Report on the Deliberation Results

March 10, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Synflorix Aqueous Suspension for Intramuscular Injection
[Nonproprietary name]	Pneumococcal 10-valent Conjugate Vaccine adsorbed (Non-Typeable *Haemophilus influenzae* [NTHi] Protein D, Diphtheria or Tetanus Toxoid Conjugates)
[Applicant]	Japan Vaccine Co., Ltd.
[Date of application]	March 28, 2014

[Results of deliberation]

In the meeting held on March 5, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years, the drug substance and drug product are both classified as a powerful drugs, and the product is classified as a biological product.

[Conditions for approval]

The applicant is required to develop and appropriately implement a risk management plan.

Review Report

February 12, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Synflorix Aqueous Suspension for Intramuscular Injection
[Nonproprietary name]	Pneumococcal 10-valent Conjugate Vaccine adsorbed (Non-Typeable *Haemophilus influenzae* [NTHi] Protein D, Diphtheria or Tetanus Toxoid Conjugates)
[Applicant]	Japan Vaccine Co., Ltd.
[Date of application]	March 28, 2014
[Dosage form/Strength]	Suspension for injection: Each 0.5-mL dose (pre-filled in a syringe) contains 1 μg each of pneumococcal capsular polysaccharide for serotypes 1, 5, 6B, 7F, 9V, 14, and 23F conjugated to protein and 3 μg each of pneumococcal capsular polysaccharide for serotypes 4, 18C, and 19F conjugated to protein.
[Application classification]	Prescription drug, (1) Drug with a new active ingredient
[Items warranting special mention]	Product subjected to prior assessment consultation
[Reviewing office]	Office of Vaccines and Blood Products

Review Results

February 12, 2015

[Brand name]	Synflorix Aqueous Suspension for Intramuscular Injection
[Nonproprietary name]	Pneumococcal 10-valent Conjugate Vaccine adsorbed (Non-Typeable *Haemophilus influenzae* [NTHi] Protein D, Diphtheria or Tetanus Toxoid Conjugates)
[Applicant]	Japan Vaccine Co., Ltd.
[Date of application]	March 28, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product for "prevention of invasive infections and pneumonia caused by *Streptococcus pneumoniae* (pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F)" has been demonstrated, and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]	Prevention of invasive infections and pneumonia caused by *Streptococcus pneumoniae* (pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F)
[Dosage and administration]	Primary immunization: The usual primary immunization series for children consist of three doses of 0.5 mL each, administered by intramuscular injection, with an interval of at least 27 days. Booster immunization: The usual booster dose for children is a single dose of 0.5 mL, administered by intramuscular injection, at least 4 months after the third dose.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

January 9, 2015

I. Product Submitted for Registration

[Brand name]	Synflorix Aqueous Suspension for Intramuscular Injection
[Nonproprietary name]	Pneumococcal 10-valent Conjugate Vaccine adsorbed (Non-Typeable *Haemophilus influenzae* [NTHi] Protein D, Diphtheria or Tetanus Toxoid Conjugates)
[Applicant]	Japan Vaccine Co., Ltd.
[Date of application]	March 28, 2014
[Dosage form/Strength]	Suspension for injection: Each 0.5-mL dose (pre-filled in a syringe) contains 1 μg each of pneumococcal capsular polysaccharide for serotypes 1, 5, 6B, 7F, 9V, 14, and 23F conjugated to protein and 3 μg each of pneumococcal capsular polysaccharide for serotypes 4, 18C, and 19F conjugated to protein.
[Proposed indication]	Prevention of invasive infections, acute otitis media, and pneumonia caused by *Streptococcus pneumoniae*
[Proposed dosage and administration]	Primary immunization: The usual primary immunization series consist of three doses of 0.5 mL each, administered by intramuscular injection, with an interval of at least 27 days. Booster immunization: The usual booster dose is a single dose of 0.5 mL, administered by intramuscular injection, at least 6 months after the last dose of primary immunization.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

With regard to this application, the data submitted by the applicant and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery, use in foreign countries, and other information

Streptococcus pneumoniae is a leading cause of otitis media, sinusitis, bronchitis, pneumonia, sepsis, and bacterial meningitis in children (*Toda's New Bacteriology*, 251-253, 2013) and is a gram-positive bacterium. *S. pneumoniae* is classified into over 90 pneumococcal serotypes, according to the antigenic properties of capsular polysaccharides (*IASR*, 2013;34:64-66). *S. pneumoniae* is transmitted via airborne droplets, colonizes in the nasopharyngeal mucosa, and then reaches the lungs through the trachea or the

middle ear via the auditory tube, causing local infections, e.g., pneumonia and otitis media, in an immunocompromised state. In some of the local infections, *S. pneumoniae* spread hematogenously throughout the body, leading to invasive pneumococcal disease (IPD).

In patients with IPDs, symptoms progress rapidly and are severe, resulting in serious sequelae or deaths despite adequate treatment in some cases (*Lancet*, 2009;374:893-902). The rate of hospitalization due to pneumonia, a pneumococcal infection, is relatively high in Japan (*Pediatr Infect Dis J*, 2013;32:e119-127), and community-acquired pneumonia (CAP) is the disease primarily responsible for pediatric hospitalization. The incidence of CAP requiring hospitalization in pediatric patients aged <5 years was 17.6 episodes per 1000 patient-years in Japan (*Epidemiol. Infect*, 2012;140:1111-1121).

In Japan, in October 2009, "pneumococcal conjugate vaccine, 7-valent adsorbed (conjugated to nontoxic variant of diphtheria toxin)" (Prevenar Suspension Liquid for S.C. Injection, hereinafter referred to as "7vPnC vaccine") was approved for "prevention of invasive infections caused by *S. pneumoniae* (serotypes of 4, 6B, 9V, 14, 18C, 19F, and 23F)" in children. In June 2013, "pneumococcal conjugate vaccine, 13-valent adsorbed (conjugated to nontoxic variant of diphtheria toxin)" (Prevenar13 Suspension Liquid for Injection) was approved for "prevention of invasive infections caused by *S. pneumoniae* (serotypes of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F)" in children. In Japan, the prevalence of IPDs in children aged less than 5 years has been decreasing since the introduction of the 7vPnC vaccine (launched in February 2010) (*Research on "Surveillance of Pediatric Bacterial Meningitis and Systemic Infections (National Surveillance)," a partial research report of the Research on Measures for Diseases and Disabilities: Research on Emerging/Re-emerging Infectious Diseases Including Novel Influenza, "Basic and Clinical Research on Efficacy, Safety, and Dosage Regimens of Newly Developed Vaccines for Hemophilus influenza type B, Streptococcus pneumoniae, Rotavirus, Human Papilloma Virus, and Other Pathogens," funded by Health and Labour Sciences Research Grants,* 2013)

Synflorix Aqueous Suspension for Intramuscular Injection (Synflorix) is a pneumococcal conjugate vaccine and contains active ingredients consisting of 10 *S. pneumoniae* polysaccharide serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) each conjugated to a carrier protein, either protein D (a cell surface protein derived from non-typeable *Haemophilus influenzae*), tetanus toxoid, or diphtheria toxoid. Synflorix was approved first in Canada in December 2008 and then has been approved for use in children in 123 countries including European countries as of December 2013. Synflorix has not been submitted for approval in the United States (US).

2. Data relating to quality

2.A Summary of the submitted data

The drug product is a pneumococcal conjugate vaccine and contains active ingredients consisting of 10 capsular polysaccharide (PS)-carrier protein conjugates in which 10 PSs derived from pneumococcal

capsular serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) are each conjugated to a carrier protein, either non-typeable *Haemophilus influenzae* protein D (PD), tetanus toxoid (TT), or diphtheria toxoid (DT). The PS content and the types of carrier proteins for individual serotypes in the drug product are shown in Table 2-1. The drug product is adjuvanted with aluminum phosphate to enhance immune response.

Table 2-1. Active ingredients of Synflorix

Serotype	1	4	5	6B	7F	9V	14	18C	19F	23F
PS content[a)]	1	3	1	1	1	1	1	3	3	1
Carrier protein	PD	PD	PD	PD	PD	PD	PD	TT	DT	PD

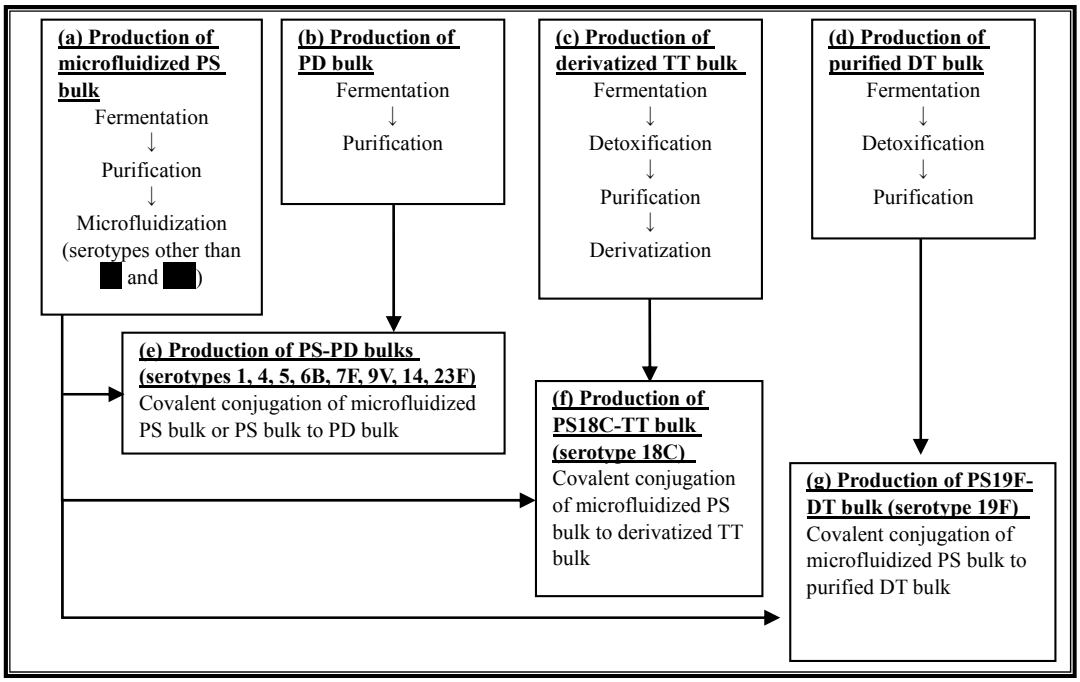
a) Content (μg) in a dose of 0.5 mL Synflorix

2.A.(1) Drug substance

2.A.(1).1) Manufacturing process

An outline of the manufacturing processes for the drug substances is shown in Figure 2-1. In Process (a), the PS bulks of 10 serotypes are produced, and then PS bulks of 8 serotypes (other than serotypes [redacted] and [redacted]) are microfluidized. The microfluidized PS bulks of the serotypes [redacted], and [redacted] and the PS bulks of the serotypes [redacted] and [redacted] are covalently conjugated to the PD bulk obtained in Process (b), the microfluidized PS bulk of the serotype 18C is covalently conjugated to the TT bulk obtained in Process (c), and the microfluidized PS bulk of the serotype 19F is covalently conjugated to the DT bulk obtained in Process (d) to produce the PS-PD bulk, PS18C-TT bulk, and PS19F-DT bulk, respectively, as the drug substances (Processes (e), (f), and (g) in Figure 2-1).

Figure 2-1. Manufacturing processes for drug substances (outline)



(a) Production of PS bulk

i) Preparation and control of *Streptococcus pneumoniae* seed

The *S. pneumoniae* seeds with serotypes 1, 4, 7F, 14, and 19F are derived from strains obtained from Professor E. Yourassowsky, M.D., Ph.D. (Brugmann University Hospital), and the seeds with serotypes 5, 6B, 9V, 18C, and 23F are derived from strains obtained from J. Henrichsen, M.D., Ph.D. (Statens Serum Institut). The parent seed was prepared from the 5th through the 16th passage (depending on the serotypes) of each of the strains obtained. The Master Seed (MS) was prepared from the first passage of the parent seed, and the Working Seed (WS) was prepared from the first passage of the MS.

Control testing shown in Table 2-2 is performed during preparation of the MS and WS to qualify them in individual tests. The MS and WS are stored at [redacted]°C. Microbial limit test has been routinely performed for the WS, and the viable microbial counts were confirmed after storage of up to [redacted] years.

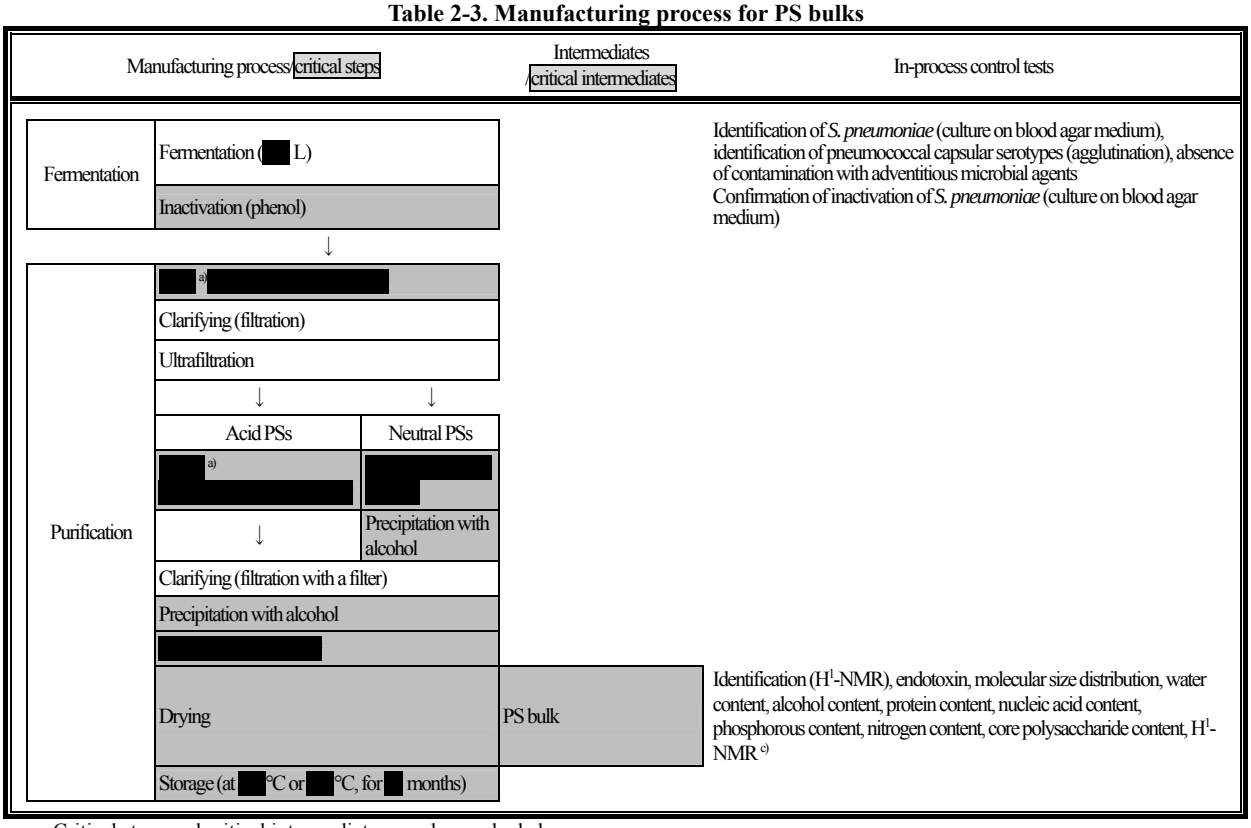
Table 2-2. Control testing for *S. pneumoniae* seed

Test items		MS	WS
Identification of *S. pneumoniae*	Culture on blood agar medium	✓	✓
	Gram staining	✓	✓
Identification of pneumococcal capsular serotypes (agglutination)		✓	✓
Absence of contamination with adventitious microbial agents	Culture in fluid thioglycollate medium and soybean casein digest medium	✓	✓
	Culture on Sabouraud agar medium	✓	✓

ii) Manufacturing process for PS bulk

The manufacturing process for the PS bulks is shown in Table 2-3. Some parts in the purification step differ between acid PSs (serotypes 1, 4, 5, 6B, 9V, 18C, 19F, and 23F) and neutral PSs (serotypes 7F and 14). Process validation was performed on the steps for the PS bulks at commercial scale and showed that the individual steps were appropriately controlled.

Table 2-3. Manufacturing process for PS bulks



Critical steps and critical intermediates are shown shaded.
a) b) Depending on serotypes. c) Contents of uronic acid (serotypes 1, 5, and 9V), hexosamines (serotypes 4, 5, 9V, 14, and 19F), methylpentoses (serotypes 6B, 7F, 18C, 19F, and 23F), and *O*-acetyl (serotypes 1, 7F, 9V, and 18C) were determined.

(b) Production of PD bulk

i) Preparation and control of PD-producing *Escherichia coli* seed

The PD-producing *Escherichia coli* seed was prepared by transfer of the plasmid containing the full-length PD gene derived from the non-typeable *Haemophilus influenzae*, obtained from A. Forsgren, M.D., Ph.D. (Lund University), into the lysogenic strain of *E. coli* AR58, obtained from the U.S. National Institute of Health. The parent seed was prepared from the strain in which plasmid retention was confirmed by drug resistance assay. The MS was prepared from the first passage of the parent seed, and the WS was prepared from the second passage of the MS.

Control testing shown in Table 2-4 is performed during preparation of the MS and WS to qualify them in individual tests. The MS and WS are stored frozen at °C. Microbial limit test has been performed every years for the WS, and the viable microbial counts were confirmed after storage for ≥ years.

Table 2-4. Control testing for PD-producing *E. coli* seed

Test items		MS	WS
Identification of *E. coli*	Gram staining	✓	✓
	Culture on LB agar medium	✓	✓
Plasmid retention rate (drug resistance)		✓	✓
Absence of contamination with adventitious microbial agents	Gram staining	✓	✓
	Culture on blood agar medium and soybean casein digest medium	✓	✓
Identification (conjugation to anti-PD antibodies)		✓	✓

ii) Manufacturing process for PD bulk

The manufacturing process for the PD bulk is shown in Table 2-5. Process validation was performed on the manufacturing process for the PD bulk at commercial scale and showed that individual steps were adequately controlled.

Table 2-5. Manufacturing process for PD bulk

Manufacturing process/critical steps		Intermediates /critical intermediates	In-process control tests
Fermentation	Prefermentation ([redacted] mL × 2)		
	Full fermentation ([redacted] L)		Identification of *E. coli* (Gram staining, fermentation on blood agar medium), absence of contamination with adventitious microbial agents
	Cell disruption		
	↓		
Purification	[redacted]		
	Clarifying (filtration)		
	[redacted]		
	Ultrafiltration		
	Filter sterilization ([redacted] μm)	PD bulk	Identification (ELISA), purity, sterility, endotoxin, protein content, PD content
	Storage (at [redacted] °C, for [redacted] months)		

Critical steps and critical intermediates are shown shaded.

(c) Production of TT bulk, purified TT bulk, and derivatized TT bulk

i) Preparation and control of *Clostridium tetani* seed

The *Clostridium tetani* seed was derived from the Harvard strain No 49205 Y-IV-4 obtained from the National Institute of Public Health and the Environment (Netherlands). The MS was prepared from the 6th passage of the strain, and the WS was prepared from the 5th passage of the MS.

Control testing shown in Table 2-6 is performed during preparation of the MS and WS to qualify them in individual tests. The MS is stored at [redacted] °C to [redacted] °C, and the WS is stored frozen at [redacted] °C. Microbial limit test has been performed every [redacted] months for the WS, and the viable microbial counts were confirmed after storage of up to [redacted] months.

Table 2-6. Control testing for *Clostridium tetani* seed

Test items		MS	WS
Absence of contamination with adventitious microbial agents	Culture on blood agar medium and trypticase soy agar medium	✓	✓
	Gram staining	✓	✓
Identification of *C. tetani* (colony morphology)		✓	✓
Hemolysis		✓	✓
Container integrity (vacuum)		✓	—

—, Undone

ii) Manufacturing process for TT bulk, purified TT bulk, and derivatized TT bulk

The manufacturing processes for the TT bulk, purified TT bulk, and derivatized TT bulk are shown in Table 2-7. Process validation was performed on the steps for individual critical intermediates at commercial scale and showed that individual steps were adequately controlled.

Table 2-7. Manufacturing process for TT bulk, purified TT bulk, and derivatized TT bulk

Manufacturing process/critical steps		Intermediates /critical intermediates	In-process control tests
Fermentation	Prefermentation (fermentation at [redacted] mL and [redacted] mL)		Absence of contamination with adventitious microbial agents
	Main fermentation ([redacted] L)		Absence of contamination with adventitious microbial agents, TT content
↓			
Detoxification	Clarifying (filtration with a filter)		
	Ultrafiltration		
	Addition of formalin		
	pH adjustment		
	Filter sterilization ([redacted] µm and [redacted] µm)		
	[redacted]		
	Agitation		Sterility, detoxification ([redacted])
↓			
Purification	Ultrafiltration		
	[redacted] ([redacted] times)		
	Ultrafiltration		
	Adjustment of [redacted] and pH		
	Filter sterilization ([redacted] µm and [redacted] µm)	TT bulk	Description, pH, identification ([redacted]), specific activity, sterility, free formaldehyde content, sodium chloride content, TT content, detoxification (*in vivo*), reversion of toxicity
	Storage (at [redacted] °C, for [redacted] months)		
↓			
Production of purified TT bulk	Ultrafiltration		
	[redacted]		TT monomer content
	Ultrafiltration		
	Filter sterilization ([redacted] µm)	Purified TT bulk	TT monomer content, protein content, specific activity, sterility, endotoxin, nitrogen content, TT content
	Storage (at [redacted] °C) [a)]		
↓			
Production of derivatized TT bulk	Dilution of purified TT bulk		
	Derivatization ([redacted] [b)] and [redacted]) and [redacted]		
	Ultrafiltration		
	Filter sterilization ([redacted] µm)	Derivatized TT bulk	TT monomer content, [redacted], protein content, sterility
	Storage (at [redacted] °C, for [redacted] months)		

Critical steps and critical intermediates are shown shaded.
a) Prior to derivatization, it is necessary to confirm that the TT monomer accounts for at least [redacted]%.
b) [redacted]

(d) Production of DT bulk and purified DT bulk

i) Preparation and control of *Corynebacterium diphtheriae* seed

The *Corynebacterium diphtheriae* seed is derived from the strain MDH#353 obtained from SmithKline Beecham (Belgium). The parent seed was prepared from the second passage of the strain. The MS was

prepared from the second passage of the parent seed, and the WS was prepared from the first passage of the MS.

Control testing shown in Table 2-8 is performed during preparation of the MS and WS to qualify them in individual tests. The MS and WS are stored frozen at [redacted]°C. Microbial limit test has been performed every [redacted] months for the WS, and the viable microbial counts were confirmed after storage of up to [redacted] months.

