluble Protein | Lowry | 80 – 120% | | | | | | | | | | | | |
| Sterility | Membrane Filtration | Meets the requirements of the test, no growth observed | | | | | | | | | | | | |

Release and Stability Tests and Justification of Specification for Liquid (Frozen) CRM₁₉₇ and Lyophilized CRM₁₉₇

| Tests | Methods | Specifications | | | Rationale for Specification |
|---------------------------|--|-------------------------------------|-------------------------------------|---|---|
| | | Release | Liquid (Frozen) Stability | Lyophilized Stability ^a | |
| Appearance | Visual Determination | Clear, colorless to slightly yellow | Clear, colorless to slightly yellow | Dry, white to off-white: granular to fibrous | Precipitation or significant color change may be indicative of aggregation, degradation or contamination. Levels of color are set to ensure consistency with clinical, production and stability experience. Discoloration of the presence of a wet cake may indicate contamination or excessive moisture. Description is consistent with clinical, production, and stability experience. |
| Appearance, Reconstituted | Visual Determination | N/A ^b | N/A | Clear, colorless to slightly yellow | Precipitation or significant color change may be indicative of aggregation, degradation or contamination. Levels of color are set to ensure consistency with clinical, production and stability experience. |
| Bioburden ^c | Membrane filtration | < 1 CFU / 25 mL | < 1 CFU / 25 mL | N/A | Specification limit is consistent with the sterility test specification of 'Meets the requirements of the test, no growth observed'. |
| DNA Content | Fluorimetric Assay | ≤ 1.0% | N/A | N/A | Limit is consistent with the historical specification for DNA content during clinical development and with process and analytical test capability. |
| Endotoxin Quantitation | Limulus Amebocyte Lysate (LAL) Kinetic-Turbidimetric Assay | < 1.0 EU/μg protein | < 1.0 EU/μg protein | N/A | Assay and specified limit required by Ph.Eur. (2150). |

| Tests | Methods | Specifications | | | Rationale for Specification |
|-------------------------------------|--|--|--|------------------------------------|--|
| | | Release | Liquid (Frozen) Stability | Lyophilized Stability ^a | |
| Enzymatic Activity | Detection of CRM ₁₉₇ toxicity | ≤ 0.0135% | N/A | N/A | Specification is supported by process capability and is well below the limit of safety concern. |
| Moisture | Coulometric Karl Fischer Titration | N/A | N/A | ≤ 7% (w/w) | Ensures material consistency for stability considerations |
| Identity (Latex Agglutination Test) | Identification of CRM ₁₉₇ | Positive | N/A | N/A | Confirms the presence of CRM ₁₉₇ protein. |
| Protein Content | Lowry assay method | ≥ 3 mg/mL | ≥ 3 mg/mL | Calculation (mg/mL) | Specification is supported by process capability as evaluated by the tolerance interval calculation and supports requirements for downstream processing. |
| | | | | | Assay required to test purity and % soluble protein. There is no quantitative specification for protein content. |
| Purity Test | Size exclusion HPLC | ≥ 95% | ≥ 95% | ≥ 95% | Specification is supported by clinical experience and process capability as evaluated by the tolerance interval calculation. |
| % Soluble Protein | Lowry assay method | N/A | N/A | 80 – 120% | Limits are consistent with the historical specification for % soluble protein during clinical development and with process and analytical test capability. |
| Sterility Test | Membrane filtration | Meets the requirements of the test, no growth observed | Meets the requirements of the test, no growth observed | N/A | Assay and specified limit required by Ph.Eur. (2150). |

a. Lyophilized CRM197 is derived from released liquid (frozen) CRM197

b. Not applicable

c. The Bioburden testing will be implemented as a release and stability specification once verification of the test according to the compendial requirements is completed. In the transition period, Sterility results will be used to confirm the ability of the material to meet the Bioburden specification

5 *Reference Standards or Materials*

The reference standard is a formulation consisting of the 13 Pneumococcal conjugates present in the 13vPnC vaccine. It is prepared using monovalent bulk conjugates (MBCs) manufactured and tested according to commercial manufacturing and testing requirements. (Stability as described in **7. Stability of the Drug Substance(s)**)

6 *Packaging and Container Closure System of the Drug Substance(s)*

Pneumococcal Polysaccharide is dispensed into 50 L stainless steel containers.

The 50 L container closure system is comprised of five major components.

The five major components are:

1. 50 L Stainless Steel vessel
2. Head plate
3. Inlet dip tube
4. Outlet dip tube
5. Silicone o-ring

The 50 L container closure system holds Pneumococcal Polysaccharide in a closed system.



7 *Stability of the Drug Substance(s)*

Real time study at 2-8°C, $-25 \pm 5^\circ\text{C}$ and $-20 \pm 5^\circ\text{C}$

Accelerated storage condition at $25 \pm 2^\circ\text{C}/60\pm 5\%\text{RH}$, $40\pm 2^\circ\text{C}$

The supported stability data has presented.

Proposed shelf life:

1. **Purified Pneumococcal Polysaccharide**

36 months at $-20 \pm 5^\circ\text{C}$ for serotype 1,6B,7F,14

24 months at $-20 \pm 5^\circ\text{C}$ for serotype 3, 5, 6A, 9V, 18C, 19A, 19F, 23F

18 months at $-20 \pm 5^\circ\text{C}$ for serotype 4

2. **Activated saccharides:** 18 months at $-20 \pm 5^{\circ}\text{C}$ except serotype 13 (12 months)
3. **Lyophilized Diphtheria CRM₁₉₇ carrier protein:** 12 months at $-25 \pm 5^{\circ}\text{C}$
4. **Pneumococcal Polysaccharide MBC:** 24 months at $2-8^{\circ}\text{C}$

II. DRUG PRODUCT

1 *Description and composition of the Drug Product*

13-Valent Pneumococcal Conjugate (13vPnC) vaccine is a sterile liquid suspension of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid-derived Diphtheria CRM₁₉₇ protein. The vaccine contains 2.2 µg/dose of each of the serotypes, except for serotype 6B at 4.4 µg/dose. The vaccine is formulated in 5 mM succinate buffer containing 0.85% NaCl and 0.02% polysorbate 80, at pH 5.8, and contains aluminum phosphate at 0.125 mg/dose aluminum, as an adjuvant. Each 1 mL syringe contains a single 0.5 mL dose of vaccine for intramuscular administration, with no preservative.

2 *Pharmaceutical Development*

Drug Substances

The stability data demonstrate that each of the thirteen conjugates maintains its antigenicity, as measured by nephelometry, within specifications throughout expiration dating in the final filled syringes.

Three 13vPnC formulations were prepared and evaluated for protein and conjugate binding to aluminum phosphate: at a low level of 2.2 µg/mL for each of the conjugates except 6B at 4.4 µg/mL; at the target level of 4.4 µg/mL for each of the conjugates except 6B at 8.8 µg/mL; and at the high level of 6.6 µg/mL for each of the conjugates except 6B at 13.2 µg/mL.

CRM₁₉₇ was chosen as the carrier protein for the 13vPnC vaccine based on previous Wyeth experience with CRM₁₉₇ in the *Haemophilus influenzae* type b polysaccharide vaccine (HibTITER®), the *Neisseria meningitidis* type C polysaccharide vaccine (Meningitec®), and the 7-valent Pneumococcal Polysaccharide vaccine (Prennar)

Multiple conjugation methods were originally explored in the development of the 7vPnC vaccine. The approach chosen for this vaccine and the 13vPnC vaccine

comprises oxidation of the polysaccharide followed by reductive amination of the activated oligosaccharides or polysaccharides to the CRM₁₉₇ carrier protein. Reductive amination of oligosaccharides to CRM₁₉₇ was also used in the Haemophilus b conjugate vaccine (HibTITER®) and in the N. meningitidis type C vaccine (Meningitec®). The activation of the polysaccharides is accomplished by the partial oxidation of adjacent (vicinal) hydroxyl groups in the carbohydrate repeat units using sodium periodate or (for Serotype 3) periodic acid. The conjugation reaction is performed in DMSO for Serotypes 6A, 6B, 7F, 19A, 19F and 23F and in an aqueous medium for Serotypes 1, 3, 4, 5, 9V, 14 and 18C.

The excipients in the 13vPnC vaccine are 5.0 mM succinate, 0.85% NaCl buffer, pH 5.8 (succinate/saline buffer), 0.02% polysorbate 80, and aluminum phosphate at 0.25 mg/mL aluminum.

