Review Report

February 8, 2016
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]	Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 μg/mL "Kitasato Daiichi Sankyo"
[Non-proprietary name]	Adsorbed cell culture-derived influenza vaccine (H5N1)
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	August 28, 2015
[Dosage form/Strength]	Suspension for injection containing the following ingredients per mL: 30 μg of hemagglutinin (HA) of inactivated influenza virus (H5N1 strain) as the active ingredient, 0.3 mg (on an aluminum-content basis) of aluminum hydroxide gel as the adjuvant, and 0.001% (w/v) thimerosal as the preservative.
[Application classification]	Prescription drug, (6) Drug with a new dosage
[Items warranting special mention]	Orphan drug (Notification No. 1211-3 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 11, 2012)
[Reviewing office]	Office of Vaccines and Blood Products

Review Results

February 8, 2016

[Brand name]	Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 μg/mL "Kitasato Daiichi Sankyo"
[Non-proprietary name]	Adsorbed cell culture-derived influenza vaccine (H5N1)
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	August 28, 2015

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product is expected to have efficacy in the prevention of pandemic influenza (H5N1) and its safety is acceptable in view of its observed benefits.

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

[Indication]	Prevention of pandemic influenza (H5N1) (No change)
[Dosage and administration]	The usual dosage is 2 doses of <u>0.1 or 0.25 mL each for persons aged 6 months to <13 years, 0.5 mL each for persons aged 13 to <20 years, and</u> 1 mL each <u>for persons aged ≥20 years,</u> injected intramuscularly at an interval of ≥2 weeks. (Underline denotes additions.)
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

January 15, 2016

I. Product Submitted for Registration

[Brand name]	Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 μg/mL "Kitasato Daiichi Sankyo"
[Non-proprietary name]	Adsorbed cell culture-derived influenza vaccine (H5N1)
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	August 28, 2015
[Dosage form/Strength]	Suspension for injection containing the following ingredients per mL: 30 μg of hemagglutinin (HA) of inactivated influenza virus (H5N1 strain) as the active ingredient, 0.3 mg (on an aluminum content basis) of aluminum hydroxide gel as the adjuvant, and 0.001% (w/v) thimerosal as the preservative.
[Proposed indication]	Prevention of pandemic influenza (H5N1) (No change)
[Proposed dosage and administration]	The usual dosage is 2 doses of <u>0.25 mL each for persons aged 6 months to <13 years, 0.5 mL each for persons aged 13 to <20 years, and</u> 1 mL each <u>for persons aged ≥20 years,</u> injected intramuscularly at an interval of ≥2 weeks. (Underline denotes additions.)

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

This application is submitted for approval of additional dosage and thus contains no new data for the "Data relating to quality" or "Non-clinical data" sections.

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

Influenza is an acute respiratory disease caused by infection with influenza viruses of the *Orthomyxoviridae* family. Influenza viruses are classified by serotype into 3 types: A, B, and C. Influenza type A viruses are further divided into 16 subtypes (H1 to H16) and 9 subtypes (N1 to N9) based on the antigenicity of the viral surface hemagglutinin (HA) and neuraminidase (NA). Many animal species, including humans, avian, swine, and horses, are known to be hosts of influenza A viruses. Influenza A virus subtypes differ by host species, while all subtypes have been isolated from avian viruses. The subtypes of influenza A viruses currently circulating in humans are H1N1 and H3N2. These subtypes undergo continuous or non-continuous antigenic change (antigenic drift or shift), and this may result in the emergence of a new influenza A virus subtype with antigenicity and species-specificity different from known ones.

Fatal human infection with highly pathogenic H5N1 avian influenza virus (HPAI H5N1 virus), first identified in Hong Kong in 1997, is known to cause serious conditions in humans, including systemic viral infection, bleeding tendency, multi-organ failure, and cytokine storm. The World Health Organization (WHO) reports that the mortality from the disease is approximately 50% (449 deaths out of 844 persons infected, as of December 14, 2015; http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/). The provisions of Article 6, paragraph 7, of the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (Act No. 114 of 1998) define novel influenza as "influenza caused by a virus that has become transmissible among humans and has the potential to affect the health and lives of people seriously, through rapid nationwide spread owing to the lack of immunity against the virus in most people." When the HPAI H5N1 virus has become transmissible among humans leading to an influenza pandemic, it may pose significant damage to human health with its high mortality.

In Japan, Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 μg/mL "Kitasato Daiichi Sankyo" (hereinafter referred to as the "H5N1 Vaccine") was approved for the indication of "the prevention of pandemic influenza (H5N1)" in March 2014. The H5N1 Vaccine is a cell culture-derived influenza vaccine containing inactivated influenza virus (H5N1 strain) as the active ingredient. It is prepared from an attenuated influenza virus strain (produced by reverse genetics) that is harvested from infected cultured cells and is inactivated with beta-propiolactone. Aluminum hydroxide gel is added as an adjuvant.