Table 2-8. Control testing for *Corynebacterium diphtheriae* seed

Test items		MS	WS
Absence of contamination with adventitious microbial agents	Fermentation on blood agar medium and trypticase soy agar medium	✓	✓
	Gram stain	✓	✓
Identification of *C. diphtheriae* (colony morphology)		✓	✓
Hemolysis		✓	✓

ii) Manufacturing process for DT bulk and purified DT bulk

The manufacturing processes for the DT bulk and the purified DT bulk are shown in Table 2-9. Process validation was performed on the steps for critical intermediates at commercial scale and showed that individual steps were adequately controlled.

Table 2-9. Manufacturing process for DT bulk and purified DT bulk

Manufacturing process/critical steps		Intermediates /critical intermediates	In-process control tests
Fermentation	Prefermentation (fermentation at [redacted] mL and [redacted] L)		Absence of contamination with adventitious microbial agents
	Main fermentation ([redacted] L)		Absence of contamination with adventitious microbial agents, DT content
↓			
Detoxification	Clarifying (filtration with a filter)		
	Addition of formalin		Sterility, detoxification ([redacted])
	Agitation		
↓			
Purification	Ultrafiltration		
	[redacted] ([redacted] times)		
	Ultrafiltration		
	Adjustment of [redacted] and pH		
	Filter sterilization ([redacted] µm and [redacted] µm)	DT bulk	Description, pH, identification ([redacted]), specific activity, sterility, free formaldehyde content, sodium chloride content, DT content, detoxification (*in vitro*), reversion of toxicity
	Storage (at [redacted]°C, for [redacted] months)		
↓			
Production of purified DT bulk	Ultrafiltration		
	[redacted]		DT monomer content
	Ultrafiltration		
	Filter sterilization ([redacted] µm)	Purified DT bulk	DT monomer content, protein content, specific activity, sterility, endotoxin, [redacted], DT content
	Storage (at [redacted]°C)[a)]		

Critical steps and critical intermediates are shown shaded.

a) Prior to conjugation, it is necessary to confirm that the DT monomer accounts for at least [redacted]%.

(e) **Production of PS-PD bulk**

The manufacturing process for the PS-PD bulk is shown in Table 2-10. The microfluidization step is omitted for serotypes [redacted] or [redacted].

Table 2-10. Manufacturing process for PS-PD bulk

Manufacturing process/critical steps		Intermediates /critical intermediates	In-process control tests
Microfluidization[a)]	Dissolution of PS bulk		
	Clarifying (filtration with a filter)		
	High pressure treatment (jet injection through a high-pressure nozzle is repeated for microfluidization of the PS bulk)		
	Filter sterilization ([redacted] µm)	Microfluidized PS bulk	Viscosity, sterility
	Storage (at [redacted] °C, for [redacted] months)		
	↓		
	Microfluidized PS and PS bulks / PD bulk		
Conjugation of PS to PD	Preparation of microfluidized PS and PS bulks / Thawing of PD bulk		
	Activation of PS bulk and microfluidized PS bulk by CDAP[b)] / Clarifying (filtration with a filter)		
	dilution		
	↓ ↓		
	Conjugation of activated PS bulk and PD bulk		
	Termination of reaction ([redacted])		
	Filtration with a filter		
	[redacted]		
	Filter sterilization ([redacted] µm)	PS-PD bulk (drug substance)	pH, specification test for drug substance[d)]
	Storage (at [redacted] °C, for [redacted] or [redacted] months [c)])		

Critical steps and critical intermediates are shown shaded.
a) Serotypes other than those [redacted] and [redacted]. b) CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate.
c) See "2.A.(1).7) Stability of the drug substance" section. d) See "2.A.(1).6) Control of drug substance" section.

Process validation was performed on the manufacturing process for the PS-PD bulk at commercial scale and showed that individual steps were adequately controlled.

(f) Production of PS18C-TT bulk

The manufacturing process for the PS18C-TT bulk is shown in Table 2-11. Process validation was performed on the manufacturing process for the PS18C-TT bulk at commercial scale and showed that individual steps were adequately controlled.

Table 2-11. Manufacturing process for PS18C-TT bulk

Manufacturing process/critical steps			Intermediates /critical intermediates	In-process control tests
Microfluidization	Dissolution of PS bulk			
	Clarifying (filtration with a filter)			
	High pressure treatment (jet injection through a high-pressure nozzle is repeated for microfluidization of the PS bulk)			
	Filter sterilization([redacted] μm)		Microfluidized PS bulk	Viscosity, sterility
	Storage (at [redacted]°C, for [redacted] months)			
	↓			
	Microfluidized PS bulk	Derivatized TT bulk		
Conjugation of PS to TT	Dilution of microfluidized PS bulk	Dilution of derivatized TT bulk		
	Activation of microfluidized PS bulk by CDAP [a)]	↓		
	↓			
	Conjugation of activated PS bulk and derivatized TT bulk			
	Termination of reaction ([redacted])			
	Clarifying (filtration with a filter)			
	[redacted]			
	Filter sterilization ([redacted] μm)		PS18C-TT bulk (drug substance)	pH, specification test for drug substance[b)]
	Storage (at [redacted]°C, for [redacted] months)			

Critical steps and critical intermediates are shown shaded.
a) CDAP, 1-cyano-4-dimethylaminopyridinium tetrafluoroborate b) See "2.A.(1).6) Control of drug substance" section.

(g) Production of PS19F-DT bulk

The manufacturing process for the PS19F-DT bulk is shown in Table 2-12. Process validation was performed on the manufacturing process for the PS19F-DT bulk at commercial scale and showed that individual steps were adequately controlled.

Table 2-12. Manufacturing process for PS19F-DT bulk

Manufacturing process/critical steps			Intermediates /critical intermediates	In-process control tests
Microfluidization	Dissolution of PS bulk			
	Clarifying (filtration with a filter)			
	High pressure treatment (jet injection through a high-pressure nozzle is repeated for microfluidization of the PS bulk)			
	Filter sterilization ([redacted] μm)		Microfluidized PS bulk	Viscosity, sterility
	Storage (at [redacted]°C, for [redacted] months)			
	↓			
	Microfluidized PS bulk	Purified DT bulk		
Conjugation of PS to DT	Dilution of microfluidized PS bulk	Dilution of purified DT bulk		DT monomer content (before dilution of purified DT bulk)
	Activation of microfluidized PS bulk by CDAP [a)]	↓		
	↓			
	Conjugation of activated PS bulk and purified DT bulk			
	Termination of reaction ([redacted])			
	Clarifying (filtration with a filter)			
	[redacted]			
	Filter sterilization ([redacted] μm)		PS19F-DT bulk (drug substance)	pH, specification test for drug substance[b)]
	Storage (at [redacted]°C, for [redacted] months)			

Critical steps and critical intermediates are shown shaded.
a) CDAP, 1-cyano-4-dimethylaminopyridinium tetrafluoroborate b) See "2.A.(1).6) Control of drug substance" section.

2.A.(1).2) Safety assessment for adventitious infectious agents

Among materials of biological origin used in the manufacturing process for the drug substance (Table 2-13), casein hydrolysate, casein peptone, and pancreatin used in the production processes for casein hydrolysate and casein peptone were qualified for the Standards for Biological Materials. Although a certificate has been issued certifying that tryptone and pancreatin used in the production process for tryptone were qualified for the Standards for Biological Materials, the details are being confirmed.

Table 2-13. Materials of biological origin used in manufacturing process for drug substance

Steps	Materials	Animals	Parts used
Fermentation step in production of PS bulk (media component)	Casein hydrolysate	Bovine	Milk
Fermentation process in preparation of *C. tetani* seed and production of TT bulk (media component)	Casein peptone	Bovine	Milk
Fermentation processes in preparation of *C. diphtheriae* seed and production of TT and DT bulks (media component)	Tryptone	Bovine	Milk
Manufacturing processes for casein hydrolysate, casein peptone, and tryptone	Pancreatin	Porcine	Pancreas Duodenum

Casein hydrolysate and pancreatin, used in the manufacturing process for casein hydrolysate, are both heated at approximately [redacted]°C for ≥[redacted] sec and then at [redacted]°C for [redacted] min. Viral clearance was evaluated for the manufacturing process for casein hydrolysate. Casein peptone and pancreatin, used in the manufacturing process for casein peptone, are each heated either at [redacted]°C for [redacted] min or [redacted]°C for [redacted] min, and medium containing casein peptone is autoclaved before use for fermentation. Tryptone and pancreatin, used in the manufacturing process for tryptone, are heated at [redacted]°C for ≥[redacted] min.

2.A.(1).3) Manufacturing process development

Major changes in the manufacturing of the drug substance are shown in Table 2-14. The drug product was initially developed as an 11-valent vaccine (11Pn-PD) formulation in which PSs of 11 serotypes (10 serotypes contained in Synflorix and serotype 3) were each conjugated to PD (Process 1). In development phase, the changes shown in Table 2-14 were made. In Study Undeca-Pn-010, a foreign clinical study, the 11Pn-PD formulation was used. Later, it was decided to use drug substances of PSs conjugated to TT and DT for serotypes 18C and 19F, respectively (PS18C-TT bulk and PS19F-DT bulk), and therefore the drug substances (active ingredients) were changed (Process 2). In addition, the drug substance of serotype 3 was removed from the final formulation of the drug product.

In Studies 10PN-PD-DIT-001 and 10PN-PD-DIT-028, foreign clinical studies, a formulation manufactured from the drug substances in Process 2 was used. In Study 10PN-PD-DIT-058, a Japanese phase III study, and Studies 10PN-PD-DIT-043 and 10PN-PD-DIT-053, foreign clinical studies, a formulation manufactured from the drug substances in Process 3 was used. The drug substances in Process 4 are proposed to be used for the final formulation intended for marketing. Quality assessment performed before and after the changes showed that the quality of drug substances was comparable among Processes 2, 3, and 4.

Table 2-14. Major changes in manufacturing process for drug substances

Process	Changes
2	・ Changes in active ingredients (conjugation of PS of serotype 18C to TT, and conjugation of PS of serotype 19F to DT) ・ Introduction of microfluidization step for PS bulks (serotypes [redacted])
3	・ Introduction of microfluidization step for PS bulk (serotype [redacted]) ・ Change of alcohol used for alcohol precipitation and [redacted] for PS bulk (serotype [redacted]) ・ Change of buffer used for [redacted] and [redacted] for PS bulks (serotypes [redacted]) ・ Change in storage temperature for PS bulks (serotypes [redacted])
4	・ Changes in conjugation scales for PS-carrier protein bulks (serotypes [redacted])

2.A.(1).4) Characterization

The critical intermediates, that is, PS bulk, microfluidized PS bulk, PD bulk, TT bulk and DT bulk, and the drug substances were characterized.

Molecular sizes of the PS bulk and/or microfluidized PS bulk for each of the 10 serotypes contained in the drug product were analyzed by size exclusion chromatography/multi-angle laser light scattering detector. The nuclear magnetic resonance (NMR) spectra (^{1}H-NMR and ^{13}C-NMR) of the PS bulks of the 10 serotypes showed that the structures of all of the PS bulks were identical to those of the PSs described in publications. *O*-acetyl content in the PS bulks and the microfluidized PS bulks of serotypes [redacted], and pyruvyl content in the PS bulks and microfluidized PS bulks of serotype [redacted] were analyzed by ^{1}H-NMR and liquid chromatography/ultraviolet spectrophotometry.

Amino acid composition analysis after hydrolysis (postcolumn derivatization), N-terminal amino acid sequence (Edman degradation), and peptide analysis after enzyme treatment (liquid chromatography/tandem mass spectrometry) were performed for the PD bulk, and the results demonstrated that the primary structure of PD was consistent with its theoretical amino acid sequence. Circular dichroism spectrum, fluorescence spectrum (spectrofluorometry), and infrared spectrum (attenuated total reflection Fourier-transform infrared spectrophotometry) were analyzed to determine the secondary structure of PD. The mean molecular weight of PD (electrospray ionization mass spectrometry) was confirmed to be consistent with its theoretical molecular weight. Electrophoresis (sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE]) under reducing and nonreducing conditions and western blotting showed a main band around [redacted] kDa, which corresponds to PD, and isoelectric focusing showed multiple bands between isoelectric points [redacted] and [redacted]. In addition, the molecular size (multi-angle laser light scattering detection) showed that PD forms a dimer in solution. Glycerophosphodiester phosphodiesterase activity was observed as a biological activity of PD.

With regard to the TT bulk, SDS-PAGE under reducing and nonreducing conditions and western blotting showed a main band around [redacted] kDa corresponding to TT, and isoelectric focusing showed multiple bands between isoelectric points [redacted] and [redacted]. In addition, size exclusion chromatography showed two peaks corresponding to a polymer or aggregate prior to the peak corresponding to the TT monomer.

With regard to the DT bulk, SDS-PAGE under reducing and nonreducing conditions and western blotting showed a main band around [redacted] kDa corresponding to DT and a minor band of an aggregate around [redacted] kDa, and isoelectric focusing showed multiple bands between isoelectric points [redacted] and [redacted]. In addition, two peaks corresponding to a polymer or aggregate were shown prior to the peak corresponding to the DT monomer in the size exclusion chromatogram. The free amino group content (mol NH_2/mol DT) was shown to be [redacted] to [redacted].

Analyses were conducted on the molecular sizes of the drug substances produced in Processes 3 and 4 of 10 serotypes (size exclusion chromatography/multi-angle laser light scattering detection), *O*-acetyl content in the drug substances for serotypes [redacted] and [redacted] (liquid chromatography/ultraviolet spectrophotometry), and pyruvyl content in the drug substance for serotype [redacted] (liquid chromatography/ ultraviolet spectrophotometry). Immunogenicity was evaluated in studies in mice and guinea pigs with the drug product formulation and adsorbed bulks for serotypes [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

2.A.(1).5) Impurities

Among impurities found in the manufacturing processes of the drug substances, protein, nucleic acid, alcohol, core polysaccharide, endotoxin, and free formaldehyde are controlled by in-process control testing. Studies were performed to determine the residual amounts of [redacted], phenol, [redacted], DNA, protein derived from *E. coli*, [redacted], [redacted], [redacted], free formaldehyde, and protein and showed that these impurities were removed consistently during the manufacturing process. In addition, studies were performed to determine the residual amounts of [redacted] and [redacted] in the drug substances of 10 serotypes and the residual amounts of [redacted] and [redacted] in the drug substance of serotype [redacted] and the results showed that these impurities were removed consistently during the manufacturing process.

2.A.(1).6) Control of drug substance

The proposed specifications for the drug substance include identification (ELISA), free polysaccharide, free carrier protein, endotoxin, sterility, molecular size distribution, protein content, polysaccharide content, and polysaccharide/protein ratio.

2.A.(1).7) Stability of the drug substance

The stability study for the drug substance is shown in Table 2-15.

In the long-term stability test, all test results were within the range of specifications during the storage period. Based on the above, shelf lives when stored at [redacted]°C to [redacted]°C in a polycarbonate container have been proposed as follows: [redacted] months for the drug substances containing serotypes [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]; and [redacted] months for the drug substances containing serotype [redacted], [redacted], [redacted], and [redacted].

Table 2-15. Stability study for drug substance

Study name	Number of batches	Temperature	Storage container	Storage period
Long-term stability testing	3 batches	[redacted]°C to [redacted]°C	Polycarbonate container	[redacted] or [redacted] months [a)]

a) Depending on serotypes.

2.A.(2) Drug product

2.A.(2).1) Formulation and development of drug product

The drug product is a solution for injection which contains PS-carrier protein conjugates as active ingredients, and each 0.5-mL dose (prefilled in a syringe) contains 1 µg each of PSs (serotypes 1, 5, 6B, 7F, 9V, 14, and 23F) along with 3 µg each of PSs (serotypes 4, 18C, and 19F). As carrier proteins conjugated to PSs, TT is used for serotype 18C, DT for 19F, and PD for the remaining 8 serotypes. The drug product contains aluminum phosphate, sodium chloride, hydrochloric acid, and sodium hydroxide as excipients. The drug product is filled into a glass syringe.

2.A.(2).2) Manufacturing process

The manufacturing process for the drug product is shown in Table 2-16. Process validation was performed on the manufacturing process at commercial scale and showed that the individual process steps were adequately controlled.

Table 2-16. Manufacturing process for drug product

Manufacturing process/critical steps		Intermediates/critical intermediates and drug product	In-process control tests
Adsorption	Mixture and agitation of aluminum phosphate and drug substances		
	pH adjustment		
	Agitation for adsorption		
	pH adjustment		
	Standing (at [redacted]°C to [redacted]°C, for [redacted] days)	Adsorbed bulks	Sterility, identification of PS-carrier protein, free polysaccharide content, rate of unadsorbed PS-carrier protein, aluminum content
	Storage of adsorbed bulks (at [redacted]°C, for [redacted] or [redacted] months [a)])		
↓			
Formulation	Addition of water for injections, sodium chloride solution, and aluminum phosphate		
	Agitation		
	pH adjustment		
	Agitation		
	Addition of each adsorbed bulk		
	Agitation		
	pH adjustment	Final bulk	Sterility
↓			
Filling	Filling		
	Labelling and packaging	Drug product (stored at 4°C, for 36 months)	Specification test for drug product[b)]

Critical steps, critical intermediates, and drug product are shown shaded.
a) Depending on serotypes b) See "2.A.(2).4) Control of drug product" section.

2.A.(2).3) Manufacturing process development

During the manufacturing process development, the conditions (pH and agitation time) in the process of adsorption to aluminum phosphate for the drug substances for serotypes [redacted], [redacted], and [redacted] were changed. Quality assessment performed on the adsorbed bulks showed that the quality was comparable between the bulks produced before and after the changes. Formulation produced in the manufacturing process before the changes was used in Japanese and foreign clinical studies.

2.A.(2).4) Control of drug product

The proposed specifications for the drug product include description, identification, pH, endotoxin, extractable volume, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, absence of abnormal toxicity, aluminum content, and assay (PS content).

2.A.(2).5) Stability of drug product

Stability studies for the drug product are shown in Table 2-17.

Table 2-17. Stability studies for the drug product

Study	Manufacturing process for drug substances	Number of batches	Storage conditions	Storage container	Storage period
Long-term stability testing	Process 3	3	2°C to 8°C	Glass syringe	36 months
	Process 4	6[a)]	2°C to 8°C	Glass syringe	36 months
Accelerated testing	Process 4	3	25°C	Glass syringe	6 months
	Process 4	6	37°C	Glass syringe	7 days
Cycle testing	Process 3	2	2°C to 8°C/25°C[b)]	Glass syringe	36 months

a) Tests for 3 batches are ongoing.
b) The drug product was stored at 2°C to 8°C for 11 or 11.5 months, then at 25°C for 14 days or 1 month, and finally at 2°C to 8°C for 24 months.

In the long-term stability test, all test results were within the range of specifications and showed no changes over time during the storage period of 36 months. In the cycle test, all test results were within the range of specifications even with temperature excursion at 25°C for up to 1 month. Based on the above, a shelf life of 36 months has been proposed for the drug product, when filled into a glass syringe and stored at 2°C to 8°C.

2.A.(3) Reference materials

The reference materials used for the assay (PS content) are subdivided drug products containing 1 μg of PSs (each for serotypes 1, 5, 6B, 7F, 9V, 14, and 23F) or 3 μg of PSs (each for serotypes 4, 18C, and 19F) and are stored at 2°C to 8°C. Regeneration criteria have been specified for the reference materials, and the proposed specifications for regenerated reference materials include description, identification, pH, endotoxin, extractable volume, sterility, aluminum content, and assay (PS content).

The PS bulks of the 10 serotypes are used as the PS reference materials in free polysaccharide tests and polysaccharide content tests and are stored at [redacted]°C. Regeneration criteria have been specified for the

reference materials, and the same specifications for the PS bulks are proposed to be used for the regenerated reference materials.

The PD bulk, derivatized TT bulk, and purified DT bulk are used as the PD reference material, derivatized TT reference material, and purified DT reference material, respectively, in free carrier protein tests and are stored at [redacted]°C, [redacted]°C, and [redacted]°C to [redacted]°C, respectively. Regeneration criteria have been defined for the reference materials, and the same specifications for the PD bulk, derivatized TT bulk, and purified DT bulk are proposed to be used for the regenerated reference materials.

2.B Outline of the review by PMDA

2.B.(1) Uniformity of dosage units

The applicant's explanation on the uniformity of the content of the active substance in the drug product:
Six syringes of the drug products (which is filled in the final container) would be necessary to determine the content of PSs specifying the strength of each active ingredient for 10 serotypes, since the content of each PS for 10 serotypes cannot be measured with 1 drug product. Accordingly, specification tests are set to determine the total PS content (i.e., total content of all PSs for 10 serotypes), not individual PS content.

In the process validation of the filling step, the individual PS contents in combined several drug products were determined at the initial, intermediate, and final stages of the filling step, and the validation showed that individual active substances were uniformly filled. The rate of active substances unadsorbed onto aluminum phosphate in the drug product is [redacted]% or less for all serotypes, and therefore, it is expected that individual PSs are filled uniformly if aluminum phosphate is uniformly filled. Process validation showed that the aluminum phosphate content was constant at the initial, intermediate, and final time points of the filling step. Based on the above, the uniformity of content of individual active substances in the drug product can be consistently assured by controlling the total PS content in the testing for uniformity of dosage units.

PMDA accepted the applicant's explanation.

2.B.(2) Novel excipients

Since the amount of aluminum phosphate contained as an excipient in the drug product exceeds that in precedent use for intramuscular administration, aluminum phosphate is deemed to be a novel excipient.

Based on the submitted data, PMDA concluded that there is no problem with the specification and stability of the excipient (aluminum phosphate). With regard to the safety, inflammatory changes with necrosis at the injection site were observed in the repeated-dose toxicity studies in which the excipient was used. PMDA therefore concluded that aluminum phosphate as an excipient at the amount should not be regarded as a general precedent use in later applications and that it is appropriate to limit the

excipient to be used for enhancement of immune response to preventive vaccines against infectious diseases.

3. Nonclinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

In primary pharmacodynamic studies, immunogenicity was evaluated for the drug formulation produced from the drug substances in Process 2 (hereinafter referred to as "10Pn-PD-DiT") [see the section "2.A.(1).3) Manufacturing process development"], 11Pn-PD&Di (Composition 1, Composition 2), and 11Pn-PD. In safety pharmacology studies, cardiovascular and respiratory effects of 11Pn-PD-DiT were evaluated. Table 3-1 shows the polysaccharide content and the type of carrier proteins by serotype contained in the substances studied.