The succinate/saline buffer (Pevnar does not contain succinate buffer) was added to the formulation to provide pH control and suitable osmolality. Succinate was chosen based on its ability to provide adequate buffering capacity with minimal impact to the binding of the conjugates to the aluminum phosphate.

The effect of pH on conjugate binding to aluminum phosphate was evaluated over the final product acceptance range of pH 5.8 ± 0.5.

Polysorbate 80 (Pevnar does not contain polysorbate 80) was added at 0.02% (w/v) to prevent loss of antigenicity resulting from both protein aggregation at air-liquid interfaces and from aggregation/degradation associated with exposure to the silicone present in the container/closure system. Concentrations of polysorbate 80 ranging from 0.01% – 0.05% were effective in preventing protein and antigenicity loss resulting from agitation of the product in the final filled syringes.

Aluminum phosphate was added as an adjuvant to enhance immunogenicity. The effect of aluminum phosphate concentration on conjugate binding was evaluated over the final product aluminum phosphate acceptance range of 0.25 ± 0.05 mg/mL aluminum. At aluminum phosphate concentrations over this range, there was significant binding of each of the conjugates to the aluminum phosphate.

Drug Product

Two formulation were tested in clinical trials.

[REDACTED]

Physicochemical and Biological Properties

The antigenicity of the vaccine is tightly controlled between 70% and 130% of the target value for each of the conjugates, specifically $4.4 \pm 1.3 \mu\text{g/mL}$ for all serotypes except 6B, at $8.8 \pm 2.6 \mu\text{g/mL}$.

Manufacturing Process Development

1. Changes to the manufacturing process through clinical trial development to commercial manufacture
2. Safety testing of the container closure components, including toxicity testing of extractables, was performed.
3. Development studies were performed to establish normal operating ranges (NOR) and proven acceptable ranges (PAR) for each of the unit operations used to formulate and fill the 13vPnC vaccine for commercial distribution
4. The $0.22 \mu\text{m}$ filter used for the sterile filtration of the conjugate pool has been validated for microbial retention, extractables, and product compatibility
5. Safety testing of the container closure components, including toxicity testing of extractables, was performed

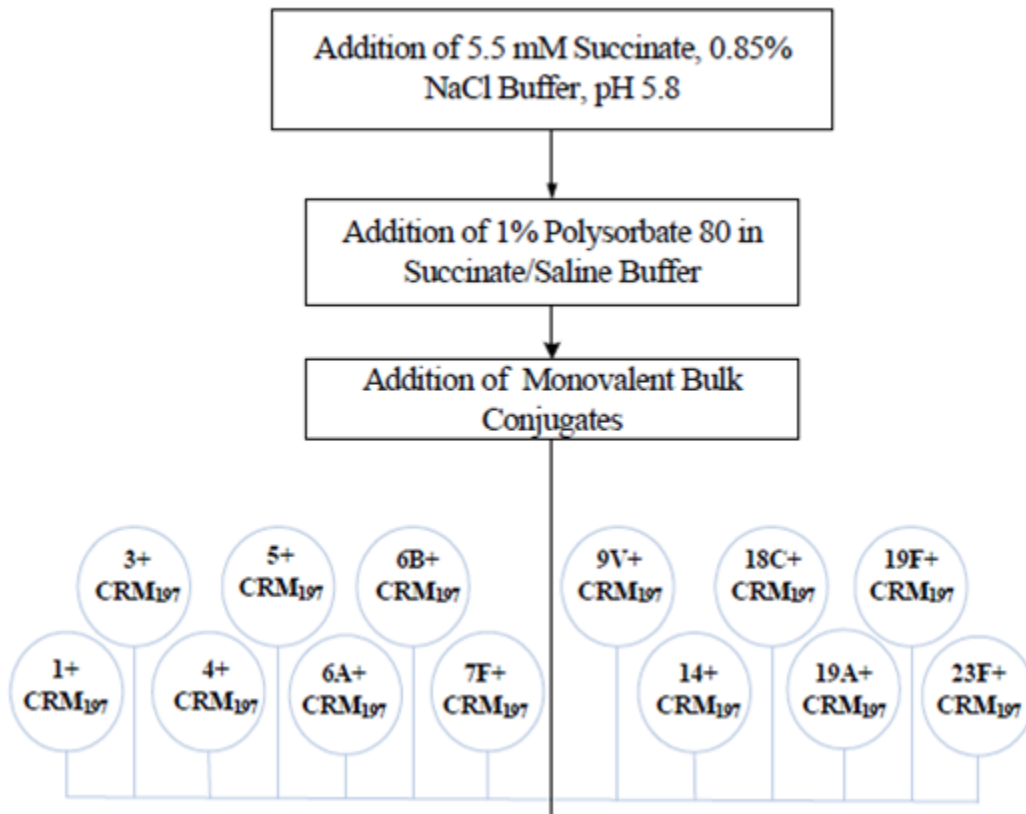
3 Manufacturing Process of the Drug Product

The vaccine for commercial distribution is formulated and filled at Wyeth in Pearl River, New York, USA, and at Baxter Pharmaceutical Solutions, LLC in Bloomington, Indiana, USA. Final product testing is performed at Wyeth, Grange Castle, Ireland, and final labeling and packaging is performed at Wyeth Havant, United Kingdom.

Manufacturing Process Step:

1. Preparation of 5.5 mM succinate, 0.85% NaCl buffer, pH 5.8 (succinate/saline buffer).
2. Preparation of 1% (w/v) polysorbate 80 in succinate/saline buffer, pH 5.8.
3. Pooling and dilution of the monovalent bulk conjugates.
4. Sterile filtration of the conjugate pool through a $0.45 \mu\text{m}$ pre-filter and two $0.22 \mu\text{m}$ filters.
5. Aseptic addition of sterile aluminum phosphate (AlPO_4).
6. Filling the bulk vaccine into 1mL syringes.
7. Inspection of the filled syringes.
8. Finishing operations, consisting of labeling, packaging and shipping of the syringes for commercial distribution.

