Report on the Deliberation Results

September 4, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Allergen Scratch Extract Positive control “TORII” Histamine Dihydrochloride
[Non-proprietary name]	Histamine dihydrochloride
[Applicant]	Japan Tobacco Inc.
[Date of application]	December 22, 2014

[Results of deliberation]
In the meeting held on August 31, 2015, the Second Committee on New Drugs concluded that the product may be approved with the following conditions and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years. The drug substance is classified as a poisonous drug. The drug product is not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

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

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Report

August 20, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Allergen Scratch Extract Positive control “TORII” Histamine Dihydrochloride
[Non-proprietary name]	Histamine dihydrochloride
[Applicant]	Japan Tobacco Inc.
[Date of application]	December 22, 2014
[Dosage form/Strength]	A solution containing 20 mg of histamine dihydrochloride per vial (2 mL)
[Application classification]	Prescription drug, (4) Drug with a new indication / (6) Drug with a new dosage / (8-2) Drug with an additional dosage form (not under re-examination)
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

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Review Results

August 20, 2015

[Brand name]	Allergen Scratch Extract Positive control “TORII” Histamine Dihydrochloride
[Non-proprietary name]	Histamine dihydrochloride
[Applicant]	Japan Tobacco Inc.
[Date of application]	December 22, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product as a positive control for evaluating skin reactions to allergens has been demonstrated and its safety is acceptable in view of its observed benefits.

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

[Indication]	Diagnostic use Positive control to evaluate skin reactions to allergens
[Dosage and administration]	Diagnostic use The product is used as a positive control for allergen screening. The surface of the skin is pricked (prick method) or scratched (scratch method) without drawing blood, and a drop of the product is applied to the site of the prick or scratch.

Review Report (1)

June 23, 2015

I. Product Submitted for Registration

[Brand name]	Scratch Histamine Dihydrochloride Positive control "TORII" (name proposed in the application)
[Non-proprietary name]	Histamine dihydrochloride
[Applicant]	Japan Tobacco Inc.
[Date of application]	December 22, 2014
[Dosage form/Strength]	A solution containing 20 mg of histamine dihydrochloride per vial (2 mL)
[Proposed indication]	Diagnostic use Positive control to evaluate skin reaction for a diagnosis of allergy
[Proposed dosage and administration]	Diagnostic use The product is used as a positive control for allergen screening. The surface of the skin is pricked (prick method) or scratched (scratch method) without drawing blood, and a drop of the product is applied to the site of the prick or scratch.

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.

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

Scratch Histamine Dihydrochloride Positive control "TORII" (hereinafter, the product) is a positive control used in skin allergy testing (skin-prick or skin-scratch test) to identify the allergen, containing histamine dihydrochloride as the active ingredient. The product was developed by ALK-Abelló A/S (Denmark) and has been approved in 18 countries, including some European countries and China as of 2014, since its first approval in Switzerland in 1985. In Japan, the Latex Allergy Safety-Measures Guideline 2013 (the Editorial Committee for the Latex Allergy Safety-Measures Guideline, the Japanese Society of Latex Allergy, Kyowa Kikaku, 2013) (hereinafter referred to as the Latex Allergy Guidelines) and the Japanese Pediatric Guideline for Food Allergy 2012 (Food Allergy Committee of Japanese Society of Pediatric Allergy and Clinical Immunology, Kyowa Kikaku, 2011) (hereinafter referred to as the Food Allergy Guidelines) recommend the use of histamine dihydrochloride solution as a positive control for skin allergy testing. In clinical practice, the solution is prepared for use from the reagent by individual healthcare practitioners, and there are problems such as the complicated process for preparing the solution, variability in skin reaction due to different preparation methods, and instability of the solution. In light of the current situation, the Japanese Society of Allergology and the Japanese Society of Pediatric Allergy and Clinical Immunology submitted a request to the Ministry of Health, Labour and Welfare (MHLW) to make this medically necessary diagnostic product available. In response to this

request, MHLW issued a notification to recruit a company to develop histamine dihydrochloride as a positive control for skin allergy testing in adults and children (Joint HPB/RDD Notification No. 0406-2 and PFSB/ELD Notification No. 0406-2, dated April 6, 2012, by the Director of Research and Development Division [RDD], Health Policy Bureau [HPB], and the Director of Evaluation and Licensing Division [ELD], Pharmaceutical and Food Safety Bureau [PFSB], MHLW). Japan Tobacco Inc. and Torii Pharmaceutical Co., Ltd. developed the product jointly, conducted a phase III study, and have now submitted an application for marketing approval of the product with data from the study.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a colorless crystal or white crystalline powder. The properties of the drug substance have been determined for including description, solubility, hygroscopicity, melting point, dissociation constant, distribution coefficient, and crystalline polymorphism.