Table 3-1. List of substances studied

Serotypes		1	3	4	5	6B	7F	9V	14	18C	19F	23F
10Pn-PD-DiT	Content [a)]	1		3	1	1	1	1	1	3	3	1
	Type [b)]	PD		PD	PD	PD	PD	PD	PD	TT	DT	PD
11Pn-PD	Content [a)]	1	1	1	1	1	1	1	1	1	1	1
	Type [b)]	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD
11Pn-PD&Di (Composition 1)	Content [a)]	3	3	3	3	10	3	3	3	3	3	5
	Type [b)]	PD	PD	PD	PD	DT	PD	PD	PD	PD	DT	DT
11Pn-PD&Di (Composition 2)	Content [a)]	5	5	5	5	10	5	5	5	5	5	5
	Type [b)]	PD	PD	PD	PD	DT	PD	PD	PD	PD	PD	DT
11Pn-PD-DiT	Content [a)]	3	3	3	3	3	3	3	3	10	3	3
	Type [b)]	PD	PD	PD	PD	TT	PD	PD	PD	DT	DT	TT

PD, protein D; TT, tetanus toxoid; DT, diphtheria toxoid
a) Polysaccharide content (μg) per 0.5 mL, b) Type of carrier protein

3.(i).A.(1) Primary pharmacodynamics

Immunogenicity studies in rabbits, mice, and guinea pigs (4.2.1.1-2, Study PIMS20[redacted]0321; 4.2.1.1-1, Studies 20[redacted]0285 and 20[redacted]0301)

In Study PIMS20[redacted]0321, 0.5 mL of physiological saline solution, 11Pn-PD&Di (Composition 1), or 11Pn-PD&Di (Composition 2) (a total of 5 doses, with an interval of 2 weeks between doses) were intramuscularly administered to rabbits (3 females per group, a total of 9 animals in 3 groups). Serum concentrations of IgG antibodies specific to each of 7 serotypes (1, 3, 5, 6B, 7F, 19F, and 23F) were measured 14 days after the second dose was administered. The percentage of rabbits with each serotype-specific IgG antibody concentration equal to or above the lower limit of quantitation was 0% for all serotypes in the saline group and 100% for all serotypes in the 11Pn-PD&Di (Composition 1) and 11Pn-PD&Di (Composition 2) groups.

In Study 20[redacted]0285, mice (40 females per group, a total of 80 animals in 2 groups) were intramuscularly administered 0.05 mL of 10Pn-PD-DiT or 11Pn-PD (a total of 3 doses, with an interval of 2 weeks between doses). In Study 20[redacted]0301, guinea pigs (20 females per group, a total of 40 animals in 2 groups) were intramuscularly administered 0.125 mL of 10Pn-PD-DiT or 11Pn-PD (a total of 3 doses, with an

interval of 2 weeks between doses). Serum concentration of each serotype-specific IgG antibody was measured 14 days (in mice) or 16 days (in guinea pigs) after the third dose was administered. In all groups of mice and guinea pigs, the percentage of animals with each serotype-specific IgG antibody concentration equal to or above the lower limit of quantitation was 100% for all serotypes except for serotype 6B (41% in the 10Pn-PD-DiT group and 44% in the 11Pn-PD group in mice; 68% in the 10Pn-PD-DiT group and 100% in the 11Pn-PD group in guinea pigs). Based on the above, the applicant explained that administration of 10Pn-PD-DiT is expected to induce the production of each serotype-specific IgG antibody.

In Studies 20[redacted]0285 and 20[redacted]0301, geometric mean concentrations of IgG antibodies (IgG GMCs) were compared for serotypes 18C and 19F for which the type of carrier protein differed between 10Pn-PD-DiT and 11Pn-PD (Table 3-1). The comparison showed that all IgG GMCs in the 10Pn-PD-DiT groups were higher than those in the 11Pn-PD groups (1.9 to 13.6 times higher). Based on the above, the applicant explained that higher immune response is expected to be induced by changing the carrier proteins from PD to TT for serotype 18C and DT for serotype 19F.

3.(i).A.(2) Safety pharmacology

3.(i).A.(2).1) Respiratory and cardiovascular effects (4.2.1.3-1, Study BVR 542/042318)

A single dose of 0.2 mL of physiological saline solution or 11Pn-PD-DiT (equivalent to approximately 5.5 times the proposed clinical dose on a body weight basis) was intramuscularly administered to rats (4 males per group, a total of 8 animals in 2 groups). Cardiovascular parameters (blood pressure, heart rate, lead II electrocardiography) and respiratory parameters (respiratory rate, tidal volume, minute volume) were measured under anesthesia from baseline to 2 hours post-dose. In 1 animal in the 11Pn-PD-DiT group, decreases in blood pressure and in respiratory rate and abnormal electrocardiograms were observed, but these parameters returned to baseline or showed a sign of recovery within approximately 30 min. No effects on cardiovascular or respiratory parameters were noted in the other 3 animals in the 11Pn-PD-DiT group.

3.(i).A.(2).2) Effects on central nervous system

Effects of 10Pn-PD-DiT on central nervous system were assessed by clinical signs, necropsy, and histopathology data in a repeat-dose toxicity study in rabbits (4.2.3.2-1, Study V7841) [see section "3.(iii).A.(2).(a) Five-time repeat-dose study in rabbits with 4-week recovery period"]. No effects on central nervous system due to 10Pn-PD-DiT were observed.

3.(i).B Outline of the review by PMDA

PMDA accepted the applicant's explanation that data from the primary pharmacodynamic studies indicate that administration of 10Pn-PD-DiT is expected to induce the production of each serotype-specific IgG antibody.

The types of carrier protein and the polysaccharide contents for serotypes 18C and 19F differ between 10Pn-PD-DiT and 11Pn-PD: the polysaccharide content in 10Pn-PD-DiT is 3 times that in 11Pn-PD (Table 3-1). The applicant explained that the relatively higher immune response in the 10Pn-PD-DiT groups than in the 11Pn-PD groups in Studies 20[redacted]0285 and 20[redacted]0301 was attributable to the changes made to the carrier protein types for serotype 18C and 19F. However, the content of polysaccharide as an antigen in 10Pn-PD-DiT is 3 times that in 11Pn-PD, suggesting that the increased polysaccharide content might contribute to the higher immune response in the 10Pn-PD-DiT groups. In order to evaluate the effects of changing the types of carrier protein, the applicant should have planned a study comparing 10Pn-PD-DiT and a substance studied containing the same polysaccharide content as but different carrier protein type from 10Pn-PD-DiT.

In light of the above, PMDA thinks that the applicant should consider conducting further pharmacological evaluation on the significance of changing the types of carrier protein in 10Pn-PD-DiT.

3.(ii) Summary of pharmacokinetic studies

No pharmacokinetic studies have been performed.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

In single-dose and repeat-dose toxicity studies, the drug formulation (hereinafter referred to as 10Pn-PD-DiT) that was produced from the drug substances obtained in Process 2, 3 and 4 was used. The drug substances obtained in Process 2, 3 and 4 had been confirmed to be of comparable quality [see the section "2.A.(1).3) Manufacturing process development"].

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1, Study V9912/02)

An intramuscular single dose of 0.5 mL 10Pn-PD-DiT (equivalent to approximately 2 times the proposed clinical dose on a body weight basis) was administered into the femoral muscle or gastrocnemius muscle of rabbits (3 per sex per group, a total of 12 in 4 groups). In the control group, rabbits (3 per sex) were intramuscularly administered a total of 1 mL of physiological saline solution, which was given as a single dose of 0.5 mL each into the femoral muscle and gastrocnemius muscle. No deaths occurred in any groups, and no findings related to administration of 10Pn-PD-DiT were observed in clinical signs or body weight. Local tolerance evaluated in these studies is discussed in the section "3.(iii).A.(6) Local tolerance studies."

3.(iii).A.(2) Repeat-dose toxicity

(a) Five-time repeat-dose study in rabbits with 4-week recovery period (4.2.3.2.1, Study V7841)

Physiological saline solution or 10Pn-PD-DiT at 0.5 mL (equivalent to approximately 1.7 times the proposed clinical dose on a body weight basis) was intramuscularly administered (a total of 5 doses, with an interval of 1 week between the first and second doses and an interval of 2 weeks between the subsequent doses) to rabbits (10 per sex per group, a total of 40 in 4 groups). No deaths occurred in any groups, and no findings related to administration of 10Pn-PD-DiT were observed in clinical signs, ophthalmic examination, rectal temperature, body weight, food consumption, or organ weights. After administration of 10Pn-PD-DiT, blood tests and blood biochemical tests showed high fibrinogen levels and low albumin/globulin ratio, and all these changes were reversible 28 days after the final administration. Necropsy performed 3 days after the final dose of 10Pn-PD-DiT was administered showed discoloration and nodules at injection site. Histopathological examination showed inflammatory changes at injection site (mild to severe cell infiltration, necrosis and edema of muscle fibers), which were reversible 28 days after the final dose was administered.

(b) Five-time repeat-dose study in rabbits with 12-week recovery period (4.2.3.2.2, Study V20046)

Physiological saline solution or 10Pn-PD-DiT at 0.5 mL (equivalent to approximately 1.7 times the proposed clinical dose on a body weight basis) was intramuscularly administered (a total of 5 doses, with an interval of 2 weeks between doses) to rabbits (20 per sex per group, a total of 80 in 4 groups). In the 10Pn-PD-DiT group, 1 male died, and 2 females were sacrificed moribund because of lumbar fracture or deterioration of the clinical conditions. In surviving animals in the 10Pn-PD-DiT group, no findings related to administration of 10Pn-PD-DiT were observed in clinical conditions, ophthalmic examination, rectal temperature, body weight, food consumption, or organ weights. After administration of 10Pn-PD-DiT, blood tests and blood biochemical tests showed high fibrinogen levels, neutrophil counts, and C-reactive protein (CRP) levels, and all these changes were reversible 29 days after the final dose was administered. Necropsy performed 3 days after the final dose of 10Pn-PD-DiT was administered showed discoloration at injection site. Histopathological examination showed inflammatory changes at injection site (moderate to severe cell infiltration as well as necrosis and degeneration of muscle fibers), which were reversible 29 days after the final dose was administered.

The rabbit that died was only partially necropsied, and the cause of death was unknown. However, the clinical observation performed before the death showed no signs leading to death. In the rabbit that was sacrificed moribund because of deterioration of the clinical condition, emaciation and dyspnea were observed after the first dose of 10Pn-PD-DiT was administered, and gross changes at necropsy after sacrifice included changes in the lungs, tracheae, and bronchi, suggesting deterioration of clinical conditions due to respiratory diseases. Since no effects were observed in the surviving rabbits in the 10Pn-PD-DiT group except for effects on injection sites in Studies V7841 and V20046, the death and deterioration of clinical conditions in the 2 rabbits were considered to be incidental and not related to administration of 10Pn-PD-DiT.

3.(iii).A.(3) Genotoxicity

No genotoxicity studies have been performed.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity studies have been performed.

3.(iii).A.(5) Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been performed.

3.(iii).A.(6) Local tolerance

Local tolerance of 10Pn-PD-DiT was evaluated in a single-dose toxicity study (Study V9912/02). Necropsy performed 3 days after administration of 10Pn-PD-DiT showed discoloration at the injection site, and histopathological examination showed inflammatory changes at the injection site (severe infiltration of inflammatory cells and necrosis of muscle fibers). While reversibility was not assessed in the single-dose toxicity study, the similar findings at the injection site were shown to be reversible in the repeat-dose toxicity studies (Studies V7841 and V20046) [see the section "3.(iii).A.(2) Repeat-dose toxicity"].

3.(iii).B Outline of the review by PMDA

PMDA concluded that there are no particular problems with the toxicity of 10Pn-PD-DiT.

4. Clinical data

4.A Summary of the submitted data

Data from 17 clinical studies were submitted as evaluation data on efficacy and safety. Data from 26 clinical studies were submitted as reference data. A summary of the evaluation data is shown in Table 4-1. The abbreviation of vaccine names is shown in Table 4-2, and the active ingredients of Synflorix and 11Pn-PD are shown in Table 4-3.

Table 4-1. Summary of clinical studies

Phase	Study name	Country	Design	Subjects	Number of enrolled subjects	Vaccination route/dose	Vaccination schedule	Co-administered vaccine	Study objectives
Evaluation data									
III	10PN-PD-DIT-058	Japan	Uncontrolled	Healthy infants	Synflorix + DPT group: 237 DPT group: 123	Synflorix, intramuscular; DPT, subcutaneous; 0.5 mL	Vaccination with Synflorix or DTP, with the first dose at 3 months of age, the second and third doses with an interval of 28 to 56 days between doses, and the fourth dose at 17 to 19 months of age	DPT (Synflorix + DPT group only); coadministration of Hib/HBV was allowed if requested	Immunogenicity/safety
III	10PN-PD-DIT-001	Finland, France, Poland	Randomized, double-blind[a)] Randomized, subject-blind[a)]	Healthy infants	Synflorix (Lot 1) group: 413 Synflorix (Lot 2) group: 409 Synflorix (Lot 3) group: 413 7vPnC group: 415	Intramuscular 0.5 mL	Vaccination with Synflorix or 7vPnC, with the first dose at 2 months of age, followed by the second and third doses with an interval of 28 to 42 days between doses	DPT-HBV-IPV/Hib [b)]	Immunogenicity (non-inferiority to 7vPnC, comparison among lots)
III	10PN-PD-DIT-002	Denmark, Norway, Slovakia, Sweden	Randomized, open-label	Healthy infants	Synflorix Group 1 (3 doses): 175 Group 2 (4 doses): 176	Intramuscular 0.5 mL	Group 1: Vaccination with Synflorix, with the first dose at 2 months of age, the second dose with an interval of 28 to 42 days, and the third dose at 11 months of age Group 2: Vaccination with Synflorix, with the first dose at 2 months of age, the second and third doses with an interval of 28 to 42 days between doses, and the fourth dose at 11 months of age	DPT-HBV-IPV/Hib or DPT-IPV/Hib [c)]	Immunogenicity
III	10PN-PD-DIT-003	Germany	Randomized, subject-blind	Healthy infants	Synflorix group: 70 7vPnC group: 64	Intramuscular 0.5 mL	Vaccination with Synflorix or 7vPnC, with the first dose at 2 months of age, followed by the second and third doses with an interval of 28 to 42 days between doses	DPT-HBV-IPV/Hib	Immunogenicity
III	10PN-PD-DIT-013	Finland	Nonrandomized	Healthy infants	Synflorix Group 1 (4 doses): 150 Group 2 (3 doses): 150 Group 3 (2 doses): 150 Group 4 (1 dose): 150	Intramuscular 0.5 mL	Group 1: Vaccination with Synflorix, with the first dose at 9 to 12 weeks of age, the second and third doses with an interval of 28 to 42 days between doses, and the fourth dose at 12 to 15 months of age Group 2: Vaccination with Synflorix, with the first dose at 7 to 11 months of age, the second dose with an interval of 28 to 42 days, and the third dose at 12 to 15 months of age Group 3: Vaccination with Synflorix, with the first dose at 12 to 23 months of age, followed by the second dose with an interval of 56 to 118 days Group 4: Vaccination with Synflorix, with the first dose at 24 months of age or older	DPT-IPV/Hib[d)]	Immunogenicity
III	10PN-PD-DIT-028	Argentina, Panama, Colombia	Randomized, assessor- and subject-blind	Healthy infants	Synflorix group: 10,211 HBV/HAV group: 10,140	Intramuscular 0.5 mL	Vaccination with Synflorix or HBV, with the first dose at 2 months of age, the second and third doses with an interval of 49 to 83 days between doses, and the booster dose (fourth dose of Synflorix or first dose of HAV) at 15 to 18 months of age	DPT-HBV-IPV/Hib or DPT-IPV/Hib[e)]	Efficacy against CAP
III /IV	10PN-PD-DIT-043	Finland	Cluster-randomized, double-blind	Healthy infants	6 weeks to 6 months of age Synflorix 2+1 group: 10,275 Synflorix 3+1 group: 10,426 HBV 2+1 and HBV 3+1 groups: 10,810 7 to 11 months of age Synflorix group: 3930 HBV group: 2017 12 to 18 months of age Synflorix group: 6616 HAV group: 3292	Intramuscular 0.5 mL	6 weeks to 6 months of age Synflorix group and HBV 2+1 group: Vaccination with Synflorix or HBV, with the first and second doses with an interval of at least 56 days between doses, and the third dose with an interval of at least 4 months Synflorix group and HBV 3+1 group: Vaccination with Synflorix or HBV, with the first, second, and third doses with an interval of at least 28 days between doses, and the fourth dose with an interval of at least 4 months 7 to 11 months of age Vaccination with Synflorix or HBV, with the first and second doses with an interval of at least 28 days between doses, and the third dose with an interval of at least 4 months 12 to 18 months of age Vaccination with Synflorix or HAV, with the first and second doses with an interval of at	None	Efficacy against IPD

Phase	Study name	Country	Design	Subjects	Number of enrolled subjects	Vaccination route/dose	Vaccination schedule	Co-administered vaccine	Study objectives
							least 6 months between doses		
III	10PN-PD-DIT-053	Finland	Cluster-randomized, double-blind	Healthy infants (including subjects who participated in Study 10PN-PD-DIT-043)	6 weeks to 6 months of age Synflorix 2+1 group: 1316 Synflorix 3+1 group: 1849 HBV 2+1 group and HBV 3+1 group: 1928 7 to 11 months of age Synflorix group: 241 HBV group: 204 12 to 18 months of age Synflorix group: 368 HAV group: 271	Intramuscular 0.5 mL	Same vaccination schedule as that in Study 10PN-PD-DIT-043	None	Immunogenicity/safety
III	Undeca-Pn-010	Czech Republic, Slovakia	Randomized, double-blind	Healthy infants	11Pn-PD group: 2489 HAV group: 2479	Intramuscular 0.5 mL	Vaccination with 11Pn-PD or HAV, with the first dose at 6 weeks to 5 months of age, the second and third doses with an interval of 21 to 97 days between doses, and the fourth dose at 12 to 15 months of age	DPT-HBV-IPV/Hib	Efficacy of 11Pn-PD against AOM
III	10PN-PD-DIT-062	India	Partially randomized[f], open-label	Subjects who participated in Study 10PN-PD-DIT-037 (reference data)	Synflorix-Synflorix9 group[g]: 100 Synflorix-Synflorix15 group[g]: 95 Hib-Synflorix group[h]: 87	Intramuscular 0.5 mL	Synflorix-Synflorix9 group: Vaccination with Synflorix at 9 to 18 months of age Synflorix-Synflorix15 group: Vaccination with Synflorix at 15 to 18 months of age Hib-Synflorix group: Vaccination with Synflorix, with the first dose at 12 to 18 months of age, the second dose with an interval of 56 to 118 days, and the third dose at 18 to 24 months of age	None	Immunogenicity of booster dose
III	10PN-PD-DIT-007	Finland, France, Poland	Partially randomized [i], subject-blind	Subjects who participated in Study 10PN-PD-DIT-001	Synflorix-Synflorix group[j]: 737 7vPnC-7vPnC group[k]: 92 7vPnC-Synflorix group[k]: 283	Intramuscular 0.5 mL	Synflorix-Synflorix group and 7vPnC-Synflorix group: Vaccination with Synflorix at 12 to 18 months of age 7vPnC-7vPnC group: Vaccination with 7vPnC at 12 to 18 months of age	DPT-HBV-IPV/Hib	Safety of booster dose
III	10PN-PD-DIT-008	Germany	Nonrandomized	Subjects who participated in Study 10PN-PD-DIT-003	Synflorix-23vPS group[l]: 60 7vPnC-23vPS group[m]: 53	Intramuscular 0.5 mL	Vaccination with 23vPS at 11 to 14 months of age	None	Immunogenicity of 23vPS after primary vaccination with Synflorix
III	10PN-PD-DIT-046	Slovakia, Sweden [n]	Nonrandomized	Healthy children (including subjects who participated in Study 10PN-PD-DIT-002)	Synflorix 4-dose group[o]: 51 Synflorix 5-dose group[p]: 59 Unprimed group[q]: 62	Intramuscular 0.5 mL	Synflorix 4-dose group: Vaccination with Synflorix at 36 to 46 months of age Synflorix 5-dose group: Vaccination with Synflorix at 36 to 46 months of age Unprimed group: Vaccination with Synflorix, with the first dose at 36 to 46 months of age, followed by the second dose with an interval of 56 to 118 days	None	Immunogenicity
II	11Pn-PD&Di-001	Germany	Randomized, open-label	Healthy infants	11Pn-PD group: 160 11Pn-PD&Di Composition 1 [r] group: 153 11Pn-PD&Di Composition 2 group: 159 11Pn-PD&Di Composition 3 group: 162 11Pn-PD&Di Composition 4 group: 152 11Pn-PD&Di Composition 1 combined with MenC[s] group: 150 11Pn-PD&Di Composition 4 combined with MenC[s] group: 153 7vPnC group: 153 MenC group: 156	Intramuscular 0.5 mL	Vaccination with the study vaccine , with the first dose at 2 months of age, followed by the second and third doses with an interval of 21 to 48 days between doses	DPT-HBV-IPV/Hib	Safety of 11Pn-PD and 11Pn-PD&Di
II	11Pn-PD&Di-007	Germany	Randomized, subject-blind	Healthy infants	11Pn-PD group: 53 11Pn-PD Composition 1[r] group: 53 11Pn-PD Composition 2 group: 50 11Pn-PD Composition 3 group: 51	Intramuscular 0.5 mL	Vaccination with the study vaccine , with the first dose at 2 months of age, followed by the second and third doses with an interval of 28 to 42 days between doses	DPT-HBV-IPV/Hib	Safety of 11Pn-PD and 11Pn-PD&Di

Phase	Study name	Country	Design	Subjects	Number of enrolled subjects	Vaccination route/dose	Vaccination schedule	Co-administered vaccine	Study objectives
					11Pn-PD&Di Composition 5 group: 52 7vPnC group: 48				
II	11PN-PD-DIT-001	Germany	Randomized, double-blind	Healthy infants	11Pn-PD group: 63 11Pn-PD-DiT Composition 1[r)] group: 57 11Pn-PD-DiT Composition 2 group: 63 11Pn-PD-DiT Composition 3 group: 59 11Pn-PD-DiT Composition 4 group: 60 11Pn-PD-DiT Composition 5 group: 63 11Pn-PD-DiT Composition 6 group: 58 11Pn-PD-DiT Composition 7 group: 65 11Pn-PD-DiT Composition 8 group: 60 7vPnC group: 64	Intramuscular 0.5 mL	Vaccination with the study vaccine , with the first dose at 2 months of age, followed by the second and third doses with an interval of 28 to 42 days between doses	DPT-HBV-IPV/Hib	Dose validation
II	11PN-PD-DIT-002	Germany	Randomized, double-blind	Healthy infants	11Pn-PD group: 62 11Pn-PD-DiT Composition A[r)] group: 61 11Pn-PD-DiT Composition B group: 66 11Pn-PD-DiT Composition C group: 63 11Pn-PD-DiT Composition D group: 61 11Pn-PD-DiT Composition E group: 60 11Pn-PD-DiT Composition F group: 64 11Pn-PD-DiT Composition G group: 62 11Pn-PD-DiT Composition H group: 65 11Pn-PD-DiT Composition I group: 65 7vPnC group: 60	Intramuscular 0.5 mL	Vaccination with the study vaccine , with the first dose at 2 months of age, followed by the second and third doses with an interval of 28 to 42 days between doses	DPT-HBV-IPV/Hib	Dose validation

CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease; AOM, acute otitis media

a) Comparison among Synflorix groups was conducted in a double-blind manner, and comparison between Synflorix and 7vPnC groups was conducted in a subject-blind manner.

b) In France, the second dose was coadministered with DPT-IPV/Hib.

c) The types of vaccines were in accordance with individual countries, and the vaccines were coadministered at the first to third doses in Group 1 and at the first, third, and fourth doses in Group 2.

d) The vaccine was coadministered in Group 1 alone.

e) In Synflorix group, DPT-HBV-IPV/Hib vaccine and DPT-IPV/Hib vaccine were coadministered at the first to third doses and at the fourth dose, respectively. In the HBV/HAV group, DPT-IPV/Hib vaccine was coadministered at the first to fourth doses.

f) Only the Synflorix-Synflorix9 and Synflorix-Synflorix15 groups were randomized.

g) Subjects who were vaccinated with 0.5 mL of Synflorix with the first dose at 6 weeks of age, the second dose at 10 weeks of age, and the third dose at 14 weeks of age in Study 10PN-PD-DIT-037 were enrolled.

h) Subjects who were assigned to the Hib group in Study 10PN-PD-DIT-037 were enrolled.

i) Only the 7vPnC-7vPnC and 7vPnC-Synflorix groups were randomized.

j) Subjects who were vaccinated with at least one dose of Synflorix in any of the Synflorix groups of Study 10PN-PD-DIT-001 were enrolled.

k) Subjects who were vaccinated with at least one dose of 7vPnC in the 7vPnC group of Study 10PN-PD-DIT-001 were enrolled.

l) Subjects who completed the 3-dose vaccination with Synflorix in the Synflorix group of Study 10PN-PD-DIT-003 were enrolled.

m) Subjects who completed the 3-dose vaccination with 7vPnC in the 7vPnC group of Study 10PN-PD-DIT-003 were enrolled.

n) The study was conducted only in 2 of 4 countries where Study 10PN-PD-DIT-002 was conducted.

o) Subjects who completed the 3-dose vaccination with Synflorix in the Group 1 (3 doses) of Study 10PN-PD-DIT-002 were enrolled.

p) Subjects who completed the 4-dose vaccination with Synflorix in the Group 2 (4 doses) of Study 10PN-PD-DIT-002 were enrolled.

q) Subjects who had not been vaccinated with pneumococcal vaccines were enrolled.

r) With regard to the polysaccharide content for each serotype, the types of composition used were as follows: 3 types (Composition 1 to 3) as well as those listed in Table 4-3 for 11Pn-PD; 5 types (Composition 1 to 5) for 11Pn-PD&Di; and 17 types (Composition 1 to 8, Composition A to I) for 11Pn-PD-DiT (see Table 4-26).

s) A vaccine formulation of 11Pn-PD&Di combined with MenC was selected as a study vaccine just before vaccination.

