Report on the Deliberation Results

June 26, 2014

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Squarekids Subcutaneous Injection Syringe
[Non-proprietary name]	Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk Vaccine) Combined Vaccine
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	February 20, 2013

[Results of deliberation]
In the meeting held on June 26, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, the re-examination period is 6 years, and the drug substance and the drug product are both classified as powerful drugs.

Review Report

June 5, 2014
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]	Squarekids Subcutaneous Injection Syringe
[Non-proprietary name]	Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk Vaccine) Combined Vaccine
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	February 20, 2013
[Dosage form/Strength]	A prefilled single-dose injection syringe containing a 0.5 mL suspension consisting of ≥4 units of *Bordetella pertussis* protective antigen, ≤15 Lf of diphtheria toxoid (≥14 international units), ≤2.5 Lf of tetanus toxoid (≥9 international units), 40 DU of inactivated poliovirus type 1 (Mahoney strain), 8 DU of inactivated poliovirus type 2 (MEF-1 strain), and 32 DU of inactivated poliovirus type 3 (Saukett strain) as active ingredients
[Application classification]	Prescription drug (2) New combination drug
[Items warranting special mention]	None
[Reviewing office]	Office of Vaccines and Blood Products

Review Results

June 5, 2014

[Brand name]	Squarekids Subcutaneous Injection Syringe
[Non-proprietary name]	Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk Vaccine) Combined Vaccine
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	February 20, 2013

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in preventing pertussis, diphtheria, tetanus, and acute poliomyelitis has been demonstrated and its safety is acceptable in view of its observed benefits. PMDA has also concluded that information on post-vaccination convulsions and febrile convulsions should be collected by post-marketing surveillance.

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

[Indication]

Prevention of pertussis, diphtheria, tetanus, and acute poliomyelitis

[Dosage and administration]

The usual primary immunization series for children consist of 3 doses of 0.5 mL administered by subcutaneous injection at intervals of at least 3 weeks.

The usual booster immunization for children is a single 0.5 mL dose administered by subcutaneous injection at least 6 months after the primary immunization.

Review Report (1)

August 9, 2013

I. Product Submitted for Registration

[Brand name]	Squarekids Subcutaneous Injection Syringe
[Non-proprietary name]	Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk) Combined Vaccine
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	February 20, 2013
[Dosage form/Strength]	A prefilled single-dose injection syringe containing a 0.5 mL suspension consisting of ≥4 units of *Bordetella pertussis* protective antigen, ≤15 Lf of diphtheria toxoid (≥23.5 units), ≤2.5 Lf of tetanus toxoid (≥13.5 units), 40 DU of inactivated poliovirus type 1 (Mahoney strain), 8 DU of inactivated poliovirus type 2 (MEF-1 strain), and 32 DU of inactivated poliovirus type 3 (Saukett strain) as active ingredients
[Proposed indication]	Prevention of pertussis, diphtheria, tetanus, and acute poliomyelitis
[Proposed dosage and administration]	The usual primary immunization series for children consist of 3 doses of 0.5 mL administered by subcutaneous injection at intervals of at least 3 weeks. The usual booster immunization for children is a single 0.5 mL dose administered by subcutaneous injection at least 6 months after the primary immunization.

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

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Squarekids Subcutaneous Injection Syringe (hereinafter referred to as "DPT-cIPV") is a combined vaccine consisting of the following: the drug substance of "Kitasato-Daiichi-Sankyo" adsorbed diphtheria-purified pertussis-tetanus (DPT) combined vaccine (listed as "Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine" in the Minimum Requirements for Biological Products) (*Bordetella pertussis* protective antigen, P; diphtheria toxoid, D; and tetanus toxoid, T) and the drug substance of Imovax Polio subcutaneous, inactivated poliomyelitis vaccine (cIPV), (listed as "Inactivated Poliomyelitis Vaccine (Salk vaccine)" in the Minimum Requirements for Biological

Products) (inactivated virulent poliovirus types 1, 2, and 3). The applicant, Kitasato Daiichi Sankyo Vaccine Co., Ltd. (formerly The Kitasato Institute), obtained approval for the above DPT vaccine on December 19, 2003. Sanofi Pasteur (currently Sanofi) obtained approval for Imovax Polio subcutaneous vaccine on April 27, 2012. Imovax Polio subcutaneous has been approved in 87 countries, and more than 293 million doses of the vaccine have been administered as either regular or combined vaccines. A single dose (0.5 mL) of DPT-cIPV contains ≥4 units of *Bordetella pertussis* protective antigen, ≤15 Lf of diphtheria toxoid (≥23.5 units), ≤2.5 Lf of tetanus toxoid (≥13.5 units), 40 DU of inactivated poliovirus type 1 (Mahoney strain), 8 DU of inactivated poliovirus type 2 (MEF-1 strain), and 32 DU of inactivated poliovirus type 3 (Saukett strain) as active ingredients and aluminum phosphate and aluminum hydroxide as adjuvants.

In Japan, a DPT vaccine developed by the applicant was introduced in 1981. (This product differs from the currently available product approved in 2003 with respect to seed control methods and use of preservatives.) Additionally, Quattrovac subcutaneous injection syringe (The Chemo-Sero-Therapeutic Research Institute) and Tetrabik subcutaneous injection syringe (The Research Foundation for Microbial Diseases of Osaka University), quadrivalent vaccines consisting of a combination of DPT vaccine and inactivated poliomyelitis vaccine (Sabin strain), were approved in July 2012.

2. Data relating to quality

2.A Summary of the submitted data

DPT-cIPV is a combined vaccine containing *Bordetella pertussis* protective antigen, diphtheria toxoid, and tetanus toxoid included in the approved Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine (DPT), and inactivated poliovirus (virulent poliovirus types 1, 2, and 3 cultured in Vero cells, purified, and inactivated in formalin). DPT-cIPV contains aluminum phosphate and aluminum hydroxide as adjuvants.

2.A.(1) Drug substance

The drug substance consists of the bulk of purified pertussis vaccine, bulk diphtheria toxoid, bulk tetanus toxoid, and bulk of inactivated poliomyelitis vaccine.

The bulk of inactivated poliomyelitis vaccine was registered in the drug master file (MF) by Sanofi Pasteur S.A. (MF No. 224MF10124).

Data for the drug substance of bulk of purified pertussis vaccine, bulk diphtheria toxoid, and bulk tetanus toxoid are summarized below:

2.A.(2) Pertussis bulk (Bulk of purified pertussis vaccine)

The pertussis bulk is a purified antigen solution containing formaldehyde-detoxified pertussis toxin (PT) and filamentous hemagglutinin (FHA) as the main protective antigens.

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

(a) Seed preparations and control

A Tohama phase I L-6 strain of *Bordetella pertussis* provided by the National Institute of Infectious Diseases (NIID) was passaged [redacted] times, divided into smaller portions, and freeze-dried to prepare master seeds (MS) in 19[redacted]. Working seeds (WS) were prepared by culturing the MS for [redacted] passages. Production seeds were prepared by culturing the WS for [redacted] passages. The MS and WS were qualified through the tests listed in Table 2-1. Production seeds are subjected to contamination, aggregation, staining, and viable count tests at the time of preparation.

Table 2-1. Control tests for *Bordetella pertussis* MS and WS

Tests	MS[a)]	WS
Staining test	○	○
Aggregation test	○	○
Growth test	○	○

○, tested

a) Retested during MS preparation in 19[redacted] and then in 20[redacted].

The MS, WS, and production seeds are stored at [redacted]°C to [redacted]°C. The stability of the MS during storage is confirmed by performing the tests listed in Table 2-1 at the time of preparation of a new WS and by manufacturing the pertussis bulk using the new WS and meeting specifications for the pertussis bulk. The stability of the WS is confirmed based on quality control tests (contamination, aggregation, staining, and viable count) of production seeds prepared every [redacted] years. A new MS or WS is prepared when the number of remaining stock is decreased to a certain level. A new MS is prepared from the MS established in 19[redacted], and a new WS is prepared from the new MS. The newly prepared MS or WS is qualified through the tests listed in Table 2-1.

(b) Manufacturing process, critical steps/intermediates, and process validation

Table 2-2 shows the manufacturing process for the bulk of purified pertussis vaccine.

Table 2-2. Summary of manufacturing process and in-process controls for bulk of purified pertussis vaccine

Manufacturing process		Intermediate/bulk	In-process controls
Culture	Pre-incubation Production seed ↓ [redacted]mL, [redacted]°C-[redacted]°C, [redacted] days shaking, Medium A[a)]		
	Main culture [redacted]-[redacted]mL, [redacted]°C-[redacted]°C, [redacted] days, Medium B[a)]	Main culture solution	Bacterial concentration, pH, Aggregation, Staining
↓			
Extrac-tion filtration	Salt precipitation ([redacted]°C-[redacted]°C, [redacted] days)		
	Centrifugation		
	[redacted]		
	Centrifugation		
	Filtration (pore sizes [redacted]µm and [redacted]µm)	Extracted antigen solution	
↓			
Crude purifica-tion	Salt precipitation[b)]		
	Centrifugation[b)]		
	Suspension[b)]		
	Dialysis[b)]		
	[redacted][c)]		
	[redacted][c)]		
	[redacted]	[redacted]	
	[redacted]	Crude purified antigen solution	
↓			
[redacted]	[redacted]	[redacted]	
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]	[redacted]	
	Concentration adjustment	[redacted]	
↓			
[redacted]	[redacted]		
	Collection		
↓			
Filtration	Filtration (pore size [redacted]µm)	Purified antigen solution	Endotoxin, Protein nitrogen content, Integrity
↓			
Detoxifi-cation	[redacted]	Detoxified antigen solution	
↓			
Pertussis bulk	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	Filtration (pore size [redacted]µm)		
	[redacted]	Pertussis bulk	Sterility, Mouse histamine sensitization, Protein nitrogen content, Endotoxin, pH, Aluminum content
↓			
Bulk composi-tion	Mixing	Bulk of adsorbed purified pertussis vaccine	

[redacted], critical steps or intermediates
a) Medium A, modified Cohen-Wheeler agar; Medium B, modified Stainer-Scholte agar
b) The process from the salt precipitation to dialysis is repeated [redacted] times.
c) [redacted]

The pertussis bulk or intermediates for each manufacturing process were evaluated for items in Table 2-3. The results demonstrated appropriate control of each process step and consistent manufacturing.

Table 2-3. Process validation/evaluation of pertussis bulk manufacturing process

Steps	Evaluated Items
Pre-incubation	Bacterial concentration (OD_{650}), Viable count
Main culture	pH, bacterial concentration (OD_{650}), Protein nitrogen content, Endotoxin content
[redacted]	Endotoxin content
[redacted]	Endotoxin content, Potency
Filtration	Sterility
Detoxification[a)]	Mouse histamine sensitization
Pertussis bulk preparation	[redacted]

a) Evaluated retrospectively

(c) Safety evaluation of adventitious agents

Table 2-4 lists the animal-derived raw materials used in manufacturing the pertussis bulk.

Table 2-4. Animal-derived raw materials used in manufacturing bulk of purified pertussis vaccine

Steps	Materials	Animal	Animal parts	Country of origin
MS and WS	Peptone	Bovine	Milk	China, New Zealand, Australia
	Casamino acid	Bovine	Milk	New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
	Horse defibrinated blood	Equine	Blood	New Zealand
	Skim milk[a)]	Bovine	Milk	US
Production seed	Peptone	Bovine	Milk	China, New Zealand, Australia
	Casamino acid	Bovine	Milk	New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
	Horse defibrinated blood	Equine	Blood	New Zealand
Pre-incubation	Peptone	Bovine	Milk	China, New Zealand, Australia
	Casamino acid	Bovine	Milk	New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
Main culture	Casamino acid	Bovine	Milk	New Zealand, Australia

a) Used in storage solution during MS and WS preparation

All animal-derived raw materials, except for skim milk, are used as culture medium ingredients. Adventitious agents derived from animals are inactivated as follows: Horse defibrinated blood is detoxified using formalin; other animal-derived raw materials are detoxified using formalin and autoclaving. Table 2-5 shows the virus reduction factor for the detoxification process, the main virus inactivation process in the manufacturing process. Autoclaved skim milk is used as an MS and WS stabilizer during storage.