The chemical structure of the drug substance has been elucidated by ultraviolet and visible (UV/Vis) absorption spectrometry, infrared (IR) spectrophotometry, nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), and mass spectrometry.

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

[redacted]

[redacted]

2.A.(1).3) Control of drug substance

The drug substance specifications have been set for strength, description (visual), identification (IR spectrophotometry and qualitative test [chloride]), pH, purity (appearance of solution, sulfate, and related substances [high-performance liquid chromatography (HPLC)]), residual solvents (gas chromatography), loss on drying, residue on ignition, and assay (endpoint detection methods in titrimetry).

2.A.(1).4) Stability of drug substance

Table 1 shows the results of main stability tests of the drug substance. Photostability testing showed that the drug substance is photolabile.

Table 1. Stability tests of the drug substance

Test	Primary batches	Storage conditions	Storage configuration	Storage period
Long-term stability	3 production batches	5°C	[redacted]	36 months
Accelerated		25°C, 60% RH		6 months

[redacted]

[redacted]

2.A.(2) Drug product

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

The drug product is a solution containing 20 mg of the drug substance per vial (2 mL). The drug product contains the following excipients: phenol, concentrated glycerin, sodium chloride, disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, and water for injections.

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

The manufacturing process for the drug product consists of dissolution, sterile filtration, dilution/stabilization, filling, and packaging/labeling. [redacted]

2.A.(2).3) Control of drug product

The drug product specifications have been established for strength, description (visual), identification (HPLC-UV), pH, foreign insoluble matter, insoluble particulate matter, sterility, phenol content and assay (HPLC).

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

Table 2 shows the results of main stability tests of the drug product. Photostability testing showed that the drug product was photostable.

Table 2. Stability tests of the drug product

Test	Primary batches	Storage conditions	Storage configuration	Storage period
Long-term stability	2 pilot scale batches 1 production batch	5°C	[redacted]	36 months
Accelerated		25°C		6 months

[redacted]

2.B Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is appropriately controlled.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

No new nonclinical pharmacology studies were conducted for this application.

3.(ii) Summary of pharmacokinetic studies

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

No new pharmacokinetic studies were conducted for this application.

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

The applicant's explanation on the omission of nonclinical pharmacokinetic studies or clinical pharmacology studies:

Histamine is an endogenous substance produced in tissues of almost all mammals and is rapidly excreted in urine as an unchanged or metabolized form. In skin-prick or skin-scratch testing, the pricked or scratched epidermal layer absorbs only a trace amount (almost undetectable) of histamine after application of the product, compared with the amount of endogenous histamine present in the skin and blood. Accordingly, conducting new nonclinical pharmacokinetic or clinical pharmacology studies was deemed unnecessary.

Given the explanation by the applicant, PMDA considered that there was no specific problem with the omission of new nonclinical pharmacokinetic and clinical pharmacology studies.

3.(iii) Summary of toxicology studies

No new toxicology studies were conducted for this application.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.*(i).A Summary of the submitted data*

No new biopharmaceutic studies were conducted for this application.

4.(ii) Summary of clinical pharmacology studies

4.*(ii).A Summary of the submitted data*

No new clinical pharmacology studies were conducted for this application.

4.(iii) Summary of clinical efficacy and safety

4.*(iii).A Summary of the submitted data*

The applicant submitted evaluation data (the results of a Japanese clinical study) for this application.

4.(iii).A.(1) Phase III study (5.3.5.1-1: Study JTE-350 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind study was conducted at a single center in Japan to evaluate the appropriateness of Scratch Histamine Dihydrochloride Positive control "TORII" (hereinafter, the product) as a positive control in skin-prick tests (SPTs) in healthy adults (target sample size, 30 subjects).

One drop each of the product and a negative control (Allergen Scratch Extract control "TORII") was applied with a dedicated dropper to different sites on the anterior forearm in a specified order. The skin surface of the application site was pricked (prick method), and the diameters of wheals and erythema were measured at 15 minutes after the pricking. A mean wheal diameter (mean of the longest and shortest diameters) ≥3 mm was considered to be a positive response. Positive response was determined in a double-blind manner.