Figure 1-5: Formulation of 13vPnC Bulk Vaccine



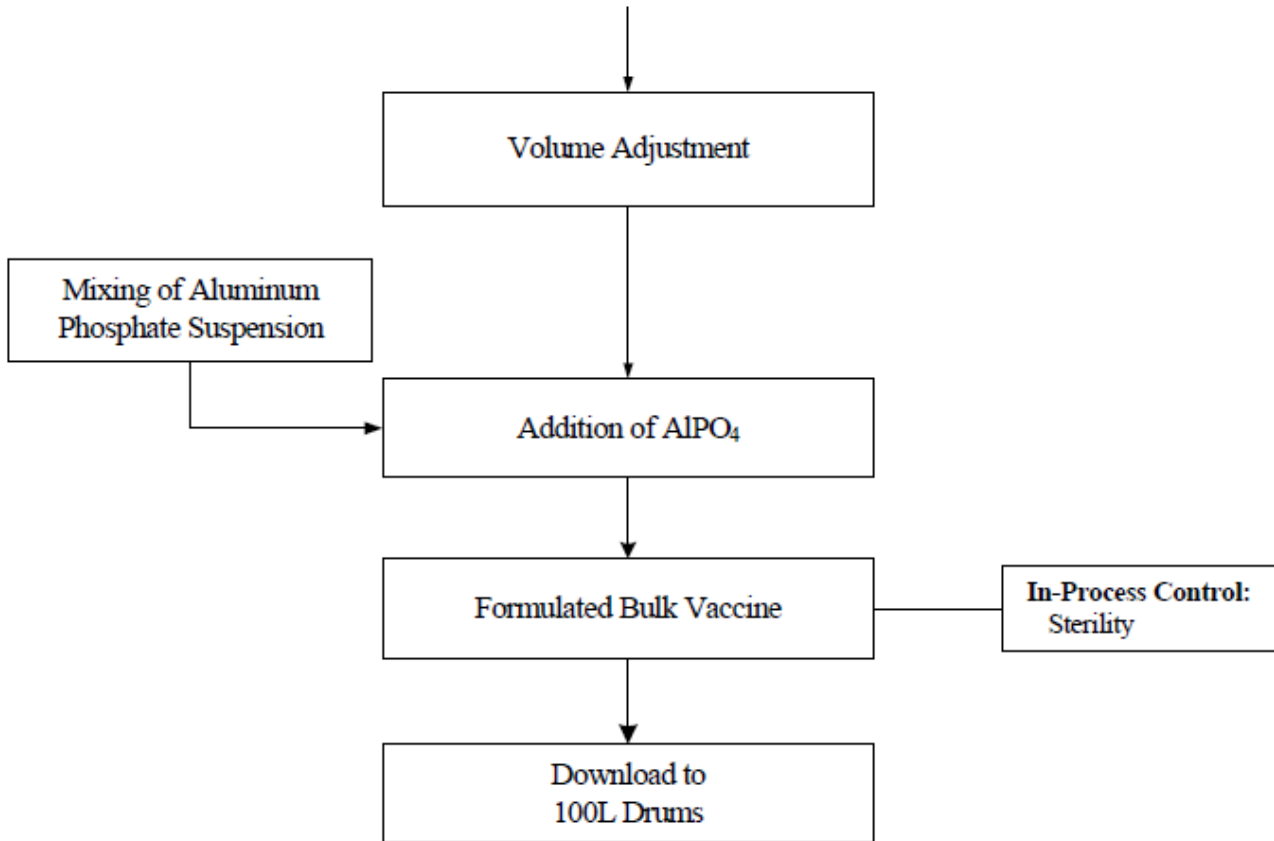
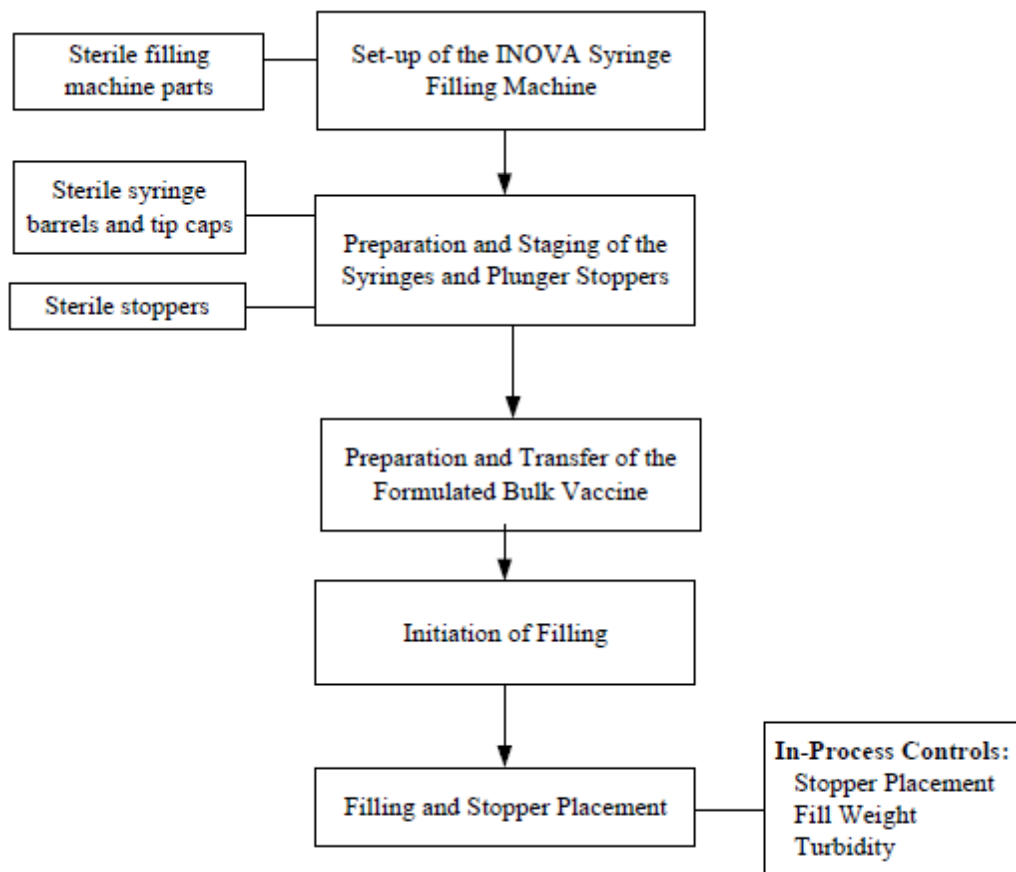


Figure 1-6 Syringe Filling Process Flow Chart



4 Control of the Adjuvant(s), Preservative(s), Stabilizer(s), and Excipients(s)

In-Process Control Tests for Succinate/Saline Buffer

| In-Process Control Test | Control Range |
|-------------------------|------------------------|
| Succinate concentration | 4.0 - 7.0 mM Succinate |
| NaCl concentration | 0.81 – 0.89% NaCl |

Specifications of Compendial Excipients

| Excipient | Quality Specifications |
|---------------------|------------------------|
| Sodium Chloride | USP; Ph.Eur.; JP |
| Succinic Acid | NF |
| Polysorbate 80 | NF; Ph.Eur.; JP |
| Water for Injection | USP/NF; Ph.Eur. |

Release and Stability Specifications for AlPO₄

| Tests | Methods | Specifications | | Justification |
|------------------|---|---|---|--|
| | | Release | Stability | |
| Aluminum Content | Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) | 2.8-3.6 mg/mL aluminum | NA ^a | The specification is based on process capability as confirmed by a statistical analysis. |
| Description | Visual Inspection | Turbid, white suspension free from evident clumps after shaking | Turbid, white suspension free from evident clumps after shaking | A change in description may be indicative of a change to AlPO ₄ quality. |
| Particle Size | Laser Diffraction Analysis | D[v,0.1]: ≥ 2.0 μm D[v,0.5]: 4.5-6.4 μm D[v,0.9]: ≤ 22.0 μm | NA ^a | The specification is based on process capability as confirmed by a statistical analysis. |
| pH | Standardized pH Meter | 5.6-6.0 | 5.4-6.0 | A change in pH may indicate a change in AlPO ₄ characteristics. |
| Sterility | Direct Inoculation | Meets the requirements of the test. No growth observed. | Meets the requirements of the test. No growth observed. | Sterility is required as AlPO ₄ is added as a component directly to a sterile drug product. |

a. Not Applicable.

5 Quality Control of the Drug Product

13vPnC drug product complies with the Ph. Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) (2150)

| Tests | Methods | Specifications | | Justification |
|--------------------------------|--|--|---|---|
| | | Release | Stability | |
| Formulated Bulk Vaccine | | | | |
| Sterility | Direct Inoculation | Meets the requirements of the test. No growth observed | NA ^a | The specification meets the requirements of Ph.Eur. (2150) and USP <71>. |
| Filled Syringes | | | | |
| Aluminum | Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) | 0.25 ± 0.05 mg/mL | NA ^a | The specification is based on the current Prevenar specification and is supported by development studies and by the tolerance interval calculation from manufacturing experience. The specification meets the requirements of Ph.Eur. (2150). |
| Antigenicity | Nephelometry (immunoassay) | 4.4 ± 1.3 µg/mL for all serotypes except Serotype 6B at 8.8 ± 2.6 µg/mL | 4.4 ± 1.3 µg/mL for all serotypes except Serotype 6B at 8.8 ± 2.6 µg/mL | The specification is ± 30% of the target value. This specification is required by Ph.Eur. (2150). |
| Appearance | Visual Inspection | Homogeneous, white suspension | Homogeneous, white suspension | A change in the appearance is indicative of product quality change. |
| Endotoxin | Limulus Amebocyte Lysate (LAL) Kinetic – Turbidimetric | ≤ 12.5 EU/mL | ≤ 12.5 EU/mL | The specification is required by Ph.Eur. (2150). |
| Identity, CRM ₁₉₇ | Slot Blot | Positive for CRM ₁₉₇ protein | NA ^a | The specification confirms the presence of CRM ₁₉₇ in the formulation. |
| Identity, Polysaccharide | Slot Blot | Positive for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F | NA ^a | The specification confirms the presence of polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in the formulation. |
| pH | Standardized pH Meter | 5.8 ± 0.5 | 5.8 ± 0.5 | A change in pH can affect product characteristics such as binding. This specification is supported by process capability as confirmed by tolerance interval calculation. |

| Tests | Methods | Specifications | | Justification |
|--|----------------------|---|---|---|
| | | Release | Stability | |
| Polysorbate 80 | RP-HPLC | 0.014 – 0.024% | NA ^a | Polysorbate 80 is used as a surfactant to stabilize the formulation in the final container. The specification limits are based on the results obtained with lots used in clinical trial testing, with the limits expressed to three decimal places, with the third decimal place value being the maximum value that would be rounded down to the results reported |
| Protein - Total | Modified Lowry Assay | 43.0 – 86.0 µg/mL | 43.0 – 86.0 µg/mL | The specification is established to determine total carrier protein concentration of the drug product. This specification is supported by production experience and shows minimum risk based on the tolerance interval calculation. |
| Protein - Bound (%) | Modified Lowry Assay | ≥ 70% | ≥ 70% | The specification is established to determine conjugate binding to adjuvant. The tolerance interval calculation recommended a specification of ≥ 61% bound protein. Manufacturing experience supports the specification of ≥ 70%. |
| Sterility | Direct Inoculation | Meets the requirements of the test. No growth observed. | Meets the requirements of the test. No growth observed. | The specification meets the requirements of Ph.Eur. (2150) and USP <71>. |
| Volume of Injection / Extractable Volume | Weight measurement | ≥ 0.5 mL | NA ^a | The volume of injection/extractable volume is determined to ensure that the volume contained in each final syringe meets or exceeds the volume stated within the label claim for 13vPnC vaccine. The method and specification comply with USP <1> and Ph.Eur. (2.9.17). |