A novel influenza (H5N1) pandemic is presumed to have a serious outcome because of the high pathogenicity of the H5N1 virus subtype. In this prospect, the H5N1 Vaccine should also be administered to pediatric populations. For the application for the initial marketing approval for the H5N1 Vaccine, however, no clinical studies were conducted in children and adolescents (the pediatric population) aged <20 years, and the dosing regimen for the pediatric population was thus decided based on data from clinical studies in adults. Recently, clinical studies were conducted in Japanese children and adolescents to determine appropriate dosing regimens for this population, and the application for partial change was filed for additional dosing regimens for the pediatric population.

The H5N1 Vaccine was designated as an orphan drug on December 11, 2012 with the intended indication of "the prevention of pandemic influenza" (Drug Designation No. 296 of 2012 [*24 yaku*]).

2. Clinical data

2.A Summary of the submitted data

Data from 2 Japanese clinical studies were submitted as evaluation data on efficacy and safety. A summary of the evaluation data is shown in Table 1. Investigational vaccine produced from the A/Indonesia/5/2005 (H5N1) strain attenuated by reverse genetics was used in both studies.

Table 1. Summary of clinical studies

Phase	Study	Design	Subjects	Number of subjects	Vaccination route/dose	Vaccination schedule	Objectives
II	KIBPCI-A-J201	Open-label, uncontrolled	Healthy children and adolescents aged 7 to <20 years	7 to <13 years: 15 subjects 13 to <20 years: 15 subjects	Intramuscular, 7 to <13 years: 0.1 mL (3 µg HA) 13 to <20 years: 0.25 mL (7.5 µg HA)	2 doses at an interval of 21 ± 7 days	Safety and immunogenicity
II/III	KIBPCI-A-J303	Open-label, uncontrolled	Healthy children and adolescents aged 6 months to <20 years	(6 months to <13 years) 3 µg HA: 63 subjects 7.5 µg HA: 63 subjects (13 to <20 years) 15 µg HA: 58 subjects	Intramuscular, 3 µg HA: 0.1 mL 7.5 µg HA: 0.25 mL 15 µg HA: 0.5 mL	2 doses at an interval of 21 ± 7 days	Immunogenicity and safety

2.A.(1) Japanese phase II clinical study (5.3.5.2-1, Study KIBPCI-A-J201 [[redacted] to [redacted]])

An open-label uncontrolled study was conducted in healthy children and adolescents aged 7 to <20 years (target sample size, 15 subjects each in a group of subjects aged 7 to <13 years [the 7- to 12-year age group] and a group of subjects aged 13 to <20 years [the 13- to 19-year age group]) at 1 center in Japan to evaluate the safety and immunogenicity of the H5N1 Vaccine.

The H5N1 Vaccine was administered intramuscularly twice at an interval of 21 ± 7 days at 0.1 mL (3 µg HA) in the 7- to 12-year age group and 0.25 mL (7.5 µg HA) in the 13- to 19-year age group.

A total of 30 subjects (15 in each group) was enrolled in the study and all of them were included in the safety analysis set and the full analysis set (FAS). The FAS was used for the primary analysis of immunogenicity.

To evaluate immunogenicity, antibody responses prior to the first vaccination, 21 days after the first vaccination, and 21 days after the second vaccination were determined by single radial hemolysis (SRH), hemagglutination inhibition (HI), and neutralization assays.

The primary endpoints were seroconversion rate (by SRH), geometric mean titer (GMT) fold-change (SRH), and seroprotection rate (by SRH). In addition, whether the immunogenicity evaluation criteria defined in the "Guideline on the Development of Prototype Vaccine against Pandemic Influenza" (Notification No. 1031-1, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated October 31, 2011; hereinafter referred to as the "prototype GL criteria") were met was assessed as a reference. The definitions of the primary endpoints and the prototype GL criteria are shown in Table 2.

Table 2. Definitions of the primary endpoints and the prototype GL criteria

Primary endpoints	Definition	Prototype GL criteria
Seroconversion rate (by SRH)	Percentage of subjects with "an SRH area of ≤4 mm^2 before the vaccination with the investigational vaccine and with that of ≥25 mm^2 after the vaccination with the investigational vaccine" or subjects with "an SRH area of >4 mm^2 before the vaccination with the investigational vaccine and a 50% increase in area after the vaccination with the investigational vaccine"	>40%
GMT fold-change (SRH)	Fold-increase from pre- to post-vaccination in geometric mean titer based on the SRH results	>2.5
Seroprotection rate (by SRH)	Percentage of subjects with an SRH area of >25 mm^2 after the vaccination with the investigational vaccine	>70%

After the second vaccination, the 3 prototype GL criteria were met in the 7- to 12-year age group, and 2 criteria, namely, seroprotection rate (by SRH) and GMT fold-change (SRH), were met in the 13- to 19-year age group.