Of 57 subjects who provided informed consent, 30 subjects received the investigational drug. All of the subjects who received the investigational drug were included in the safety analysis set and the full analysis set (FAS). The FAS was the primary population for efficacy analysis.

The primary efficacy endpoint was positive response rate based on a mean wheal diameter at the application site of the product (positive response rate = [the number of subjects with positive response in the mean wheal diameter / the number of subjects undergoing SPTs] × 100). All 30 subjects had a mean wheal diameter ≥3 mm at the application site of the product. The positive response rate was thus 100% (30 of 30 subjects) (95% confidence interval [CI], 88.4%, 100%). The lower limit of the 95% CI was higher than the pre-specified margin of 75%. None of the subjects showed positive response (i.e., a mean wheal diameter ≥3 mm) on the application site of the negative control.

The secondary endpoint was positive response rate based on the longest wheal diameter at the application site of the product (positive response rate = [the number of subjects with positive response in the longest wheal diameter / the number of subjects undergoing SPTs] × 100). In all 30 subjects, the longest wheal diameter at the application site of the product was ≥3 mm. The positive response rate was thus 100% (30 of 30 subjects) (95% CI, 88.4%, 100.0%).

The longest, shortest, and mean diameters of wheals at the application site of histamine dihydrochloride were 8.65 ± 1.66 mm, 6.87 ± 1.04 mm, and 7.758 ± 1.051 mm (mean ± standard deviation [SD]), respectively, and no wheals were produced by the negative control. The longest, shortest, and mean diameters of erythema at the application site of histamine dihydrochloride were 34.42 ± 9.79 mm, 24.50 ± 7.40 mm, and 29.458 ± 8.103 mm (mean ± SD), respectively. The longest, shortest, and mean diameters of erythema at the application site of the negative control were 3.52 ± 1.02 mm, 2.88 ± 0.87 mm, and 3.200 ± 0.915 mm, respectively.

Symptoms and findings at the application sites in SPT and adverse events were assessed for safety evaluation. No adverse events occurred. Table 3 shows symptoms and findings observed at the application site within 2 hours post-SPT.

Table 3. Symptoms and findings at application sites in SPT (Safety analysis set)

Symptoms	Histamine dihydrochloride		Negative control	
	Within 2 hours post-SPT	At 2 hours post-SPT	Within 2 hours post-SPT	At 2 hours post-SPT
Symptoms present	30 (100%)	1 (3.3%)	29 (96.7%)	0 (0%)
Itching	26 (86.7%)	0 (0%)	2 (6.7%)	0 (0%)
Pain	2 (6.7%)	0 (0%)	1 (3.3%)	0 (0%)
Wheals	30 (100%)	0 (0%)	0 (0%)	0 (0%)
Erythema	30 (100%)	1 (3.3%)	29 (96.7%)	0 (0%)
Others	0 (0%)	0 (0%)	1* (3.3%)	0 (0%)

N = 30
Number of subjects (%)
* Feeling strange

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

4.(iii).B.(1) Efficacy

The applicant's explanation on the efficacy of the product:

The product has long been used as a positive control for SPTs after approval in Europe and other countries. In Japan also, histamine dihydrochloride 10 mg/mL solution is recommended to be used as a positive control for skin allergy testing, according to the Latex Allergy Guidelines and the Food Allergy Guidelines. As histamine dihydrochloride 10 mg/mL solution has been accepted as an effective, well-tolerated, and safe positive control for SPTs and is widely used for both adults and children in clinical practice worldwide, only a single phase III clinical study was adequate to evaluate the efficacy of the product for SPTs. In the phase III study, the product was administered by prick method to 30 healthy adults. All subjects showed a wheal diameter of ≥3 mm (positive response rate = 100%). The product was thus shown to be effective as a positive control for SPTs.

PMDA concluded that the efficacy of the product as a positive control solution has been demonstrated, for the following reasons: (1) Histamine is a well-known main allergen that induces immediate allergic reactions. (2) In overseas countries, the product has long been used as a positive control for SPTs to identify the allergens. (3) In Japan, histamine dihydrochloride (reagent) has been used as a positive control in clinical practice, as recommended by the Japanese guidelines. (4) The phase III study showed 100% positive response rate for wheals at the application sites of the product and 0% positive response rate for wheals at the application sites of the negative control.