a. NA: not applicable

Analytical Procedures

| Method | Principle |
|---|--|
| Aluminum | Quantitation of aluminum is performed by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES). With ICP-OES, the intensity of the emitted light at predetermined wavelengths is proportional to the concentration of the element unique to these wavelengths. The computer uses a calibration curve to convert the intensity measured in voltage to a value representing the actual concentration of the element. |
| Antigenicity | Rate nephelometry is used to determine the total antigenicity of individual serotypes present in the 13vPnC drug product samples. Rate nephelometry is based on the measurement of light scattering resulting from immunoprecipitation of antigen and antibody at optimal concentrations. The amount of light scattered at a certain concentration of antibody is proportional to the concentration of antigen. Standard curves are generated for all 13 serotypes using a 13-valent standard prepared in a matrix similar to the sample. The concentrations of the samples are determined by linear regression analysis. |
| Appearance | The appearance test method is used to determine the color and opalescence of drug product samples. The assay is performed by visual examination of the test samples in comparison to established standards with acceptable color and opalescence. Observations for color and opalescence are determined under diffuse overhead fluorescence light against white and black backgrounds, respectively. |
| Endotoxin | Endotoxin concentration is determined by the kinetic turbidimetric limulus amoebocyte lysate method. The assay complies with Ph.Eur. (2.6.14) and USP <85> requirements. |
| Identity (Saccharides and CRM ₁₉₇ protein) | The slot blot assay is used to confirm the presence of each of the 13 pneumococcal polysaccharide serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) and CRM ₁₉₇ protein in 13vPnC drug product samples, using type-specific antibodies prepared for each antigen. The method is based on the binding of antibodies to unique epitopes on the polysaccharides and protein. 13vPnC samples are applied to a nitrocellulose membrane, incubated with specific antibodies, and detected using an antibody binding reagent and detection system. Positive identification is the development of purple bands significantly darker than the negative controls. A negative result remains white or exhibits faint bands considerable lighter than positive bands. |
| pH | pH is determined using a pH meter. The assay complies with Ph.Eur. (2.2.3) and USP <791> requirements. |
| Polysorbate 80 | Polysorbate 80 (polyoxyethylene sorbitan monooleate) concentration in 13vPnC drug product samples is determined by HPLC. Samples are hydrolyzed to release oleic acid, which is quantitated by the HPLC analysis. The oleic acid elutes as a single peak that is easily separated from other components and detected by UV spectrophotometry at 200 nm. A standard curve is used to determine percent polysorbate 80. |

| Method | Principle |
|--|--|
| Protein – Total and Bound | <p>A modified Lowry procedure is used to determine the protein concentration in 13vPnC drug product samples. The method is based on the reaction of peptidic nitrogens with copper, under alkaline conditions, followed by reaction with Folin-Ciocalteu phenol reagent. The reduction of the phenol reagent produces a deep blue color, measured at 750 nm, which is proportional to protein concentration.</p> <p>To measure the amount of protein bound to aluminum phosphate, the sample is centrifuged, the supernatant is removed, and an equivalent volume of buffer is added to the pellet, which contains the bound protein. The bound protein is then measured by the modified Lowry method and compared to the total protein in the sample.</p> |
| Sterility | Sterility is determined using the Direct Inoculation method. The assay complies with Ph.Eur. (2.6.1) and USP <71> requirements. |
| Volume of Injection / Extractable Volume | Volume of Injection / Extractable Volume is determined by weighing the 13vPnC vaccine expelled from individual syringes. The assay complies with Ph.Eur. (2.9.17) and USP <1> requirements. |

6 Reference Standards and Materials

A reference standard for the Nephelometry assay is the only reference standard or material used for testing 13vPnC Drug Product. The reference standard is used in the Nephelometry assay to prepare a standard curve for quantitation of the antigenicity of each of the individual conjugates in the formulated vaccine.

The reference standard is a formulation consisting of the thirteen pneumococcal conjugates present in the 13vPnC vaccine. It is prepared using monovalent bulk conjugates (MBCs) manufactured and tested according to commercial manufacturing and testing requirements. The reference standard is re-qualified initially at an established time point based on the previous standard, and then e-qualified annually.

7 Packaging and Container Closure System of the Drug Product

The container closure system for the 13vPnC vaccine is a 1 mL type 1 botosilicate glass syringe with latex-free rubber tip cap, sealed with a latex-free rubber stopper. The syringe presentation includes the following non-product contact components: plunger rod, backstop, and plastic rigid tip cap (PRTC) overseal.

A 25G x 5/8" (0.5 x 16 mm) or 25G x 1" (0.5 x25 mm) needle may be included in the outer carton of the syringe package.

8 Stability of the Drug Product

1. Wyeth (3.2.P.3.5 Process Validation and /or Evaluation – Pearl River, Process Validation of 13vPnC Formulation at Pearl River)

Maximum Hold Times During 13vPnC Formulation

| Stage | Maximum Hold Time |
|---|--|
| 5.5 mM Succinate, 0.85% NaCl Buffer, pH 5.8 | 15 hours at room temperature (prior to starting formulation) |
| Conjugate Pool | 20 hours at room temperature (prior to sterile filtration) |
| Formulated Bulk Vaccine | 19 hours prior to download to the 100L drums 24 hours at room temperature, followed by 14 days at 2-8 °C (prior to filling) |

2. Baxter (3.2.P.3.5 Process Validation and /or Evaluation – Baxter, Process Validation of 13vPnC Formulation at Baxter)

Maximum Hold Times During 13vPnC Formulation

| Stage | Maximum Hold Time |
|---|--|
| 5.5 mM Succinate, 0.85% NaCl Buffer, pH 5.8 | 72 hours at room temperature (prior to starting formulation) |
| Conjugate Pool | 20 hours at room temperature (prior to starting formulation) |
| Formulated Bulk Vaccine | 24 hours at room temperature, followed by 4 days at 2-8°C (prior to filling) |

Recommended storage condition of final lot: 24 months at 2-8°C, and 6 months at 25±2°C/60 ±5%RH

3.2.P.8.1. *Stability Summary and Conclusion*, 3.2.P.8.3 *Stability data*, the data demonstrate that 13vPnC is stable through:

Thermal cycling of three periods of 2-4 days storage each at 2-8°C and at 25°C , followed by long-term storage at 2-8°C

Thermal cycling of three periods of 2-4 days storage each at -5°C and at 25°C , followed by long-term storage at 2-8°C

Storage at 25°C for 1 month , followed by long-term storage at 2-8°C
Thermal stress at 40°C for 28 days, with decreasing serotype 19A levels beyond 7 days
exposure.

ICH requirement for photo stability.

III. APPENDICES

The following information may be needed on a case by case basis.