Table 2-5. Virus reduction factor (log_{10}) for detoxification process (5 weeks)

Virus	Influenza virus	Canine parvovirus	Feline calicivirus
Virus reduction factor (log_{10})	> 6.5	> 3.9	> 6.4

(d) Manufacturing process development

The remaining stock of the MS prepared in 19[redacted] had diminished. To avoid a further passage from the remaining MS for preparation of a new MS, a new control system using production seeds was introduced in 20[redacted]. [redacted] Additionally, the results of specification tests for bulk manufactured using production seeds and those without using them were compared, and the bulks before and after the introduction of production seeds were confirmed to be comparable.

2.A.(2).2) Characterization

[redacted]

2.A.(2).3) Impurities

The removal of endotoxin, Impurity A, and Impurity B, all process-related impurities, was investigated using the pertussis bulk. The results confirmed the following: Endotoxin concentrations were below [redacted] EU/mL; concentrations of Impurities A and B were below detection limits; and removal of these impurities during manufacture was adequate.

2.A.(2).4) Specifications

Specifications for pertussis bulk include sterility, inactivation, heat-labile toxin, endotoxin, mouse histamine sensitization, formaldehyde content, aluminum content, protein nitrogen content, and adsorbed purified pertussis vaccine antigen potency.

2.A.(2).5) Standards

As standards, the Standard Pertussis Vaccine provided by NIID is used for the antigen potency test and the Reference Pertussis Vaccine provided by NIID for the mouse histamine sensitization test. Both standards are stored at 2°C to 8°C.

2.A.(2).6) Stability

Table 2-6 lists stability studies for the pertussis bulk.

Table 2-6. Stability tests for pertussis bulk

Study	No. of batches	Storage conditions	Container	Storage period
Long term	3	[redacted]°C-[redacted]°C, light-protected	Borosilicate glass container	[redacted] months[a)]
Photostability	1	25±2°C, Overall illumination of ≥1.2 million lux × hr and integrated near ultraviolet energy of ≥200 W × hr/m^2	Borosilicate glass container	–
			Borosilicate glass container (light-protected by aluminum foil)	

a) Planned to be conducted for [redacted] months

No deviations were noted during the long-term stability studies. [redacted] Additionally, stability studies of 4 light-protected batches of the bulk used in clinical studies or drug product stability studies (storage periods of [redacted], [redacted], [redacted], and [redacted] months) were performed and the obtained results were submitted. No deviations were observed with any study at any time point. Based on the results of the [redacted]-month study, a shelf life of [redacted] years has been proposed for the pertussis bulk when stored protected from light.

2.A.(3) Diphtheria bulk (Bulk diphtheria toxoid)

The diphtheria bulk is an antigen solution containing diphtheria toxoid produced by toxoiding of diphtheria toxin using formalin.

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

(a) Seed preparations and control

Park-Williams No. 8 strain of *Corynebacterium diphtheriae* provided by NIID was passaged [redacted] times to prepare MS in 20[redacted]. A new WS was prepared by culturing the MS for [redacted] passages. Both the MS and WS were qualified through the tests listed in Table 2-7.

Table 2-7. Control tests for *Corynebacterium diphtheriae* MS and WS

Tests	MS	WS
Toxigenicity test	○	○
Staining test	○	○

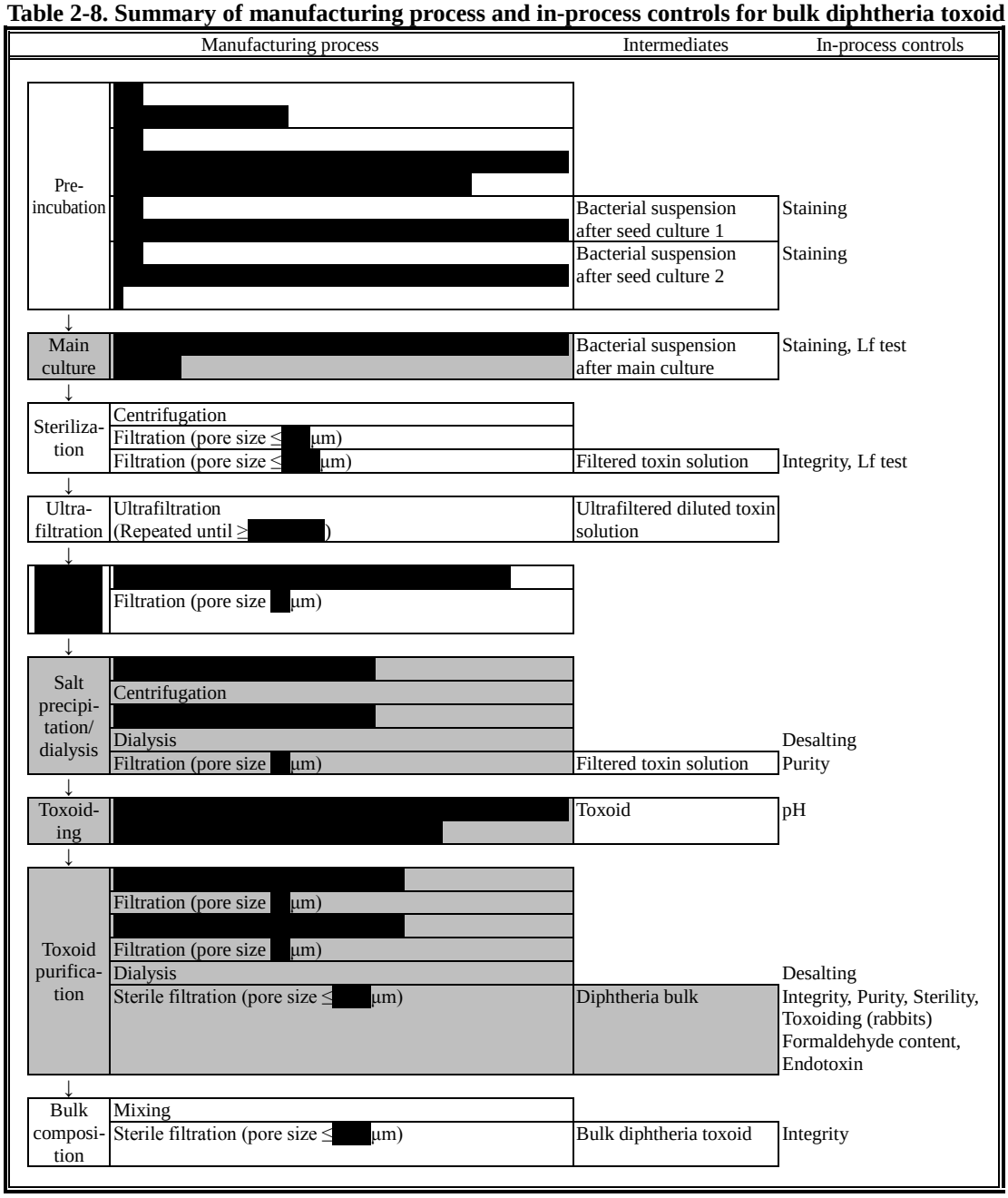
○, tested

The MS and WS are stored at [redacted]°C to [redacted]°C. The stability of the MS during storage is confirmed by performing the tests listed in Table 2-7 at the time of preparation of a new WS and by manufacturing diphtheria bulk using the new WS, and qualifying based on specifications for the diphtheria bulk. The stability of the WS is confirmed by Lf test, an in-process test that is part of the main culture process of the bulk prepared using the WS. A new MS or WS is prepared when the number of remaining stock is decreased to a certain level. A new MS is prepared from the MS established in 20[redacted], and a new WS is prepared from the new MS. The newly prepared MS or WS is qualified through the tests listed in Table 2-7.

(b) Manufacturing process, critical steps/intermediates, and process validation

Table 2-8 shows the manufacturing process for the bulk diphtheria toxoid.

Table 2-8. Summary of manufacturing process and in-process controls for bulk diphtheria toxoid



[redacted], critical steps or critical intermediates

The diphtheria bulk or the intermediates for the manufacturing process were evaluated for the items listed in Table 2-9. The results demonstrated appropriate control of each process step and consistent manufacturing.

Table 2-9. Process validation/evaluation of bulk diphtheria toxoid manufacturing process

Steps	Evaluated items
Main culture	pH, Turbidity, Absorbance, and Lf (diphtheria antitoxin)
Purification	HPLC
Sterile filtration	Purity (Lf test, protein nitrogen content) and HPLC
Ultrafiltration	Purity (Lf test, protein nitrogen content) and HPLC
[redacted]	Purity (Lf test, protein nitrogen content) and HPLC
Salt precipitation/dialysis	Purity (Lf test, protein nitrogen content) and HPLC
Toxoid purification	HPLC
Toxoiding	Toxoiding
Bulk composition	Filter sterilization performance

(c) Safety evaluation of adventitious agents

Table 2-10 shows the animal-derived raw materials used in manufacturing bulk diphtheria toxoid.

Table 2-10. Animal-derived raw materials used in manufacturing bulk diphtheria toxoid

Steps	Materials	Animal	Used parts	Country of origin
MS	Peptone	Bovine	Milk	China, New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
	Sheep serum	Ovine	Blood	
	Horse serum	Equine	Blood	
	Skim milk	Bovine	Milk	US
WS	Horse serum	Equine	Blood	
	Peptone	Bovine	Milk	China, New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
	Skim milk	Bovine	Milk	US
Pre-incubation	Horse serum	Equine	Blood	
	Peptone	Bovine	Milk	China, New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
Main culture	Peptone	Bovine	Milk	China, New Zealand, Australia
	Pancreatin	Porcine	Pancreas	

Animal-derived raw materials are used as medium ingredients. Adventitious agents derived from animals are inactivated as follows: Horse serum and sheep serum are detoxified using formalin; the other animal-derived raw materials are detoxified by autoclaving and formalin. Table 2-11 shows the virus reduction factor for the detoxification (toxoiding) process, the main virus inactivation process in the manufacturing process.

Table 2-11. Virus reduction factor (log_{10}) for toxoiding process (5 weeks)

Virus	Influenza virus	Canine parvovirus	Feline calicivirus
Virus reduction factor (log_{10})	> 7.7	> 3.2	> 6.0

(d) Manufacturing process development

To ensure long-term and consistent production of the diphtheria bulk, a new MS was prepared in 20[redacted] and a [redacted]-tiered seed lot system was introduced to be replaced with the seed control system with which MS and WS had been prepared from the same source. Diphtheria bulk will be produced with WS prepared by the [redacted]-tiered seed lot system. [redacted] Additionally, bulks prepared from WS before and after the introduction of the [redacted]-tiered seed lot system were compared by analyzing the results of specification tests and WS comparability before and after introduction of the [redacted]-tiered seed lot system was confirmed.

2.A.(3).2) Characterization

[redacted]

2.A.(3).3) Impurities

Process-related impurities were investigated using the bulk diphtheria toxoid. [redacted] Additionally, formaldehyde decreased to ≤[redacted] w/v%. These findings confirmed adequate removal of process-related impurities.

2.A.(3).4) Specifications

Specifications for the bulk diphtheria toxoid include sterility, purity, toxoiding (guinea pigs), toxoiding (rabbits), adsorbed diphtheria toxoid potency, and bacterial endotoxin.

2.A.(3).5) Standards and reference materials

As standards, the Reference Diphtheria Antitoxin (for flocculation) provided by NIID is used for the purity test; Schick Test Toxin (animal) for the toxoiding test; and Reference Adsorbed Diphtheria Toxoid, Diphtheria Test Toxin, and Standard Diphtheria Antitoxin for potency tests. The Reference Diphtheria Antitoxin (for flocculation) is stored at 5±2°C, the Reference Adsorbed Diphtheria Toxoid at ≤-70°C, and the other standards at 2 to 8°C.

2.A.(3).6) Stability of diphtheria bulk

Table 2-12 lists stability tests for the diphtheria bulk.

Table 2-12. Stability tests for diphtheria bulk

Tests	No. of batches	Storage conditions	Container	Storage period
Long term	3	[redacted]°C-[redacted]°C, light-protected	Borosilicate glass container	[redacted] months[a)]
Photostability	1	25±2°C, Overall illumination of ≥1.2 million lux × hr and integrated near ultraviolet energy of ≥200 W × hr/m^2	Borosilicate glass container	–
			Borosilicate glass container (light-protected by aluminum foil)	

a) Planned to be conducted for [redacted] months

No deviations were observed during the long-term storage test. [redacted] Additionally, the results of stability tests of 4 light-protected batches of the bulk including those used in drug product stability tests (storage periods of [redacted], [redacted], [redacted], and [redacted] months) were submitted. Although no deviations were noted with any test at any time point, a shelf life of [redacted] years has been proposed for the diphtheria bulk when stored protected from light.