4.(iii).B.(2) Safety

The applicant's explanation on the safety of the product:

In the European Periodic Safety Update Reports (PSURs) of Soluprick Positive control (the overseas brand name of the product), no deaths or other serious adverse reactions have been reported during any postmarketing surveillance periods since its launch in 1995. In the Japanese phase III study, no subjects experienced adverse events. Although some subjects presented with symptoms or findings at the application sites of the product or the negative control, these symptoms and findings resolved

immediately and were not considered as adverse events. Accordingly, the product was confirmed safe to be used as a positive control for skin tests.

PMDA's view:
The product has no clinically significant problems in terms of safety, given the following facts: (1) Only non-serious adverse events have been reported as adverse reactions to Soluprick in the overseas postmarketing safety reports. (2) No subjects experienced adverse events in the Japanese phase III study. (3) Although histamine directly induces allergic reactions, the amount of histamine administered during SPTs is so marginal relative to the endogenous histamine levels that excessive reactions or systemic reactions are very unlikely to occur following administration of histamine dihydrochloride.

4.(iii).B.(3) Dosage and administration
PMDA asked the applicant to explain whether 10 mg/mL is the optimal concentration of histamine dihydrochloride as the active ingredient of the product and to provide the rationale for 10 mg/mL concentration.

The applicant's response:
In a study on the reproducibility of SPT results using histamine dihydrochloride 1, 5, and 10 mg/mL (Taudorf E *et al*., *Allergy*. 1985;40:344-9), the threshold for positive response was defined as a wheal ≥15 mm^2. In the study, some subjects receiving histamine dihydrochloride 1 or 5 mg/mL had wheals <15 mm^2, but all subjects receiving histamine dihydrochloride 10 mg/mL had wheals ≥15 mm^2. Therefore, the authors concluded that 10 mg/mL of histamine dihydrochloride is appropriate as positive control for SPTs because of its high reproducibility. Similar results were reported on the positive response rate with histamine dihydrochloride 10 mg/mL in SPTs in another study (Dreborg S *et al*., *Clin Allergy*. 1987;17:537-50). In this study, although some subjects receiving histamine dihydrochloride 1 mg/mL did not show wheals ≥7 mm^2 (with a diameter ≥3 mm), all subjects receiving histamine dihydrochloride 10 mg/mL had wheals ≥7 mm^2. In addition, in the Japanese phase III clinical study that used 10 mg/mL, all treated subjects showed a good degree of response to evaluate the efficacy of the product (histamine dihydrochloride 10 mg/mL). Outside Japan, approximately 7.5 million people are estimated to have been exposed to Soluprick between January 1, 2003 and June 30, 2014, according to the number of sales. No deaths or other serious adverse reactions have been reported, and only 32 events of non-serious adverse reactions were reported between January 1, 1995 and June 16, 2014 (PSURs for Soluprick Positive control and Soluprick Negative control). While no data comparing the safety profile of 10 mg/mL histamine dihydrochloride with other concentrations are available, the safety information obtained from substantial clinical use poses no concerns for the safety of 10 mg/mL histamine dihydrochloride. In Japan, as the Food Allergy Guidelines and the Latex Allergy Guidelines state that "a positive control (histamine dihydrochloride 10 mg/mL) should be used," individual healthcare practitioners prepare histamine dihydrochloride solution as a positive control at a concentration of 10 mg/mL from the reagent. As described above, histamine dihydrochloride 10 mg/mL shows a high reproducibility, which is essential for a positive control, and has no safety problems. The optimal concentration of histamine dihydrochloride as a positive control is thus 10 mg/mL.

PMDA asked the applicant to provide the rationale and justification for the criterion for positive response for the product in skin allergy testing, taking into account the fact that the positive response was defined as "a wheal diameter ≥3 mm at 15 minutes after pricking" in the Japanese phase III study, whereas the positive response to the allergens approved in Japan for skin-scratch testing is defined as "a wheal diameter of ≥5 mm or twice the wheal control diameter at 15 to 30 minutes after scratching."

The applicant's response:
A wheal of 1 to 2 mm in diameter may develop from the pricking procedure itself (Dreborg S, The skin-prick test: methodological studies and clinical applications. Linköping University Medical Dissertations No. 239, 1987). Thus, the position paper jointly released by the Global Allergy and Asthma European Network and the Allergic Rhinitis and its Impact on Asthma (Bousquet J *et al*., *Allergy*. 2012;67:18-24) and the Summary of Product Characteristics (SPC) of Soluprick define a wheal diameter ≥3 mm as a positive response. Additionally, in Japan, the Latex Allergy Guidelines clearly specify that histamine dihydrochloride produces a wheal with a diameter of 3 to 8 mm on the anterior forearm, and it is well known that administration of histamine dihydrochloride in SPTs results in a wheal with a diameter of ≥3 mm. Therefore, the criterion of "a wheal with a diameter of ≥3 mm as a positive response" in the phase III study is appropriate.