1 *Equipment and Facilities*

1. **Polysaccharide Manufacturing:**

Pearl River: Type 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F

Andover: Type 1, 3, 5, 6A, 19A

Manufacture, Quality control testing, release and stability testing

Sanford, NC: Cell bank storage, Quality control testing including release and stability testing of pneumococcal cell banks, Alternate site for performing anthrone and residual protein testing of pneumococcal polysaccharides

Contract cell bank storage facility: Fisher BioServices, Lofstrand Land, Rockville, United States

Contract Testing Laboratory:

BioReliance Corp.: sterility test

Spectral Data Services, Inc.: NMR test

2. **CRM197 (*Corynebacterium diphtheriae* C7(β 197)/pPX3520 (plasmid CRM197))Manufacturing:**

Wyeth Sanford, NC (Manufacturing, Cell bank storage, Quality Control testing including release and stability testing of CRM197) **Contract cell bank storage facility** :Fisher BioServices, Lofstrand Land, Rockville, United States

3. **Conjugate Manufacturing:** Manufacturing, Quality Control testing including release and stability testing

Sanford B101: Type 4, 14, 18C, 23F

Sanford B110: Type 3, 6B, 9V, 19A

Grange Castle Ireland: Type 1, 5, 6A, 7F, 19F

Contract Sterility Testing Laboratory: Molecular Epidemiology

4. **Fill and Formulation:**

Wyeth, Pearl River, NY: AlPO4 manufacture 13vPnC vaccine formulation and syringe filling Quality control testing of AlPO4 and Drug Product syringes including stability testing

Baxter Healthcare (Bloomington, IN): 13vPnC vaccine formulation and syringe filling Quality control testing of Drug Product syringes

Wyeth Medica Ireland Grange Castle Business Park: Release testing of Drug Product syringes

Contract Testing Site: International Laboratory Services Ltd: sterility testing site for release of Drug Product syringes

5. **Labeling and packaging:** Wyeth, Havant, UK

6. **QP Release:** Wyeth, Havant, UK

2 *Evaluation of the Safety of Adventitious Agents*

The animal derived ingredients used in 13vPnC production are excluded from the scope of the October 2003 revision to the TSE guideline. Nevertheless, Wyeth has been vigilant in assuring proper use and control of animal derived materials by :

- Working with our suppliers to collect the most up-to-date information on animal derived materials used in our process;
- Working with the United States Drug Administration (USDA) for updates on regulations and practices to control TSE in the US;
- Working with other agencies worldwide, including the Committee for Medicinal Products for Human Use (CHMP), when needed, to keep abreast of any changes in compliance expectations.

The TFDA recommended on the Quality Dossiers as The followings:

1. Drug Substance
 - Cell Bank Characterization (ทั้ง Cell bank for Pneumococcal Polysaccharide production และ CRM₁₉₇ production ให้แนบบวิธี Genotype identify test ทั้ง test method, method validation และ data of testing)
 - Raw material ทั้งที่สำหรับ Cell bank process เช่น Soy, L-Cysteine HCl, Phenol red etc, รวมถึง Raw material ที่ใช้ใน Pneumococcal Polysaccharid fermentation and purification เช่น Sodium Deoxycholate, HB reagent etc และ Raw material ที่ใช้ในการสังเคราะห์ CRM₁₉₇ รวมถึง aluminium phosphate suspension ในกรณีที่เป็น non-compendial specification ขอให้แนบ CoA จาก supplier ด้วย
 - ให้แนบ CoA of Aluminium Phosphate suspension ไว้ใน แฟ้ม C19/19
 - Stability of Drug Substance แฟ้ม C1/19 ข้อ 2.5 conclusion: Stability ของ activated saccharide serotype 1 ให้แก้ไข recommended long term storage condition จาก 20+/- 5°C เป็น -20+/-5 °C
 - อธิบายระบบการกำหนด batch numbering และ batch size เนื่องจากเอกสารระบุ consecutive แต่เลขที่แสดงไม่ต่อเนื่องกัน
 - แจ้งคุณลักษณะและขนาดcontainer สำหรับ Pneumococcal polysaccharide MBC
 - แจ้ง batch size ของ Activated Pneumococcal polysaccharide
 - แสดงรายละเอียด MBC lot ที่ใช้เป็น reference standard การกำหนด control range value การกำหนดหมายเลข lot no. การเก็บรักษา ผลการใช้งาน (trend analysis)
 - ขอให้จัดตารางสรุป (Test, Method, Specification) ใน ภาพรวมของการควบคุมคุณภาพ drug substance ทั้ง 13 serotype โดยแยก

ตารางตามหัวข้อดังนี้

- 1.1 Release test and Characterization ของ Master cell Bank
- 1.2 Release test and Characterization ของ Working cell Bank
- 1.3 Release and Stability Tests and Justification of Specification for Pneumococcal polysaccharide
- 1.4 Release and Stability Tests and Justification of Specification for Activated Saccharide
- 1.5 Release and Stability Tests and Justification of Specification for Pneumococcal Saccharide-CRM₁₉₇ Conjugate
 - ขอ SOP determination of molecule weight average by SEC-MALLS, SOP determination of dry weight, SOP determination of free protein by SE-HPLC, SOP determination of residual nucleic acid, SOP determination of residual protein
2. Drug Product
 - ชื่อยาใน Certificate of a Medicinal Product เป็น Prevenar 13 ไม่ตรงกับชื่อยาที่แจ้งในเอกสารอื่นๆใช้เป็น Prevnar 13
 - อธิบายรายละเอียด batch formulation อย่างละเอียดทุกขั้นตอน
 - อธิบายระบบการกำหนด batch numbering และ batch size

เนื่องจากเอกสารระบุ consecutive แต่เลขที่แสดงไม่ต่อเนื่องกัน

- แสดง stability data ในส่วนของการศึกษาที่แจ้งว่า pending ใน

เอกสาร 3.2.P.8.1 Stability Summary and Conclusion

- ขอ SOP ของทุกการทดสอบใน final container

The company responded to the above recommendations as the followings:

All documents were submitted as recommended

TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON QUALITY ASPECTS

In conclusion data and information submitted for evaluation support good quality of product appropriate for marketing authorization.

BASED ON THE RESULTS THESE QUALITY ASPECT COULD BE ACCEPTED

2.3 Non Clinical aspects

Introduction

Prevnar 13 ประกอบด้วย pneumococcal capsular Polysaccharides ของ 13 serotypes แต่ละ

serotype conjugated กับ Diphtheria CRM₁₉₇ protein และมี Aluminum phosphate เป็น adjuvant ขึ้นทะเบียน เป็น vaccine สำหรับ active immunization สร้างภูมิคุ้มกันต่อโรคที่เกิดจาก *Streptococcus pneumoniae* serotype ทั้ง 13 ชนิด ในเด็กตั้งแต่ 2 เดือน ถึง 5 ปี

I. PHARMACOLOGY

1 Pharmacodynamic studies (immunogenicity of the vaccine)

Primary pharmacodynamics มีการประเมินความสามารถในการสร้างภูมิคุ้มกันของ Prevnar 13 หรือ 13vPnC ในหนู rats, rabbits และ cynomolgus monkeys วัด Ab ที่เฉพาะเจาะจงกับแต่ละ serotype หลังจากให้ vaccine แบบ repeat dose ให้ผลการตอบสนองการสร้าง Ab เจาะจงกับ pneumococcal serotype-specific capsular polysaccharide ตามที่คาดหมายทั้ง 13 serotypes

Secondary pharmacodynamics จาก clinical pathology และ histology แสดงถึง systemic inflammatory response

Safety pharmacology มีการประเมิน CNS function, respiratory system ก่อนและหลังให้ 13vPnC ไม่พบอาการที่ related vaccine

2 Pharmacodynamic studies of adjuvant(s) (if applicable)

Polysaccharide ของแต่ละ serotype จับกับ Diphtheria CRM₁₉₇ protein และ Aluminum phosphate เป็น adjuvant จึงมีการวิเคราะห์ Ab ต่อ Diphtheria toxoid เฉพาะใน cynomolgus monkeys ส่วน Aluminum phosphate เป็น adjuvant ที่ใช้มานานแล้ว อย่างไรก็ตาม ในการศึกษาจะมีกลุ่มควบคุมโดยให้ เฉพาะ ซึ่งพบว่าทำให้เกิด inflammation บริเวณที่ฉีด

II. PHARMACOKINETICS

ไม่มีการประเมินเภสัชจลนศาสตร์ของวัคซีน

III. TOXICOLOGY

1. General toxicology

Single-dose toxicity ใน rats, rabbits และ cynomolgus monkeys ขนาด 0.5 ml/injection (หรือ 0.15 ml ใน juvenile rats) ไม่ทำให้สัตว์ตาย repeat-dose toxicity 1 dose/2 week 7 เข็มฉีด SC ใน rats และ monkeys ฉีด IM ให้ 5 เข็ม ในกระต่ายทั้งเพศผู้และเพศเมีย ไม่พบ adverse effect ต่อสุขภาพทั่วไปของ rats ไม่พบ systemic toxicity มี local effect ได้แก่ erythema, edema เป็นอาการ inflammatory ทั้ง 2 เพศตอบสนองไม่แตกต่างกัน ส่วนในกระต่ายก็พบ inflammatory ที่ตำแหน่งที่ฉีด vaccine หรือ AlPO₄ vehicle control กลุ่มที่ให้ 13 vPnC จะมีความรุนแรงของ inflammatory มากกว่า control ไม่พบ effect ต่อสุขภาพทั่วไป สัตว์ทดลองมีระดับ Ab ต่อ

serotype แต่ละชนิดหลังฉีด 13 vPnC ในลิงก็พบ nodules, erythema, edema ไม่พบ systemic toxicity มีการตรวจ Ab ต่อ 13 serotypes พบว่ามี Ab และมี Ab ต่อ Diphtheria toxoid

Local tolerance was evaluated in a single-dose IM irritation study of 13vPnC vaccine with or without adjuvant in male rabbits at a dose volume of 0.5 mL/injection. The vaccine was well tolerated and did not produce irritation at the injection site.