Table 4-2. List of abbreviations for vaccines

Synflorix	10-valent pneumococcal conjugate vaccine adsorbed (PD, TT, DT conjugates)
11Pn-PD	11-valent pneumococcal conjugate vaccine adsorbed (PD conjugates)
11Pn-PD-DiT	11-valent pneumococcal conjugate vaccine adsorbed (PD, TT, DT conjugates)
11Pn-PD&Di	11-valent pneumococcal conjugate vaccine adsorbed (PD, DT conjugates)
23vPS	23-valent pneumococcal polysaccharide vaccine
DPT	Adsorbed diphtheria-purified pertussis-tetanus combined vaccine
HAV	Hepatitis A vaccine
HBV	Hepatitis B vaccine
Hib	Freeze-dried *Haemophilus influenzae* type b vaccine (tetanus toxoid conjugate)
IPV	Inactivated poliovirus vaccine (Salk vaccine)
MenC	*Neisseria meningitidis* group C protein conjugate vaccine
7vPnC	7-valent pneumococcal conjugate vaccine adsorbed (nontoxic variant of diphtheria toxin conjugate)

PD, non-typeable *Haemophilus influenzae* protein D; TT, tetanus toxoid; DT, diphtheria toxoid

Table 4-3. Active ingredients of Synflorix and 11Pn-PD

Serotypes		1	3	4	5	6B	7F	9V	14	18C	19F	23F
Synflorix	Content [a)]	1		3	1	1	1	1	1	3	3	1
	Type [b)]	PD		PD	PD	PD	PD	PD	PD	TT	DT	PD
11Pn-PD	Content [a)]	1	1	1	1	1	1	1	1	1	1	1
	Type [b)]	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD

PD, non-typeable *Haemophilus influenzae* protein D; TT, tetanus toxoid; DT, diphtheria toxoid
a) Polysaccharide content (μg) per 0.5 mL, b) Type of carrier protein

4.A.(1) Japanese phase III clinical study (5.3.5.1.10, 5.3.5.1.43, 5.3.5.1.60, Study 10PN-PD-DIT-058 [December 2009 to September 2011])

An uncontrolled study was conducted in healthy infants aged 3 months (target sample size, 240 in Synflorix + DPT group and 120 in DPT group) at 16 centers in Japan to compare the immunogenicity against 10 pneumococcal capsular serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F; hereinafter referred to as "the pneumococcal serotypes in Synflorix") in subjects receiving Synflorix, with the immunogenicity observed in the Synflorix group (Lots 1 to 3 combined, hereinafter referred to as "the pooled Synflorix group") in foreign Study 10PN-PD-DIT-001 (hereinafter referred to as "Study 001").

In the Synflorix + DPT group, subjects received 3-dose primary vaccination with Synflorix 0.5 mL with an interval of 28 to 56 days (primary epoch) followed by a booster dose of Synflorix 0.5 mL (booster epoch) at 17 to 19 months of age. Synflorix was intramuscularly administered alternately in the left or right leg, and DPT 0.5 mL was subcutaneously coadministered with Synflorix alternately on the left or right arm. In the DPT group, subjects received subcutaneous doses of DPT 0.5 mL alone.

All 360 enrolled subjects (237 in the Synflorix + DPT group and 123 in the DPT group) were included in the "Total vaccinated cohort for primary epoch" and the safety analysis in primary epoch. All 348 subjects (228 in the Synflorix + DPT group and 120 in the DPT group) who received the fourth dose of the study vaccine were included in the "Total vaccinated cohort for booster epoch" and the safety analysis in booster epoch. Of 360 enrolled subjects, 353 subjects (231 in the Synflorix + DPT group and 122 in the DPT group) were included in the "According-to-Protocol (ATP) cohort for immunogenicity for primary epoch" and the primary analysis for immunogenicity in primary epoch. The excluded 7

subjects included those who concomitnatly received prohibited drugs. Of 348 subjects who received the fourth dose of the study vaccine, 331 subjects (216 in the Synflorix + DPT group and 115 in the DPT group) were included in the "ATP cohort for immunogenicity for booster epoch" and the primary analysis for immunogenicity in booster epoch. The excluded 17 subjects included those who deviated from the blood sampling schedule.

For evaluation of immunogenicity, the following parameters were determined prior to the first dose, 1 month after the third dose (after primary immunization), prior to the fourth dose, and 1 month after the fourth dose (after booster immunization) of the study vaccine: serum concentrations of serotype-specific IgG antibodies (IgG antibody concentrations) and serotype-specific opsonophagocytic activity (OPA antibody titer) against the pneumococcal serotypes in Synflorix; IgG antibody concentrations and OPA antibody titers against pneumococcal serotypes 6A and 19A (not contained in Synflorix); concentrations of antibodies against PD; and concentrations of antibodies against the antigens in DPT.

The primary endpoint was IgG antibody concentrations against the pneumococcal serotypes in Synflorix after the third dose of the study vaccine, and the following criterion was set for the main objectives. Results (Table 4-4) met the criterion.

- The upper limit of the 95% confidence interval of the ratios (Study 001/Study 058) of the geometric mean concentrations of IgG antibodies (IgG GMCs) against the pneumococcal serotypes in Synflorix after the third dose of the study vaccine in the pooled Synflorix group in Study 001 to those in the Synflorix + DPT group in the Study 10PN-PD-DIT-058 (Study 058) should not exceed 2 for all pneumococcal serotypes in Synflorix.

Table 4-4. IgG GMCs against pneumococcal serotypes in Synflorix after the third dose of the study vaccine (ATP cohort for immunogenicity for primary epoch)

Serotypes	Study 058 (Synflorix + DPT group)				Study 001 (Pooled Synflorix group)				Ratio[a)] [95% CI]
	Predose		After 3rd dose		Predose		After 3rd dose		
	N	IgG GMC	N	IgG GMC	N	IgG GMC	N	IgG GMC	
1	227	0.05	231	6.52	1102	0.04	1100	1.05	0.16 [0.14, 0.18]
4	230	0.03	231	6.54	1101	0.04	1106	1.45	0.22 [0.20, 0.25]
5	228	0.06	231	6.54	1099	0.05	1104	1.70	0.26 [0.23, 0.29]
6B	227	0.05	231	1.71	1102	0.07	1100	0.33	0.19 [0.16, 0.23]
7F	229	0.06	231	6.11	1102	0.09	1107	1.72	0.28 [0.25, 0.31]
9V	228	0.05	231	5.42	1098	0.06	1103	1.32	0.24 [0.22, 0.27]
14	229	0.24	231	10.03	1097	0.36	1100	2.90	0.29 [0.25, 0.33]
18C	230	0.08	231	16.59	1096	0.09	1102	1.66	0.10 [0.09, 0.12]
19F	226	0.14	229	17.39	1095	0.19	1104	1.84	0.11 [0.09, 0.12]
23F	231	0.07	231	2.17	1098	0.09	1102	0.53	0.25 [0.21, 0.29]

N, number of subjects with IgG antibody concentrations determined after primary immunization
a) Ratio of IgG GMCs after the third dose (IgG GMC from Study 001/IgG GMC from Study 058)

Results of evaluation on the immunogenicity of DPT in the Synflorix + DPT group and the DPT group in Study 058 are as shown in Table 4-5. The applicant explained that IgG GMCs against diphtheria and tetanus antigens tended to be higher in the Synflorix + DPT group because no decreases in seroprotection

rates against the DPT antigens or IgG GMCs occurred following covaccination with Synflorix and Synflorix contains DT and TT as carrier proteins (Table 4-3).

Table 4-5. Seroprotection rates against DPT antigens and IgG GMCs after the third and fourth dose of the study vaccine
(ATP cohorts for immunogenicity for primary epoch and booster epoch)

	DPT antigens	Seroprotection rates [c]		IgG GMC			
		Synflorix + DPT group	DPT group	Synflorix + DPT group		DPT group	
		n/N (%)	n/N (%)	N	GMC [95% CI]	N	GMC [95% CI]
Post Dose 3	Diphtheria	229/229 (100)	120/120 (100)	229	5.36 [5.00, 5.75]	120	3.83 [3.46, 4.23]
	Tetanus	230/230 (100)	120/120 (100)	230	5.43 [4.94,5.96]	120	3.63 [3.17, 4.14]
	PT [a]	231/231 (100)	120/120 (100)	231	123.17 [115.2, 131.7]	120	133.09 [119.5, 148.3]
	FHA [b]	231/231 (100)	121/121 (100)	231	308.56 [284.8, 334.3]	121	365.0 [327.9, 406.2]
Post Dose 4	Diphtheria	214/214 (100)	114/114 (100)	214	15.977 [14.573, 17.515]	114	10.814 [9.684, 12.075]
	Tetanus	214/214 (100)	114/114 (100)	214	11.057 [9.949, 12.287]	114	6.278 [5.334, 7.389]
	PT [a]	213/213 (100)	114/114 (100)	213	158.4 [143.7, 174.7]	114	204.0 [176.7, 235.6]
	FHA [b]	214/214 (100)	113/113 (100)	214	460.6 [421.2, 503.7]	113	584.5 [512.6, 666.6]

N, number of subjects with available data for immunogenicity; n, number of subjects who retained antibodies
a) Pertussis toxoid, b) Filamentous hemagglutinin,
c) Percentage of subjects with antibody concentrations that were equal to or above the prespecified levels (0.1 IU/mL for diphtheria toxoid, 0.1 IU/mL for tetanus toxoid, 5 EU/mL for PT, and 5 EU/mL for FHA).

With regard to safety, Table 4-6 shows solicited local adverse events (injection site pain, injection site erythema, injection site swelling) and solicited general adverse events (somnolence, pyrexia, irritability, appetite impaired) and adverse reactions that occurred by Day 7 after each dose of the study vaccine. Solicited local adverse events were all collected as adverse reactions. In the Synflorix + DPT group, only solicited local adverse events that occurred at the Synflorix injection site, not the DPT injection site, were noted. The applicant described that the incidences of solicited local adverse events after the booster immunization tended to be higher than those after the primary immunization in all groups and that the overall incidences of solicited general adverse events in the Synflorix + DPT group tended to be higher than those in the DPT group.

Table 4-6. Solicited local adverse events and solicited general adverse events/adverse reactions (Total vaccinated cohort for primary epoch and booster epoch)

	Synflorix + DPT group				DPT group			
	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 4th dose	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 4th dose
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Solicited local adverse events [a)]								
Injection site pain	74/237 (31.2)	61/235 (26.0)	55/233 (23.6)	114/228 (50.0)	19/123 (15.4)	26/123 (21.1)	23/122 (18.9)	47/120 (39.2)
Injection site erythema	161/237 (67.9)	171/235 (72.8)	153/233 (65.7)	178/228 (78.1)	71/123 (57.7)	96/123 (78.0)	84/122 (68.9)	102/120 (85.0)
Injection site swelling	112/237 (47.3)	121/235 (51.5)	112/233 (48.1)	154/228 (67.5)	33/123 (26.8)	75/123 (61.0)	65/122 (53.3)	90/120 (75.0)
Solicited general adverse events								
Somnolence	67/237 (28.3)	67/235 (28.5)	41/233 (17.6)	69/228 (30.3)	24/123 (19.5)	34/123 (27.6)	25/122 (20.5)	30/120 (25.0)
Pyrexia	61/237 (25.7)	65/235 (27.7)	51/233 (21.9)	90/228 (39.5)	20/123 (16.3)	22/123 (17.9)	21/122 (17.2)	24/120 (20.0)
Irritability	100/237 (42.2)	88/235 (37.4)	80/233 (34.3)	90/228 (39.5)	43/123 (35.0)	45/123 (36.6)	31/122 (25.4)	35/120 (29.2)
Appetite impaired	32/237 (13.5)	27/235 (11.5)	25/233 (10.7)	48/228 (21.1)	12/123 (9.8)	7/123 (5.7)	7/122 (5.7)	17/120 (14.2)
Solicited general adverse reactions								
Somnolence	24/237 (10.1)	26/235 (11.1)	15/233 (6.4)	19/228 (8.3)	6/123 (4.9)	9/123 (7.3)	10/122 (8.2)	7/120 (5.8)
Pyrexia	20/237 (8.4)	31/235 (13.2)	21/233 (9.0)	41/228 (18.0)	5/123 (4.1)	7/123 (5.7)	2/122 (1.6)	11/120 (9.2)
Irritability	40/237 (16.9)	30/235 (12.8)	31/233 (13.3)	36/228 (15.8)	12/123 (9.8)	12/123 (9.8)	10/122 (8.2)	10/120 (8.3)
Appetite impaired	4/237 (1.7)	7/235 (3.0)	5/233 (2.1)	12/228 (5.3)	1/123 (0.8)	2/123 (1.6)	0/122 (0)	2/120 (1.7)

N, number of subjects receiving each dose of the study vaccine; n, number of subjects reporting the event/reaction
a) All events were collected as adverse reactions.

The overall incidences of unsolicited adverse events (adverse events other than the solicited local and general adverse events shown in Table 4-6) that occurred by 30 days after each dose of the study vaccine were 81.4% (193 of 237 subjects) after the primary immunization and 57.9% (132 of 228 subjects) after the booster immunization in the Synflorix + DPT group; and 78.9% (97 of 123 subjects) after the primary immunization and 55.0% (66 of 120 subjects) after the booster immunization in the DPT group. Of these, adverse events that occurred in ≥5% of subjects in any group are shown with the adverse reactions and incidences in Table 4-7.

Table 4-7. Adverse events with an incidence of ≥5% in any group and adverse reactions among them (Total vaccinated cohort for primary epoch and booster epoch)

	Primary immunization								Booster immunization							
	Synflorix + DPT group (N = 237)				DPT group (N = 123)				Synflorix + DPT group (N = 228)				DPT group (N = 120)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Upper respiratory tract infection	64	27.0	1	0.4	33	26.8	0	0	13	5.7	0	0	5	4.2	0	0
Eczema	45	19.0	0	0	20	16.3	0	0	6	2.6	1	0.4	7	5.8	0	0
Injection site induration	39	16.5	39	16.5	18	14.6	18	14.6	28	12.3	28	12.3	9	7.5	9	7.5
Nasopharyngitis	32	13.5	0	0	17	13.8	0	0	15	6.6	0	0	11	9.2	0	0
Diarrhoea	23	9.7	0	0	8	6.5	0	0	7	3.1	0	0	6	5.0	0	0
Gastroenteritis	15	6.3	0	0	3	2.4	0	0	4	1.8	0	0	2	1.7	0	0
Dermatitis diaper	15	6.3	0	0	8	6.5	0	0	2	0.9	0	0	1	0.8	0	0
Conjunctivitis	14	5.9	0	0	7	5.7	1	0.8	4	1.8	0	0	3	2.5	0	0
Bronchitis	12	5.1	1	0.4	7	5.7	0	0	5	2.2	0	0	9	7.5	0	0
Rhinorrhoea	12	5.1	0	0	2	1.6	0	0	2	0.9	0	0	2	1.7	0	0
Erythema	10	4.2	1	0.4	11	8.9	1	0.8	1	0.4	1	0.4	0	0	0	0
Upper respiratory tract inflammation	7	3.0	0	0	3	2.4	0	0	34	14.9	0	0	17	14.2	0	0
Impetigo	3	1.3	0	0	7	5.7	0	0	2	0.9	0	0	1	0.8	0	0
Hand-foot-and-mouth disease	2	0.8	0	0	0	0	0	0	5	2.2	0	0	6	5.0	0	0

N, number of subjects receiving at least one dose of the study vaccine; n, number of subjects with adverse events/adverse reactions

Serious adverse events that occurred between the first dose and 30 days after the fourth dose of the study vaccine were reported by 28 subjects (47 episodes) in the Synflorix + DPT group (pneumonia [7 episodes]; respiratory syncytial virus infection [5 episodes]; gastroenteritis and bronchitis [4 episodes each]; upper respiratory tract infection, asthma, otitis media, convulsion, gastroenteritis rotavirus, and febrile convulsion [2 episodes each]; and upper respiratory tract inflammation, pharyngotonsillitis, exanthema subitum, respiratory syncytial virus bronchiolitis, pneumonia bacterial, myelitis transverse, pyrexia, meningitis staphylococcal, ear malformation, rectal polyp, laryngitis, sudden infant death syndrome, bronchopneumonia, pneumonia adenoviral, and Kawasaki's disease [1 episode each]) and by 19 subjects (28 episodes) in the DPT group (croup infectious and bronchitis [3 episodes each]; urinary tract infection and pharyngitis [2 episodes each]; and asthma, pharyngotonsillitis, respiratory syncytial virus infection, pneumonia, respiratory syncytial virus bronchiolitis, gastroenteritis rotavirus, bronchopneumonia, food allergy, faciodigitogenital dysplasia, pneumonia respiratory syncytial viral, tuberculid, acute tonsillitis, strabismus, intussusception, viral pharyngitis, fibrinous bronchitis, influenza, and gastroenteritis norovirus [1 episode each]). A causal relationship to the study vaccine was ruled out for all these events. Death occurred in a subject in the Synflorix + DPT group (sudden infant death syndrome), but a causal relationship between the event and the study vaccine was ruled out. Except for the death case, 3 subjects in the Synflorix + DPT group discontinued the study due to adverse events (allergy to vaccine, Kawasaki's disease, and myelitis transvers [1 episode each], a total of 3 adverse events). Of these events, allergy to vaccine in 1 subject was assessed as related to the study vaccine.

4.A.(2) Foreign phase III/IV clinical studies (5.3.5.1.55, Study 10PN-PD-DIT-043 [May 2009 to January 2012]; 5.3.5.1.56, 5.3.5.1.57, 5.3.5.1.58, 5.3.5.1.61, Study 10PN-PD-DIT-053 [February 2009 to December 2011])

Study 10PN-PD-DIT-043 (Study 043) was conducted in healthy infants aged 6 weeks to 6 months, 7 to 11 months, and 12 to 18 months at 790 centers in Finland. Study 043 was a cluster-randomized, double-blind, parallel group comparative study and was conducted to evaluate the effectiveness of Synflorix in preventing bacteriologically culture-confirmed IPD due to vaccine pneumococcal serotypes (VT-IPD) after Synflorix vaccination in comparison with HBV (HAV for subjects aged 12 to 18 months) as control. In Study 043, the municipalities of the participating health care centers were mapped into 72 clusters with average yearly birth cohort, ranging from around 400 to 1350 subjects. Study 10PN-PD-DIT-053 (Study 053) was conducted at 15 centers to evaluate the immunogenicity following Synflorix vaccination in a part of the subjects enrolled in Study 043 and additional subjects.

Table 4-8 shows the target sample size by vaccine group and age group of Studies 043 and 053. Table 4-9 shows the dosage regimens in each age group in Study 043 (the same dosage regimens were used in Study 053).

Table 4-8. Target sample size of each group in Studies 043 and 053 [a)]

Age	Vaccine groups		
6 weeks to 6 months	Synflorix 3+1 group	Synflorix 2+1 group	Pooled HBV group [b)]
	12,180 (1840)	12,180 (1840)	12,180 (1840)
7 to 11 months	Synflorix group		HBV group
	4698 (432)		2349 (216)
12 to 18 months	Synflorix group		HAV group
	6832 (432)		3416 (216)

a) The target sample sizes for Study 053 are shown in parentheses.
b) A pooled group of the HBV 3+1 and HBV 2+1 groups

Table 4-9. Dosage regimens in Study 043

Age	Dosage regimen	
6 weeks to 6 months	Synflorix 3+1 group HBV 3+1 group	Three doses of Synflorix or HBV at 0.5 mL were intramuscularly administered in the leg with an interval of at least 28 days (primary immunization), and a booster dose was administered at least 4 months after the third primary dose (booster immunization).
	Synflorix 2+1 group HBV 2+1 group	Two doses of Synflorix or HBV at 0.5 mL were intramuscularly administered in the leg with an interval of at least 56 days (primary immunization), and a booster dose was administered at least 4 months after the second primary dose (booster immunization).
7 to 11 months	Synflorix group HBV group	Two doses of Synflorix or HBV at 0.5 mL were intramuscularly administered in the leg with an interval of at least 28 days (primary immunization), and a booster dose was administered at least 4 months after the second primary dose (booster immunization).
12 to 18 months	Synflorix group HAV group	Two doses of Synflorix or HAV at 0.5 mL were intramuscularly administered in the leg or arm with an interval of at least 6 months.