Table 3. Seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH) after the first and second vaccination (FAS)

	Group	Antigen level	Seroconversion rate (by SRH)		GMT fold-change (SRH)	Seroprotection rate (by SRH)	
			n	(%) [95% CI]	Value [95% CI]	n	(%) [95% CI]
Post first vaccination	7-12 years of age (N = 15)	3 μg HA	2	13.33 [1.66, 40.46]	1.398 [0.907, 2.154]	2	13.33 [1.66, 40.46]
	13-19 years of age (N = 15)	7.5 μg HA	1	6.67 [0.17, 31.95]	1.179 [0.739, 1.881]	1	6.67 [0.17, 31.95]
Post second vaccination	7-12 years of age (N = 15)	3 μg HA	12	80.00 [51.91, 95.67]	5.356 [3.456, 8.301]	12	80.00 [51.91, 95.67]
	13-19 years of age (N = 15)	7.5 μg HA	7	46.67 [21.27, 73.41]	3.333 [1.941, 5.724]	7	46.67 [21.27, 73.41]

N, number of subjects analyzed; n, number of subjects meeting the criteria in Table 2.
Shaded values meet the prototype GL criterion.

The safety analysis revealed that the incidences of adverse events during the period between the day of the first vaccination and the 21st day after the second vaccination ("observation period") were 73.3% (11 of 15 subjects) in the 7- to 12-year age group and 86.7% (13 of 15 subjects) in the 13- to 19-year age group. These adverse events include adverse reactions, which were reported in 10 of 15 subjects (66.7%) in the 7- to 12-year age group and 10 of 15 subjects (66.7%) in the 13- to 19-year age group. Table 4 shows the solicited adverse events (injection site erythema, injection site swelling, injection site induration, injection site pain, injection site warmth, injection site pruritus, malaise, pyrexia, and headache) and adverse reactions occurring during the observation period. Unsolicited adverse events and/or adverse reactions occurring in ≥2 subjects in either group were laboratory test abnormal only (Table 5).

Table 4. Solicited adverse events and adverse reactions (safety analysis set)

	7-12 years of age (N = 15)				13-19 years of age (N = 15)			
	Adverse events		Adverse reactions		Adverse events		Adverse reactions	
	n	%	n	%	n	%	n	%
Injection site pain	5	33.3	5	33.3	8	53.3	8	53.3
Injection site induration	3	20.0	3	20.0	0	0	0	0
Injection site warmth	2	13.3	2	13.3	1	6.7	1	6.7
Injection site erythema	2	13.3	2	13.3	0	0	0	0
Malaise	1	6.7	1	6.7	3	20.0	2	13.3
Injection site swelling	1	6.7	1	6.7	1	6.7	1	6.7
Pyrexia [a)]	1	6.7	1	6.7	0	0	0	0
Headache	0	0	0	0	2	13.3	2	13.3
Injection site pruritus	0	0	0	0	0	0	0	0

N, number of subjects analyzed; n, number of subjects with an adverse event/adverse reaction
[a)] Defined as fever of ≥37.5°C

Table 5. Unsolicited adverse events and/or adverse reactions occurring in ≥2 subjects in either group (safety analysis set)

		7-12 years of age(N = 15)				13-19 years of age (N = 15)			
		Adverse events		Adverse reactions		Adverse events		Adverse reactions	
		n	%	n	%	n	%	n	%
Laboratory test	Aspartate aminotransferase increased	2	13.3	2	13.3	2	13.3	2	13.3
	Protein urine present	2	13.3	0	0	2	13.3	0	0
	Alanine aminotransferase increased	1	6.7	1	6.7	2	13.3	2	13.3

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

No serious adverse events, adverse events leading to the discontinuation of the study, or deaths occurred during the observation period in either group.

2.A.(2) Japanese phase II/III clinical study (5.3.5.1-1, Study KIBPCI-A-J303 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, open-label, uncontrolled study was conducted in healthy children and adolescents aged 6 months to <20 years (target sample size, 50 subjects each in the 3 μg HA group [6 months to 12 years of age], 7.5 μg HA group [6 months to 12 years of age], and 15 μg HA group [13-19 years of age]) at 10 centers in Japan to evaluate the immunogenicity and safety of the H5N1 Vaccine.

The H5N1 Vaccine was administered intramuscularly twice at an interval of 21 ± 7 days at 0.1 mL in the 3 μg HA group, 0.25 mL in the 7.5 μg HA group, and 0.5 mL in the 15 μg HA group.

A total of 184 subjects (63 in the 3 μg HA group, 63 in the 7.5 μg HA group, and 58 in the 15 μg HA group) were enrolled and all of them were included in the safety analysis set and the FAS. The FAS was used for the primary analysis of immunogenicity. Non-compliance with the dosing regimen of the investigational vaccine was identified in 1 subject in the 3 μg HA group (the vaccine was injected subcutaneously in the left upper arm instead of intramuscularly in the right upper arm) [see "III.2. PMDA's conclusion on the results of GCP on-site inspection"]. However, the non-compliance did not meet the exclusion criteria for the FAS (a subject who received no dose of the investigational vaccine), and the subject was not excluded from the FAS.

Antibody responses prior to the first vaccination, 21 days after the first vaccination, and 21 days after the second vaccination were determined by SRH and neutralization assays to evaluate immunogenicity.

The primary endpoints were seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH), and the fulfillment of the prototype GL criteria was assessed. The 3 prototype GL criteria were met after the second vaccination in all groups (Table 6).