During repeated dose toxicity studies, local tolerance

There were no objection against the studies design and results of these “Repeat-dose toxicity” studies. However, in “Single-dose toxicity” studies which were evaluated using data collected after first dose administration to the animals in the “Repeat-dose toxicity” studies could not be taken into the account as “Single-dose toxicity” studies in the part of “General toxicity”. Single-dose toxicity” studies in this sense should reflect the toxicity of vaccine at different increasing doses but being given as single dose. Therefore, Single-dose toxicity” studies were not really done. In addition, there were no special toxicity studies related to “Reproductive toxicity” and “Development toxicity”, and also no data about the excretion of the vaccine into breast milk. However the company states that this vaccine is intended to us in infants and young children aged below 6 years; therefore the expert would suggest adding this sentence “this vaccine is intended to use in infants and young children aged below 6 years” into “Warnings” in the product package insert.

2. Special toxicology for vaccines (when applicable)

Genotoxicity ไม่มีการศึกษา เหตุผลคือ polysaccharide ที่จับกับ protein ไม่สามารถทำปฏิกิริยา กับ DNA สอดคล้องกับ WHO และ EMEA Guidance

Carcinogenicity ไม่ได้ศึกษา สอดคล้องกับ WHO และ EMEA Guidance Reproductive and Development Toxicity vaccine 13 vPnC ให้ใช้ใน infant ไม่แนะนำให้ใช้ในสตรีที่อาจตั้งครรภ์ได้ จึงไม่มีการศึกษา อย่างไรก็ตาม มีการศึกษา 8 week SC repeat-dose toxicity ใน juvenile rat เพื่อสนับสนุนการฉีด SC ในเด็ก ในประเทศญี่ปุ่น ซึ่งพบเฉพาะ effect ที่ตำแหน่งที่ฉีดเป็น nodule, erythema และ edema การเกิด SC inflammation มี degenerate necrosis ที่ตำแหน่งที่ฉีด ไม่พิจารณาว่าเป็น adverse effect

Local tolerance ฉีด IM ในกระต่าย พบว่า well tolerated ที่เกิด irritation ที่ injection site

2.1 Special immunological investigations

- Toxicity studies in special population

No studies

- Genotoxicity and carcinogenicity studies, when applicable

No studies

- Reproductive toxicity studies for vaccines to be administered to pregnant women or individuals of fertile age.

No studies ยกเว้นการฉีด SC ใน juvenile rats เพื่อเป็นข้อมูลการฉีด SC ในทารกในครรภ์

3. SPECIAL CONSIDERATIONS (if applicable)

3.1 Live attenuated vaccines.

Not applicable

3.2 New substances incorporated into the formulation

Not applicable

4. TFDA PTL AND EXTERNAL EXPERT'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

เอกสารกำกับยาหน้า 1 ผิด 1 แห่ง ปรับปรุงข้อความ 1 แห่ง

ในเอกสารทั้งภาษาไทยและอังกฤษ ควรเพิ่มข้อความใน "คำเตือน" ทำนองว่า "ไม่ให้วัคซีนนี้ในผู้ที่มีอายุเกินกว่า 6 ปีบริบูรณ์" ถึงแม้จะมีข้อความทำนองนี้ในหัวข้อ "Pediatric use" แล้ว ทั้งนี้ เพื่อให้ผู้บริโภคเข้าใจได้ง่าย ("ภายใต้คำเตือน") โดยไม่จำเป็นต้องเสียเวลาดูในหัวข้อผู้สูงอายุ หญิงมีครรภ์ หรือหญิงที่ให้นมบุตร

5. TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON NON-CLINICAL ASPECTS

1. Prevnar 13 หรือ 13 vPnC เมื่อให้แบบ repeat-dose ทั้งใน adult และ juvenile rats, rabbits, cynomolgus monkeys ไม่ว่าจะฉีด SC หรือ IM ให้ผล immune response ตามความคาดหมาย

2. Single-dose safety pharmacology ศึกษาใน rats และ cynomolgus monkeys และ repeat-dose toxicity ใน juvenile และ adult rats, rabbits และ cynomolgus monkeys แสดงผลว่า 5-7 dose (เทียบเท่า clinical dose) ฉีด SC หรือ IM ทุก 2-3 week สัตว์ทดลองทนได้ดี ไม่มี adverse effects ส่วน inflammatory changes ที่สัมพันธ์กับ 13vPnC และ $AlPO_4$ ที่เป็น adjuvant ณ ตำแหน่งที่ฉีดเป็นการเปลี่ยนแปลงที่คาดหมาย ไม่พิจารณาว่าเป็น adverse effects ไม่มีผลต่อสุขภาพโดยรวมของสัตว์ทดลอง

โดยสรุป Prevnar 13 มีความปลอดภัยและมี efficacy สมควรให้การรับรอง

BASED ON THE STUDIES DESIGN AND RESULTS THESE NON-CLINICAL ASPECT COULD BE ACCEPTED

2.4 Clinical aspects

Introduction

เนื่องจากการขึ้นทะเบียนของ Prevnar 7 แล้ว มีการศึกษาเพิ่มเติมต่ออีก 6 serotypes (1,3,5,6A, 7F และ 19A) พบมีความครอบคลุมมากขึ้น ในประเทศไทย Prevnar 7 ครอบคลุมเชื้อ *S. pneumoniae* serotype ได้ประมาณ 70-75% หากเพิ่มเป็น 13 serotype จะครอบคลุมได้กว้างขึ้นถึง 88%

1. REPORTS OF CLINICAL STUDIES

1 Phase I Studies

ผ่านได้

มีการศึกษาความปลอดภัยใน 12 การศึกษาใน

Infant และ toddler

1 study in older infants

1 study in adults

ผลปรากฏว่า ความปลอดภัยอยู่ในเกณฑ์ที่น่าพอใจ แสดงว่ามีความปลอดภัย ไม่พบว่ามี SAE มีอาสาสมัครเสียชีวิต 4 ราย แต่ไม่มีรายใดที่เกี่ยวข้องกับวัคซีนทดลองเลย Tolerabilityไม่แตกต่างไปจากวัคซีนที่ได้รับการจดทะเบียนก่อนแล้ว

2 Phase II Studies

ผ่านได้

มีการศึกษาในการตอบสนองในการสร้างแอนติบอดีและ

ติดตามสำรวจเมื่อครบ 6 เดือน ผลการศึกษาแสดงว่ามีการตอบสนองที่ดีสูงกว่า 90 % และมีความปลอดภัยสูง ไม่แตกต่างจากวัคซีนเดิม นับว่าอยู่ในเกณฑ์ที่น่าพอใจ

3 Phase III Studies

ผ่านได้ มีข้อมูลการศึกษามากเพียงพอ

มีการดำเนินการศึกษาในสหรัฐ 43 แห่ง เป็นการศึกษา randomized, active control, double blind, multicenter studies in parallel study กับ 7-valent vaccine. Sample size = 1,216, assay 36560 assays, ELISA test 24,960 assays ในเยอรมนีมีการทดสอบอีก 56 ศูนย์ เป็น parallel group, randomized, active control, double blind, 6,000 subjects (2 groups) ผลการศึกษาแสดงว่าการสนองตอบต่อนิวโมค็อกคัส แอนติเจน ดี เป็นไปตามวัตถุประสงค์

4 Special Considerations

ได้รับการจดทะเบียนแล้วในประเทศผู้ผลิตและยังได้รับ การจดทะเบียนแล้วในประเทศอื่นๆอีกหลาย

ประเทศ

ควรมีการเฝ้าติดตามเรื่อง serotype ที่ไม่ได้อยู่ใน Prevnar 13 ว่ามี replacement ในเด็กไทยในแง่ Colonization และการที่ serotype ที่ไม่ได้อยู่ใน วัคซีน (replacement serotype) ว่าจะก่อโรคน้อยแค่ไหน และเป็นเชื้อ *S. pneumoniae* ที่ดื้อยาปฏิชีวนะหรือไม่

5 Adjuvant(s)

ไม่มี

6 Phase IV Studies and / or Pharmacovigilance plan (if applicable)

ผ่าน

7 Non-inferiority Studies (for combined vaccines, or approved vaccines prepared by new manufacturers)

ผ่าน

8 Co-administration Studies with other Vaccines

ผ่าน (มีหลายวัคซีนที่ฉีดรวมกันได้ แต่ต่างตำแหน่ง)