Of 31,511 subjects aged 6 weeks to 6 months and randomized in Study 043 (10,275 in the Synflorix 3+1 group, 10,426 in the Synflorix 2+1 group, and 10,810 in the pooled HBV group), 30,528 subjects (10,273 in the Synflorix 3+1 group, 10,054 in the Synflorix 2+1 group, and 10,201 in the pooled HBV group) were included in the "Infant vaccinated cohort for usefulness" and the primary efficacy analysis. A total of 983 subjects were excluded from the infant vaccinated cohort, the reasons of which included an error in the randomization program (in the Synflorix 2+1 group and the HBV 3+1 group, treatment code was assigned the other way around). The program error was identified during the preceding enrollment in Study 053.

The primary endpoint was the occurrence of VT-IPD after the first dose of the study vaccine in the Synflorix 3+1 group, and the superiority of Synflorix 3+1 vaccination over HBV vaccination was demonstrated as shown in Table 4-10. While 371 subjects in the pooled HBV group were excluded from the primary efficacy analysis population because of the erroneous allocation to study vaccine, a similar result for the superiority of Synflorix (vaccine effectiveness [%] of 100 [82.1, 100]) was observed in an analysis population (ITT infant population) in which the 371 subjects were included as an intended cohort.

Table 4-10. Incidence of VT-IPD after the first dose of the study vaccine (per 1000 subject-years) (Study 043, Infant vaccinated cohort for usefulness)

	N	n	Incidence (per 1000 subject-years)	Vaccine effectiveness (%)[a)] [95% CI]	P-value[b)]
Synflorix 3+1 group	10,273	0	0	100 [82.8, 100]	<0.0001
Pooled HBV group	10,201	12	0.564		

N, number of subjects analyzed; n, number of VT-IPD reported after the first dose of the study vaccine
a) Vaccine effectiveness (%) = [1 − ratio of VT-IPD incidence (Synflorix group/pooled HBV group)] × 100
b) Using a Poisson regression model with treatment group as an explanatory variable and log of observation period as an offset variable and a two-sided significance level of 0.05%

For safety evaluation, only serious adverse events that occurred from the first dose to the end of the study (until when the study was unblinded) were collected from the subjects in Study 043, and adverse events that occurred by 30 days after each dose of the study vaccine were collected from the subjects in Study 053.

In Study 043, randomized were 31,511 subjects aged 6 weeks to 6 months (10,275 in the Synflorix 3+1 group, 10,426 in the Synflorix 2+1 group, and 10,810 in the pooled HBV group), 5947 subjects aged 7 to 11 months (3930 in the Synflorix group and 2017 in the HBV group), and 9908 subjects aged 12 to 18 months (6616 in the Synflorix group and 3292 in the HAV group). Of these randomized subjects, 983 subjects (aged 6 weeks to 6 months), 159 subjects (aged 7 to 11 months), and 247 subjects (aged 12 to 18 months) were excluded from the "Total vaccinated cohort for safety" for reasons including the erroneous allocation to study vaccine due to the error in the randomization program, which was identified during the preceding enrollment in Study 053, and the remaining subjects were included in the Total vaccinated cohort for safety and the safety analysis. Specifically, the data analyzed for safety were those collected from the subjects aged 6 weeks to 6 months included in the Infant vaccinated cohort for usefulness, 5788 subjects aged 7 to 11 months (3880 in the Synflorix group and 1908 in the HBV group), and 9661 subjects aged 12 to 18 months (6535 in the Synflorix group and 3126 in the HAV group).

In Study 053, 5093 subjects aged 6 weeks to 6 months (1849 in the Synflorix 3+1 group, 1316 in the Synflorix 2+1 group, 1069 in the HBV 3+1 group, and 859 in the HBV 2+1 group), 445 subjects aged 7 to 11 months (241 in the Synflorix group and 204 in the HBV group), and 639 subjects aged 12 to 18 months (368 in the Synflorix group and 271 in the HAV group) were randomized, and all of them were included in the "Total vaccinated cohort for safety" and the safety analysis.

Table 4-11 shows solicited local adverse events (injection site pain, injection site erythema, injection site swelling) and solicited general adverse events (somnolence, pyrexia, irritability, appetite impaired) and adverse reactions that occurred by 4 days after each dose of the study vaccine in the Synflorix 3+1 and HBV 3+1 groups in Study 053. Solicited local adverse events were all collected as adverse reactions. The applicant described that all incidences of solicited local adverse events tended to be higher in the Synflorix 3+1 group than in the HBV 3+1 group.

Table 4-11. Solicited local adverse events and solicited general adverse events/adverse reactions (Study 053, Total vaccinated cohort for safety)

	Synflorix 3+1 group				HBV 3+1 group			
	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 4th dose	Post 1st dose	Post 2nd dose	Post 3 dose	Post 4 dose
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Solicited local adverse events[a)]								
Injection site pain	807/1846 (43.7)	662/1827 (36.2)	538/1808 (29.8)	888/1758 (50.5)	146/1066 (13.7)	114/1056 (10.8)	102/1052 (9.7)	250/1024 (24.4)
Injection site erythema	936/1846 (50.7)	996/1827 (54.5)	963/1808 (53.3)	913/1758 (51.9)	270/1066 (25.3)	254/1056 (24.1)	300/1052 (28.5)	345/1024 (33.7)
Injection site swelling	636/1846 (34.5)	686/1827 (37.5)	676/1808 (37.4)	716/1758 (40.7)	88/1066 (8.3)	114/1056 (10.8)	144/1052 (13.7)	229/1024 (22.4)
Solicited general adverse events								
Somnolence	1070/1846 (58.0)	868/1828 (47.5)	645/1808 (35.7)	721/1757 (41.0)	462/1066 (43.3)	332/1056 (31.4)	293/1052 (27.9)	307/1024 (30.0)
Pyrexia	388/1846 (21.0)	380/1828 (20.8)	347/1808 (19.2)	391/1757 (22.3)	82/1066 (7.7)	78/1056 (7.4)	110/1052 (10.5)	142/1024 (13.9)
Irritability	1325/1846 (71.8)	1254/1828 (68.6)	1115/1808 (61.7)	1124/1757 (64.0)	577/1066 (54.1)	532/1056 (50.4)	496/1052 (47.1)	491/1024 (47.9)
Appetite impaired	499/1846 (27.0)	434/1828 (23.7)	349/1808 (19.3)	549/1757 (31.2)	202/1066 (18.9)	187/1056 (17.7)	178/1052 (16.9)	260/1024 (25.4)
Solicited general adverse reactions								
Somnolence	1054/1846 (57.1)	855/1828 (46.8)	638/1808 (35.3)	699/1757 (39.8)	453/1066 (42.5)	329/1056 (31.2)	285/1052 (27.1)	300/1024 (29.3)
Pyrexia	381/1846 (20.6)	373/1828 (20.4)	336/1808 (18.6)	371/1757 (21.1)	78/1066 (7.3)	78/1056 (7.4)	106/1052 (10.1)	134/1024 (13.1)
Irritability	1298/1846 (70.3)	1236/1828 (67.6)	1100/1808 (60.8)	1085/1757 (61.8)	565/1066 (53.0)	523/1056 (49.5)	492/1052 (46.8)	481/1024 (47.0)
Appetite impaired	480/1846 (26.0)	419/1828 (22.9)	336/1808 (18.6)	513/1757 (29.2)	196/1066 (18.4)	181/1056 (17.1)	172/1052 (16.3)	253/1024 (24.7)

N, number of subjects receiving each dose of the study vaccine; n, number of subjects reporting the event/reaction
a) All events were collected as adverse reactions.

In Study 053, the overall incidences of unsolicited adverse events (adverse events other than the solicited local and general adverse events shown in Table 4-11) that occurred by 30 days after each dose of the study vaccine were 59.8% (1105 of 1849 subjects) after the primary immunization and 29.2% (521 of 1786 subjects) after the booster immunization in the Synflorix 3+1 group; and 51.8% (554 of 1069 subjects) after the primary immunization and 26.6% (277 of 1043 subjects) after the booster immunization in the HBV 3+1 group. Of these, adverse events that occurred in ≥5% of subjects in any group are shown with the adverse reactions and the incidences in Table 4-12.

Table 4-12. Adverse events with an incidence of ≥5% in any group and adverse reactions among them (Study 053, Total vaccinated cohort for safety)

	Primary immunization								Booster immunization							
	Synflorix 3+1 group (N = 1849)				HBV 3+1 group (N = 1069)				Synflorix 3+1 group (N = 1786)				HBV 3+1 group (N = 1043)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Injection site induration	376	20.3	373	20.2	47	4.4	44	4.1	118	6.6	118	6.6	29	2.8	29	2.8
Upper respiratory tract infection	172	9.3	10	0.5	98	9.2	10	0.9	89	5.0	3	0.2	47	4.5	4	0.4
Rhinitis	121	6.5	7	0.4	90	8.4	15	1.4	41	2.3	4	0.2	20	1.9	3	0.3
Diarrhoea	106	5.7	33	1.8	65	6.1	33	3.1	41	2.3	18	1.0	12	1.2	5	0.5

N, number of subjects receiving at least one dose of the study vaccine; n, number of subjects with the adverse event/reaction

In subjects who were included in the Total vaccinated cohort for safety in Study 043 but were not enrolled in Study 053, serious adverse events that occurred from the first dose until the end of the study (until when the study was unblinded) were reported in 0.07% of subjects (18 of 27,477 subjects) in the Synflorix groups and 0.09% of subjects (12 of 13,704 subjects) in the control vaccine groups. The following episodes of these serious adverse events were assessed as related to the study vaccine: 1 episode in 1 subject in the Synflorix 3+1 group (pyrexia); 3 episodes in 2 subjects in the Synflorix 2+1 group (1 episode each of injection site reaction, irritability, and febrile convulsion); 2 episodes in 2 subjects aged 7 to 11 months in the Synflorix group (1 episode each of febrile convulsion and Kawasaki's disease); 1 episode in 1 subject aged 12 to 18 months in the Synflorix group (Kawasaki's disease); 2 episodes in 2 subjects in the HBV 3+1 group (1 episode each of convulsion and hypotonic-hyporesponsive episode); 2 episodes in 1 subject aged 7 to 11 months in the HBV group (1 episode each of convulsion and syncope); and 1 episode in 1 subject aged 12 to 18 months in the HAV group (febrile convulsion). Discontinuation of the study due to an adverse event occurred in 0.004% of subjects (1 of 27,477 subjects) in the Synflorix groups. The event was Kawasaki's disease in subjects aged 7 to 11 months in the Synflorix group and was assessed as related to the study vaccine. Deaths occurred in 4 subjects with 4 episodes of events (1 episode each of Krabbe's disease, death, sudden infant death syndrome, and sepsis) in the Synflorix 3+1 group, 4 subjects with 5 episodes of events (1 episode each of sudden death, myocarditis, Gaucher's disease, laryngitis, and foreign body) in the Synflorix 2+1 group, 3 subjects with 4 episodes of events (1 episode each of accidental death, Reye's syndrome, road traffic accident, and asphyxia) in the HBV 3+1 group, and 1 subject with 1 episode of an event (asphyxia) who was aged 12 to 18 months in the HAV group. All deaths were assessed as unrelated to the study vaccine.

In subjects who were included in the Total vaccinated cohort for safety in Study 053, serious adverse events that occurred from the first dose to the end of the study (until when the study was unblinded) were reported in 8.1% of subjects (306 of 3774 subjects) in the Synflorix groups and 7.6% of subjects (183 of 2403 subjects) in the control vaccine groups. Of these serious adverse events, the following episodes of events were assessed as related to the study vaccine: 4 episodes in 4 subjects in the Synflorix 3+1 group (convulsion [2 episodes], and sepsis and pyrexia [1 episode each]); 1 episode in 1 subject in the HBV 3+1 group (petit mal epilepsy); and 1 episode in 1 subject in the HBV 2+1 group (pyrexia). Discontinuation of the study due to adverse events occurred in 0.5% of subjects (19 of 3774 subjects) in the Synflorix groups and 0.4% of subjects (10 of 2403 subjects) in the control vaccine groups. The following episodes of these events were assessed as related to the study vaccine: 8 episodes in 8 subjects in the Synflorix 3+1 group (irritability [3 episodes] and convulsion, swelling, lethargy, injection site swelling, and injection site pain [1 episode each]); 2 episodes in 2 subjects in the Synflorix 2+1 group (immobile); 1 episode in 1 subject aged 7 to 11 months in the Synflorix group (pyrexia); and 2 episodes in 2 subjects in the HBV 3+1 group (petit mal epilepsy and irritability [1 episode each]). Death occurred in 1 subject with 1 episode of an event (sudden death) in the Synflorix 2+1 group and was assessed as unrelated to the study vaccine.

4.A.(3) Foreign phase III clinical study (5.3.5.1.51, 5.3.5.1.52, 5.3.5.1.53, Study 10PN-PD-DIT-028 [June 2007 to July 2011])

A randomized, assessor- and subject-blind, parallel-group comparative study was conducted in healthy infants aged 2 months (target sample size: 12,000 in Synflorix group, 12,000 in HBV/HAV group) at 61 centers in Argentina, Panama, and Colombia to evaluate the effectiveness of Synflorix vaccination in preventing likely bacterial CAP (B-CAP) in comparison with HBV (primary immunization) or HAV (booster immunization). In this study, study vaccine storage managers, dispensers, and vaccinators were not blinded, and subjects, investigators (and subinvestigators), clinical research coordinator, and the sponsor were blinded to assignment.

Subjects received 3 primary vaccination doses of Synflorix 0.5 mL or HBV 0.5 mL at an interval of 49 to 83 days (primary epoch) followed by an booster dose of Synflorix 0.5 mL or HAV 0.5 mL (booster epoch). All vaccines were administered intramuscularly. In the Synflorix group, DPT-HBV-IPV/Hib 0.5 mL and DPT-IPV/Hib 0.5 mL were coadministered intramuscularly with Synflorix as primary immunization and booster immunization, respectively. In the HBV/HAV group, DPT-IPV/Hib 0.5 mL was coadministered intramuscularly with HBV or HAV. Synflorix and the control vaccines were injected into the right arm or right leg, and the coadministered vaccines were injected into the left arm or left leg to avoid confounding injection sites.

In this study, an interim analysis was to be performed as per protocol ≥15 days after the third dose of the study vaccine when ≥535 first B-CAP episodes were reported, and the results of interim analysis were to be the efficacy results for Synflorix if the efficacy of Synflorix was validated in the interim analysis. Of 23,819 subjects (11,911 in the Synflorix group and 11,908 in the HBV/HAV group) randomized at the time of the interim analysis, 20,496 subjects (10,295 in the Synflorix group and 10,201 in the HBV/HAV group) were included in the "ATP cohort for efficacy against CAP" and were primarily analyzed for efficacy. Excluded were 3323 subjects for the reasons including no contact available by 14 days after the third dose of the study vaccine.

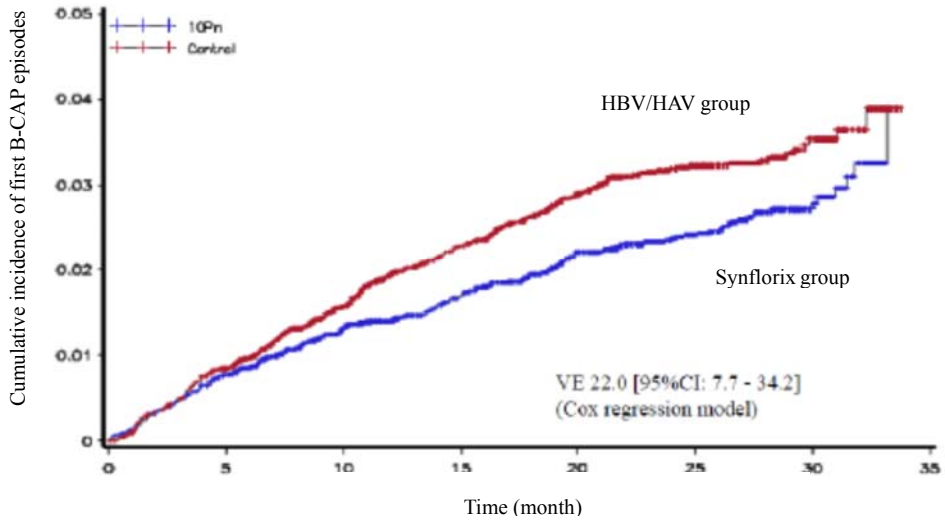
B-CAP was defined as CAP with alveolar infiltration/pleural effusion on the chest X-ray (CXR) or CAP with abnormal CXR findings without alveolar infiltration but with CRP of ≥40 mg/L. The primary endpoint was the first B-CAP episode ≥15 days after the third dose of the study vaccine, and the results of the interim analysis on the ATP cohort for efficacy against CAP are shown in Table 4-13. The superiority of Synflorix over HBV/HAV was validated in the interim analysis. Figure 4-1 shows the time course of cumulative incidence of the first B-CAP episodes ≥15 days after the third dose of the study vaccine.

Table 4-13. Incidence of first B-CAP episode ≥15 days after the third dose of the study vaccine (per 1,000 subject-years) (Interim analysis, ATP cohort for efficacy against CAP)

	N	n	Incidence (per 1,000 subject-years)	Vaccine effectiveness (%) [a),b)] [95% CI]	P-value [b),c)]
Synflorix group	10,295	240	12.30	22.0 [7.7, 34. 2]	0.0020
HBV/HAV group	10,201	304	15.78		

N, number of subjects analyzed; n, number of occurrence
a) Vaccine effectiveness (%) = [1 − ratio of incidence (Synflorix group/[HBV/HAV group])] × 100
b) The time to the first B-CAP episode ≥15 days after the third dose of the study vaccine, or on or after the day of the first dose of Synflorix was evaluated by using a Cox regression model with treatment group as an explanatory variable.
c) The one-sided significance level was determined to be 0.0175 for the interim analysis and 0.0119 for the final analysis (with an assumption of 1045 first B-CAP episodes) according to a Pocock-type alpha spending function.

Figure 4-1. Cumulative incidence of the first B-CAP episodes ≥15 days after the third dose of the study vaccine (ATP cohort for efficacy against CAP)



Number at risk

Synflorix group	10295	10122	9623	8619	7538	4651	1408	193
HBV/HAV group	10201	10032	9532	8483	7376	4578	1373	178

Of the CAP diagnosed according to the World Health Organization (WHO) criteria (*Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children*, WHO, 2001, *Pneumonia: the forgotten killer of children*, WHO, 2006) (C-CAP), the incidence of first C-CAP episodes that occurred ≥15 days after the third dose of the study vaccine was evaluated as a secondary endpoint (Table 4-14).

Table 4-14. Incidence of first C-CAP ≥15 days after the third dose of the study vaccine (per 1,000 subject-years) (Interim analysis, ATP cohort for efficacy against CAP)

	N	n	Incidence (per 1,000 subject-years)	Vaccine effectiveness (%)[a)] [95% CI]
Synflorix group	10,295	155	7.90	25.7 [8.4, 39.6]
HBV/HAV group	10,201	206	10.64	

N, number of subjects analyzed; n, number of first C-CAP episodes ≥15 days after the third dose of the study vaccine
a) Vaccine effectiveness (%) = [1 – incidence ratio (Synflorix group/[HBV/HAV group])] × 100

For safety analysis, solicited local and general adverse events were collected from the Total vaccinated cohort from the "Immuno and reacto" subset. In addition, all unsolicited adverse events (adverse events other than the solicited local and general adverse events) were collected from the Total vaccinated cohort enrolled in Panama, and serious adverse events were collected from the Total vaccinated cohort. Table 4-15 shows the breakdown of individual analysis sets.

Table 4-15. Breakdown of safety analysis cohorts

Analysis set	Description
Total vaccinated cohort from the "Immuno and reacto" subset	Of first 1001 subjects (501 in the Synflorix group and 500 in the HBV/HAV group) enrolled in the study in Panama and Argentina, 739 subjects (374 in the Synflorix group and 365 in the HBV/HAV group) were included in the cohort, and 262 subjects were excluded because of invalid informed consent.
Total vaccinated cohort enrolled in Panama	Of 7355 subjects (3679 in the Synflorix group and 3676 in the HBV/HAV group) enrolled in the study in Panama, 7214 subjects (3602 in the Synflorix group and 3612 in the HBV/HAV group) were included in the cohort, and 141 subjects were excluded for reasons including invalid informed consent.
Total vaccinated cohort	Of all 23,819 subjects (11,911 in the Synflorix group and 11,908 in the HBV/HAV group) enrolled in this study, 23,597 subjects (11,798 in the Synflorix group and 11,799 in the HBV/HAV group) were included in the cohort, and 222 subjects were excluded for reasons including invalid informed consent.

Table 4-16 shows solicited local adverse events (injection site pain, injection site erythema, injection site swelling) and solicited general adverse events (somnolence, pyrexia, irritability, appetite impaired) and adverse reactions that occurred by 3 days after each dose of the study vaccine in the Total vaccinated cohort from the "Immuno and reacto" subset. Solicited local adverse events were all collected as adverse reactions. In Table 4-16, only solicited local adverse events that occurred at the Synflorix injection site are shown for the Synflorix group, and for the HBV/HAV group, the table shows only solicited local adverse events that occurred at the HBV injection site after the first, second, and third vaccination doses and those occurred at the HAV injection site after the fourth vaccination dose. The applicant described that the incidences of solicited adverse events tended to be higher in the Synflorix group than in the HBV/HAV group.

Table 4-16. Solicited local adverse events and solicited general adverse events/adverse reactions (Total vaccinated cohort from the "Immuno and reacto" subset)

	Synflorix group				HBV/HAV group[a)]			
	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 4th dose	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 4th dose
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Solicited local adverse events[b)]								
Injection site pain	199/366 (54.4)	183/359 (51.0)	149/357 (41.7)	129/317 (40.7)	112/354 (31.6)	93/350 (26.6)	78/340 (22.9)	89/303 (29.4)
Injection site erythema	109/366 (29.8)	114/359 (31.8)	97/357 (27.2)	104/317 (32.8)	66/354 (18.6)	68/350 (19.4)	61/340 (17.9)	73/303 (24.1)
Injection site swelling	84/366 (23.0)	81/359 (22.6)	75/357 (21.0)	74/317 (23.3)	45/354 (12.7)	45/350 (12.9)	52/340 (15.3)	55/303 (18.2)
Solicited general adverse events								
Somnolence	162/366 (44.3)	134/358 (37.4)	110/357 (30.8)	74/317 (23.3)	118/354 (33.3)	75/350 (21.4)	63/339 (18.6)	65/303 (21.5)
Pyrexia	128/366 (35.0)	158/358 (44.1)	113/357 (31.7)	93/317 (29.3)	41/354 (11.6)	72/350 (20.6)	53/339 (15.6)	73/303 (24.1)
Irritability	208/366 (56.8)	196/358 (54.7)	159/357 (44.5)	121/317 (38.2)	139/354 (39.3)	123/350 (35.1)	105/339 (31.0)	95/303 (31.4)
Appetite impaired	61/366 (16.7)	70/358 (19.6)	65/357 (18.2)	51/317 (16.1)	39/354 (11.0)	37/350 (10.6)	32/339 (9.4)	46/303 (15.2)
Solicited general adverse reactions								
Somnolence	156/366 (42.6)	133/358 (37.2)	109/357 (30.5)	72/317 (22.7)	115/354 (32.5)	75/350 (21.4)	62/339 (18.3)	61/303 (20.1)
Pyrexia	126/366 (34.4)	157/358 (43.9)	111/357 (31.1)	90/317 (28.4)	41/354 (11.6)	71/350 (20.3)	52/339 (15.3)	68/303 (22.4)
Irritability	202/366 (55.2)	194/358 (54.2)	157/357 (44.0)	113/317 (35.6)	135/354 (38.1)	123/350 (35.1)	104/339 (30.7)	91/303 (30.0)
Appetite impaired	60/366 (16.4)	70/358 (19.6)	65/357 (18.2)	49/317 (15.5)	38/354 (10.7)	36/350 (10.3)	30/339 (8.8)	42/303 (13.9)

N, number of subjects receiving each dose of the study vaccine; n, number of subjects reporting the event/reaction

a) In the HBV/HAV group, HBV was administered at the first, second, and third vaccinations, and HAV was administered at the fourth vaccination.

b) All events were collected as adverse reactions.