2.A.(4) Tetanus bulk (Bulk tetanus toxoid)

The tetanus bulk is an antigen solution containing tetanus toxoid produced by toxoiding of tetanus toxin using formalin.

2.A.(4).1) Manufacturing process

(a) Seed preparations and control

Harvard/47 strain of *Clostridium tetani* provided by NIID was passaged to prepare a pre-master seed in 19[redacted]. A new MS was prepared by culturing the pre-master seed for [redacted] passages and a new WS by culturing the MS for [redacted] passages. Both the MS and WS were qualified through the tests listed in Table 2-13.

Table 2-13. Control tests for *Clostridium tetani* MS and WS

Tests	MS	WS
Toxin production test	○	○
Staining test	○	○

○, tested

The MS and WS are stored at [redacted]°C to [redacted]°C. The stability of the MS during storage is confirmed by performing the tests listed in Table 2-13 when preparing a new WS and by preparing tetanus bulk using the new WS and qualifying based on specifications for the tetanus bulk. The stability of the WS is confirmed by conducting the Lf test, an in-process test that is part of the main culture process of the bulk prepared using the WS. Before its use, MS or WS is qualified through the tests listed in Table 2-13. When the number of remaining stock is decrease to a certain level, a new MS or WS is prepared and qualified through the tests listed in Table 2-13. A new MS is prepared from the MS made in 20[redacted], and a new WS is prepared from the newly prepared MS.

(b) Manufacturing process, critical steps/intermediates, and process validation

Table 2-14 describes the manufacturing process for the bulk tetanus toxoid.

Table 2-14. Summary of manufacturing process and in-process controls for bulk tetanus toxoid

Manufacturing process		Intermediates	In-process controls
Pre-incubation	Culture WS [redacted] ampoules ↓ [redacted] mL, [redacted] °C-[redacted] °C, [redacted] days ↓ [redacted] L, [redacted] °C-[redacted] °C, [redacted] days	Bacterial suspension after seed culture	Staining
Main culture	Culture [redacted] L, [redacted] °C-[redacted] °C, [redacted] days	Bacterial suspension after main culture	Staining
Purification	Filtration (pore size ≤[redacted] μm)	Filtered toxin solution	Integrity, Lf test, Sterility
	Ultrafiltration (Molecular weight cut-off [redacted])	Ultrafiltered concentrated toxin solution	Lf test
	[redacted]		
	Dialysis (Permeable molecular weight [redacted])	Centrifuged (1st-run) toxin solution	
	[redacted]		
	Filtration (pore size [redacted] μm)		
	[redacted]		
	Dialysis (Permeable molecular weight [redacted])	Centrifuged (2nd-run) toxin solution	
	Filtration (pore size ≤[redacted] μm)	Filtered toxin pooled solution	Purity
	[redacted]	[redacted]	Purity
Toxoiding	[redacted]		pH
Toxoid purification	Filtration (equivalent to pore size [redacted] μm)		
	[redacted]		
	Dialysis (Permeable molecular weight [redacted])		Desalting
	Sterile filtration (pore size ≤[redacted] μm)	Tetanus bulk	Integrity, Purity, Sterility, Toxoiding, Formaldehyde content, Endotoxin test
Bulk composition	Mixing of bulk tetanus toxoid		
	Sterile filtration (pore size ≤[redacted] μm)	Bulk tetanus toxoid	Integrity

[redacted], critical steps or critical intermediates

The tetanus bulk or intermediates for each manufacturing process were evaluated for the items described in Table 2-15. As a result, appropriate control of each process step and consistent manufacturing were demonstrated.

Table 2-15. Process validation/evaluation of bulk tetanus toxoid manufacturing process

Steps	Evaluated items
Culture	Cultured bacterial suspension (pH, turbidity, Lf test)
Purification	Filtered toxin solution (toxin content, protein nitrogen content and HPLC), Ultrafiltered concentrated toxin solution (toxin content, protein nitrogen content and HPLC), Centrifuged (1st-run) toxin solution (toxin content, protein nitrogen content and HPLC), Centrifuged (2nd-run) toxin solution (toxin content, protein nitrogen content and HPLC), Filtered toxin pooled solution (toxin content, protein nitrogen content and HPLC), [redacted]
Toxoiding	Toxoiding
Bulk composition	Filter sterilization performance

(c) Safety evaluation of adventitious agents

Table 2-16 lists the animal-derived raw materials used in manufacturing the bulk tetanus toxoid.

Table 2-16. Animal-derived raw materials used in manufacturing bulk tetanus toxoid

Steps	Materials	Animals	Used parts	Country of origin
MS and WS	Peptone	Bovine	Milk	China, New Zealand, Australia
	Pancreatin	Porcine	Pancreas	
	Horse defibrinated blood	Equine	Blood	
	Skim milk	Bovine	Milk	US
Pre-incubation and main culture	Peptone	Bovine	Milk	China, New Zealand, Australia
	Pancreatin	Porcine	Pancreas	

Animal-derived raw materials are used as medium ingredients. Adventitious agents derived from animals are inactivated as follows: Horse defibrinated serum is detoxified using formalin; the other animal-derived raw materials are detoxified by autoclaving and treatment with formalin. Table 2-17 shows the virus clearance for toxoiding, a detoxification process that is part of the main virus inactivation process during manufacture.

Table 2-17. Virus reduction factor (log_{10}) for toxoiding process (5 weeks)

Virus	Influenza virus	Canine parvovirus	Feline calicivirus
Virus reduction factor (log_{10})	> 7.7	> 3.9	> 7.1

(d) Manufacturing process development

[redacted]

2.A.(4).2) Characterization

[redacted]

2.A.(4).3) Impurities

Process-related impurities were investigated using [redacted] batches of the bulk tetanus toxoid. [redacted] Additionally, formaldehyde decreased to ≤[redacted] w/v%. The above findings confirmed adequate removal of process-related impurities.

2.A.(4).4) Specifications

Specifications for the bulk tetanus toxoid include purity, sterility, toxoiding, adsorbed tetanus toxoid potency, and bacterial endotoxins.

2.A.(4).5) Standards and reference materials

As standards, the Reference Tetanus Antitoxin (for flocculation) provided by NIID is used for the Lf test, and the Reference Adsorbed Tetanus Toxoid and Tetanus Test Toxin provided by NIID are used for the potency test. The Reference Tetanus Antitoxin (for flocculation) is stored at 5±2°C, the Reference Adsorbed Tetanus Toxoid at ≤-70°C, and the Tetanus Test Toxin at 2 to 8°C.

2.A.(4).6) Stability of tetanus bulk

Table 2-18 lists stability studies for the tetanus bulk.

Table 2-18. Stability tests for tetanus bulk

Study	No. of batches	Storage conditions	Container	Storage period
Long term	3	[redacted]°C-[redacted]°C, light-protected	Borosilicate glass container	[redacted] months[a)]
Photostability	1	25±2°C, Overall illumination of ≥1.2 million lux × hr and integrated near ultraviolet energy of ≥200 W × hr/m^2	Borosilicate glass container	–
			Borosilicate glass container (light-protected by aluminum foil)	

a) Planned to be conducted for [redacted] months

No deviations were observed during the long-term stability studies. [redacted] Additionally, the results of stability studies of 4 light-protected batches of the bulk used in clinical studies, drug product stability studies, and commercial production of DPT (storage periods of [redacted], [redacted], [redacted], and [redacted] months) were submitted. Although no deviations were noted with any study at any time point, a shelf life of [redacted] years has been proposed for the tetanus bulk when stored protected from light.

2.A.(5) Drug product

2.A.(5).1) Description and composition of the drug product and formulation development

Each 0.5 mL dose of the drug product in a prefilled glass syringe contains the following: ≥4 units of *Bordetella pertussis* protective antigen, ≤15 Lf of diphtheria toxoid, and ≤2.5 Lf of tetanus toxoid, 40 D-antigen units (DU) of inactivated poliovirus type 1 (Mahoney strain), 8 DU of inactivated poliovirus type 2 (MEF-1 strain), and 32 DU of inactivated poliovirus type 3 (Saukett strain) as active ingredients; 0.21 mg of sodium hydroxide, 0.81 mg of trisodium phosphate, and 0.90 mg of aluminum chloride as adjuvants; and ≤0.05 mg of formaldehyde, 0.28 mg of dibasic sodium phosphate hydrate, 0.32 mg of sodium dihydrogen phosphate, and M199 as excipients.

2.A.(5).2) Manufacturing process

(a) Manufacturing process

Table 2-19 shows the manufacturing process for the drug product.

Table 2-19. Summary of manufacturing process and in-process controls for the drug product

Manufacturing process	Intermediates	In-process controls
Pertussis vaccine: [redacted]		
Agitation	Portioned bulk of adsorbed purified pertussis vaccine	
Diphtheria toxoid: Bulk of diphtheria toxoid vaccine		
Filtration (pore size [redacted]μm)		
Addition of aluminum hydroxide gel		
Agitation	Bulk adsorbed purified diphtheria toxoid	
Tetanus toxoid: Bulk of tetanus toxoid vaccine		
Filtration (pore size [redacted]μm)		
Addition of aluminum hydroxide gel		
Agitation	Bulk of adsorbed tetanus toxoid vaccine	
Final bulk preparation Mix and stir the portioned bulk of adsorbed purified pertussis vaccine, bulk adsorbed purified diphtheria toxoid, bulk of adsorbed tetanus toxoid vaccine, and inactivated poliomyelitis vaccine. Adjust volumes using phosphate buffered saline as needed.	Final bulk	
↓		
Filling ([redacted]mL)		Test for filling volume, Visual inspection
↓		
Packaging		Packaging check
↓		
Inspection, labeling, and testing		

, critical steps or critical intermediates

a) [redacted]

(b) Development history

No changes have been made in manufacturing process from that of the investigational product.

2.A.(5).3) Specifications

Specifications for the drug product include pH, aluminum content, formaldehyde content, sterility, freedom from abnormal toxicity, endotoxins, mouse histamine sensitization, diphtheria toxin toxoiding, tetanus toxin toxoiding, adsorbed purified pertussis vaccine potency, adsorbed diphtheria toxoid potency, adsorbed tetanus toxoid potency, D-antigen content, protein content, osmolality, description, foreign insoluble matter, extractable volume, insoluble particulate matter, adsorbed purified pertussis vaccine label check, adsorbed diphtheria toxoid label check, adsorbed tetanus toxoid label check, inactivated poliomyelitis vaccine label check, and content uniformity (protein and aluminum).

2.A.(5).4) Standards

In addition to the standards used for testing the bulks, the Reference Adsorbed Tetanus Toxoid (for combined vaccine potency) provided by NIID is used for the tetanus toxoid potency test, and the In-house Reference Standard provided by Sanofi Pasteur S.A. is used for the D-antigen content test. These standards are stored at 2°C to 8°C and at -70°C, respectively.

2.A.(5).5) Stability

Table 2-20 lists the stability studies for the drug product.

Table 2-20. Stability tests for the drug product

Study	No. of batches	Storage conditions	Container	Storage period
Long term	6	10±[redacted]°C, light-protected	Syringe, gasket, top cap	[redacted] months[a)]
Accelerated	3	25±2°C, light-protected	Syringe, gasket, top cap	[redacted] months
Photostability	1	25±2°C, Overall illumination of ≥1.2 million lux × hr and integrated near ultraviolet energy of ≥200 W × hr/m^2	Syringe, gasket, top cap	–
			Syringe, gasket, top cap (light-protected by aluminum foil)	
			Syringe, gasket, top cap (commercial packaging)	

a) [redacted]. All are planned to be conducted for [redacted] months.

The data submitted in the application included the results of the long-term stability studies up to 30 months ([redacted] of the 6 batches), and no deviations from the specifications were found. [redacted] Based on the above, a shelf life of 30 months has been proposed for the drug product when stored protected from light.

2.B Outline of the review by PMDA

Based on the submitted data, PMDA considers that there are no significant quality problems that would affect the evaluation of non-clinical and clinical studies. PMDA asked the applicant for further clarification of the manufacturing process and controls for the drug product, and the conclusion of PMDA's review will be summarized in Review Report (2).

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The results of pharmacology studies with the proposed product (DPT-cIPV) were submitted for the evaluation of primary pharmacodynamics. The results of immunogenicity studies were submitted as reference data.