2. TFDA PTL AND EXTERNAL EXPERT'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

เหมาะสม

3. TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSION ON CLINICAL ASPECTS

เหมาะสม น่าจะขึ้นทะเบียน อย ได้ โดยให้มีการเฝ้าระวัง

Post-marketing ที่สมบูรณ์เพื่อติดตามผลข้างเคียงต่างๆและทฤษฎี replacement serotype จากเชื้อแบคทีเรีย *S. pneumoniae* ซึ่งบริษัทจะส่งข้อมูล “Monitoring for replacement of *S.pneumoniae* with non-pneumococcal bacteria in the nasopharyngeal flora of children” ซึ่งเป็นส่วนหนึ่งของ EU risk management plan เมื่อรายงานการตรวจติดตามดังกล่าวเสร็จสมบูรณ์แล้ว

BASED ON THE STUDIES DESIGN AND RESULTS THESE NON-CLINICAL ASPECT COULD BE ACCEPTED

2.5 Pharmacovigilance (If applicable)

.....ข้อนี้สำหรับกรณีและผู้เชี่ยวชาญมีความเห็นให้ทำการศึกษา Pharmacovigilance

2.6 Overall Conclusion on Risk/benefit Assessment and Recommendation

Efficacy

The 13-valent pneumococcal conjugate vaccine (Prevnar 13) was demonstrated to induce an immune response to all 13 serotypes. The vaccine induced a functional immune response as measured by opsonophagocytic (OPA) assay. The majority of subjects who received a 3-dose primary series achieved an antibody concentration $>0.35\mu\text{g/ml}$ (90.5-99.5%) and an OPA titre $>1:8$ (84-100%), except for certain serotypes. For 12 of the 13 serotypes (except serotype 3), a good priming effect of the 3-dose and 2-dose schedules was shown with an anamnestic response following a booster dose. These data indicate the presence of an immune memory. The immune response to routine paediatric vaccines co-administered with Prevenar 13 was assessed and no clinically relevant immune interferences were observed.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Benefits

The introduction of Prevnar in the childhood immunisation program in the US in the year 2000 have resulted in a dramatic decline in rates of IPD due to the 7 vaccine serotypes in the target group, as well as in unvaccinated older subjects (herd protection). Significant reductions of pneumococcal AOM and pneumonia in children have also been demonstrated. Prevnar has 80 to 90% serotype coverage in the US, but somewhat lower in Europe (60-80%) and in other continents (40-80%). The Prevnar 13 vaccine with the additional serotypes 1, 3, 5, 6A, 7F and 19A is expected to provide an increased coverage of approximately 90% of serotypes responsible for IPD in children aged <5 years in most regions of the world, and more than 73-100% of isolates in Europe.

Uncertain benefits include the efficacy of the Prevnar 13 vaccine against serotypes 1, 3, and 5 in pneumonia and otitis media. The results demonstrated that functional immune response elicited by Prevnar 13 was lower for 3 of the 6 additional serotypes compared with all the other vaccine serotypes. The OPA GMTs for the concerned additional serotypes in Prevnar 13 lay in the same range as those for 19F and 6A in Prevnar. For protection against non-invasive disease higher antibody titres are required and it is questioned whether the OPA titres observed for serotypes 1, 3 and 5 would be sufficient to protect against pneumonia and otitis media due to these serotype. The poor boostability observed for serotype 3 is of unknown clinical relevance, but may result in reduced vaccine efficacy against pneumococcal disease due to this serotype.

The safety profile of Prevnar 13 is comparable to the licensed 7-valent pneumococcal conjugate vaccine (Prevnar) and no new or significant risks have been identified. The Prevnar 13 vaccine is commonly associated with range of local and systemic reactions. These adverse events are not often of severe intensity and the safety profile would not preclude the use of Prevnar 13 for primary vaccination, booster vaccination or catch-up vaccination.

Data showing that after introduction of earlier vaccines, e.g. 7-valent pneumococcal conjugate vaccine and Hib vaccine, diseases caused by vaccine-related serotypes decreased dramatically and an increase of infections caused by other serotypes (e.g. pneumococcal serotype 19A) was noticed. Serotype replacement is considered as an important potential risk which must be included in the risk management plan. Data showing that after introduction of Prevnar, diseases caused by vaccine serotypes decreased dramatically and an increase of infections caused by other serotypes in particular 19A was noticed. Risk minimisation measures are in place. Monitoring of replacement with non-pneumococcal bacteria, like staphylococci, have also been included in the risk management plan.

The Prevnar 13 may induce suboptimal vaccine efficacy to certain serotypes with a risk of breakthrough infections and only short term persistence of efficacy.

The 2-dose primary schedule in infants resulted in lower immune responses than the 3-dose primary series, in particular with regard to serotypes 6B and 23F, which could result in suboptimal protection against IPD and AOM during the pre-booster period.

It has to be noted that there are no data demonstrated for use in the populations at high risk for infection with the pneumococcus. Any use in these populations may not provide satisfactory protection and could result in break-through infections.

Recommendations

The TFDA and external experts have reviewed the clinical studies and found them evidently supportive; therefore positive opinion was given towards the approval of marketing authorization of **Prevnar 13** with no conditions.

Analytical Procedures
used for Pneumococcal polysaccharide, activated
saccharide and MBC

| Method | Principle |
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| Appearance | Visually compare polysaccharide, activated saccharide, and MBCs to WFI and appropriate turbidity and color standards to determine the appropriate sample description. Lyophilized samples are examined for the appearance of moisture, for texture and for color. |
| Degree of Oxidation | Used for determining the degree of oxidation (DO) of activated saccharides. The DO is defined as the ratio of the sugar repeat units in the polysaccharide, based on weight, to the aldehyde groups generated when the polysaccharide is oxidized by sodium periodate. The numerical value of DO is inversely proportional to the amount of aldehyde formed. The moles of sugar repeat unit is obtained from the appropriate saccharide assay (e.g., Anthrone assay or Uronic Acid assay) and the moles of aldehyde is obtained from the appropriate aldehyde assay (e.g., Park Johnson assay, Bicinchoninic Acid [BCA] assay, 3-methyl-2-benzothiazolone hydrazone [MBTH] assay or 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole [AHMT] assay). |
| Dry weight | Used for determination of the dry weight of all pneumococcal polysaccharides. The method is based on drying a liquid sample to a constant weight by a known volume of a liquid sample brought to dryness under application of heat and vacuum. |
| Endotoxin | Determine endotoxin concentration in polysaccharides, activated saccharides, MBCs as per compendial methods Ph. Eur. 2.6.14 and USP <85>. |
| Free protein by SE-HPLC | Determination of unconjugated (free) protein in samples of MBCs and in-process MBCs for all serotypes. Method is based on the use of Size-Exclusion HPLC to separate free protein (CRM197) from the conjugate product. |
| Free saccharide | <u>Monovalent Bulk Conjugates 1, 4, 5, 6B, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F</u> Determination of the amount of unbound saccharide in samples of MBCs and in-process MBCs. Method is based on the binding of protein and covalently bound saccharide to aluminum hydroxide gel and subsequent removal by centrifugation. The protein concentration of the sample must be determined prior to initiating this test. Samples are mixed with phosphate buffered aluminum hydroxide gel to bind protein and conjugated saccharide. Aliquots of the mixture are tested before centrifugation to determine total saccharide and after centrifugation to determine free saccharide in the supernatant. Free saccharide is defined as that portion of the total saccharide that is not covalently bound to the carrier protein. |
| Free saccharide by Deoxycholic Acid | <u>Monovalent Bulk Conjugate 3</u> Determination of the amount of unbound saccharide in sample of MBC and in-process MBC sample. This method is based on binding of Deoxycholic acid to the protein portion of the conjugate, precipitation of the conjugate at low pH with the addition of hydrochloric acid. Then quantitation of any free saccharide in the supernatant is determined by using an appropriate saccharide assay (e.g., Anthrone Assay). |
| Identity by Slot Blot | The method is used to confirm the identity of individual polysaccharides, and MBCs, or CRM197 protein using type-specific antibodies prepared for each antigen. The Method is based on the binding of antibodies to specific epitopes on the analytes of interest. Polysaccharides, MBCs or CRM197 are applied to a nitrocellulose membrane by vacuum filtration, followed by incubation with specific antibodies. After blocking with bovine serum albumin (BSA), the nitrocellulose membrane is probed with protein A/G conjugated to horseradish peroxidase (HRP) and then visualized using a 4 chloro-naphthol (CN) peroxidase substrate. |
| Molecular weight average by SEC-MALLS | Determine the average molecular weight and distribution of molecular weight. Based on the fractionation of the pneumococcal polysaccharides using Size Exclusion Chromatography (SEC). Refractive index (RI), and multi-angle laser light scattering (MALLS) detectors are used for the determination of the weight average molar mass distribution for pneumococcal polysaccharides. Activated Saccharides Serotypes 1, 3, 5, 6A, 7F, 19A, 19F and Polysaccharide Serotypes 1, 3, 5, 6A, 7F, 19A |