In the Total vaccinated cohort enrolled in Panama, the overall incidences of unsolicited adverse events (adverse events other than the solicited local and general adverse events shown in Table 4-16) that occurred by 30 days after each dose of the study vaccine were 89.5% (3224 of 3602 subjects) after the primary immunization and 50.8% (1542 of 3033 subjects) after the booster immunization in the Synflorix group; and 86.6% (3129 of 3612 subjects) after the primary immunization and 49.5% (1496 of 3022 subjects) after the booster immunization in the HBV/HAV group. Of these, adverse events that occurred in ≥5% of subjects in any group are shown with the adverse reactions and the incidences in Table 4-17.

Table 4-17. Adverse events with an incidence of ≥5% in any group and adverse reactions among them (Total vaccinated cohort enrolled in Panama)

	Primary immunization								Booster immunization							
	Synflorix group (N = 3602)				HBV/HAV group (N = 3612)				Synflorix group (N = 3033)				HBV/HAV group (N = 3022)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Nasopharyngitis	1937	53.8	58	1.6	1998	55.3	54	1.5	654	21.6	5	0.2	634	21.0	4	0.1
Pyrexia	1728	48.0	1531	42.5	1209	33.5	915	25.3	324	10.7	182	6.0	208	6.9	88	2.9
Diarrhoea	509	14.1	55	1.5	460	12.7	34	0.9	150	5.0	2	0.1	165	5.5	5	0.2
Bronchiolitis	379	10.5	6	0.2	379	10.5	4	0.1	25	0.8	0	0	32	1.1	0	0
Irritability	368	10.2	325	9.0	298	8.3	252	7.0	32	1.1	27	0.9	19	0.6	12	0.4
Injection site pain	352	9.8	352	9.8	189	5.2	189	5.2	76	2.5	76	2.5	22	0.7	22	0.7
Anaemia	273	7.6	0	0	279	7.7	0	0	29	1.0	0	0	29	1.0	0	0
Injection site erythema	243	6.8	243	6.8	155	4.3	155	4.3	36	1.2	36	1.2	22	0.7	22	0.7
Overweight	217	6.0	0	0	213	5.9	0	0	29	1.0	0	0	28	0.9	0	0
Rhinitis	197	5.5	1	0	163	4.5	7	0.2	17	0.6	1	0	18	0.6	0	0

N, number of subjects receiving at least one dose of the study vaccine; n, number of subjects with the adverse event/adverse reaction

Serious adverse events that occurred between the first dose of the study vaccine and the end of the study (at the time of confirmation of the interim analysis results for B-CAP) were reported in 21.5% of subjects (2534 of 11,798 subjects) in the Synflorix group and 22.6% of subjects (2668 of 11,799 subjects) in the HBV/HAV group. Of these events, 1 episode of an event in 1 subject in the HBV/HAV group (apparent life threatening event) was assessed as related to the study vaccine. Discontinuation of the study due to adverse events occurred in 0.3% of subjects (35 of 11,798 subjects) in the Synflorix group and 0.4% of subjects (43 of 11,799 subjects) in the HBV/HAV group, but a causal relationship to the investigational drug were ruled out for all the events. Death occurred in 19 subjects in the Synflorix group (asphyxia [2 subjects]; burn; craniocerebral injury; ventricular arrhythmia; acid base balance abnormal, cardio-respiratory arrest, and electrocution; bronchiolitis, pneumonia, and septic shock; cardio-respiratory arrest; dehydration, gastroenteritis, and shock; electrocution; hepatic failure, disseminated intravascular coagulation, and multi-organ failure; dehydration and gastroenteritis; pneumonia, pleural effusion, and septic shock; acute pulmonary oedema; cardiac failure and intracardiac mass; brain neoplasm and aspiration bronchial; pertussis, acute lung injury, pneumonia, pulmonary sepsis, septic shock, and systemic candida; aspiration bronchial; and Hypoxic-ischaemic encephalopathy and interstitial lung disease [1 subject each]), and 26 subjects in the HBV/HAV group (aspiration bronchial [3 subjects]; asphyxia; septic shock [2 subjects each]; meningitis pneumococcal and septic shock; interstitial lung disease; road traffic accident; acute respiratory failure and aspiration; acute pulmonary oedema; burns second degree, pneumonia, and sepsis; sudden infant death syndrome; meningitis pneumococcal and sepsis; bronchiolitis, bronchial obstruction, pneumonia, and respiratory distress; dehydration, intussusception, pneumonia, respiratory distress, and sepsis; pneumonia and sepsis; pneumonia; bronchopneumonia, respiratory distress, and septic shock; sudden death; multiple injuries; heart disease congenital, cardiac failure, hypokalaemia, pneumonia, pulmonary oedema, and anaemia; interstitial lung disease and septic shock; brain oedema and subdural haematoma; and abscess, intracranial pressure increased, porencephaly, and nosocomial infection [1 subject each]). A causal relationship to the study vaccine was ruled out for all the deaths.

4.A.(4) Foreign phase III clinical study (5.3.5.1.15, 5.3.5.1.16, Study Undeca-Pn-010 [October 2000 to June 2004])

Study Undeca-Pn-010 (Study U-010) was conducted with an 11-valent vaccine formulation, 11Pn-PD (see Table 4-3), instead of Synflorix, in healthy infants aged 6 weeks to 5 months (target sample size, 2500 subjects in the 11Pn-PD group and 2500 subjects in the HAV group) at 168 centers in the Czech Republic and Slovakia. Study U-010 was designed as a randomized, double-blind, parallel-group comparative study to evaluate the effectiveness of vaccination with the 11Pn-PD vaccine in preventing acute otitis media (AOM) caused by 11 pneumococcal capsular serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F (hereinafter referred to as serotypes contained in 11Pn-PD) using HAV as a control vaccine.

Subjects were administered intramuscularly 3 primary vaccination doses of 11Pn-PD 0.5 mL or HAV 0.5 mL with an interval of 21 to 97 days (primary epoch) followed by a booster dose of 11Pn-PD 0.5

mL or HAV 0.5 mL at 12 to 15 months of age (booster epoch). During primary epoch, DPT-HBV-IPV/Hib 0.5 mL was coadministered intramuscularly with 11Pn-PD or HAV in both groups. 11Pn-PD and HAV were injected into the right leg, and the coadministered vaccine was injected into the left leg to avoid confounding injection sites.

All randomized 4968 subjects (2489 in the 11Pn-PD group and 2479 in the HAV group) were included in the "Total vaccinated cohort for primary epoch" and the safety analysis in primary epoch. All 4919 subjects (2461 in the 11Pn-PD group and 2458 in the HAV group) who received the fourth dose of the study vaccine were included in the "Total vaccinated cohort for booster epoch" and the safety analysis in booster epoch. Of the randomized 4968 subjects, 4907 subjects (2455 in the 11Pn-PD group and 2452 in the HAV group) were included in the "ATP cohort for efficacy" and the primary efficacy analysis, and 61 subjects were excluded from the cohort for reasons including discontinuation of the study before the third dose of the study vaccine.

The primary endpoint was the first episode of otolaryngologist-diagnosed bacterial AOM that occurred ≥15 days after the third dose of the study vaccine and was caused by serotypes contained in 11Pn-PD.

When all of the findings stated below were observed, bacterial examinations were performed, and the diagnosis of bacterial AOM episode caused by serotypes contained in 11Pn-PD was confirmed if any pneumococcal serotypes contained in 11Pn-PD were detected in the samples.

- Abnormal appearance of the tympanic membrane including redness, bulging, or loss of light reflex, or the presence of middle ear effusion
- At least 2 of the following clinical symptoms: ear pain, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting, and diarrhea.

With regard to the threshold for the primary endpoint, the vaccine effectiveness of 11Pn-PD against bacterial AOM caused by serotypes contained in 11Pn-PD was to be demonstrated when the lower limit of the two-sided 95% confidence interval was greater than 30%, and the criterion was achieved (Table 4-18).

Table 4-18. Incidence of the first episode of bacterial AOM caused by serotypes contained in 11Pn-PD occurring ≥15 days after the third dose of the study vaccine (per 1,000 subject-years) (ATP cohort for efficacy)

	N	n	Incidence (per 1,000 subject-years)	Vaccine effectiveness (%) [a] [95% CI]
11Pn-PD group	2455	57	14.4	52.6 [35.0, 65.5]
HAV group	2452	118	30.4	

N, number of subjects analyzed; n, number of the first episode of bacterial AOM ≥15 days after the third dose of the study vaccine
a) Vaccine effectiveness (%) = [1 – incidence ratio (11Pn-PD group/HAV group)] × 100

With regard to safety, Table 4-19 shows solicited local adverse events (injection site pain, injection site erythema, injection site swelling) and solicited general adverse events (somnolence, pyrexia, irritability, appetite impaired) and adverse reactions that occurred by 7 days after each dose of the study vaccine. Solicited local adverse events were all collected as adverse reactions. In Table 4-19, only solicited local adverse events that occurred at the 11Pn-PD injection site and HAV injection site are shown for the 11Pn-PD group and HAV group, respectively.

Table 4-19. Solicited local adverse events and solicited general adverse events/adverse reactions (Total vaccinated cohort for primary epoch and booster epoch)

	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 4th dose
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
11Pn-PD group				
Solicited local adverse events[a)]				
Injection site pain	618/2489 (24.8)	508/2476 (20.5)	422/2470 (17.1)	632/2461 (25.7)
Injection site erythema	619/2489 (24.9)	693/2476 (28.0)	686/2470 (27.8)	716/2461 (29.1)
Injection site swelling	443/2489 (17.8)	458/2476 (18.5)	447/2470 (18.1)	463/2461 (18.8)
Solicited general adverse events				
Somnolence	981/2489 (39.4)	702/2476 (28.4)	530/2471 (21.4)	540/2461 (21.9)
Pyrexia	787/2489 (31.6)	710/2476 (28.7)	498/2471 (20.2)	435/2461 (17.7)
Irritability	1198/2489 (48.1)	1038/2476 (41.9)	832/2471 (33.7)	826/2461 (33.6)
Appetite impaired	557/2489 (22.4)	409/2476 (16.5)	344/2471 (13.9)	432/2461 (17.6)
Solicited general adverse reactions				
Somnolence	715/2489 (28.7)	552/2476 (22.3)	399/2471 (16.1)	406/2461 (16.5)
Pyrexia	696/2489 (28.0)	626/2476 (25.3)	396/2471 (16.0)	321/2461 (13.0)
Irritability	908/2489 (36.5)	816/2476 (33.0)	633/2471 (25.6)	635/2461 (25.8)
Appetite impaired	390/2489 (15.7)	295/2476 (11.9)	229/2471 (9.3)	294/2461 (11.9)
HAV group				
Solicited local adverse events[a)]				
Injection site pain	290/2479 (11.7)	245/2470 (9.9)	188/2466 (7.6)	248/2458 (10.1)
Injection site erythema	413/2479 (16.7)	491/2470 (19.9)	485/2466 (19.7)	463/2458 (18.8)
Injection site swelling	221/2479 (8.9)	261/2470 (10.6)	260/2466 (10.5)	204/2458 (8.3)
Solicited general adverse events				
Somnolence	810/2479 (32.7)	537/2470 (21.7)	416/2466 (16.9)	397/2458 (16.2)
Pyrexia	439/2479 (17.7)	467/2470 (18.9)	378/2466 (15.3)	320/2458 (13.0)
Irritability	970/2479 (39.1)	830/2470 (33.6)	692/2466 (28.1)	579/2458 (23.6)
Appetite impaired	441/2479 (17.8)	324/2470 (13.1)	303/2466 (12.3)	353/2458 (14.4)
Solicited general adverse reactions				
Somnolence	575/2479 (23.2)	378/2470 (15.3)	295/2466 (12.0)	273/2458 (11.1)
Pyrexia	378/2479 (15.2)	378/2470 (15.3)	273/2466 (11.1)	197/2458 (8.0)
Irritability	679/2479 (27.4)	610/2470 (24.7)	507/2466 (20.6)	423/2458 (17.2)
Appetite impaired	275/2479 (11.1)	212/2470 (8.6)	197/2466 (8.0)	231/2458 (9.4)

N, number of subjects receiving each dose of the study vaccine; n, number of subjects reporting the event/reaction.

a) All events were collected as adverse reactions.

The overall incidences of unsolicited adverse events (adverse events other than the solicited local and general adverse events shown in Table 4-19) that occurred by 30 days after each dose of the study vaccine were 47.7% (1188 of 2489 subjects) after the primary immunization and 20.9% (515 of 2461 subjects) after the booster immunization in the 11Pn-PD group and 49.8% (1234 of 2479 subjects) after the primary immunization and 21.7% (534 of 2458 subjects) after the booster immunization in the HAV group. Of these, adverse events that occurred in ≥5% of subjects in any group are shown with adverse reactions and the incidences in Table 4-20.

Table 4-20. Adverse events with an incidence of ≥5% in any group and adverse reactions among them (Total vaccinated cohort for primary epoch and booster epoch)

	Primary immunization								Booster immunization							
	11Pn-PD group (N = 2,489)				HAV group (N = 2,479)				11Pn-PD group (N = 2,461)				HAV group (N = 2,458)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Nasopharyngitis	256	10.3	9	0.4	235	9.5	7	0.3	87	3.5	4	0.2	85	3.5	2	0.1
Rhinitis	201	8.1	4	0.2	233	9.4	6	0.2	44	1.8	0	0	47	1.9	1	0
Bronchitis	188	7.6	6	0.2	166	6.7	4	0.2	61	2.5	0	0	68	2.8	1	0
Viral infection	134	5.4	7	0.3	147	5.9	5	0.2	59	2.4	1	0	55	2.2	1	0
Pharyngitis	114	4.6	3	0.1	131	5.3	2	0.1	56	2.3	1	0	62	2.5	2	0.1

N, number of subjects receiving at least one dose of the study vaccine; n, number of subjects with the adverse event/adverse reaction

Serious adverse events that occurred between the first dose and the end of the study were reported in 19.7% of subjects (491 of 2489 subjects) in the 11Pn-PD group and 20.5% of subjects (508 of 2479 subjects) in the HAV group. Of these serious adverse events, 12 episodes in 10 subjects in the 11Pn-PD group (viral infection [2 episodes] and lymphadenitis, vomiting, pyrexia, hypersensitivity, immunisation reaction, depressed level of consciousness, agitation, breath holding, purpura, and haemorrhage [1 episode each]) and 4 episodes in 4 subjects in the HAV group (hypersensitivity [2 episodes] and epilepsy and angiopathy [1 episode each]) were assessed as related to the study vaccine. Discontinuation of the study due to adverse events occurred in 0.4% of subjects (9 of 2489 subjects) in the 11Pn-PD group and 0.5% of subjects (13 of 2479 subjects) in the HAV group. Of these events, 4 episodes in 4 subjects in the HAV group (hypersensitivity [2 episodes] and epilepsy and vomiting [1 episode each]) were assessed as related to the study vaccine. Death occurred in 1 subject in the 11Pn-PD group (a subject with epilepsy) and 3 subjects in the HAV group (sudden death, haematuria, cardiac failure, and cardiomegaly [1 subject], lymphocytic leukaemia [1 subject], and asphyxia and drowning [1 subject]), and a causal relationship to the study vaccine was ruled out for the deaths.

4.B Outline of the review by PMDA

4.B.(1) Clinical data package and review policy

The applicant's explanation on the structure of clinical data package in Japan:

After the market launch of 7vPnC, a pneumococcal conjugate vaccine, the WHO Technical Report Series (TRS) recommend that immunogenicity based on IgG antibody concentrations be directly compared between a new pneumococcal conjugate vaccine and the 7vPnC vaccine, for which efficacy in preventing IPD has been demonstrated, to show the efficacy of the new vaccine against IPD (*WHO TRS 927 Annex2*, WHO, 2005, *Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines, Proposed replacement of TRS 927, Annex 2*, WHO, 2009). According the WHO's recommendation, the non-inferiority of Synflorix to 7vPnC was validated on the basis of IgG antibody concentrations in Study 10PN-PD-DIT-001 (Study 001) conducted outside Japan to explain the efficacy of Synflorix against IPD. In Japan, however, since pneumococcal conjugate vaccines including the 7vPnC vaccine were not approved at the time of development of Synflorix, a

direct comparison of immunogenicity between Synflorix and 7vPnC was not performed, and instead, IgG antibody concentrations following Synflorix vaccination in Japanese Study 058 were compared with those in Study 001. The effectiveness of Synflorix in preventing IPD was evaluated also in foreign Study 043.

The effectiveness of Synflorix in preventing CAP was evaluated in foreign Study 028. As exploratory analyses of Study 028 suggested a correlation between OPA antibody titers and the preventive effectiveness against CAP, OPA antibody titers following Synflorix vaccination were compared between Studies 028 and 058 for a comparison of immune response between Japanese and non-Japanese subjects.

The effectiveness of Synflorix in preventing AOM was evaluated in Study U-010, a foreign study, by using 11Pn-PD (Table 4-2) instead of the final formulation of Synflorix and was secondarily evaluated also in Study 028. Since exploratory analyses of Studies 028 and U-010 suggested a correlation between OPA antibody titers and the preventive effectiveness against AOM, OPA antibody titers following Synflorix vaccination were compared between Studies U-010 and 058 for a comparison of immune response between Japanese and non-Japanese subjects.

In light of the above, the following data were primarily used to demonstrate the efficacy of Synflorix: data from Studies 001 and 058, for the efficacy against IPD; data from Studies 028 and 058, for the efficacy against CAP; and data from Studies U-010 and 058, for the efficacy against AOM. Data from Study 028 in which the efficacy of Synflorix against AOM was secondarily evaluated were also used as supplemental data for demonstration of the efficacy of Synflorix against AOM. In addition, data from Study 043 in which the effectiveness of Synflorix in preventing IPD was evaluated were used as supplemental data to demonstrate the efficacy of Synflorix against IPD.

PMDA's view:

The efficacy of Synflorix against IPD should be more appropriately demonstrated on the basis of data from Study 043 because it has a higher level of evidence in that the effectiveness of Synflorix in preventing IPD was evaluated, and a comparison of immunogenicity between Study 058 and foreign studies should be used for discussion for efficacy in Japanese subjects. Therefore, PMDA reviewed the efficacy of Synflorix against IPD mainly on the basis of data from Study 043 and also on the basis of data from Study 058; and the efficacy of Synflorix against CAP mainly on the basis of data from Study 028, in which the effectiveness of Synflorix in preventing CAP was evaluated, and also on the basis of data from Study 058. In contrast, the applicant evaluated the efficacy of Synflorix against AOM in Study U-010 in which the 11Pn-PD formulation, not the final Synflorix formulation, was used. It is not appropriate to review the data from Study U-010 as the data for Synflorix because of the differences between the 11Pn-PD formulation and Synflorix in the following respects: the serotypes contained; the active substances for serotypes 18C and 19F; and the active substance contents for serotypes 4, 18C, and 19F (Table 4-3).

PMDA's review of the safety of Synflorix was conducted on the basis of data from Study 058, a Japanese

study, and additionally data from the foreign clinical studies and foreign postmarketing safety information submitted as evaluation data,.

4.B.(2) Efficacy

4.B.(2).1) Efficacy against IPD

PMDA's view on the efficacy of Synflorix against IPD:

In Study 043, the superiority of Synflorix over the control vaccine was validated from the data of incidences (per 1,000 subject-years) of VT-IPD that occurred on or after the day of the first dose of the study vaccine in the Synflorix 3+1 group and the control group (pooled HBV group) (Table 4-10). Based on the results, PMDA concluded that the effectiveness of Synflorix in preventing VT-IPD has been demonstrated.

The WHO TRS specify IgG antibody concentrations and OPA antibody titers as evaluation indicators related to the effectiveness in prevention of IPD. According to them, IgG antibody concentrations and OPA antibody titers were compared between Japanese and non-Japanese subjects. PMDA compared the IgG GMCs and OPA GMTs between the Synflorix 3+1 group in Study 053, in which immunogenicity was evaluated in some subjects enrolled in Study 043, and the Synflorix + DPT group, in which Japanese subjects received 4 doses of Synflorix in Study 058, to review the ethnic differences in immunogenicity (Table 4-21).

Table 4-21. IgG GMCs and OPA GMTs for serotypes contained in Synflorix after the third or fourth dose of Synflorix
(Studies 058 and 053, ATP cohorts for immunogenicity for primary epoch and booster epoch)

Serotypes	Post 3rd dose				Post 4th dose			
	Study 058 (Synflorix + DPT group)		Study 053 (Synflorix 3+1 group)		Study 058 (Synflorix + DPT group)		Study 053 (Synflorix 3+1 group)	
	N	IgG GMC	N	IgG GMC	N	IgG GMC	N	IgG GMC
1	231	6.52	208	1.86	214	7.81	189	2.13
4	231	6.54	208	2.47	213	12.89	189	3.61
5	231	6.54	208	2.73	214	8.81	189	3.27
6B	231	1.71	208	0.51	214	3.66	189	1.43
7F	231	6.11	209	2.90	214	10.68	189	4.25
9V	231	5.42	208	2.23	214	12.79	188	3.98
14	231	10.03	209	5.00	214	15.72	189	6.40
18C	231	16.59	209	6.51	213	34.90	189	10.43
19F	229	17.39	209	5.91	214	28.72	189	8.04
23F	231	2.17	208	0.68	214	7.68	189	2.30
Serotypes	Post Dose 3				Post Dose 4			
	Study 058 (Synflorix + DPT group)		Study 053 (Synflorix 3+1 group)		Study 058 (Synflorix + DPT group)		Study 053 (Synflorix 3+1 group)	
	N	OPA GMT	N	OPA GMT	N	OPA GMT	N	OPA GMT
1	223	619.8	202	52.8	214	2320.7	184	305.6
4	221	1184.6	199	845.6	214	3863.1	184	1745.7
5	224	335.1	199	65.9	214	686.7	185	191.6
6B	222	1926.6	195	740.6	214	1682.9	181	736.3
7F	216	7905.9	197	3894.8	214	14144.3	184	5219.7
9V	219	4063.4	194	2798.0	214	4693.7	183	3491.2
14	217	3392.4	198	1831.3	213	6209.0	185	2657.2
18C	217	893.2	192	543.3	214	2181.0	183	1066.1
19F	219	1254.6	196	649.6	212	3496.3	183	1026.0
23F	218	4312.1	196	1900.7	214	7057.2	184	3248.2

N, Subjects with immunogenicity measurements after the third or fourth dose of Synflorix

The comparison showed that IgG GMCs and OPA GMTs in Japanese subjects following the third and fourth dose of Synflorix in Study 058 were higher for all 10 serotypes than those in subjects in Study 053.