Table 6. Seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH) after the first and second vaccination (FAS)

	Group	Age at vaccination	Seroconversion rate (by SRH)		GMT fold-change (SRH)	Seroprotection rate (by SRH)	
			n	(%) [95% CI]	value [95% CI]	n	(%) [95% CI]
Post first vaccination	3 µg HA (N = 63)	6 months to 12 years	4	6.35 [1.76, 15.47]	1.500 [1.270, 1.771]	3	4.76 [0.99, 13.29]
	7.5 µg HA(N = 63)		14	22.22 [12.72, 34.46]	2.126 [1.705, 2.651]	11	17.46 [9.05, 29.10]
	15 µg HA (N = 58)	13-19 years	12	20.69 [11.17, 33.35]	1.916 [1.505, 2.439]	11	18.97 [9.87, 31.41]
Post second vaccination	3 µg HA (N = 63)	6 months to 12 years	46	73.02 [60.35, 83.43]	7.288 [5.838, 9.098]	47	74.60 [62.06, 84.73]
	7.5 µg HA(N = 63)		59	93.65 [84.53, 98.24]	11.699 [10.206, 13.411]	58	92.06 [82.44, 97.37]
	15 µg HA (N = 57)	13-19 years	45	78.95 [66.11, 88.62]	9.375 [7.415, 11.852]	44	77.19 [64.16, 87.26]

N, number of analyzed subjects with measurements; n, number of subjects meeting the criteria in Table 2.
Shaded values meet the prototype GL criterion.

The safety analysis revealed that the incidences of adverse events during the observation period were 73.0% (46 of 63 subjects) in the 3 µg HA group, 82.5% (52 of 63 subjects) in the 7.5 µg HA group, and 84.5% (49 of 58 subjects) in the 15 µg HA group. These adverse events include adverse reactions, which were reported in 36 of 63 subjects (57.1%) in the 3 µg HA group, 42 of 63 subjects (66.7%) in the 7.5 µg HA group, and 46 of 58 subjects (79.3%) in the 15 µg HA group. Table 7 shows the solicited adverse events (injection site erythema, injection site induration, injection site pain, injection site pruritus, injection site warmth, injection site swelling, malaise, and pyrexia) and adverse reactions occurring during the observation period. Table 8 shows unsolicited adverse events and adverse reactions occurring at an incidence of ≥5% in any group during the observation period.

Table 7. Solicited adverse events and adverse reactions (safety analysis set)

	6 months to 12 years of age								13-19 years of age			
	3 µg HA (N = 63)				7.5 µg HA (N = 63)				15 µg HA (N = 58)			
	Adverse events		Adverse reactions		Adverse events		Adverse reactions		Adverse events		Adverse reactions	
	n	%	n	%	n	%	n	%	n	%	n	%
Injection site pain	23	36.5	23	36.5	32	50.8	32	50.8	42	72.4	42	72.4
Injection site erythema	12	19.0	12	19.0	14	22.2	14	22.2	9	15.5	9	15.5
Injection site swelling	11	17.5	11	17.5	9	14.3	9	14.3	10	17.2	10	17.2
Injection site induration	9	14.3	9	14.3	9	14.3	9	14.3	6	10.3	6	10.3
Pyrexia [a)]	8	12.7	6	9.5	7	11.1	6	9.5	5	8.6	5	8.6
Injection site warmth	6	9.5	6	9.5	7	11.1	7	11.1	10	17.2	10	17.2
Malaise	5	7.9	4	6.3	3	4.8	2	3.2	12	20.7	12	20.7
Injection site pruritus	3	4.8	3	4.8	5	7.9	5	7.9	3	5.2	3	5.2

N, number of subjects analyzed; n, number of subjects with an adverse event/adverse reaction
[a)] ≥37.5°C

Table 8. Unsolicited adverse events and adverse reactions occurring at an incidence of ≥5% in any group (safety analysis set)

		6 months to 12 years of age								3-19 years of age			
		3 μg HA (N = 63)				7.5 μg HA (N = 63)				15 μg HA (N = 58)			
		Adverse events		Adverse reactions		Adverse events		Adverse reactions		Adverse events		Adverse reactions	
		n	%	n	%	n	%	n	%	n	%	n	%
Systemic	Upper respiratory tract inflammation	7	11.1	0	0	6	9.5	0	0	0	0	0	0
	Nasopharyngitis	5	7.9	0	0	6	9.5	0	0	5	8.6	0	0
	Rhinorrhoea	5	7.9	0	0	2	3.2	0	0	0	0	0	0
	Abdominal pain	0	0	0	0	1	1.6	0	0	3	5.2	2	3.4

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

No serious adverse events, adverse events leading to the discontinuation of study, or deaths occurred in any of the groups during the observation period.

2.B Outline of the review by PMDA

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

The applicant's explanation on the structure of clinical data package for the partial change application:
Two clinical studies listed in Table 1 (a Japanese phase II clinical study [Study J201] and a Japanese phase II/III clinical study [Study J303]) were conducted in the Japanese pediatric population to seek approval for an additional pediatric dosing regimen of the H5N1 Vaccine.