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

3.(i).A.(1).1) Immunogenicity studies of *Bordetella pertussis* protective antigen, diphtheria toxoid, and tetanus toxoid in rats (4.2.1.1.1-1 [reference data], Study NH07374; 4.2.1.1.1-2 [reference data], Study DD-687-P01)

Rats (5 rats/sex/group, a total of 20 rats in 2 groups) were immunized by subcutaneously injecting 0.5 mL of either DPT-cIPV or saline (a total of 2 injections at an interval of 2 weeks). Serum samples were collected before the first injection and at 7 days after the second injection. Antibody titers against pertussis protective antigen, diphtheria toxoid, and tetanus toxoid (active ingredients of the Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine [DPT components]) were measured by ELIZA,

blood anti-toxoid assay, and latex agglutination assay, respectively. Antibody titers against all DPT components increased in all rats in the DPT-cIPV group, while those increased in none of the rats in the saline group.

3.(i).A.(1).2) Pharmacology study of inactivated poliovirus in rats (4.2.1.1.2-1, Study DD-687-A)

Rats (10 females/group, a total of 150 rats) were immunized by a single injection with the following dosage regimen in the 15 groups: by subcutaneously injecting 0.5 or 1 mL of DPT-cIPV; by subcutaneously injecting 0.5 mL of DPT-cIPV diluted at 1:2, 1:4, or 1:16; by intramuscularly injecting 0.5 or 1 mL (2 groups for each dose) of the in-house reference inactivated poliomyelitis vaccine[1] (referred to as "the IPV-containing combined vaccine"); or by intramuscularly injecting 0.5 mL of the IPV-containing combined vaccine diluted at 1:2, 1:4, or 1:16 (2 groups for each dilution). At 21 days after injection, serum samples were collected to measure neutralizing antibody titers against each poliovirus type and to calculate mean neutralizing antibody titers per group. For both the DPT-cIPV groups and the IPV-containing combined vaccine groups, mean neutralizing antibody titers against all poliovirus types increased in a dose-dependent manner. Mean neutralizing antibody titers in the DPT-cIPV groups were either comparable to or above those in the IPV-containing combined vaccine groups at each dilution.

3.(i).A.(1).3) Potency studies of *Bordetella pertussis* protective antigen, diphtheria toxoid, and tetanus toxoid in mouse (4.2.1.1.3-1, Study DD-687-P02; 4.2.1.1.3-2, Study DD-687-P03; 4.2.1.1.3-3, Study DD-687-P04)

The relative potency of DPT-cIPV and DPT to the standards and references for the DPT components was measured in accordance with the requirements of "Potency test for Adsorbed Purified Pertussis Vaccine," "Potency test for Adsorbed Diphtheria Toxoid," and "Potency test for Adsorbed Tetanus Toxoid" for the standard "Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine" listed in the Minimum Requirements for Biological Products, which are used for determining the potency of the DPT components in Japan (Table 3-1). Each of DPT components in DPT-cIPV satisfied the specifications required in the Minimum Requirements for Biological Products. The applicant considered there were no marked differences in the relative potency of DPT components between DPT-cIPV and comparator (an approved DPT vaccine).

Table 3-1. Relative potency of DPT antigens

	Pertussis vaccine (U/mL)	Diphtheria toxoid (U/mL)	Tetanus toxoid (U/mL)
	Mean [95% CI]	Mean [95% CI]	Mean [95% CI]
DPT-cIPV	18.99 [9.98, 37.26]	86.74 [60.03, 134.60]	97.65 [64.64, 151.56]
Approved DPT	23.47 [12.59, 44.70]	123.34 [83.68, 203.39]	136.37 [106.23, 178.95]

[1] Adsorbed vaccine containing inactivated poliomyelitis vaccine, acellular pertussis vaccine, diphtheria toxoid, tetanus toxoid, and Haemophilus influenza conjugate vaccine. The D antigen contents for poliovirus types 1, 2 and 3 was 51.6, 11.2 and 39.6 DU/mL, respectively.

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

No safety pharmacology studies have been performed. Effects of DPT-cIPV on central nervous, cardiovascular, and respiratory systems were investigated in a rat 8-week subcutaneous toxicity study. As a result, no effects attributable to DPT-cIPV were seen.

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

Since DPT-cIPV increased neutralizing antibody titers against poliovirus in the rat pharmacology study, PMDA concluded that the immunogenicity of DPT-cIPV against poliovirus can be expected. Additionally, DPT-cIPV increased antibody titers against the pertussis protective antigen, diphtheria toxoid, and tetanus toxoid, and there were no marked differences in potency in DPT components between DPT-cIPV and an approved DPT in the pharmacology studies. PMDA concluded that the immunogenicity of DPT-cIPV in terms of DPT can be expected.

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

Single-dose toxicity, repeated-dose toxicity and local tolerance studies were performed as toxicity studies for DPT-cIPV.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1, Study IP07325)

Rats (10 rats/sex/group) were subcutaneously injected with 10 mL/kg of saline, 1 mL/kg of DPT-cIPV, or 10 mL/kg of DPT-cIPV. No deaths occurred. The approximate lethal dose was considered to be above 10 mL/kg (about 100 times the proposed clinical dose).

3.(iii).A.(2) Repeated-dose toxicity (4.2.3.2, Study IP07326)

Rats (10 rats/sex/group) were subcutaneously injected in the back of the neck with 10 mL/kg of saline, 1 mL/kg of DPT-cIPV, or 10 mL/kg of DPT-cIPV for a total of 5 injections at 2-week intervals. Cumulative local tolerance was also evaluated by injecting into the same area. Histopathological findings in the DPT-cIPV group included foreign matter reactions against vaccine residues (mononuclear cell infiltration, fibrosis, macrophage accumulation, and edema), bleeding, and musculocutaneous degeneration and necrosis in the subcutaneous tissue at the injection site. Hematology findings were mostly seen in the 10 mL/kg group and included the following findings: low hemoglobin and hematocrit counts related to injection site changes; high white blood cell count; high neutrophil, monocyte, eosinophil, and large non-stained cell counts within the leukocyte classification; and extended activated partial thromboplastin time. Clinical chemistry findings included high α2-globulin, high β-globulin, low albumin, and low A/G, mostly for the 10 mL/kg group. Excluding injection site changes, the no observed adverse effect level was 10 mL/kg.

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. Histopathological findings obtained by a repeated-dose toxicity study showed no effects on male or female reproductive organs.

3.(iii).A.(6) Local tolerance (4.2.3.6, Study IP07327)

Rabbits (8 rabbits/sex/group) were subcutaneously injected into the abdomen with 0.5 mL/site of either saline or DPT-cIPV. As a result, foreign matter reactions against vaccine residues (inflammatory cell infiltration and macrophage accumulation) were seen, but no findings indicative of irritability such as bleeding, ulcer, or subcutaneous degeneration or necrosis were observed. Injection site changes found were considered to be typical local inflammatory reactions (foreign body reactions) to a combined vaccine using aluminum adjuvants.

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

PMDA concluded that there are no specific concerns about toxicity of DPT-cIPV.

4. Clinical data

4.A Summary of the submitted data

The results of the 3 clinical studies indicated in Table 4-1 were submitted as data for evaluating efficacy and safety.

Table 4-1. Summary of clinical studies

Phase	Study	Design	Subjects	Enrollment	Dosage and administration	Administration schedule
I	A-J101	Open-label uncontrolled	Healthy adult males (≥20 years and <40 years)	DPT-cIPV group, n = 10	0.5 mL subcutaneous	Single injection
II	A-J201	Open-label uncontrolled	Healthy infants (3-8 months)	DPT-cIPV group, n = 115	0.5 mL subcutaneous	Primary immunization: 3 injections at intervals of 30-56 days Booster immunization: a single injection 6-18 months after the primary immunization
III	A-J301	Randomized double-blinded	Healthy children (3-68 months)	Group A, n = 248 (DPT-cIPV[a] + OPV Placebo) Group B, n = 129 (DPT[a] + OPV)	0.5 mL subcutaneous	・ DPT-cIPV (Group A) or DPT (Group B) Primary immunization: 3 injections at intervals of 21-57 days Booster immunization: a single injection 6-18 months after the third injection ・ OPV or OPV placebo 2 doses: the 1st dose, 4-6 weeks after the third injection of DPT-cIPV or DPT; the 2nd dose, 6-10 weeks after the 1st dose

DPT, Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine (S Hokken Syringe); OPV, Live Oral Poliomyelitis Vaccine
a) Simultaneous administration was allowed only for freeze-dried Haemophilus influenza type b vaccine (Hib).

4.A.(1) Japanese phase I clinical study (5.3.5.2-1, Study A-J101; Study period, [redacted], 20[redacted] to [redacted], 20[redacted])

An open-label uncontrolled study was performed at a single center in Japan to investigate safety of DPT-cIPV in healthy adult males aged ≥20 to <40 years (target sample size of 10). Subjects received a single 0.5 mL dose of DPT-cIPV by subcutaneous injection.

All 10 subjects registered received the investigational product, and they were included in the safety analysis set. Safety was evaluated on the follow-up day set in the period from Day14 to Day 17 after injection (counting from the day after injection; the same hereinafter, unless otherwise noted).

During the period from injection to follow-up day, at least 1 adverse event was observed in 7 of the 10 subjects (70%). All adverse events were injection site reactions related to the investigational product, and all subjects who experienced those events recovered with time (Table 4-2). No clinically significant changes were observed in clinical laboratory data. No deaths or serious adverse events occurred.

Table 4-2. Adverse events classified by severity (safety analysis set)

Adverse events (N = 10)	Number of subjects		Severity	
	n	%	Grade A[a)]	Grade B[b)]
Injection site erythema	7	70	3	4
Injection site induration	2	20	2	0
Injection site pain	3	30	3	0
Injection site swelling	2	20	1	1

N, number of analyzed subjects; n, number of subjects with adverse event
a) Grade A
Injection site erythema, injection site induration, and injection site swelling: <2 cm in the longest diameter
Injection site pain: Painful but tolerable
b) Grade B
Injection site erythema, injection site induration, and injection site swelling: 2-5 cm in the longest diameter
Injection site pain: Painful and requiring a single dose of analgesics

4.A.(2) Japanese phase II clinical study (5.3.5.2-2, Study A-J201; Study period, [redacted], 20[redacted] to [redacted], 20[redacted])

A multicenter, open-label, uncontrolled study was performed at 8 centers in Japan to investigate safety and immunogenicity of DPT-cIPV in healthy infants 3 to 8 months of age at the initiation of primary immunization (target sample size of 110).

Subjects received a total of 4 doses of 0.5 mL of DPT-cIPV by subcutaneous injection: 3 doses at intervals of 30 to 56 days (primary immunization) and a single dose 6 to 18 months after the third dose (booster immunization).

All 115 subjects enrolled in the study received DPT-cIPV at least once, and all were included in the safety analysis set. Of these subjects, 1 subject who failed to complete the primary immunization (voluntary consent withdrawal) was excluded from the full analysis set (FAS) and the per protocol set (PPS; consisting of the remaining 114 subjects) for primary immunization. Additionally, with the exclusion of 4 subjects (for protocol non-compliance in 2 subjects and voluntary consent withdrawal in

2 subjects), 110 subjects remained in the FAS and PPS for booster immunization. The PPS was used for the primary analysis for immunogenicity.

With respect to safety, 113 of the 115 subjects (98.3%) reported at least 1 adverse event during all of observation periods (7 days after each injection for adverse events of special interest, 30 days after each injection for other adverse events, the period from enrollment to final hospital visit for serious adverse events) and 104 of the 115 subjects (90.4%) reported at least 1 adverse reaction. A total of 13 of the 115 subjects (11.3%) had 14 serious adverse events (pneumonia [2]; bronchitis, cytomegalovirus infection, exanthema subitum, viral gastroenteritis, hand-foot-and-mouth disease, tympanitis, RS virus pneumonia, urinary tract infection, bacterial upper respiratory infection, RS virus bronchitis, febrile convulsion, and inguinal hernia [1 each]). The causal relationship was ruled out for all the patients, and all the events eventually resolved and resulted in recovery. Table 4-3 shows adverse events and adverse reactions with ≥10% incidence. No deaths or adverse events resulting in study discontinuation occurred.