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| | <p>The HPLC system (e.g., tandem SynChroPak® GPC 1000 + GPC 100 columns with an autosampler, optional UV/VIS detector, RI detector, and MALLS detector) is set to defined parameters (e.g., flow rate of 0.5 mL/min, column temperature of 25°C, sample tray temperature of 2 to 8°C). Polysaccharide Serotypes 4, 6B, 9V, 14, 18C, 19F, 23F</p> <p>The HPLC system (e.g., Tandem SynChroPak® GPC 1000 columns with an autosampler, optional UV/VIS detector, RI detector, and MALLS detector) is set to defined parameters (e.g., flow rate of 0.5 mL/min).</p> |
| Molecular Size 50% Kd (CL-4B) | <p><u>Activated Saccharide Serotypes 4, 6B, 9V, 14, 18C, and 23F</u></p> <p>Determination of the size profile of Activated Pneumococcal Polysaccharides. The method is based on size exclusion chromatography (SEC), which separates macromolecules according to molecular size. Molecules that are larger than the average pore size of the column packing are excluded and elute faster than smaller molecules, which can penetrate into these pores as they pass through the column. The Kd value is determined using the Ve (elution volume) of the sample at 50% saccharide and the calibration V0 and Vi values. Therefore, the 50% Kd is the Kd value at which 50% of the product has eluted from the column</p> |
| Molecular Size % Saccharide ≤ 0.3 Kd (CL-4B) | <p>Used for the determination of the size profile of MBCs and in-process MBCs. The method is based on size exclusion chromatography (SEC), which separates macromolecules according to molecular size. Molecules that are larger than the average pore size of the column packing are excluded and elute faster than smaller molecules, which can penetrate into these pores as they pass through the column. The 30% Kd (% < 0.3 Kd) is the Kd value at which 30% of the product has eluted from the column. The "Kd profile" is created using the results from the detection assay performed on the collected fractions.</p> |
| Nuclear Magnetic Resonance | <p>The Nuclear Magnetic Resonance (NMR) test method is used for structure verification, and quantification of functional groups and impurities (C-Polysaccharide) in Pneumococcal Polysaccharides. This method is based on magnetically active atomic nuclei with a non-integral magnetic quantum number, such as 1H, 13C, 31P, aligning themselves in specific energetic positions in the presence of a strong magnetic field. When the alignment is perturbed by the introduction of an external Radio Frequency (RF) field, the nuclei exhibit precessional frequency which is unique to a given nuclei type. This frequency (Larmor frequency) is detected as a signal and is used in obtaining chemical information of chemical functional groups based on their structure and local environments.</p> |
| pH | <p>Determine pH of polysaccharides and MBCs as per compendial methods Ph. Eur. 2.2.3 and USP <791></p> |
| Protein concentration- Lowry | <p>Determine protein concentration in samples of MBCs and in-process. Method is based on the Lowry procedure, which involves the reaction of peptidic nitrogens, with copper, under alkaline conditions, followed by reaction of the moiety thus formed with Folin-Ciocalteu phenol reagent.</p> |
| Residual Cyanide by instrumental assay | <p>Determine the concentration of residual cyanide in MBCs and in-process MBCs prepared by reductive amination. The assay is performed using an automated cyanide analyzer.</p> |
| Residual DMSO by HPLC | <p><u>Monovalent Bulk Conjugates 6A, 6B, 7F, 19A, 19F, 23F</u></p> <p>Determine the level of DMSO in samples of MBCs. The method is based on the separation of residual DMSO in MBC from other species, using SE-HPLC. DMSO peak is detected at 210nm.</p> |
| Residual Moisture | <p>Used for the determination of water content in lyophilized activated saccharides as per compendial methods Ph. Eur. 2.5.12 and USP <921></p> |
| Residual Nucleic Acid | <p>Determine the concentration of nucleic acid in pneumococcal polysaccharides. Based on quantitation of the concentration of nucleic acid by UV spectrophotometry and the fact that a 50 µg/mL solution of nucleic acid has an absorbance of 1.0 at 260 nm</p> |
| Residual Protein | <p>Determination of residual protein in samples of polysaccharides for all serotypes. The method is based on a modified Lowry procedure, which involves the reaction of peptidic nitrogens, with copper, under alkaline conditions. This reaction is followed by the reduction of phosphomolybdic/phosphotungstic acid to form a blue chromogen. The resulting absorbance, measured at 750 nm, is proportional to the protein concentration in the sample.</p> |

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| Saccharide Concentration Anthrone | <u>Polysaccharides, Activated Saccharides, and Monovalent Bulk Conjugates 3, 4, 6B, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F</u> Determine the concentration of saccharide in samples of polysaccharides, activated saccharides, MBCs and in-process MBCs. The method is based on the reaction of the Anthrone reagent with hexoses, which are generated from the polysaccharides by the action of sulfuric acid and heat. The hexoses and the Anthrone reagent form a yellow-green colored complex the absorbance of which is read spectrophotometrically at 625 nm. |
| Saccharide Concentration Uronic | <u>Polysaccharides, Activated Saccharides, and Monovalent Bulk Conjugates 1 and 5</u> Determine the concentration of saccharide in samples of polysaccharides, activated polysaccharides, MBCs and in-process MBCs. Method is based on the reaction of Uronic acid, which is generated from the polysaccharide by the action of Sulfuric acid, Sodium tetraborate and heat. The uronic acid reacts with 3-phenyphenol to form a fushia colored complex, the absorbance of which is read spectrophotometrically at 520 nm. |
| Saccharide to Protein Ratio | Determine the ratio of saccharide to protein concentration for MBCs. Ratio in the conjugate is determined by the conjugation reaction conditions, and is calculated using results obtained from the appropriate saccharide assay (Uronic Acid or Anthrone) and from the Lowry Assay for protein. |
| % Soluble Protein | Determine the % non-aggregated soluble protein in MBCs and intermediates. This method is based on the Lowry procedure, as described in the Total Protein procedure. |
| Sterility | Determine sterility of polysaccharides (Membrane Filtration or Direct Inoculation) and MBCs (Membrane Filtration) as per compendial methods Ph. Eur. 2.6.1 and USP <71>. |
| Total Aldehyde by BCA | <u>Activated Saccharide Serotype 4</u> Used for the determination of the concentration of aldehyde groups in activated saccharide sample. The method is based on the ability of the aldehyde functional group, in alkaline solution, to reduce Cu ²⁺ to Cu ¹⁺ . Cu ¹⁺ forms a complex with bicinchoninic acid (BCA) to form a chromophore, which absorbs light at a wavelength of 560 nm. |
| Total Aldehyde by AHMT | <u>Activated Saccharide Serotypes 5, 18C, 19F</u> Used for the determination of the concentration of aldehyde groups on activated saccharide. Based on the reaction of 4-amino-3-hydrazino-5-mercapto-1,2,4-trizole (AHMT; Purpald®) with aliphatic aldehyde to form a fuschia color that can be read at 540 nm on a suitable device. |
| Total Aldehyde by MBTH | <u>Activated Saccharide Serotype 19A</u> Determine concentration of aldehyde groups on the activated saccharide. Based on the reaction of 3-methyl-2-benzothiazolone hydrazone (MBTH) with aldehyde to form an azine intermediate. The excess MBTH oxidizes with FeCl ₃ to form a reactive cation. The reactive cation and azine intermediate react to form a blue chromophore, which is read at 650 nm. |
| Total Aldehyde by Park Johnson | <u>Activated Saccharide Serotypes 1, 3, 6A, 6B, 7F, 9V, 14, 23F</u> Determine concentration of aldehyde groups on the activated saccharide. The method is based on the reaction of aldehydes with potassium ferricyanide, after the addition of Fe ³⁺ , to form the chromophore, ferric ferrocyanide (Prussian blue), which produces an absorbance at 690 nm. |

Pneumococcal Saccharide-CRM₁₉₇ Conjugate is in compliance with Ph.Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) (2150) and ICH Harmonized tripartite guideline, Impurities: Guideline for Residual Solvents Q3C(R3).