In a pediatric clinical study of Adsorbed Egg Culture-derived H5N1 Influenza Vaccine "Kitasato Daiichi Sankyo" (hereinafter referred to as the "egg culture-derived vaccine"), a similar egg culture-derived influenza vaccine, pyrexia was observed frequently in subjects aged <7 years. On the ground of the results, Study J201 was conducted in a small number of children aged ≥7 years to evaluate the tolerability and immunogenicity of the H5N1 Vaccine [see "2.B.(4) Dosage and administration"]. Based on the data on vaccination with the H5N1 Vaccine at 3 μg HA in children aged 7 to 12 years in Study J201, Study J303 was designed to cover the pediatric population aged ≥6 months to evaluate the immunogenicity and tolerability of the H5N1 Vaccine following vaccination at 3 μg HA or 7.5 μg HA in children aged 6 months to 12 years. In addition, based on the data on vaccination with the H5N1 Vaccine at 7.5 μg HA in pediatric subjects aged 13 to 19 years in Study J201, the immunogenicity and tolerability of the H5N1 Vaccine at 15 μg HA in pediatric subjects aged 13 to 19 years were evaluated in Study J303. In principle, the prototype GL requires the 3 prototype GL criteria to be met in a study population with groups of ≥50 subjects. Accordingly, immunogenicity was evaluated in a study population consisting of groups of ≥50 subjects.

In accordance with the prototype GL, therefore, the proposed pediatric dosing regimen was determined on the basis of data from Study J303.

PMDA accepted the applicant's explanation on the clinical data package and reviewed mainly data from Study J303 for the additional pediatric dosing regimen of the H5N1 Vaccine.

2.B.(2) Efficacy

2.B.(2).1) Primary endpoints

The applicant's rationale for the use of seroconversion rate (by SRH), GMT fold-change rate (SRH), and seroprotection rate (by SRH) as the primary endpoints of Study J303 (Table 2):

At present, although there are no guidelines stipulating criteria for evaluation of the immunogenicity of novel influenza (H5N1) vaccines in Japan, the prototype GL has been published as guidelines for prototype vaccines produced from novel influenza virus strains that are not currently circulating in humans. The applicant considered that the prototype GL criteria (Table 2) would be applicable to the H5N1 Vaccine, a vaccine against novel influenza (H5N1) virus. The prototype GL requires that vaccine immunogenicity be assessed on the basis of antibody titers determined by HI or SRH assay, and the antibody titers are correlated with the prophylactic effects of existing seasonal influenza HA vaccines, and that all 3 endpoints, namely, seroconversion rate, GMT fold-change, and seroprotection rate, meet the prototype GL criteria in groups of ≥50 subjects in principle. The prototype GL also states that the prototype GL criteria are applicable to the pediatric population aged <20 years.

Thus, the immunogenicity endpoints based on antibody titers determined by the SRH assay, namely, seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH), were used as the primary endpoints of Study J303 to assess whether the prototype GL criteria were met.

PMDA accepted the applicant's explanation and concluded that the use of seroconversion rate (by SRH), GMT fold-change (by SRH), and seroprotection rate (by SRH) as the primary endpoints of Study J303 was acceptable.

2.B.(2).2) Efficacy of the product in pediatrics

The applicant's explanation on immunogenicity of the H5N1 Vaccine in pediatrics:
In Study J303, the prototype GL criteria for seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH) were all met after the second vaccination in all of the 3 and 7.5 μg HA groups of subjects aged 6 months to 12 years and the 15 μg HA group of subjects aged 13 to 19 years (Table 6).

The results showed the efficacy of the H5N1 Vaccine in the prevention of pandemic influenza (H5N1) infection in children aged 6 months to 12 years at one-tenth to one-quarter the adult dose (adult dose, 2 doses of 30 μg HA each) and adolescents aged 13 to 19 years at one-half the adult dose.

PMDA accepted the applicant's explanation and concluded that the proposed doses of the H5N1 Vaccine are expected to prevent influenza infection in the pediatric population.

2.B.(3) Safety

The applicant's explanation on the safety of the H5N1 Vaccine in clinical studies in pediatrics:
The adverse events reported in Studies J201 and J303 (Tables 4, 5, 7, and 8) were observed also in clinical studies of the H5N1 Vaccine in adults (*Review Report on Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 μg/mL "Kitasato Daiichi Sankyo," Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 60 μg/mL "Kitasato Daiichi Sankyo," dated February 7, 2014*) (in Japanese only) and following the use of the egg culture-derived vaccine and seasonal influenza HA vaccines approved in Japan. In Studies J201 and J303, no deaths or serious adverse events occurred in any age or dose groups.

Severe adverse events reported in Studies J201 and J303 are shown in Table 9. Pyrexia and urticaria (1 subject each) in the age group of 6 months to 12 years resolved with medication, and the other events resolved without any treatment.