Table 4-3. Adverse events and reactions observed with ≥10% incidence during all of observation periods (safety analysis set)

		Adverse events (N = 115)		Adverse reactions (N = 115)	
		n	%	n	%
Injection site reaction	Injection site erythema	93	80.9	93	80.9
	Injection site induration	74	64.3	74	64.3
	Injection site swelling	66	57.4	66	57.4
	Injection site pain	23	20.0	23	20.0
Systemic reaction	Fever	51	44.3	45	39.1
	Irritability	43	37.4	32	27.8
	Diarrhea	38	33.0	23	20.0
	Nasopharyngitis	38	33.0	0	0
	Somnolence	35	30.4	31	27.0
	Decreased appetite	28	24.3	19	16.5
	Rhinorrhoea	28	24.3	17	14.8
	Crying	26	22.6	24	20.9
	Upper respiratory tract inflammation	25	21.7	0	0
	Bronchitis	20	17.4	1	0.9
	Cough	20	17.4	16	13.9
	Vomiting	20	17.4	15	13.0
	Pharyngitis	17	14.8	0	0
	Exanthema subitum	17	14.8	0	0
	Diaper dermatitis	13	11.3	0	0

N, number of analyzed subjects; n, number of subjects with adverse event or adverse reaction

The primary immunogenicity endpoints were the prevalence of antibodies and the rate of positive antibody conversion at 1 month after the third injection. Disease protection levels for anti-diphtheria toxoid antibody titers and anti-tetanus toxoid antibody titers were ≥0.01 IU/mL, anti-pertussis PT antibody titers and anti-pertussis FHA antibody titers ≥10 EU/mL, and poliovirus type 1, 2, and 3 neutralizing antibody titers ≥8-fold. The prevalence of antibodies was defined as the ratio of numbers of subjects with the antibody titers exceeding above-mentioned antibody titers at 1 month after the third injection to numbers of all subjects in whom antibody titers were measured. Additionally, the rate of positive antibody conversion was defined as the ratio of numbers of subjects with antibody titers exceeding the above-mentioned antibody titers at 1 month after the third injection to the numbers of all

subjects in whom antibody titers were measured except subjects with antibody titers exceeding the above-mentioned antibody titers before primary immunization. Table 4-4 shows the prevalence of antibodies and the rate of positive antibody conversion at 1 month after the third injection of DPT-cIPV.

Table 4-4. Antibody prevalence and antibody positive conversion at 1 month after the third injection of DPT-cIPV (PPS)

	Antibody prevalence		Antibody positive conversion	
	n/N	% [95% CI]	n/N[a)]	% [95% CI]
Anti-PT antibody titer	113/114	99.1 [95.2, 99.8]	109/109	100 [96.6, 100.0]
Anti-FHA antibody titer	114/114	100 [96.7, 100.0]	105/105	100 [96.5, 100.0]
Anti-diphtheria toxoid antibody titer	114/114	100 [96.7, 100.0]	70/70	100 [94.8, 100.0]
Anti-tetanus toxoid antibody titer	114/114	100 [96.7, 100.0]	35/35	100 [90.1, 100.0]
Poliovirus type 1 antibody titer	114/114	100 [96.7, 100.0]	95/95	100 [96.1, 100.0]
Poliovirus type 2 antibody titer	114/114	100 [96.7, 100.0]	88/88	100 [95.8, 100.0]
Poliovirus type 3 antibody titer	114/114	100 [96.7, 100.0]	106/106	100 [96.5, 100.0]

N, number of analyzed subjects; n, number of subjects with neutralizing antibody or antibody positive conversion
a) Excluding subjects in whom antibody titers exceeded protective levels before primary immunization

4.A.(3) Japanese phase III clinical study (5.3.5.1-1, Study A-J301; Study period, [redacted], 20[redacted] to [redacted], 20[redacted])

A multicenter, randomized, double-blinded parallel study was performed at 23 centers in Japan to investigate the safety and immunogenicity of DPT-cIPV in healthy children 3 to 68 months of age (target sample size of 374 subjects, 249 subjects for the DPT-cIPV group and 125 subjects for the comparator group).

DPT-cIPV and an oral solution not containing attenuated strains of poliovirus (OPV placebo) were used for the DPT-cIPV group while DPT and OPV were used for the comparator group. Subjects received a total of 4 doses of 0.5 mL of DPT-cIPV or DPT by subcutaneous injection: 3 doses at intervals of 3 to 8 weeks (primary immunization), and a single dose 6 to 18 months after the third dose (booster immunization). An oral dose of 0.05 mL of OPV placebo or OPV was administered twice at 4 to 6 weeks and at 6 to 10 weeks after the third injection of DPT-cIPV or DPT of the primary immunization. If necessary, simultaneous administration of freeze-dried Haemophilus influenza type b vaccine with DPT-cIPV or DPT was permitted.

A total of 377 subjects (248 subjects in the DPT-cIPV group and 129 subjects in the comparator group) were enrolled in the study. Of them, 376 subjects (248 subjects in the DPT-cIPV group and 128 subjects in the comparator group) were included in the safety analysis set, excluding 1 subject who failed to receive the investigational product. For primary immunization, the FAS included 370 subjects (245 subjects in the DPT-cIPV group and 125 subjects in the comparator group). Excluded were 6 subjects in whom a course of 5 administration (3 injections of DPT-cIPV or DPT for primary immunization and 2 doses of OPV or OPV placebo) was not completed. The PPS consisted of 355 subjects (235 subjects in the DPT-cIPV group and 120 subjects in the comparator group). Excluded were 15 subjects who exhibited deviations (blood sampling timing deviations in 6 subjects, use of prohibited concomitants or vaccines in 6 subjects, vaccination timing deviations in 3 subjects). For booster immunization, the FAS included 367 subjects (242 subjects in the DPT-cIPV group and 125 subjects in the comparator group). Excluded were 7 subjects who failed to receive DPT-cIPV or comparator and 2 subjects who exhibited

deviations (lacking test results). The PPS consisted of 363 subjects (241 subjects in the DPT-cIPV group and 122 subjects in the comparator group). Excluded were 4 subjects who exhibited deviations (use of prohibited concomitants or vaccines).

The primary endpoint of the study was the prevalence of neutralizing antibodies above the protective level against poliovirus types 1, 2, and 3 at 1 month after the third injection of DPT-cIPV (≥8-fold neutralizing antibody titer).

For the DPT-cIPV group, the prevalence of neutralizing antibodies against poliovirus types 1, 2, and 3 after primary immunization was 100% [95% CI, 98.4, 100.0] (235 of 235 subjects). The lower limit of 95% confidence interval was above the pre-defined level of 90% (Table 4-5).

Table 4-5. Prevalence of neutralizing antibodies against poliovirus types 1, 2, and 3 at 1 month after the third injection for the DPT-cIPV group (PPS)

	DPT-cIPV group	
	n/N	% [95% CI]
Anti-polio type 1	235/235	100.0 [98.4, 100.0]
Anti-polio type 2	235/235	100.0 [98.4, 100.0]
Anti-polio type 3	235/235	100.0 [98.4, 100.0]

N, number of analyzed subjects;
n, number of subjects with neutralizing antibody

Table 4-6 shows the geometric mean and the 95% confidence interval of neutralizing antibody titers against poliovirus types 1, 2, and 3 for the DPT-cIPV and comparator groups.

Table 4-6. Geometric mean of neutralizing antibody titers against poliovirus types 1, 2, and 3 at each time point (PPS)

	V01[a)]	V04[b)]	V06[c)]	V07[d)]	V08[e)]
	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]
DPT-cIPV group	N = 235[f)]	N = 235[f)]	N = 235[f)]	N = 241[f)]	N = 241[f)]
Type 1	3.02 [2.73, 3.35]	1019.47 [892.32, 1164.74]	454.34 [397.40, 519.45]	287.21 [256.51, 321.58]	2672.22 [2388.02, 2990.24]
Type 2	4.58 [4.00, 5.24]	1953.61 [1747.67, 2183.81]	880.98 [760.22, 1020.93]	678.69 [589.14, 781.86]	4582.21 [4128.56, 5085.71]
Type 3	2.60 [2.46, 2.75]	1048.45 [917.69, 1197.84]	283.42 [242.41, 331.36]	161.58 [138.89, 187.97]	3441.83 [3001.78, 3946.39]
Comparator group	N = 120[f)]	N = 120[f)]	N = 120[f)]	N = 122[f)]	N = 122[f)]
Type 1	3.25 [2.77, 3.81]	2.14 [2.00, 2.30]	520.94 [409.14, 663.30]	300.13 [245.68, 366.64]	290.08 [239.96, 350.66]
Type 2	6.54 [5.27, 8.12]	2.69 [2.32, 3.13]	1452.34 [1181.38, 1785.46]	534.28 [441.41, 646.68]	497.66 [408.28, 606.62]
Type 3	2.80 [2.56, 3.06]	2.21 [2.10, 2.33]	129.88 [92.80, 181.77]	72.94 [54.17, 98.22]	65.48 [49.01, 87.47]

N, number of analyzed subjects
a) V01, Visit 01 (immediately before first injection of DPT-cIPV or DPT, which corresponds to the time before administration of IPV and OPV)
b) V04, Visit 04 (1 month after third injection of DPT-cIPV or DPT, which corresponds to the time after third injection of IPV and before administration of OPV)
c) V06, Visit 06 (1 month after second administration of OPV or OPV placebo, which corresponds to the time after third injection of IPV and second administration of OPV)
d) V07, Visit 07 (immediately before fourth injection of DPT-cIPV or DPT, which corresponds to the time after third injection of IPV and second administration of OPV)
e) V08, Visit 08 (1 month after fourth injection of DPT-cIPV or DPT, which corresponds to the time after fourth injection of IPV and second administration of OPV)
f) V01, 04 and 06 for the PPS of primary immunization; V07 and 08 for the PPS of booster immunization

The secondary endpoint of the study was the prevalence of neutralizing antibodies (anti-diphtheria toxoid and anti-tetanus toxoid, ≥0.01 IU/mL; anti-PT and anti-FHA, ≥10 EU/mL) at 1 month after the third injection of DPT-cIPV. Table 4-7 shows the prevalence of antibodies and the 95% confidence interval.

Table 4-7. Prevalence of neutralizing antibodies against *Bordetella pertussis* (PT and FHA), diphtheria toxoid and tetanus toxoid at 1 month after the third injection of DPT-cIPV or comparator (PPS)

	DPT-cIPV group		Comparator group	
	n/N	% [95% CI]	n/N	% [95% CI]
Anti-PT	232/235	98.7 [96.3, 99.7]	118/120	98.3 [94.1, 99.8]
Anti-FHA	235/235	100.0 [98.4, 100.0]	120/120	100.0 [97.0, 100.0]
Anti-diphtheria toxoid	235/235	100.0 [98.4, 100.0]	120/120	100.0 [97.0, 100.0]
Anti-tetanus toxoid	235/235	100.0 [98.4, 100.0]	120/120	100.0 [97.0, 100.0]

N, number of analyzed subjects; n, number of subjects with neutralizing antibody

Table 4-8 summarizes changes in the geometric mean of antibody titers against each antigen for the DPT-cIPV and comparator groups.

Table 4-8. Geometric mean of antibody titers against *Bordetella pertussis* (PT and FHA), diphtheria toxoid, and tetanus toxoid at each time point (PPS)

	V01[a)]	V04[b)]	V07[c)]	V08[d)]
	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]
DPT-cIPV group	N = 235[e)]	N = 235[e)]	N = 241[e)]	N = 241[e)]
Anti-PT (EU/mL)	1.18 [1.03, 1.34]	67.20 [61.74, 73.14]	16.20 [14.54, 18.05]	61.47 [56.06, 67.40]
Anti-FHA (EU/mL)	2.35 [2.04, 2.70]	164.34 [152.03, 177.63]	58.27 [52.15, 65.09]	255.65 [234.63, 278.55]
Anti-diphtheria toxoid (IU/mL)	0.01 [0.01, 0.02]	5.21 [4.48, 6.06]	2.55 [2.23, 2.92]	23.78 [21.29, 26.57]
Anti-tetanus toxoid (IU/mL)	0.04 [0.03, 0.04]	2.12 [1.86, 2.41]	1.43 [1.20, 1.71]	6.10 [5.41, 6.88]
Comparator group	N = 120[e)]	N = 120[e)]	N = 122[e)]	N = 122[e)]
Anti-PT (EU/mL)	1.21 [1.00, 1.46]	61.58 [54.55, 69.53]	16.40 [13.79, 19.49]	52.24 [45.27, 60.28]
Anti-FHA (EU/mL)	2.28 [1.87, 2.79]	134.87 [118.27, 153.81]	48.66 [41.68, 56.82]	208.72 [183.41, 237.52]
Anti-diphtheria toxoid (IU/mL)	0.01 [0.01, 0.02]	3.79 [3.21, 4.48]	1.66 [1.41, 1.96]	13.76 [11.68, 16.21]
Anti-tetanus toxoid (IU/mL)	0.04 [0.03, 0.05]	1.74 [1.44, 2.10]	1.04 [0.79, 1.37]	3.85 [3.16, 4.71]

N, number of analyzed subjects
a) V01, Visit 01 (immediately before first injection of DPT-cIPV or DPT)
b) V04, Visit 04 (1 month after third injection of DPT-cIPV or DPT)
c) V07, Visit 07 (immediately before fourth injection of DPT-cIPV or DPT)
d) V08, Visit 08 (1 month after fourth injection of DPT-cIPV or DPT)
e) V01 and 04 for PPS of primary immunization; V07 and 08 for the PPS of booster immunization

Adverse events were reported by all 248 subjects (100%) in the DPT-cIPV group and 127 of the 128 subjects (99.2%) in the comparator group during the observation periods (7 days after each injection for adverse events of special interest, 20 days after each injection for other adverse events, and the period from enrollment to final hospital visit for serious adverse events). Of these adverse events, 97.6% (242 of the 248 subjects) for the DPT-cIPV group and 97.7% (125 of the 128 subjects) for the comparator group were adverse reactions. Table 4-9 shows adverse events and adverse reactions with ≥5% incidence in either group.