Based on the above, PMDA concluded that the efficacy of Synflorix against IPD caused by the serotypes contained in Synflorix is consistent in light of immunogenicity and can be expected in Japanese people.

4.B.(2).2) Efficacy against CAP

The applicant's explanation on the efficacy of Synflorix against CAP:

In Study 028, the superiority of Synflorix over control vaccines was validated for incidences (per 1000 subject-years) of first B-CAP episodes ≥15 days after the third dose of the study vaccine in the Synflorix group and the control group (HBV/HAV group) (Table 4-13). In the study, C-CAP (pneumonia with alveolar infiltration or pleural effusion) diagnosed according to the WHO criteria (*Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children*, WHO, 2001, *Pneumonia: the forgotten killer of children*, WHO, 2006) was assessed as a secondary endpoint, and the vaccine effectiveness [95% confidence interval] of Synflorix against C-CAP was 25.7% [8.4, 39.6] with a lower limit of the 95% confidence interval above 0 (Table 4-14). Based on the above, the effectiveness of Synflorix in preventing CAP has been demonstrated.

The IgG antibody concentrations and OPA antibody titers were compared in the Synflorix group in Study 028 and the Synflorix + DPT group in Japanese Study 058. The comparison showed that IgG GMCs and OPA GMTs in Japanese subjects following the third and fourth dose of Synflorix in Study 058 were higher than those in subjects in Study 028 for all 10 serotypes, except for OPA GMTs for serotype 18C after the fourth vaccine dose (Table 4-22). The OPA GMTs for serotype 18C after the fourth vaccine dose did not largely differ between Studies 028 and 058.

Based on the above, the efficacy of Synflorix against pneumonia has been demonstrated.

Table 4-22. IgG GMCs and OPA GMTs for serotypes contained in Synflorix after the third or fourth dose of Synflorix
(Studies 058 and 028, ATP cohorts for immunogenicity for primary epoch and booster epoch)

Serotypes	Post 3rd dose				Post 4th dose			
	Study 058 (Synflorix + DPT group)		Study 028 (Synflorix group)		Study 058 (Synflorix + DPT group)		Study 028 (Synflorix group)	
	N	IgG GMC	N	IgG GMC	N	IgG GMC	N	IgG GMC
1	231	6.52	334	2.51	214	7.81	219	3.58
4	231	6.54	334	3.26	213	12.89	217	6.55
5	231	6.54	334	4.20	214	8.81	219	5.73
6B	231	1.71	334	1.34	214	3.66	217	3.32
7F	231	6.11	334	3.86	214	10.68	218	5.77
9V	231	5.42	334	3.15	214	12.79	218	7.34
14	231	10.03	334	4.55	214	15.72	219	9.31
18C	231	16.59	334	5.32	213	34.90	219	16.38
19F	229	17.39	334	5.33	214	28.72	219	9.40
23F	231	2.17	334	1.99	214	7.68	218	4.02
Serotypes	Post 3rd dose				Post 4th dose			
	Study 058 (Synflorix + DPT group)		Study 028 (Synflorix group)		Study 058 (Synflorix + DPT group)		Study 028 (Synflorix group)	
	N	OPA GMT	N	OPA GMT	N	OPA GMT	N	OPA GMT
1	223	619.8	306	139.5	214	2320.7	209	357.5
4	221	1184.6	310	771.7	214	3863.1	207	2853.5
5	224	335.1	313	224.8	214	686.7	196	306.1
6B	222	1926.6	315	689.7	214	1682.9	203	1123.4
7F	216	7905.9	302	4656.7	214	14144.3	205	4336.3
9V	219	4063.4	312	1690.4	214	4693.7	200	3763.0
14	217	3392.4	308	908.5	213	6209.0	209	2659.6
18C	217	893.2	308	310.9	214	2181.0	188	2426.0
19F	219	1254.6	304	383.0	212	3496.3	199	657.5
23F	218	4312.1	317	2167.4	214	7057.2	206	4278.3

N, Subjects with immunogenicity measurements after the third or fourth dose of Synflorix

PMDA's view:

No relevant indicators have been established for evaluation of the effectiveness in prevention of CAP caused by *S. pneumoniae*. However, it is meaningful to compare the data on IgG antibody concentrations and OPA antibody titers, both of which are widely used as evaluation indicators related to clinical prevention of IPD, between Japanese and foreign clinical studies to discuss the ethnic difference in immunogenicity. From an immunogenic point of view, no discrepancy has been found between the data from Study 028, in which the effectiveness of Synflorix in preventing CAP demonstrated, and the data from Japanese Study 058.

Based on the above, PMDA concluded that the efficacy of Synflorix against CAP can be expected in Japanese people.

4.B.(2).3) Efficacy against AOM

As described in "4.B.(1) Clinical data package and review policy," PMDA considers it difficult to explain the efficacy of Synflorix against AOM on the basis of data from Study U-010, in which the 11Pn-PD was used instead of the final Synflorix formulation. PMDA requested the applicant to discuss the data on the effectiveness of Synflorix in preventing AOM, which was secondarily evaluated in Study 028. The applicant responded as follows.

When Study 028 was planned, the first episode of clinical AOM (C-AOM) diagnosed by otolaryngologists according to the pre-specified criteria that occurred ≥15 days after the third dose of the study vaccine was to be assessed as a primary endpoint in subjects enrolled in Panama (hereinafter referred to as "ATP cohort for efficacy against AOM"). During the study, however, the number of occurrences of overall AOM was found to be lower than expected, and the primary endpoint was thus changed to a secondary endpoint. Data from Study 028 showed that the lower limit of the 95% confidence interval for the vaccine effectiveness of Synflorix against C-AOM episode was lower than 0, indicating no statistically significant difference in the occurrence of C-AOM episodes between the Synflorix group and the control vaccine group (HAV/HBV group) (Table 4-23). Meanwhile, a similar analysis was performed for the occurrence of C-AOM caused by the serotypes contained in Synflorix (hereinafter referred to as "VT-C-AOM") and showed a statistically significant difference, albeit in the secondary endpoint, between the Synflorix group and the control vaccine group.

Accordingly, data on VT-C-AOM following Synflorix vaccination suggest that the effectiveness of Synflorix in preventing AOM can be expected.

Table 4-23. Incidences of first episode of C-AOM or VT-C-AOM ≥15 days after the third dose of the study vaccine (per 1,000 subject-years)
(Study 028, ATP cohort for efficacy against AOM)

		N	n	Incidence (per 1,000 subject-years)	Vaccine effectiveness (%) [95% CI]
C-AOM	Synflorix group	3010	204	28.91	16.14 [−1.09, 30.43]
	HBV/HAV group	2979	239	34.1	
VT-C-AOM	Synflorix group	3010	6	0.85	67.1 [17.0, 86.9]
	HBV/HAV group	2979	18	2.58	

N, number of subjects analyzed; n, number of first episodes of C-AOM or VT-C-AOM ≥15 days after the third dose of the study vaccine
a) Vaccine effectiveness (%) = [1 − incidence ratio (Synflorix group/[HBV/HAV group])] × 100

PMDA's view on the efficacy of Synflorix against AOM:

PMDA concluded that the efficacy of Synflorix against AOM has not been demonstrated because the clinical data submitted in this application do not include study results to evaluate the effectiveness of Synflorix in preventing AOM. PMDA considers that the VT-C-AOM results have no clinical significance, in light of the following: VT-C-AOM was assessed as a secondary endpoint; the number of VT-C-AOM episodes in Study 028 was very small (6 episodes in 204 C-AOM episodes in the Synflorix group and 18 episodes in 239 C-AOM episodes in the control vaccine group [Table 4-23]) and

accordingly the expected occurrence of VT-C-AOM was not detected.

4.B.(3) Safety

The applicant explained the safety data obtained in clinical studies in and out of Japan as follows.

4.B.(3).1) Safety data in clinical studies

In Japanese Study 058, the incidence of Grade 3 solicited local adverse events occurring at Synflorix injection site in the Synflorix + DPT group tended to be higher than those occurring at DPT injection site in the DPT group (Table 4-24). In addition, the incidence of solicited local adverse events was higher after booster immunization than after primary immunization in both Synflorix + DPT group and DPT group (Tables 4-6 and 4-24). In the Synflorix + DPT group, most of Grade 3 solicited local adverse events occurring at Synflorix injection site resolved in several days after onset, except for 1 event in 1 subject (injection site erythema, 32 mm), which developed after the fourth vaccine dose and persisted beyond 7 days after the dose. The event was confirmed to have resolved by 12 days after the dose. In the Synflorix + DPT group, no solicited local adverse events leading to discontinuation of the study occurred, and all events resolved.

The incidence of solicited general adverse events was compared between the Synflorix + DPT group (those events after coadministration of Synflorix and DPT) and the DPT group (those events after administration of DPT alone). As a result, the incidence was generally higher in the Synflorix + DPT group than in the DPT group (Table 4-6). However, there were no Grade 3 solicited general adverse events that occurred with an incidence of >5% even in the Synflorix + DPT group, and the most frequently observed Grade 3 solicited general adverse event was irritability after the fourth dose with an incidence of 3.5% (Table 4-24).

In the Synflorix + DPT group, convulsion and febrile convulsion occurred in the primary epoch and booster epoch, respectively, in 1 subject each by 30 days after each study vaccination. In the subject with convulsion, it occurred with pneumonia and gastroenteritis rotavirus 30 days after the third dose of Synflorix and DPT. In the subject with febrile convulsion, the event onset was 28 days after the fourth dose of Synflorix and DPT. Both events were assessed as unrelated to the vaccination with the study vaccine.

Table 4-24. Grade 3[a] solicited local adverse events and solicited general adverse events/adverse reactions (Study 058, Total vaccinated cohort for primary epoch and booster epoch)

	Synflorix + DPT group				DPT group			
	Primary immunization			Booster immunization	Primary immunization			Booster immunization
	1st dose	2nd dose	3rd dose	4th dose	1st dose	2nd dose	3rd dose	4th dose
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Solicited local adverse events [b]								
Injection site pain	1/237 (0.4)	0/235 (0)	1/233 (0.4)	12/228 (5.3)	0/123 (0)	0/123 (0)	0/122 (0)	0/120 (0)
Injection site erythema	9/237 (3.8)	19/235 (8.1)	16/233 (6.9)	52/228 (22.8)	0/123 (0)	4/123 (3.3)	0/122 (0)	20/120 (16.7)
Injection site swelling	13/237 (5.5)	24/235 (10.2)	24/233 (10.3)	41/228 (18.0)	0/123 (0)	4/123 (3.3)	1/122 (0.8)	18/120 (15.0)
Solicited general adverse events								
Somnolence	3/237 (1.3)	2/235 (0.9)	0/233 (0)	3/228 (1.3)	0/123 (0)	0/123 (0)	0/122 (0)	3/120 (2.5)
Pyrexia	1/237 (0.4)	0/235 (0)	2/233 (0.9)	6/228 (2.6)	0/123 (0)	0/123 (0)	0/122 (0)	0/120 (0)
Irritability	6/237 (2.5)	4/235 (1.7)	3/233 (1.3)	8/228 (3.5)	3/123 (2.4)	0/123 (0)	0/122 (0)	2/120 (1.7)
Appetite impaired	0/237 (0)	0/235 (0)	0/233 (0)	4/228 (1.8)	0/123 (0)	0/123 (0)	0/122 (0)	1/120 (0.8)
Solicited general adverse reactions								
Somnolence	2/237 (0.8)	2/235 (0.9)	0/233 (0)	2/228 (0.9)	0/123 (0)	0/123 (0)	0/122 (0)	0/120 (0)
Pyrexia	1/237 (0.4)	0/235 (0)	0/233 (0)	1/228 (0.4)	0/123 (0)	0/123 (0)	0/122 (0)	0/120 (0)
Irritability	3/237 (1.3)	1/235 (0.4)	1/233 (0.4)	3/228 (1.3)	2/123 (1.6)	0/123 (0)	0/122 (0)	0/120 (0)
Appetite impaired	0/237 (0)	0/235 (0)	0/233 (0)	1/228 (0.4)	0/123 (0)	0/123 (0)	0/122 (0)	0/120 (0)

N, number of subjects vaccinated with the study vaccine; n, number of subjects with the adverse event/adverse reaction

a) Adverse events were classified into 3 grades (Grade 1 to 3) according to severity. Grade 3 solicited events were defined as follows: Injection site pain, cried when limb was moved/spontaneously painful; Injection site erythema or injection site swelling, >30 mm; Somnolence, prevented normal daily activity; Pyrexia, >39.5°C; Irritability, crying that could not be comforted/prevented normal daily activity; Appetite impaired, not eating at all.

b) In the Synflorix + DPT group, only solicited local adverse events that occurred at Synflorix injection site were collected.

Results of a pooled analysis of foreign clinical studies in which the 7vPnC vaccine was used as a control vaccine (primary immunization, Studies 001, 003, 011, 027, 012, and 036; booster immunization, Studies 007, 017, 018, 027, and 063) are shown in Table 4-25 and indicate that the incidences of the solicited adverse events did not largely differ between the Synflorix group and the 7vPnC group.

Table 4-25. Solicited local and general adverse events[a]
(Studies 001, 003, 011, 027, 012, 036, 007, 017, 018, 027, and 063, Total vaccinated cohort)

	Primary immunization		Booster immunization	
	Synflorix group	7vPnC group	Synflorix group	7vPnC group
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Solicited local adverse events				
Injection site pain	2461/3932 (62.6)	840/1453 (57.8)	2092/3490 (59.9)	540/1006 (53.7)
Injection site erythema	2710/3932 (68.9)	991/1453 (68.2)	1932/3490 (55.4)	570/1006 (56.7)
Injection site swelling	2299/3932 (58.5)	793/1453 (54.6)	1588/3490(45.5)	455/1006 (45.2)
Solicited general adverse events				
Somnolence	2855/3932 (72.6)	1011/1453 (69.6)	1442/3489 (41.3)	400/1006 (39.8)
Irritability	3278/3932 (83.4)	1184/1453 (81.5)	2050/3489 (58.8)	563/1006 (56.0)
Appetite impaired	2060/3932 (52.4)	730/1453 (50.2)	1162/3489 (33.3)	349/1006 (34.7)
Pyrexia	2373/3932 (60.4)	823/1453 (56.6)	1292/3489 (37.0)	380/1006 (37.8)

N, number of subjects receiving at least one vaccination dose; n, number of subjects with the adverse event

a) These events were collected up to 3 days after study vaccination.

4.B.(3).2) Serious adverse reactions

In clinical studies in and out of Japan (11 studies in the evaluation data and 26 studies in the reference data, a total of 37 studies), 15 episodes of serious adverse reactions occurred in 15 of 22,429 subjects vaccinated with Synflorix as primary immunization (pyrexia [4 episodes], convulsion [2 episodes], and

crying, sudden death, injection site abscess, lower respiratory tract infection, sepsis, vaccination complication, febrile convulsion, nephrotic syndrome, and apparent life threatening event [1 episode each]), and 10 episodes of serious adverse reactions occurred in 7 of 19,466 subjects vaccinated with Synflorix as booster immunization (febrile convulsion [4 episodes], pyrexia [2 episodes], and injection site erythema, oedema peripheral, pharyngitis, and somnolence [1 episode each]). No serious adverse reactions occurred in Japanese Study 058.

Serious adverse reactions that persisted for ≥1 week were 1 episode each of nephrotic syndrome (duration unknown), injection site abscess (54 days), pyrexia (10 days), and sepsis (9 days). All the reactions except nephrotic syndrome were confirmed to have resolved. The subject with nephrotic syndrome was receiving steroid therapy at the time of follow-up approximately 1 year after the onset. All serious adverse reactions lasting for <1 week resolved without sequelae.

Deaths occurred in 21 of 22,429 subjects in the primary epoch and 8 of 19,466 subjects in the booster epoch. In Study 058, 1 subject in the Synflorix + DPT group died, but a causal relationship to Synflorix vaccination was ruled out. The subject died 10 days after the second dose of the study vaccine, and a diagnosis of sudden infant death syndrome was made. The subject had a history of intrauterine growth retardation, and the subject's elder sibling had died of sudden infant death syndrome, too. Among the deaths, only 1 case of sudden death in primary epoch in Study 10PN-PD-DIT-034 (reference data) was assessed as related to Synflorix vaccination. The sudden death occurred after injection in the subject on the day of the first coadministration of Synflorix, DPT-HBV/Hib, and OPV.

4.B.(3).3) Foreign postmarketing safety information

Approximately 55.08 million doses of Synflorix were supplied during the reporting period (December 11, 2012 to December 10, 2013) of the current version, version 2, of Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR). During the period, 1696 episodes of serious adverse events and 2559 episodes of non-serious adverse events were spontaneously reported. Of the serious adverse events, main events were pyrexia (170 episodes) and hyperpyrexia (temperature of ≥41.1°C or hyperpyrexia diagnosed by the reporter [physician]) (18 episodes), followed by hypotonic-hyporesponsive episode (145 episodes), febrile convulsion (71 episodes) and convulsion (34 episodes), and crying (64 episodes). Non-serious adverse events accompanying the serious adverse events are included in the above number of episodes. Deaths in 10 vaccinees were reported during the reporting period. Background information and clinical course to death were reviewed for individual vaccinees, and it was concluded that there was no information affecting the safety profile of Synflorix.

In the Core Data Sheet (CDS) of Synflorix, anaphylaxis and hypotonic-hyporesponsive episodes are listed as events that developed after Synflorix vaccination while those were not detected in clinical studies. In addition, convulsion, allergic reaction including anaphylaxis, and thrombocytopenic purpura were assessed as shown below.

(a) Convulsions

In the PBRER/PSUR version 2, febrile convulsion and convulsion were reported in 76 vaccinees and 27 vaccinees, respectively. Febrile convulsion and convulsion have been reported in 204 vaccinees and 70 vaccinees, respectively, during the period from the launch of Synflorix on the foreign market to the data lock point of the PBRER/PSUR version 2, and pyrexia concomitantly occurred in many cases reported as convulsion. Among the reported vaccinees, convulsions occurred after vaccination with Synflorix alone in 52 of 127 vaccinees in Brazil, 1 of 38 vaccinees in Netherlands, and 17 of 109 vaccinees in other countries.

(b) Anaphylaxis

Allergic reactions were reported in 55 vaccinees (0.094 vaccinees per 100,000 doses) in the PBRER/PSUR version 2. These events included urticarial in 38 vaccinees, angioedema in 4 vaccinees, eye swelling in 3 vaccinees, and anaphylactic shock in 2 vaccinees. Cases of anaphylactic shock and angioedema were difficult to be assessed because of lack of information. Anaphylaxis possibly related to Synflorix vaccination have been reported in 3 vaccinees since the launch of Synflorix, and remission or recovery was reported in all of the vaccinees. Based on the above, the CDS states that appropriate medical treatment and supervision should always be readily available in case of anaphylaxis.

(c) Thrombocytopenic purpura

A total of 71 cases of purpura-related cases (thrombocytopenic purpura, idiopathic thrombocytopenic purpura, and thrombocytopenia) have been reported during the period from the launch of Synflorix on the market to the data lock point of the PBRER/PSUR version 2. Among 7 vaccinees with available information for evaluation of causality to Synflorix, 6 vaccinees had been coadministered with other vaccines.

PMDA's view on the tolerability of Synflorix:

PMDA considers that Synflorix is well-tolerated in light of the following facts: no serious adverse reactions occurred in Japanese Study 058; among serious adverse events reported in foreign clinical studies including those submitted as the reference data, only 1 event of nephrotic syndrome had not recovered; and in Japanese and foreign clinical studies submitted as evaluation data, there were no deaths assessed as related to Synflorix vaccination. In the foreign postmarketing setting, rare adverse events (e.g., anaphylaxis) that had not been identified in clinical studies have been reported, but no events seem specific to Synflorix.

Based on the review on the safety as shown in above sections 4.B.(3).1) and 4.B.(3).2), PMDA concluded that the safety profile of Synflorix is tolerable.

4.B.(4) Clinical positioning

In Japan, pneumococcal conjugate vaccines including the 7vPnC vaccine and "pneumococcal conjugate vaccine, 13-valent adsorbed (conjugated to nontoxic variant of diphtheria toxin)" (13vPnC) were not approved at the time of development of Synflorix. However, now as of 2014, the 13vPnC vaccine is used routinely for prevention of IPD caused by serotypes contained in the 13vPnC. Since Synflorix does not contain serotypes 3, 6A, or 19A, which are included in 13 serotypes in the 13vPnC vaccine, PMDA asked the applicant to explain the significance of introduction of Synflorix in Japan.

The applicant's explanation:

Synflorix contains serotypes 6B and 19F which have similar structures to serotypes 6A and 19A, respectively. Therefore, immunological cross-reaction can be expected between 6A and 6B and between 19A and 19F. In Study 058, immunogenicity against serotypes 6A and 19A was observed after Synflorix vaccination. In addition, the efficacy of Synflorix for prevention of IPD caused by serotypes 6A and 19A is suggested in epidemiological studies conducted outside Japan (*Lancet Respir. Med*, 2014;2:464-471, *Vaccine*, 2014;32:1501-1506, *8th WSPID* abstract, 2013, *Nordic Vaccine Meeting*, 2014).

The incidence of IPD caused by serotype 3 was reported to account for 1.1% of overall pediatric IPDs by surveillance conducted approximately 3 years after the introduction of the 7vPnC vaccine in Japan (surveillance period: January 2013 to December 2013), and the rate is known to be low (*Research on "Basic and Clinical Research on Efficacy, Safety, and Adverse Reactions of Vaccines for Hemophilus influenzae type B, Streptococcus pneumoniae, Rotaviruses, Human Papilloma Viruses, and Other Pathogens," "Surveillance of Pediatric Bacterial Meningitis and Invasive Infections (National Surveillance)," Research Project on Emerging/Re-emerging Infectious Diseases Including Novel Influenza, funded by Health and Labour Sciences Research Grants,* 2013). In addition, reportedly, preventive effect of the 13vPnC and 23vPS vaccines on IPDs caused by serotype 3 has not been suggested (*Pediatr Infect Dis J*, 2013;32:984-989), and it is thus presumed that the effectiveness of vaccines in preventing IPD caused by serotype 3 is limited.