Table 9. Severe[a)] adverse events reported in Studies J201 and J303

Age group	Event	Study	Antigen level	Time to onset of an adverse event from the last vaccination with the investigational vaccine	Duration of an adverse event	Causal relationship with the investigational vaccine	Treatment	Outcome
6 months to 12 years	Pyrexia	J303	3 μg HA	1 day	3 days	Related	None	Recovered/resolved
	Pyrexia	J303	3 μg HA	17 days	3 days	Unrelated	Medication	Recovered/resolved
	Injection site erythema	J303	7.5 μg HA	0 day	5 days	Related	None	Recovered/resolved
	Injection site swelling	J303	7.5 μg HA	0 day	5 days	Related	None	Recovered/resolved
	Injection site induration	J303	7.5 μg HA	0 day	22 days	Related	None	Recovered/resolved
	Urticaria	J303	7.5 μg HA	9 days	5 days	Unrelated	Medication	Recovered/resolved
13-19 years	Injection site swelling	J201	7.5 μg HA	0 day	3 days	Related	None	Recovered/resolved
	Injection site swelling	J303	15 μg HA	1 day	6 days	Related	None	Recovered/resolved
	Injection site induration	J303	15 μg HA	1 day	6 days	Related	None	Recovered/resolved

[a)] Pyrexia, ≥39.0°C; injection site erythema/ injection site swelling/ injection site induration, >5.0 cm in diameter; urticarial, requiring treatment for ≥2 days

Based on the above, the safety of the H5N1 Vaccine in the pediatric population is considered acceptable.

PMDA accepted the applicant's explanation and concluded that the safety of the H5N1 Vaccine in the pediatric population is acceptable.

2.B.(4) Dosage and administration

The applicant's explanation about the proposed pediatric dosing regimen is presented in the sections below.

2.B.(4).1) Dosage and administration in persons aged 6 months to <13 years

In the pediatric clinical study of the similar egg culture-derived vaccine (Study KIB-PIA03, funded by the Health and Labour Sciences Research Grants [Large Scale Clinical Trial Network Project, Clinical

Trial on Development of New Drugs and Medical Devices], "*Adsorbed inactivated influenza vaccine (H5N1 strain),*" FY 2009 General Research Report, 2010), pyrexia was reported frequently, especially in subjects aged <7 years: the incidence of pyrexia (temperature ≥ 37.5°C) was 65.3% (62 of 95 subjects) in subjects aged 6 months to 6 years and 29.3% (27 of 92 subjects) in subjects aged 7 to 19 years. Because of pyrexia reported frequently in this age group, Study J201 was conducted to evaluate the tolerability of the H5N1 Vaccine in subjects aged ≥7 years. In Study J201, pyrexia (temperature ≥ 37.5°C) occurred in 1 of 15 subjects (6.7%) aged 7 to 12 years and no subjects aged 13 to 19 years (Table 4), and no pyrexia (temperature ≥ 39°C) occurred (Table 9). There were no adverse events of concern. In light of the study results, Study J303 was conducted in subjects aged 6 months to 19 years, which was designed to include children aged <7 years.

In Study J201, the 3 prototype GL criteria were met after the second vaccination at 3 μg HA in 15 subjects aged 7 to 12 years (Table 3), and the tolerability of the H5N1 Vaccine at the dose was confirmed. However, of 12 subjects who achieved the seroconversion (by SRH) after receiving the H5N1 Vaccine at 3 μg HA, 6 showed SRH zone areas (i.e., antibody titer) of 25 to 30 mm^2, which are close to the seroconversion criterion (the zone area of "25 mm^2"). Therefore, Study J303 evaluated 7.5 μg HA in addition to 3 μg HA. In Study J303, the prototype GL criteria were all met for all the endpoints of seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH) after the second vaccination in the 3 μg HA and 7.5 μg HA groups of subjects aged 6 months to 12 years. All the values were higher in the 7.5 μg HA group than in the 3 μg HA group (Table 6). The safety analysis revealed that severe injection site erythema, injection site swelling, injection site induration, and urticaria occurred in 1 subject each in the 7.5 μg HA group and severe pyrexia occurred in 2 subjects in the 3 μg HA group (Table 9). All the events resolved, suggesting that 3 μg HA and 7.5 μg HA are both tolerable.

Based on the above results, the 7.5 μg of the HA antigen is expected to induce higher immunity and has been demonstrated to be tolerable in children aged 6 months to <13 years. The appropriate vaccination regimen of the H5N1 Vaccine for this population thus consists of 2 single doses of 0.25 mL each, equivalent to 7.5 μg HA (antigen content).

2.B.(4).2) Dosage and administration in persons aged 13 to <20 years

In Study J201, the seroprotection rate (by SRH) after the second dose of 7.5 μg HA was 46.67% in 15 subjects aged 13 to 19 years (Table 3), which was below the prototype GL criterion of "70%" (Table 2). Because of the results suggesting the need of evaluation at a higher dose, 15 μg HA was evaluated in Study J303. In the 15 μg HA group in Study J303, the prototype GL criteria were met for all endpoints, of seroconversion rate (by SRH), GMT fold-change (SRH), and seroprotection rate (by SRH) after the second vaccination (Table 6). The safety analysis revealed that, in the 15 μg HA group, severe injection site swelling and injection site induration occurred in 1 subject each (Table 9), but both events resolved, suggesting the acceptable safety of the H5N1 Vaccine at the dose.