Table 4-9. Adverse events and reactions observed with ≥5% incidence during the observation periods in either group (safety analysis set)

		DPT-cIPV group (N = 248)				Comparator group (N = 128)			
		Adverse events		Adverse reactions		Adverse events		Adverse reactions	
		n	%	n	%	n	%	n	%
Injection site	Injection site erythema	228	91.9	228	91.9	117	91.4	117	91.4
	Injection site induration	180	72.6	180	72.6	105	82.0	105	82.0
	Injection site swelling	149	60.1	149	60.1	83	64.8	83	64.8
	Injection site pain	55	22.2	55	22.2	31	24.2	31	24.2
Others	Nasopharyngitis	134	54.0	6	2.4	58	45.3	1	0.8
	Irritability	115	46.4	89	35.9	60	46.9	50	39.1
	Diarrhea	103	41.5	67	27.0	50	39.1	39	30.5
	Rhinorrhoea	94	37.9	51	20.6	48	37.5	30	23.4
	Fever	93	37.5	79	31.9	51	39.8	37	28.9
	Somnolence	76	30.6	56	22.6	45	35.2	38	29.7
	Crying	71	28.6	52	21.0	37	28.9	31	24.2
	Decreased appetite	61	24.6	32	12.9	46	35.9	27	21.1
	Vomiting	59	23.8	38	15.3	35	27.3	25	19.5
	Cough	52	21.0	32	12.9	30	23.4	22	17.2
	Rash	41	16.5	28	11.3	19	14.8	15	11.7
	Upper respiratory tract inflammation	41	16.5	1	0.4	20	15.6	0	0.0
	Gastroenteritis	35	14.1	2	0.8	10	7.8	1	0.8
	Bronchitis	29	11.7	2	0.8	9	7.0	0	0.0
	Exanthema subitum	31	12.5	0	0.0	21	16.4	0	0.0
	Diaper dermatitis	29	11.7	0	0.0	9	7.0	0	0.0
	Eczema	24	9.7	4	1.6	10	7.8	2	1.6
	Tympanitis	19	7.7	0	0.0	6	4.7	0	0.0
	Conjunctivitis	18	7.3	0	0.0	10	7.8	2	1.6
	Eye discharge	17	6.9	1	0.4	6	4.7	0	0.0
	Pediatric eczema	16	6.5	0	0.0	5	3.9	0	0.0
	Pruritus	15	6.0	8	3.2	16	12.5	12	9.4
	Miliaria rubra	15	6.0	0	0.0	3	2.3	0	0.0
	Urticaria	14	5.6	8	3.2	6	4.7	5	3.9
	Hand-foot-and-mouth disease	14	5.6	0	0.0	5	3.9	0	0.0
	Constipation	13	5.2	4	1.6	6	4.7	2	1.6
	Influenza	11	4.4	0	0.0	9	7.0	0	0.0
	Dermatitis	3	1.2	0	0.0	7	5.5	0	0.0

N, number of analyzed subjects; n, number of subjects with adverse event or adverse reaction

During the observation periods, 53 serious adverse events were reported by 37 of 248 subjects (14.9%) in the DPT-cIPV group; 15 serious adverse events were reported by 12 of 128 subjects (9.4%) in the comparator group. Of these, the causal relationship to the investigational product could not be ruled out for 1 subject in the DPT-cIPV group (fever) or 1 subject in the comparator group (cardiac failure and tamponade). The case involving cardiac failure had not resolved by the time of final visit.

Additionally, 7 cases of febrile convulsion were reported by 6 of the 248 subjects (2.4%) in the DPT-cIPV group during the observation periods. None of the cases in all these subjects were related to the investigational product. Of them, the cases in 4 subjects were serious adverse events.

Adverse events resulting in study discontinuation occurred in 2 subjects in the DPT-cIPV group (Kawasaki disease in both subjects, serious but resolving) and 1 subject in the comparator group (cardiac failure and tamponade, both serious and cardiac failure had not resolved). No deaths were observed.

4.B Outline of the review by PMDA

4.B.(1) Clinical data package

The applicant explained the data comprising the clinical data package as follows:

Squarekids (DPT-cIPV) is a quadrivalent combined vaccine consisting of approved DPT and IPV approved in Japan in 2012 and produced by Sanofi Pasteur (currently Sanofi, hereinafter referred to as SP) and the strengths of each active ingredient are the same as those of the approved products. The safety and efficacy of DPT-cIPV were evaluated for its indication of "the prevention of pertussis, diphtheria, tetanus, and acute poliomyelitis," based on the results of the Japanese phase I study (Study A-J101), phase II study (Study A-J201), and phase III study (Study A-J301).

DPT-cIPV consists of adjuvant-free IPV and adjuvant-containing DPT. Because the antigenicity of IPV can be higher than that of IPV monotherapy, PMDA asked the applicant to provide rationales for not conducting a dose range-finding study for the D antigen of IPV.

The applicant responded as follows:

The D-antigen contents in IPV matches those (40, 8, and 32 DU of inactivated poliovirus types 1, 2, and 3, respectively) specified in the WHO guidelines to ensure the efficacy (WHO TRS No. 673, 1982). The effects of DPT and IPV interference on efficacy and safety were investigated based on overseas clinical studies conducted in Chile. In these studies of investigational products manufactured by SP, simultaneous vaccination of DPT with IPV (DPT + IPV) and a combined vaccine of DPT and IPV (combined vaccine) were administered (CHILE Study). The D-antigen contents in both IPV alone and the combined vaccine used in this study were equal to those in DPT-cIPV. In both groups in the CHILE study, the prevalence of serum neutralizing antibodies against polioviruses was 100% for all types, and no marked differences existed in the prevalence of DPT neutralizing antibody between the 2 groups (Table 4-10).

Table 4-10. Prevalence of neutralizing antibodies (%) against each antigen at 1 month after the third injection of combined vaccine or simultaneous vaccination of DPT with IPV (CHILE Study, ITT)

Vaccine	Injection time (Age)	Pertussis		Diphtheria	Tetanus	Polio		
		Anti-PT	Anti-FHA			Type 1	Type 2	Type 3
Protective level		≥ 4-fold		≥ 0.01 IU/mL		≥ 5-fold		
DPT + IPV group (n/N)	2,4, and 6 months	97.5% (117/120)	94.1% (112/119)	100% (134/134)	100% (134/134)	100% (110/110)	100% (110/110)	100% (110/110)
Combined vaccine group (n/N)	2,4, and 6 months	88.6% (109/123)	93.2% (110/118)	100% (129/129)	100% (129/129)	100% (107/107)	100% (107/107)	100% (107/107)

N, number of analyzed subjects; n, number of subjects with neutralizing antibody

In the CHILE Study, the subjects received investigational products by intramuscular injection. However, DPT-cIPV is to be injected subcutaneously. The effects of administration routes on efficacy were investigated. Literature has reported that when IPV was administered subcutaneously or OPV was administered orally, neutralizing antibodies against each poliovirus type were detected in 99% of the children receiving IPV, and geometric mean values at least comparable to those following OPV were achieved (*Am J Epidemiol*, 1988;128:615-628), indicating that immunogenicity does not diminish when DPT-cIPV is administered subcutaneously. Even without a dose range-finding study, this indicates that

DPT-cIPV can achieve efficacy equivalent to that of simultaneously administered DPT and IPV, and thus, the prevalence of neutralizing antibodies against each antigen can be achieved.

In the CHILE Study, there were no marked differences between the 2 groups in systemic reactions (DPT + IPV group, 42 of 135 subjects, 31.1%; combined vaccine group, 51 of 131 subjects, 38.9%) and local adverse reactions (DPT + IPV group, 34 of 135 subjects for DPT, 25.2% and 3 of 135 subjects for IPV, 2.2%; combined vaccine group, 28 of the 131 subjects, 21.4%) after the third administration. The aluminum content used as an adjuvant for DPT-cIPV is lower than that used in the CHILE Study. Additionally, there were no marked differences in serious adverse reactions or systemic adverse reactions between differing administration routes (*Pediatrics*. 1996;97(2):236-242), indicating no dose range-finding study is required.

Based on the above, the applicant considered that no dose range-finding study appeared necessary from the standpoint of efficacy and safety evaluations.

PMDA considers as follows:
With respect to the D-antigen content in DPT-cIPV, taking the following points and the applicant's explanation into account, the D-antigen content in the vaccine used in the phase III study was understandable. The WHO guidelines (WHO TRS, No.673, 1982) suggest that immunoreactions are induced at higher rates with such level of antigen. Vaccine products containing equivalent D-antigen contents have been used for a long time outside Japan. Additionally, an overseas clinical study of a similar vaccine product containing the same D–antigen contents revealed no marked differences in safety between simultaneous vaccination of DPT with IPV and a combined vaccine of DPT and IPV. Furthermore, Study A-J301 has shown the immunogenicity and safety of the combined product of DPT and IPV. PMDA has concluded that the clinical data package without a dose range-finding study is acceptable.

4.B.(2) Efficacy

4.B.(2).1) Selection of the primary endpoint

The primary endpoint of Study A-J301 was the prevalence of neutralizing antibodies exceeding the protective level against poliovirus types 1, 2, and 3 (neutralizing antibody titers of 8-fold) at 1 month after primary immunization (3 injections).

The applicant explained the primary endpoint as follows:
In clinical development, the antibody titer of poliomyelitis prevention is often set to 8-fold (*Ann N Y Acad Sci*. 1995;754:289-299), the value recommended by the WHO (WHO TRS, No.673, 1982) and literature in Japan (*Scand J Infect Dis*. 2008;40:247-253). Thus, the primary endpoint was set as the prevalence of ≥8-fold neutralizing antibody titers against each polio antigen at 1 month after the third injection of DPT-cIPV.

PMDA considers as follows:

IPV had yet to be approved at the time of the development of DPT-cIPV. Understandably, the immunogenicity of IPV, a new drug, was set as the primary endpoint, and the effects of combined IPV on the immunogenicity of DPT were investigated based on the comparison to the approved DPT as a secondary endpoint. Based on the above-mentioned applicant's explanation and reference materials (National Institute of Health Research Associate ed. *Vaccine Handbook*. 1994:120-129, *J Infect Dis*. 2012;205:237-243, *N Engl J Med*. 2007;356:1536-1544, *Manual for the virological investigation of polio*, WHO/EPI/GEN/97.01, WHO, 1997, Plotkin, *et al. Vaccines*. 6th ed. 2013:573-597), PMDA has concluded that the prevalence of neutralizing antibodies against poliovirus types 1, 2, and 3 following the third injection of DPT-cIPV is appropriate as the primary endpoint.

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

The applicant explained the efficacy of DPT-cIPV for the prevention of polio as follows:

The herd immunity needed to avoid epidemic for polio is reported to be 80% to 86% (*Epidemiol Rev*. 1993;15:265-302). The primary endpoint of Study A-J301 was as follows: the lower limit of 95% confidence interval for the prevalence of neutralizing antibodies against each poliovirus type after the third injection exceeds the predefined level of 90%. The prevalence of neutralizing antibodies against all poliovirus types at 1 month after the third injection of DPT-cIPV was 100% [95% CI, 98.4, 100] [see "4.A.(3) Japanese phase III clinical study"]. The lower limit of the 95% confidence interval of the prevalence of neutralizing antibodies exceeded 90% (the predetermined limit), verifying the immunogenicity of DPT-cIPV against polioviruses. The booster effects of DPT-cIPV were seen at 1 month after the fourth injection (booster immunization). The geometric mean of neutralizing antibody titers against types 1, 2, and 3 after the fourth injection was 9.30-, 6.75-, and 21.30-fold, respectively, compared to that before the fourth injection. As a secondary endpoint, the non-inferiority of IPV to OPV was demonstrated in terms of the prevalence of neutralizing antibodies against polioviruses.