Accordingly, with respect to the preventive effect caused by serotypes contained, no clinical differences exist between the 13vPnC vaccine and Synflorix, which does not contain serotypes 3, 6A, or 19A, and it is considered significant to introduce Synflorix to Japan.

PMDA's view on the clinical positioning of Synflorix:

Immunogenicity against serotypes 6A and 19A has been demonstrated after Synflorix vaccination, but the clinical significance of the immunogenicity in prevention of IPD is not clear. It is difficult to accept the applicant's explanation that no clinical differences exist between the 13vPnC vaccine and Synflorix, which does not contain serotypes 3, 6A, or 19A, mainly on the ground of demonstrated immunogenicity.

IPD is a serious disease that should be prevented from affecting infants because of its severity and

mortality. As described in "4.B.(2) Efficacy," the effectiveness of Synflorix in preventing IPD caused by the 10 serotypes contained in the vaccine was clinically validated (Table 4-10). In contrast, with regard to the evidence for the approved 13vPnC vaccine, the efficacy was evaluated only in comparison of immunogenicity with the 7vPnC vaccine for which the effectiveness in preventing IPD caused by 7 serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) had been demonstrated. The effectiveness for prevention of IPD related to 13 serotypes contained in the 13vPnC vaccine was not directly validated (Review Report on Prevenar13 Suspension Liquid for Injection, dated May 7, 2014). The effectiveness of Synflorix in preventing IPD caused by the 10 serotypes contained in the vaccine was directly validated, making the high level evidence available.

It is important that, based on the above findings, the higher level evidence has been obtained for Synflorix as compared with the 13vPnC vaccine, and Synflorix is considered to be an option for pneumococcal conjugate vaccines in Japan.

4.B.(5) Indication

As discussed in "4.B.(2) Efficacy," Synflorix is expected to be effective for prevention of IPD and CAP caused by the serotypes contained in the vaccine.

Pneumonia is classified into CAP and hospital-acquired pneumonia: the former is caused by microorganisms in community settings, and the latter by those in healthcare facilities (*Jpn. J. Chemother.*, 2014;62:1-109). The efficacy of Synflorix against CAP has been demonstrated in clinical studies, and the results seem to reflect the efficacy of Synflorix for prevention of pneumonia caused by *S. pneumoniae*, including hospital-acquired pneumonia. PMDA therefore considers that it is appropriate to use the term pneumonia, instead of CAP, in the indication of Synflorix.

Based on the above discussion, PMDA concluded that Synflorix should be approved for the indication of "prevention of invasive infections and pneumonia caused by *S. pneumoniae* (pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F)."

4.B.(6) Dosage and administration

4.B.(6).1) Dosage and vaccination route

The applicant's explanation on the dosage (active substance contents) per dose and route of vaccination:
The doses of Synflorix were evaluated in foreign clinical studies using 11Pn-PD, 11Pn-PD-DiT, and 11Pn-PD&Di formulations (Studies 11Pn-PD&Di-001, 11Pn-PD&Di-007, 11PN-PD-DIT-001, and 11PN-PD-DIT-002). Immunogenicity and safety were evaluated in various formulations with different combination of 5 pneumococcal capsular polysaccharide contents (1, 2, 3, 5, and 10 μg) per 0.5 mL for each serotype (Table 4-26). Based on the results, the pneumococcal capsular polysaccharide contents per 0.5 mL were determined to be 3 μg for serotypes 4, 18C, and 19F; and 1 μg for the other 7 serotypes.

Table 4-26. List of study vaccines

Serotypes		1	3	4	5	6B	7F	9V	14	18C	19F	23F
Synflorix	Content [a)]	1		3	1	1	1	1	1	3	3	1
	Type [b)]	PD		PD	PD	PD	PD	PD	PD	TT	DT	PD
11Pn-PD	Content [a)]	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3
	Type [b)]	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD
11Pn-PD-DiT	Content [a)]	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1 or 3	1, 3, or 10	3	1 or 3
	Type [b)]	PD	PD	PD	PD	TT	PD	PD	PD	DT or TT	DT	PD or TT
11Pn-PD&Di	Content [a)]	3 or 5	2, 3, or 5	2, 3, or 5	3 or 5	5 or 10	3 or 5	2, 3, or 5	2, 3, or 5	2, 3, or 5	3 or 5	5
	Type [b)]	PD	PD	PD	PD	DT	PD	PD	PD	PD	DT or PD	DT

PD, protein D; TT, tetanus toxoid; DT, diphtheria toxoid
a) Polysaccharide content (μg) per 0.5 mL, b) Type of carrier protein

The effectiveness of Synflorix in preventing IPD and pneumonia was validated, and data from Japanese Study 058 demonstrated the immunogenicity and tolerability of Synflorix in Japanese subjects. Therefore, the proposed polysaccharide content for each serotype is considered appropriate for Japanese people.

With regard to the vaccination route, intramuscular vaccination with Synflorix was evaluated in foreign clinical studies, and the effectiveness of intramuscularly administered Synflorix in prevention of IPD and pneumonia was validated in these studies. Local reactions were more severe when vaccines (including Synflorix) with aluminum adjuvant were subcutaneously administered than when intramuscularly administered, and higher immunogenicity was noted when the vaccines were intramuscularly administered than when subcutaneously administered (*Vaccine*, 2008;26:6299-6304, *Vaccine*, 1999;17:2067-2072). In addition, data from Study 058 in which Synflorix was administered intramuscularly demonstrated the immunogenicity and tolerability in Japanese subjects. Based on the above findings, intramuscular administration of Synflorix is considered appropriate for Japanese people.

PMDA accepted the applicant's explanation. Given that the administration route of Synflorix differs from that of the approved 13vPnC vaccine, which is subcutaneously administered, PMDA recommends that precautionary statement about the difference in administration route between the vaccines be included in information materials.

4.B.(6).2) Vaccination schedule

(a) Interval for primary doses

The applicant proposed the interval between primary Synflorix doses (first, second, third doses) to be "at least 27 days" and explained the grounds as follows.

In Study 043 in which the effectiveness of Synflorix in preventing IPD caused by the serotypes contained in Synflorix was evaluated, Synflorix was administered at least 28 days after the previous doses, namely an interval of at least 27 days between the doses, in the Synflorix 3+1 group. Meanwhile, in Study 058, Synflorix was administered 28 to 56 days after the previous doses, namely an interval of 27 to 55 days between the doses, in the primary epoch. Primary doses with Synflorix with an interval of 56 days or longer has not been evaluated in Japanese people. However, the world's most widely used clinical

textbook on vaccines (*Plotkin Vaccines, 6th ed.*, Elsevier, 2013) states that in multiple dose schedule, immune memory is induced by the first dose and remains intact even if the second or subsequent dose is administered later than the recommended schedule. Therefore, the "interval of at least 27 days" used in the primary epoch in Study 043 can be proposed for the interval between the primary Synflorix doses.

PMDA concluded that the proposed "interval of at least 27 days" for primary doses with Synflorix is appropriate.

(b) Interval for a booster dose

The applicant proposed the interval between the last primary dose (third dose) and the booster dose (fourth dose) to be "at least 6 months" and explained the grounds as follows.

In the Synflorix 3+1 group in Study 043, the planned interval between the third and fourth doses was set to be at least 4 months while the recommended interval was 6 months. The 6-month interval was recommended according to (i) the above textbook (*Plotkin Vaccines, 6th ed.*, Elsevier, 2013) that stated that good immune response is available with an interval of at least 4 to 6 months and (ii) the WHO position paper (*Wkly Epidemiol Rec*, 87: 129-144, 2007) that recommended an interval of at least 6 months for pneumococcal conjugate vaccines. Following the clinical study, the median interval between the third and fourth doses was found to be 6 months, and the mean interval 6.7 months.

In foreign Study 10PN-PD-DIT-062 (Study 062), 2 groups (the Synflorix-Synflorix9 group and the Synflorix-Synflorix15 group in Table 4-1) were set in which subjects received the booster dose of Synflorix at 9 to 18 months of age and at 15 to 18 months of age, respectively. The immunogenicity and safety of Synflorix vaccination were evaluated by comparing the 2 groups with an interval of 5.5 to 14.5 months (in the Synflorix-Synflorix9 group) and 11.5 to 14.5 months (in the Synflorix-Synflorix15 group) between the third and fourth doses (Table 4-27). As a result, antibody titers in the Synflorix-Synflorix15 group were generally higher than those in the Synflorix-Synflorix9 group but did not differ significantly with a maximum difference of approximately 2-fold. Also with regard to safety, no consistent pattern depending on the intervals was observed (Table 4-28).

Table 4-27. Immunogenicity 1 month after booster immunization by interval (Study 062, ATP cohorts for immunogenicity)

Serotypes	Synflorix-Synflorix9 group (interval of 5.5 to 14.5 months)				Synflorix-Synflorix15 group (interval of 11.5 to 14.5 months)			
	Percentage of subjects with IgG antibody n/N (%)	IgG GMC	Percentage of subjects with OPA n/N (%)	OPA GMT	Percentage of subjects with IgG antibody n/N (%)	IgG GMC	Percentage of subjects with OPA n/N (%)	OPA GMT
1	79/80 (98.8)	4.78	77/79 (97.5)	1138.3	60/61 (98.4)	5.98	57/58 (98.3)	2096.7
4	79/81 (97.5)	7.28	79/79 (100)	3368.8	63/63 (100)	11.56	58/58 (100)	7202.1
5	80/81 (98.8)	5.86	78/79 (98.7)	452.7	61/62 (98.4)	7.20	57/58 (98.3)	834.6
6B	78/81 (96.3)	2.82	77/79 (97.5)	1556.6	60/64 (93.8)	2.98	53/57 (93.0)	1781.2
7F	79/81 (97.5)	6.30	79/79 (100)	7814.8	63/63 (100)	7.89	57/57 (100)	11064.4
9V	79/81 (97.5)	8.03	79/79 (100)	4440.0	63/64 (98.4)	9.76	58/58 (100)	7870.3
14	80/81 (98.8)	10.18	78/79 (98.7)	2057.1	63/64 (98.4)	11.85	57/57 (100)	4407.5
18C	79/81 (97.5)	33.39	78/79 (98.7)	1889.7	63/63 (100)	42.43	57/58 (98.3)	3643.2
19F	79/81 (97.5)	13.68	76/78 (97.4)	1672.9	63/64 (98.4)	13.64	57/58 (98.3)	2404.4
23F	78/81 (96.3)	5.54	77/79 (97.5)	3812.3	62/63 (98.4)	6.48	56/58 (96.6)	5937.2

N, number of subjects analyzed; n, number of subjects with an IgG antibody concentration of ≥0.2 μg/mL or an OPA antibody titer of ≥8

Table 4-28. Solicited local and general adverse events by interval (Study 062, Total vaccinated cohort)

	Synflorix-Synflorix9 group (interval of 5.5 to 14.5 months)	Synflorix-Synflorix15 group (interval of 11.5 to 14.5 months)
	n/N (%)	n/N (%)
Solicited local adverse events		
Injection site pain	31/93 (33.3)	25/85 (29.4)
Injection site erythema	16/93 (17.2)	12/85 (14.1)
Injection site swelling	14/93 (15.1)	14/85 (16.5)
Solicited general adverse events		
Somnolence	5/92 (5.4)	4/85 (4.7)
Pyrexia	20/92 (21.7)	13/85 (15.3)
Irritability	19/92 (20.7)	9/85 (10.6)
Appetite impaired	14/92 (15.2)	9/85 (10.6)

N, number of subjects analyzed; n, number of subjects with adverse events

In Study 058, subjects received the booster dose at 17 to 19 months of age. In Japanese subjects, an interval of 12 to 14 months only was studied between the third and fourth doses. However, the data of Study 062 suggests that the immunogenicity and safety are not significantly affected by the difference in the dose interval. In light of the fact that the fourth dose of Synflorix was scheduled to be administered at least 4 months apart from the third dose with a recommendation of a 6-month interval in Study 043, the proposed interval of at least 6 months between the third and fourth doses is considered reasonable.

PMDA's view:

An interval of at least 4 months should be allowed between the third and fourth doses of Synflorix, based on the following: in Study 043, the interval between the third and fourth doses was set to be at least 4 months, and some subjects received the doses with an interval of less than 6 months; the effectiveness of Synflorix in preventing IPD caused by the serotypes contained in the vaccine was evaluated in Study 043; and there seems to be no positive grounds supporting an interval of at least 6 months between the third and fourth doses.

Based on the above review, PMDA concluded that the dosage and administration section should be changed as shown below. In addition, PMDA considers that, in order to clarify Synflorix is not indicated for vaccination in the elderly, "children" should be included in the dosage and administration section in

contrast with the approved 13vPnC, which is indicated for the population.

[Dosage and administration]
Primary immunization: The usual primary immunization series for children consist of three doses of 0.5 mL each, administered by intramuscular injection, with an interval of at least 27 days.
Booster immunization: The usual booster dose for children is a single dose of 0.5 mL, administered by intramuscular injection at least 4 months after the third dose.

4.B.(7) Postmarketing investigations

The applicant plans to conduct a drug use-results survey with a target sample size of 1000 vaccinees to evaluate the safety of Synflorix in routine clinical use. PMDA is reviewing the details of the plan, and the survey plan will be reported with PMDA's review results in the Review Report (2).

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. The inspection and assessment revealed no particular problems. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.10, 5.3.5.1.43, 5.3.5.1.60). PMDA concluded that overall clinical studies were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application documents. The following matter, while having a less effect on the evaluation of the entire study, was found at some medical institutions, and a notification was issued to the heads of the medical institutions to improve it.

Matter to be improved
Medical institutions
・Protocol deviation (noncompliance with rules for reporting serious adverse events)

IV. Overall Evaluation

As described in "II.4.B.(2) Efficacy" and "II.4.B.(3) Safety" sections, PMDA concluded that the efficacy of Synflorix for the proposed indication has been demonstrated and its safety is acceptable. PMDA considers that this application may be approved if Synflorix is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 12, 2015

I. Product Submitted for Registration

[Brand name]	Synflorix Aqueous Suspension for Intramuscular Injection
[Nonproprietary name]	Pneumococcal 10-valent Conjugate Vaccine adsorbed (Non-Typeable *Haemophilus influenzae* [NTHi] Protein D, Diphtheria or Tetanus Toxoid Conjugates)
[Applicant]	Japan Vaccine Co., Ltd.
[Date of application]	March 28, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy and indication

The expert advisors supported the PMDA's conclusion that Synflorix is expected to be effective in the prevention of invasive pneumococcal disease (IPD) and pneumonia caused by serotypes contained in the vaccine and that the efficacy of Synflorix in prevention of acute otitis media (AOM) has not been demonstrated. Furthermore, the expert advisors supported the PMDA's conclusion that Synflorix should be indicated for "prevention of invasive infections and pneumonia caused by *S. pneumoniae* (pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F)."

Besides, the following comments on the efficacy of Synflorix were raised from the expert advisors at the Expert Discussion:

- It is presumed that the definition of likely bacterial community-acquired pneumonia (B-CAP) case used in Study 10PN-PD-DIT-028 (Study 028) allowed cases of pneumonia caused by bacteria other than *S. pneumoniae* to be included in the B-CAP cases. In view of this, it is considered that the actual vaccine effectiveness of Synflorix in pneumonia caused by serotypes contained in it may be greater than the listed value 22.0 [7.7, 34.2] (Table 4-13, Review Report [1]).
- In Study Undeca-Pn-010 (Study U-010), the effectiveness of the 11Pn-PD formulation, a 11-valent formulation, instead of the final Synflorix formulation, in preventing AOM was evaluated, and the incidence of clinical AOM caused by serotypes contained in the 11Pn-PD was reported to be 30.4

(per 1,000 subject-years) in the control group (Table 4-18, Review Report [1]). In contrast, in Study 028, the incidence of clinical AOM caused by serotypes contained in Synflorix was reported to be 2.58 (per 1000 subject-years) in the control group [see the column "VT-C-AOM" in Table 4-23, Review Report (1)]. The incidences of clinical AOM in the control groups largely differed between the 2 studies. PMDA concluded that the effectiveness of Synflorix in preventing AOM was not clearly demonstrated in Study 028 because of the low incidence in the control group, and the conclusion made by PMDA is considered reasonable.

Protein D of non-typeable *Haemophilus influenzae* (NTHi) is used as a carrier protein in Synflorix (Table 4-3, Review Report [1]). Occurrence of AOM caused by NTHi was assessed as a secondary endpoint in Study 028, the data of which were included in the application data, and no difference in the incidences was observed between the Synflorix and control groups (Table 1). The expert advisors commented on the results, stating that the effectiveness of Synflorix in preventing AOM caused by NTHi contained in the vaccine has not been clearly demonstrated and that information on the results should be provided in an appropriate manner, for instance using information materials.

Table 1. Incidence of first episode of AOM caused by NTHi [a] ≥15 days after the third dose of study vaccine (per 1000 subject-years)
(Study 028, ATP cohort for efficacy against AOM)

	N	n	Incidence (per 1000 subject-years)	Vaccine effectiveness (%)[b] [95% CI]
Synflorix group	3010	12	1.70	15.0 [−83.8, 60.7]
HBV/HAV group	2979	14	2.00	

N, number of subjects analyzed; n, number of first episodes of AOM ≥15 days after the third dose of study vaccine

a) When all of the following findings were observed, bacterial examinations were performed, and the diagnosis was confirmed if NTHi was detected in the samples.

- Abnormal appearance of the tympanic membrane including redness, bulging, loss of light reflex or the presence of middle ear effusion; and
- At least 2 of the following clinical symptoms: ear pain, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting, and diarrhea.

b) Vaccine effectiveness (%) = [1 − incidence ratio (Synflorix group/[HBV/HAV group])] × 100

Given that Synflorix, a 10-valent pneumococcal conjugate vaccine, will be introduced in Japan in addition to the 13vPnC vaccine, the expert advisors commented that a scheme should be established in Japan to monitor changes over time in serotypes isolated from pediatric patients with pneumococcal infections (IPD, AOM, pneumonia).

(2) Safety

The expert advisors supported the PMDA's conclusion that the safety of Synflorix is acceptable based on the data from all clinical studies submitted.

According to the Review Report (1), among adverse events in the Standardized MedDRA Query "anaphylactic reaction," anaphylaxis possibly related to Synflorix vaccination was reported in 3 vaccinees in foreign postmarketing experience during the period from the market launch to April 24,

2012 [see "II.4.B.(3).3).(b) Anaphylaxis"]. The applicant reported that 6 vaccinees experienced anaphylaxis possibly related to Synflorix vaccination during the period from April 25, 2012 to February 3, 2015. In 1 of the 6 vaccinees, occurrence of anaphylactic shock was only reported, and no further information, including outcome, is available. In the other 5 vaccinees, the outcomes of the event were assessed as resolving or resolved.

Shock and anaphylaxis are listed as clinically significant adverse reactions in the package insert to call attention to their occurrence because these require appropriate monitoring and treatment.

(3) Dosage and administration

Based on the dosage regimen used in Study 10PN-PD-DIT-043 (Study 043) in which the effectiveness of Synflorix in preventing IPD was evaluated, PMDA has concluded that the primary doses (first to third doses) should be administered with an interval of "at least 27 days" between doses and that the booster dose (fourth dose) should be administered with an interval of "at least 4 months" after the last primary dose (third dose). This conclusion made by PMDA was supported by the expert advisors. Additionally, PMDA has concluded that, in order to clarify Synflorix is not indicated for vaccination in the elderly, "children" should be included in the dosage and administration section in contrast with the pneumococcal conjugate vaccine, 13-valent adsorbed (conjugated to nontoxic variant of diphtheria toxin) (13vPnC), which is indicated also for the elderly. The conclusion made by PMDA was also supported by the expert advisors.

Based on the above, the expert advisors supported the PMDA's conclusion that the dosage and administration section should be changed as follows.

[Dosage and administration]

Primary immunization: The usual primary immunization series for children consist of three doses of 0.5 mL each, administered by intramuscular injection, with an interval of at least 27 days.

Booster immunization: The usual booster dose for children is a single dose of 0.5 mL, administered by intramuscular injection, at least 4 months after the third dose.

The expert advisors commented that healthcare professionals should be appropriately informed of differences in the target population and the dosage and administration (vaccination route, vaccination schedule, number of doses) between Synflorix and other similar vaccines, namely the 23-valent pneumococcal vaccine and the 13vPnC vaccine, in order to prevent errors in administration of vaccines.

PMDA requested the applicant to address the matter, and the applicant responded that they would take appropriate measures including preparation of information materials for healthcare professionals and parents or legal guardians of vaccine recipients.

(4) Risk management plan (draft)

PMDA concluded that the safety specifications shown in Table 2 should be included in the current risk management plan for Synflorix (draft) and that the additional pharmacovigilance and risk minimization activities shown in Table 3 should be conducted in a proper manner.

Table 2. Safety specification and efficacy specification in risk management plan (draft)

Safety Specification		
Important identified risks	Important potential risks	Important missing information
• Convulsion • Apnea in premature infants	• Shock, anaphylaxis • Kawasaki's disease • Thrombocytopenic purpura • Sudden death • Errors in selecting injection site • Administration errors due to confusion with other pneumococcal vaccines	• Safety in persons for whom caution is needed in vaccination • Safety of coadministration with other vaccines
Efficacy specification		
None		

Table 3. Summary of additional pharmacovigilance and risk minimization activities in risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early postmarketing phase vigilance • Drug use-results survey	• Early postmarketing phase vigilance • Preparation and provision of information materials for healthcare professionals (Instructions for proper use)

Table 4. Outline of drug use-results survey (draft)

Objective	To capture any problems or questions on safety of Synflorix in routine clinical use
Format	Central registration
Subjects	Vaccinees who have received Synflorix for the first time
Follow-up period	First 30 days after each vaccination
Planned sample size	1,000
Main survey items	• Convulsion • Safety in persons for whom caution is needed in vaccination (those who have underlying diseases such as cardiovascular diseases, those who have experienced pyrexia within 2 days after a vaccination) • Safety of coadministration with other vaccines • Solicited adverse events (injection site pain, injection site redness, injection site swelling, somnolence, pyrexia [≥37.5°C], irritability, appetite impaired) • Unsolicited adverse events (adverse events other than solicited adverse events)

(5) Quality

As described in "II.2.A.(1).2) Safety assessment for adventitious infectious agents" in Review Report (1), conformance of tryptone and pancreatin used in the production process for tryptone to the Standards for Biological Materials was being verified. PMDA has confirmed that the two substances conform to the standards. Based on the above review, PMDA has concluded that the quality of Synflorix is appropriately controlled.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration statements as shown below, with the following conditions. The re-examination period is 8 years because the product is classified as a drug with new active ingredients. The drug substance and drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication]	Prevention of invasive infections and pneumonia caused by *Streptococcus pneumoniae* (pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F)
[Dosage and administration]	Primary immunization: The usual primary immunization series for children consist of three doses of 0.5 mL each, administered by intramuscular injection, with an interval of at least 27 days. Booster immunization: The usual booster dose for children is a single dose of 0.5 mL, administered by intramuscular injection, at least 4 months after the third dose.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.