The above results showed that the H5N1 Vaccine containing 15 µg HA met the prototype GL criteria and demonstrated its tolerability in adolescents aged 13 to <20 years. The appropriate regimen of the H5N1 Vaccine for this population thus consists of 2 single doses of 0.5 mL each, equivalent to 15 µg of HA antigen content.

PMDA's view:

1) The proposed regimen for children aged 6 months to <13 years

In Study J303, the 3 prototype GL criteria were met after the second vaccination in both the 3 µg HA and 7.5 µg HA groups, and the tolerability of the H5N1 Vaccine was demonstrated. Therefore, the dose of 0.25 mL (equivalent to 7.5 µg of HA antigen) proposed by the applicant is acceptable. Meanwhile, the dose of 0.1 mL (equivalent to 3 µg of HA antigen) is also deemed appropriate, given lower doses generally result in less frequent adverse events such as local reaction and are considered safer. The H5N1 Vaccine is intended to prevent novel influenza (H5N1) infection, and whether to select 0.1 or 0.25 mL may depend on the mortality, seriousness, or other relevant factors of novel influenza (H5N1) that actually emerges. Therefore, PMDA concluded that both 0.1 and 0.25 mL should be recommended for children aged 6 months to <13 years.

2) The proposed regimen for adolescents aged 13 to <20 years

PMDA accepted the applicant's explanation.

Based on the above, PMDA concluded that the "Dosage and Administration" section of the package insert should state as follows:

[Dosage and administration]

The usual dosage is 2 doses of <u>0.1 or 0.25 mL each for persons aged 6 months to <13 years, 0.5 mL each for persons aged 13 to <20 years, and</u> 1 mL each <u>for persons aged ≥20 years,</u> injected intramuscularly at an interval of ≥2 weeks.

(Underline denotes additions.)

2.B.(5) Post-marketing investigations

The applicant has a plan for a drug use-results survey (target sample size of 3000 vaccine recipients) to evaluate the safety of the H5N1 Vaccine in a pandemic in accordance with the prototype GL (the *Review Report on Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 µg/mL "Kitasato Daiichi Sankyo," Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 60 µg/mL "Kitasato Daiichi Sankyo," dated February 7, 2014*) (in Japanese only). The target population of the survey is those vaccinated with the H5N1 Vaccine in line with the National Action Plan for Pandemic Influenza and New Infectious Diseases (http://www.cas.go.jp/jp/seisaku/ful/keikaku.html). This includes children and adolescent aged 6 months to <20 years vaccinated with the H5N1 Vaccine.

PMDA concluded that no new drug use-results survey needs to be conducted because pediatric safety information will be available from the planned drug use-results survey.

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

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

Document-based compliance inspection and data integrity assessment were conducted for the data submitted in the application in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no problems, PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection took place for the data submitted in the application (5.3.5.1-1) in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that clinical studies were conducted in compliance with GCP as a whole and that there should be no problem with conducting a regulatory review based on the submitted application documents. The inspection revealed the following finding at 1 site; it did not affect the evaluation of the entire study significantly but was notified to the head of the medical institution (study site) as a matter to be corrected.

Finding requiring corrective action

At a study site

- Protocol deviation (non-compliance with dosing regimen for the investigational vaccine)

IV. Overall Evaluation

As described in "II.2.B.(2) Efficacy" and "II.2.B.(3) Safety," PMDA concluded that the product is expected to have efficacy for the proposed indication in the pediatric population and its safety is acceptable. Based on this conclusion, PMDA considers that the application may be approved if the product is not considered to have any particular problem based on comments from the Expert Discussion.

Review Report (2)

February 5, 2016

I. Product Submitted for Registration

[Brand name]	Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30 μg/mL "Kitasato Daiichi Sankyo"
[Non-proprietary name]	Adsorbed cell culture-derived influenza vaccine (H5N1)
[Applicant]	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
[Date of application]	August 28, 2015

II. Content of the Review

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

(1) Efficacy

In Study J303, efficacy was evaluated based on the 3 immunogenicity criteria defined in the "Guideline on the Development of Prototype Vaccine against Pandemic Influenza" (Notification No. 1031-1, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated October 31, 2011) ("prototype GL") (Table 2 of the Review Report [1]). The 3 immunogenicity criteria were met in all treatment groups, the 3 and 7.5 μg HA groups of subjects aged 6 months to 12 years and the 15 μg HA group of subjects aged 13 to 19 years (Table 6 of the Review Report [1]). Based on the results, PMDA concluded that the H5N1 Vaccine is expected to have efficacy in preventing novel influenza (H5N1) infection after 2 doses of 3 μg HA (0.1 mL) or 7.5 μg HA (0.25 mL) each for persons aged 6 months to 12 years and 15 μg HA (0.5mL) each for persons aged 13 to 19 years. The conclusion by PMDA was supported by the expert advisors.

(2) Safety

PMDA concluded that the safety of the H5N1 Vaccine in children is acceptable, based on the submitted clinical study data showing that all severe adverse events reported in the clinical studies resolved and no deaths or serious adverse events occurred. The conclusion by PMDA was supported by the expert advisors.