PMDA concluded that the results of Study A-J301 demonstrated the immunogenicity and booster effects of DPT-cIPV against each poliovirus and that DPT-cIPV would have a prophylactic effect against poliomyelitis.

4.B.(2).3) Efficacy against pertussis, diphtheria, and tetanus

The applicant explained the efficacy of DPT-cIPV for the prevention of pertussis, diphtheria, and tetanus as follows:

In Study A-J301, the secondary endpoint was the prevalence of neutralizing antibodies against pertussis (PT and FHA antigens), diphtheria toxoid, and tetanus toxoid at 1 month after the third injection of DPT-cIPV; the prevalence was to be verified when measured neutralizing antibodies were 10 EU/mL, 10 EU/mL, 0.01 IU/mL, and 0.01 IU/mL, respectively, which are above the protective levels in accordance with the infection surveillance standards employed by the National Institute of Infectious Diseases[2].

[2] Tuberculosis and Infectious Diseases Control Division, HSB, MHLW, and Infectious Disease Surveillance Center, National Institute of Infectious Diseases. Annual Report 1996, 1998, 2003 National Epidemiological Surveillance of Vaccine-Preventable Diseases

Furthermore, the lower limit of the 95% confidence interval for the difference in the prevalence of neutralizing antibodies against each antigen at 1 month after 3 injections between 2 groups (DPT-cIPV group minus comparator [DPT + OPV] group) exceeded -10%, a predetermined non-inferiority limit (Table 4-11). The above data indicate the immunogenicity of DPT-cIPV.

Table 4-11. Prevalence and geometric mean of neutralizing antibody titers against each DPT antigen after 3 injections of DPT-cIPV or comparator (Study A-J301, PPS)

Antigen	Product group (DPT-cIPV)			Comparator group (DPT+ OPV)			Difference in antibody prevalence (DPT-cIPV group - comparator group) [95% CI]
	Antibody prevalence		Antibody titers (Geometric mean [95% CI])	Antibody prevalence		Antibody titers (Geometric mean [95% CI])	
	n/N	(%)		n/N	(%)		
PT	232/235	98.7	67.20 [61.74, 73.14]	118/120	98.3	61.58 [54.55, 69.53]	0.39 [-2.30, 4.68]
FHA	235/235	100.0	164.34 [152.03, 177.63]	120/120	100.0	134.87 [118.27, 153.81]	0.00 [-1.61, 3.10]
Diphtheria	235/235	100.0	5.21 [4.48, 6.06]	120/120	100.0	3.79 [3.21, 4.48]	0.00 [-1.61, 3.10]
Tetanus	235/235	100.0	2.12 [1.86, 2.41]	120/120	100.0	1.74 [1.44, 2.10]	0.00 [-1.61, 3.10]

N, number of analyzed subjects; n, number of subjects with neutralizing antibody; 95% CI, 95% confidence interval

The WHO has set the protective levels of antibody titers against diphtheria at 0.1 IU/mL. PMDA asked the applicant to provide the rationale for setting the positive level of neutralizing antibody titer against diphtheria toxoid at 0.01 IU/mL.

The applicant responded as follows:

The cut-off value for diphtheria toxoid antibody titer of 0.01 IU/mL is appropriate as it has been reported "An antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection" (Plotkin, *et al*. *Vaccines.* 4th ed. Saunders; 2004:211-228). However, an epidemic prediction survey conducted by the National Institute of Infectious Diseases found that 0.1 IU/mL was the protective level and the WHO reported that 0.1 IU/mL is a reliable protective level (*Wkly Epidemiol Rec*. 2006;81:21-32). Thus, the data from the study in which the secondary endpoint was set as the positive level of neutralizing antibody titer of 0.1 IU/mL were investigated. In Study A-J301, when the positive level of neutralizing antibody titer was set at 0.1 IU/mL, the prevalence of neutralizing antibody against diphtheria toxoid at 1 month after the third injection of DPT-cIPV was 99.1% [95% CI, 97.0, 99.9] and the value at 1 month after the fourth injection was 100% [95% CI, 98.5, 100.0] (Table 4-12). The above findings indicate that DPT-cIPV is sufficiently immunogenic against diphtheria toxoid.

Table 4-12. Prevalence of neutralizing antibodies against diphtheria toxoid with a cut-off value of 0.1 IU/mL (Study A-J301, PPS)

	Product group (DPT-cIPV)		Comparator group (DPT + OPV)	
	n/N	% [95% CI]	n/N	% [95% CI]
After 3 injections	233/235	99.1 [97.0, 99.9]	120/120	100 [97.0, 100.0]
After booster immunization	241/241	100 [98.5, 100.0]	122/122	100 [97.0, 100.0]

N, number of analyzed subjects; n, number of subjects with neutralizing antibody levels

PMDA considers as follows:

In view of the literature submitted by the applicant and other data (Plotkin *et al*. *Vaccines*. 6th ed. Saunders; 2013:573- 597), the positive level of neutralizing antibody titer against diphtheria toxoid should have been defined as 0.1 IU/mL. However, as explained by the applicant, immunogenicity has been confirmed with either 0.01 or 0.1 IU/mL, and DPT-cIPV is not inferior to the approved DPT in

terms of the geometric mean of neutralizing antibody titers against diphtheria toxoid in Study A-J301 (Table 4-8). This suggests DPT-cIPV is effective in preventing diphtheria.

The protective level for tetanus toxoid proposed in this application is the same level used by the WHO (*Wkly Epidemiol Rec*. 2006;81:21-32, *Wkly Epidemiol Rec*. 2006;81:197-208), suggesting that the positive level of neutralizing antibody titer was appropriate. On the other hand, the clinical significance of the positive levels for PT and FHA antibody titers has not been fully elucidated. In Study A-J301, however, antibody prevalence and geometric mean of neutralizing antibody titers against pertussis, diphtheria, and tetanus toxoid were similar in the DPT-cIPV group and the comparator (DPT + OPV) group. PMDA therefore accepted the applicant's explanation that the efficacy of DPT-cIPV for the prevention of pertussis, diphtheria, and tetanus is comparable to the approved DPT.

4.B.(3) Safety

Based on the following review, PMDA concluded that the safety of DPT-cIPV is acceptable, since there is no notable difference between DPT-cIPV and the approved DPT and OPV. However, the number of subjects evaluated in the submitted data was limited. More information concerning unknown adverse reactions and factors impacting safety must be collected through post-marketing surveillance.

4.B.(3).1) Comparison of safety

The applicant explained that the safety of DPT-cIPV is acceptable because there were no marked differences in adverse events and adverse reactions between the DPT-cIPV group and comparator (DPT + OPV) group in Study A-J301 (Table 4-13).

Table 4-13. Incidence of adverse events and reactions reported with maximum severity (Grade ≥3) (Study A-J301, FAS)

	Primary immunization				Booster immunization			
	DPT-cIPV group N = 248		Comparator group N = 128		DPT-cIPV group N = 244[a)]		Comparator group N = 125	
	Adverse events n (%)	Adverse reactions n (%)	Adverse events n (%)	Adverse reactions n (%)	Adverse events n (%)	Adverse reactions n (%)	Adverse events n (%)	Adverse reactions n (%)
Systemic adverse events and reactions of special interest[b)]								
Fever[c)]	2 (0.8)	1 (0.4)	0 (0)	0 (0)	3 (1.2)	3 (1.2)	0 (0)	0 (0)
Decreased appetite[d)]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.4)	1 (0.8)	0 (0)
Irritability[e)]	0 (0)	0 (0)	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea[f)]	0 (0)	0 (0)	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria[g)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Other adverse events and reactions[h)]								
Fever[i)]	0 (0)	0 (0)	2 (1.6)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)
Hot feeling at injection site[i)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)

N, number of analyzed subjects; n, number of subjects with adverse event or adverse reaction
a) Adverse events of special interest following booster immunization were analyzed in 243 of the 244 subjects in the safety analysis set after excluding 1 subject for whom data on events of special interest could not be obtained.
b) Number and incidence of events within 7 days of each injection (3 primary immunization injections and 1 booster immunization injection) of DPT-cIPV or comparator
c) Grade 3, Temperature of ≥39.0°C lasting ≤1 day
d) Grade 3, Minimal food intake
e) Grade 3, No response to treatment
f) Grade 3, Increase in frequency of bowel movements to ≥9 times/day
g) Grade 3, Required therapy lasting ≥2 days
h) Number and incidence of events within 20 days of each injection (3 primary immunization injections and 1 booster immunization injection) of DPT-cIPV or comparator

i) Grade 3, Severe adverse events (severe symptoms requiring hospitalization or invasive therapy/induction voltage regulator/transfusion/endoscopic therapy/surgery)

PMDA concluded as follows:

With respect to systemic adverse events and adverse reactions of special interest in Study A-J301, Grade ≥3 fever (1 of 248 subjects following primary immunization and 3 of 243 subjects following booster immunization) and decreased appetite (1 of 243 subjects following booster immunization) were reported only in the DPT-cIPV group. All the events eventually resolved. A serious adverse reaction of fever was reported by 1 of 248 subjects in the DPT-cIPV group at 19 days after the first dose of OPV placebo. This reaction eventually resolved. A total of 6 subjects experienced 7 episodes of serious or non-serious febrile convulsion, but a causal relationship to DPT-cIPV was ruled out for all 7 episodes of the event.

Based on the above, PMDA concluded that the safety of DPT-cIPV is acceptable, but information concerning the incidences of fever and febrile convulsion should be collected through post-marketing surveillance.

4.B.(3).2) Clinically significant adverse reactions

The package insert of the approved DPT lists “shock, anaphylaxis, thrombocytopenic purpura, encephalitis and convulsion” as clinically significant adverse reactions. The applicant explained that these reactions would be listed on the package insert of DPT-cIPV. As clinically significant risks of IPV, the applicant explained convulsion and anaphylaxis have been identified based on the clinical data of IPV monotherapy in Japan and abroad.

Clinical studies of DPT-cIPV revealed no new notable adverse reactions compared to approved DPT or IPV. PMDA concluded that it is appropriate to list “shock, anaphylaxis, thrombocytopenic purpura, encephalitis and convulsion” as clinically significant adverse reactions for DPT-cIPV. The incidences of these reactions were low; more information on the reactions should be collected through post-marketing surveillance.

4.B.(4) Clinical positioning and indication

The applicant explained the clinical positioning of DPT-cIPV as follows:

DPT-cIPV is a combined vaccine which can be an alternative to DPT and IPV. At present, a monovalent IPV containing the same poliovirus strains as DPT-cIPV and a quadrivalent vaccine containing IPV manufactured from another strain (Sabin strain) are approved and administered as routine vaccinations. Combining IPV and DPT vaccines will reduce the number of immunizations to be administered, reduce burdens on infants, and make it easier to schedule immunizations. Furthermore, DPT-cIPV contributes to the secure distribution of DPT-IPV vaccines.

PMDA considers the clinical positioning of DPT-cIPV as follows:

DPT-cIPV is expected to be effective in preventing poliomyelitis since Study A-J301 demonstrated the immunogenicity of DPT-cIPV against poliovirus. Additionally, DPT-cIPV is also effective in preventing

pertussis, diphtheria, and tetanus, and its safety is acceptable. DPT-cIPV is clinically significant because it provides another therapeutic option besides the available DPT-IPV vaccines (Quattrovac subcutaneous injection syringe and Tetrabik subcutaneous injection syringe) [see "4.B.(2).2) Efficacy against polio," "4.B.(2).3) Efficacy against pertussis, diphtheria, and tetanus," and "4.B.(3) Safety"].

Based on the above, PMDA concluded that DPT-cIPV should be indicated for "the prevention of pertussis, diphtheria, tetanus, and acute poliomyelitis" as proposed.

4.B.(5) Dosage and administration

The results of the clinical studies of DPT-cIPV demonstrated the immunogenicity of DPT-cIPV against pertussis, diphtheria, tetanus, poliovirus types 1, 2, and 3. DPT-cIPV is tolerable [see "4.B.(2) Efficacy" and "4.B.(3) Safety"]. PMDA concluded that the following dosage and administration proposed by the applicant is acceptable.

[Dosage and administration]
The usual primary immunization series for children consist of 3 doses of 0.5 mL administered by subcutaneous injection at intervals of at least 3 weeks.
The usual booster immunization for children is a single 0.5 mL dose administered by subcutaneous injection at least 6 months after the primary immunization.

4.B.(6) Simultaneous vaccination with other vaccines

Hib is likely to be administered simultaneously with DPT-cIPV. Its potential effects on the safety and immunogenicity of DPT-cIPV were investigated. Study A-J301 allowed simultaneous administration of DPT-cIPV with Hib. Table 4-14 summarizes the immunogenicity of subjects receiving DPT-cIPV alone or DPT-cIPV in combination with Hib; simultaneous vaccination of DPT-cIPV with Hib had no impact on the immunogenicity of DPT-cIPV. With respect to safety, systemic adverse events of special interest after the completion of primary immunization were reported by 11 of 15 subjects (73.3%) in the simultaneous group and by 125 of 170 subjects (73.5%) in the non-simultaneous group. Systemic adverse events of special interest after the completion of booster immunization were reported by 11 of 15 subjects (73.3%) in the simultaneous group and 87 of 228 subjects (38.2%) in the non-simultaneous group. Irritability, somnolence, and decreased appetite were the systemic adverse events of special interest after the completion of booster immunization more commonly reported in the simultaneous vaccination group. Grade ≥3 systemic adverse events of special interest were reported only in the non-simultaneous group (4 of 228 subjects, 1.8%). Based on the above, the applicant explained that simultaneous administration with Hib posed no marked differences in safety.

Table 4-14. Geometric mean of neutralizing antibody titers against poliovirus with or without simultaneous vaccination with Hib at each time point (Study A-J301, PPS)

	V01[a)]	V04[b)]	V07[c)]	V08[d)]
	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]	Geometric mean [95% CI]
Non-simultaneous group (DPT-cIPV alone)	N = 163[e)]	N = 163[e)]	N = 164[f)]	N = 164[f)]
Type 1	3.00 [2.64, 3.40]	970.98 [831.05, 1134.47]	259.26 [225.78, 297.72]	2529.93 [2210.91, 2894.99]
Type 2	4.41 [3.76, 5.19]	1825.87 [1602.48, 2080.39]	621.87 [519.91, 743.83]	4533.30 [3983.54, 5158.92]
Type 3	2.47 [2.32, 2.63]	952.58 [817.19, 1110.40]	148.72 [124.38, 177.81]	3812.02 [3238.23, 4487.48]
Simultaneous group (DPT-cIPV plus Hib)	N = 15[e)]	N = 15[e)]	N = 9[f)]	N = 9[f)]
Type 1	2.90 [2.09, 4.02]	1203.74 [648.04, 2235.96]	322.54 [207.35, 501.70]	2580.32 [1325.67, 5022.42]
Type 2	3.74 [2.40, 5.82]	2640.64 [1674.15, 4165.10]	574.69 [369.45, 893.94]	4423.94 [2522.91, 7757.39]
Type 3	3.03 [2.23, 4.14]	977.76 [611.48, 1563.43]	181.01 [62.36, 525.42]	3378.65 [1010.54, 11296.19]

N, number of analyzed subjects
a) V01, Visit 01 (immediately before first injection of DPT-cIPV)
b) V04, Visit 04 (1 month after third injection of DPT-cIPV)
c) V07, Visit 07 (immediately before fourth injection of DPT-cIPV)
d) V08, Visit 08 (1 month after fourth injection of DPT-cIPV)
e) Of the 235 subjects in the PPS for primary immunization, 163 subjects who did not receive Hib throughout primary immunization period were included in the non-simultaneous group. Additionally, of the 72 subjects who received Hib simultaneously at least once, 15 subjects who received Hib at all 3 injections of DPT-cIPV were included in the simultaneous group.
f) Of the 241 subjects in the PPS for booster immunization, 164 subjects who did not receive Hib throughout the study were included in the non-simultaneous group. Of the 77 subjects who received Hib simultaneously at least once, 9 subjects who received Hib at all 4 injections of DPT-cIPV were included in the simultaneous group.

PMDA concluded that simultaneous vaccination of DPT-cIPV with Hib is unlikely to markedly compromise the safety and immunogenicity of DPT-cIPV. Nevertheless, only a limited number of children have received simultaneous administration of DPT-cIPV and Hib. In clinical settings, DPT-cIPV is likely to be simultaneously administered with other vaccines. Post-marketing surveillance must focus on not only Hib but also other vaccines administered simultaneously with DPT-cIPV. Safety information collected through the surveillance should be analyzed and, as necessary, provided to healthcare professionals [see "4.B.(7) Post-marketing investigations"].

4.B.(7) Post-marketing investigations

The applicant submitted the following post-marketing surveillance plan:

A use-results survey will be conducted in children scheduled to receive a total of 4 injections of DPT-cIPV for primary and booster immunizations. The target number of children vaccinated with DPT-cIPV is 750 at each injection (i.e. 3000 injections). The safety of DPT-cIPV in clinical settings will be investigated in children vaccinated with DPT-cIPV at least once. In Study A-J301, Grade ≥3 fever was observed after primary immunization, and the duration of administration of DPT-cIPV overlapped with the time when febrile convulsion was frequently reported. Thus, the survey was designed to investigate 750 children vaccinated with DPT-cIPV at each of the 4 injections to elucidate the incidences of fever and convulsion (including febrile convulsion) in clinical settings.

PMDA concluded that the fever and convulsion (including febrile convulsion) should be items to be investigated in the post-marketing surveillance, as proposed by the applicant. Additionally, more information need to be collected on the safety of simultaneous vaccination of DPT-cIPV with other

vaccines and on the incidences of clinically significant adverse reactions (shock, anaphylaxis, thrombocytopenic purpura, encephalitis, and convulsion), because only limited data have been obtained from clinical studies. Furthermore, post-marketing surveillance should collect information on unknown adverse reactions and factors impacting safety.

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

The results are currently being evaluated.

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

The results are currently being evaluated.

IV. Overall Evaluation

As described in "4.B.(2) Efficacy" and "4.B.(3) Safety," PMDA concludes that the efficacy of Squarekids (DPT-cIPV) for the proposed indication has been demonstrated and that its safety is acceptable. The product may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion

Review Report (2)

September 30, 2013

I. Product Submitted for Registration

[Brand name]	Squarekids Subcutaneous Injection Syringe
[Non-proprietary name]	Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk) Combined Vaccine
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	February 20, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described 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 following conclusion by PMDA was supported by the expert advisors:

Based on the submitted clinical study data, the efficacy of Squarekids (DPT-cIPV) can be expected and the indication for the product should be "the prevention of pertussis, diphtheria, tetanus, and acute poliomyelitis."

2. Safety

Based on the submitted clinical study data, PMDA has concluded that the safety profile of DPT-cIPV is tolerable. This decision was supported by the expert advisors.

3. Dosage and administration

PMDA has concluded that the dosage and administration of DPT-cIPV should be as follows. This decision was supported by the expert advisors.

[Dosage and administration]

The usual primary immunization series for children consist of 3 doses of 0.5 mL administered by subcutaneous injection at intervals of at least 3 weeks.

The usual booster immunization for children is a single 0.5 mL dose administered by subcutaneous injection at least 6 months after the primary immunization.

4. Risk management plan (draft)

Based on the investigations described in "4.B.(7) Post-marketing investigations" of Review Report (1), a use-results survey will be carried out to investigate incidences of fever and convulsion (including febrile convulsion) and to collect and evaluate safety information regarding simultaneous administration of DPT-cIPV with other vaccines. This decision was supported by the expert advisors.

PMDA concluded that, at present, the risk management plan for DPT-cIPV should include the safety specifications shown in Table 1, the additional pharmacovigilance activities and risk minimization activities listed in Table 2, and the use-results survey listed in Table 3.

Table 1. Safety and efficacy investigation items in the risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	・ Convulsion ・ Shock and anaphylaxis ・ Thrombocytopenic purpura ・ Encephalopathy	・ Safety of simultaneous administration of DPT-cIPV with other vaccines
Efficacy specification		
None		

Table 2. Summary of additional pharmacovigilance and risk minimization activities in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
・ Early post-marketing phase vigilance ・ Use-results survey (target sample size, 750 children [3000 injections])	・ Early post-marketing phase vigilance

Table 3. Outline of use-results survey plan (draft)

Objective	Ascertain safety in clinical settings and factors impacting safety.
Survey method	Central registration system
Population	Children scheduled to receive DPT-cIPV in primary (3 injections) and booster immunizations
Observation period	For 1 week following each injection (3 injections for the primary immunization, 1 injection for booster immunization)
Target sample size	750 children
Major survey items	・ Fever ・ Convulsion (including febrile convulsion)

5. Quality

PMDA investigated the additional explanations and additional items submitted by the applicant in response to the requirement described in "2.B Outline of the review by PMDA" of Review Report (1), and concluded that the quality of DPT-cIPV was appropriately controlled. During the review, it was decided that specifications for the drug product should include content uniformity for *Bordetella pertussis* protective antigen, diphtheria toxoid, and tetanus toxoid, to ensure content uniformity of each active ingredient.

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

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. The results showed no particular problems, and PMDA 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 (5.3.5.1-1, 5.3.5.2-2). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the above review, PMDA has concluded that Squarekids (DPT-cIPV) may be approved with the following indication and dosage and administration. The re-examination period of the product should be the same as the remaining re-examination period of Imovax Polio subcutaneous, one of the active ingredients of the proposed combination product (i.e., until April 26, 2020). Both the drug substance and the drug product are classified as powerful drugs and biological products.

[Indication]

Prevention of pertussis, diphtheria, tetanus, and acute poliomyelitis

[Dosage and administration]

The usual primary immunization series for children consist of 3 doses of 0.5 mL administered by subcutaneous injection at intervals of at least 3 weeks.

The usual booster immunization for children is a single 0.5 mL dose administered by subcutaneous injection at least 6 months after the primary immunization.

Review Report (3)

June 5, 2014

I. Product Submitted for Registration

[Brand name]	Squarekids Subcutaneous Injection Syringe
[Non-proprietary name]	Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk Vaccine) Combined Vaccine
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	February 20, 2013

II. Content of the Review

A problem identified in commercial-scale process validation (PV) necessitated the continuation of the review after the completion of Review Report (2) in September 2013. The review process after the completion of Review Report (2) is described below.

The information and data submitted initially in the application for Squarekids included the description of the manufacturing process for and the study data of the vaccine manufactured on a small scale. The results of the review of the application are described in Review Reports (1) and (2). In the first PV run conducted after the regulatory submission, content uniformity, one of the specifications for PV batches, failed to meet acceptance criteria; this information was revealed in September 2013. This failure appears attributable to malfunctions in the filling process, because of which the bulk was not properly stirred in accordance with the stirring specifications and was then filled in syringes. After the equipment issues were addressed, the second PV run showed that content uniformity was within the specification. However, potency for diphtheria toxoid was out of the specification. This was considered attributable to improperly adjusted pH of aluminum hydroxide gel, an excipient. The third PV run was performed by scaling down the commercial scale production proposed in the application, and all 3 PV batches met the specifications. The results were submitted in June 2014; the applicant explained that DPT-cIPV could be manufactured consistently on the modified commercial scale. According to the modified production scale that satisfied the specifications, the applicant modified the application to change the volume of final bulk and each drug substance used in the formulation process.

PMDA has concluded that the modified volume of final bulk and each drug substance for the formulation process is appropriate since the volume was defined based on the results of the third PV run which satisfied all the specifications.

III. Other

The proposed product (DPT-cIPV) is a new combination drug containing the same active ingredients as Imovax Polio subcutaneous. In view of the non-proprietary name of Imovax Polio subcutaneous, the non-proprietary name of the proposed product in the application was changed from “Adsorbed

Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk) Combined Vaccine" to "Adsorbed Diphtheria-Purified Pertussis-Tetanus-Inactivated Polio (Salk Vaccine) Combined Vaccine." In a partial revision of the Minimum Requirements for Biological Products (MHLW Ministerial Announcement No. 294 issued on September 12, 2013), the unit for diphtheria toxoid and tetanus toxoid potencies was changed to "IU/mL." After completion of Review Reports (1) and (2), unit descriptions in the application and submitted data were revised accordingly.

IV. Overall Evaluation

At the time of discussion included in Review Report (2), the remaining re-examination period of Imovax Polio subcutaneous was more than 6 years. Thus, the re-examination period of Squarekids was set to be equal to this remaining time (i.e., until April 26, 2020). However, the remaining re-examination period is currently less than 6 years because of the prolonged review process. PMDA has therefore concluded that the re-examination period of Squarekids should be changed to 6 years.