(3) Dosage and administration

In Study J303 showed that all of the 3 prototype GL criteria were met in subjects aged 6 months to 12 years receiving the second dose in both 3 μg HA (0.1 mL) and 7.5 μg HA (0.25 mL) groups,

demonstrating the H5N1 Vaccine is tolerable. PMDA concluded that both 0.1 and 0.25 mL doses of the H5N1 Vaccine should be recommended for children aged 6 months to <13 years. The H5N1 Vaccine is intended for the prevention of pandemic influenza (H5N1) infection and, therefore, the choice of the 0.1 or 0.25 mL dose may depend on mortality, seriousness, etc. of an actual novel influenza (H5N1) outbreak. PMDA also concluded that a vaccination regimen consisting of 2 doses of the H5N1 Vaccine 0.5 mL each, equivalent to 15 µg of HA antigen, is appropriate for persons aged 13 to <20 years, because the H5N1 Vaccine at 15 µg HA has been proven to meet the 3 prototype GL criteria and be tolerable in this population. These conclusions by PMDA were supported by the expert advisors.

Accordingly, PMDA concluded that the Dosage and Administration of the H5N1 Vaccine should be stated in the package insert as follows. The conclusion by PMDA was supported by the expert advisors.

[Dosage and administration]
The usual dosage is 2 doses of 0.1 or 0.25 mL each for persons aged 6 months to <13 years, 0.5 mL each for persons aged 13 to <20 years, and 1 mL each for persons aged ≥20 years, injected intramuscularly at an interval of ≥2 weeks.

(Underline denotes additions.)

The H5N1 Vaccine must be administered by intramuscular injection, not by subcutaneous injection. The expert advisors commented that this precautionary advice should be given to healthcare professionals in an appropriate manner. PMDA instructed the applicant to ensure that healthcare professionals are informed of the correct route of administration, and the applicant agreed to respond to the instruction accordingly.

(4) Risk management plan (draft)
The initial marketing approval for the H5N1 Vaccine included a drug use-results survey (target sample size, 3000 subjects) planned based on the prototype GL for the evaluation of the safety of the product in a pandemic. The target population of the survey is those who are vaccinated with the H5N1 Vaccine in line with the National Action Plan for Pandemic Influenza and New Infectious Diseases (http://www.cas.go.jp/jp/seisaku/ful/keikaku.html). The survey will include children and adolescents aged 6 months to <20 years receiving the H5N1 Vaccine. Considering that pediatric safety data would be collected from the survey, PMDA concluded that no additional survey is needed. The conclusion by PMDA was supported by the expert advisors.

PMDA also concluded that the safety and efficacy specifications shown in Table 1 should be included in the current risk management plan (draft) and that additional pharmacovigilance and risk minimization activities shown in Table 2 should be implemented in the risk management plan.

Table 1. Safety and efficacy specification in the risk management plan (draft)

Safety Specification		
Important identified risks	Important potential risks	Important missing information
None	・ Shock, anaphylaxis ・ Acute disseminated encephalomyelitis (ADEM) ・ Guillain-Barre syndrome ・ Convulsion ・ Hepatic function disorder, jaundice ・ Asthmatic attack ・ Thrombocytopenic purpura, platelets decreased ・ Vasculitis (Allergic purpura, allergic granulomatous angiitis, leukocytoclastic vasculitis, etc.) ・ Interstitial pneumonia ・ Encephalitis/encephalopathy, myelitis, optic neuritis ・ Oculomucocutaneous syndrome (Stevens-Johnson syndrome) ・ Nephrotic syndrome ・ Facial palsy	・ Safety in the elderly ・ Safety in pregnant women, women in labor, and lactating women ・ Safety in specific populations in which the H5N1 Vaccine should be used with caution
Efficacy specification		
・ Immunogenicity in the elderly		

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

Additional pharmacovigilance activities	Additional risk minimization activities
・ Early post-marketing phase vigilance ・ Drug use-results survey (see Table 3) ・ Post-marketing clinical study in the elderly	・ Early post-marketing phase vigilance

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

Objective	To confirm the safety of the H5N1 Vaccine in a pandemic caused by an influenza A virus of subtype H5N1.
Survey method	To be determined depending on the vaccination program for the pandemic caused by an influenza A virus of subtype H5N.
Target population	Individuals vaccinated with the H5N1 Vaccine (in line with the National Action Plan for Pandemic Influenza and New Infectious Diseases)
Observation period	Up to 14 days after each vaccination dose
Target sample size	3000 vaccine recipients
Main investigation items	Injection site reactions (pain, erythema, feeling hot, swelling, induration, and pruritus) and systemic reactions (headache, malaise, and pyrexia)

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved, with the following conditions, after modifying the dosage and administration statements as shown below. The re-examination period for this application is the remainder of the re-examination period for the initial approval of the product (until March 23, 2024).

[Indication] Prevention of pandemic influenza (H5N1)

(No change)

[Dosage and administration] The usual dosage is 2 doses of 0.1 or 0.25 mL each for persons aged 6 months to <13 years, 0.5 mL each for persons aged 13 to <20 years, and 1 mL each for persons aged ≥20 years, injected intramuscularly at an interval of ≥2 weeks.

[Conditions for approval] The applicant is required to develop and appropriately implement a risk management plan.