Reading the reaction at 15 minutes after pricking is recommended in the above-mentioned position paper (Bousquet J *et al*., *Allergy*. 2012;67:18-24) and the SPC in Europe as well as the Latex Allergy Guidelines and the Food Allergy Guidelines in Japan. The timing of assessing the reaction (at 15 minutes after pricking) in the phase III study is thus appropriate.

While the product was administered only in skin-prick testing in the Japanese phase III clinical study, the use in skin-scratch testing is mentioned in the proposed dosage and administration. Therefore, PMDA asked the applicant to provide the rationale for considering that the product is effective also in skin-scratch testing, and to explain whether the efficacy and safety of the product in skin-scratch testing are equivalent to those in skin-prick testing.

The applicant's response:
Both prick and scratch methods have been used for skin testing with allergen extracts since the 1960s. In a study on skin tests with allergen extracts, Matsumura *et al*. evaluated test methods including prick and scratch methods, reporting that either type of the tests yielded stable results when performed by well-trained and experienced personnel (Scratch Test Workshop, *Jpn J. Allergol*. 1972;21:50-63). The package inserts of 72 products of Allergen Scratch Extract "TORII" marketed by Torii Pharmaceutical Co., Ltd. in Japan describe their dosage and administration without differentiating prick method and scratch method, as with the proposed dosage and administration for the proposed product. The package inserts of the 72 products state that "The surface of the skin is pricked (prick method) or scratched (scratch method) without drawing blood, and a drop of the product is applied to the site of the prick or scratch. The reactions are read after 15 to 30 min, and a wheal diameter of ≥5 mm or twice the control

wheal diameter is considered to be positive." In Japanese clinical practice, the scratch method has been used similarly with the prick method since the 1960s when the first Allergen Scratch Extract "TORII" was approved in Japan. Based on the above, both scratch and prick methods of skin tests with allergen extracts yield stable results when performed by well-trained and experienced personnel and have been used similarly, and therefore, the efficacy of histamine dihydrochloride in the scratch tests is comparable to that in the prick tests.

Skin testing is an *in vivo* method to evaluate the effects of chemical substances such as histamine released from the mast cells by antigen loading. Skin-prick testing has the lowest antigen load, followed by scratch testing, and intradermal testing (Chinuki and Morita. *Allergol & Immunol*. 2010;17:116-22; Chinuki and Morita. *MB Derma*. 2013;203:19-24; Hirai. *Visual Dermatology*. 2013;12:354-7). The Latex Allergy Guidelines and the Food Allergy Guidelines, which recommend histamine dihydrochloride as a positive control, list both scratch and prick methods for skin testing, and the scratch method is also widely used in Japan, as with the prick method.

The surface of the skin is incised in the skin-scratch testing. Histamine administered in the skin-scratch testing may therefore penetrate into the skin tissues in a larger amount, compared with histamine given in the skin-prick testing in which the skin is penetrated with a lancet with a needle tip of 1 mm. The European SPC of Soluprick describes that the amount of solution applied epicutaneously at skin-prick testing corresponds to 0.003 μL, which is equivalent to 0.018 μg of histamine. When skin-scratch testing is assumed to produce a wound of 3 to 5 mm in length (Chinuki and Morita, *Allergol & Immunol.* 2010;17:116-22; Adachi, *MB Derma*. 2009;151:57-64) and skin-prick testing a wound of 1 mm in diameter, skin scratch testing produces a wound area up to 5-fold a wound area produced by skin-prick testing, probably resulting in up to a 5-fold amount of histamine penetrating the skin. The total amount of endogenous histamine in human skin is calculated to be 33,440 μg based on published data (Feldberg W *et al*., *J Physiol*. 1954;126:286-92; Hanano *et al*., Pharmacokinetics for drug development: theory and experiments, Soft Science Inc., 1985:477). Meanwhile, the amount of histamine penetrating the skin in skin-scratch testing is calculated to be only 0.091 μg even with a 5-fold higher penetration amount than that in skin-prick testing, and is very small as compared with the total amount of histamine present in human skin. As shown above, the amount of histamine penetrating the skin in skin-scratch testing is likely to be higher than that in skin-prick testing, but is actually marginal as compared with the total amount of endogenous histamine in human skin. Although no safety data with skin-scratch testing were obtained in the Japanese phase III study, other data on the amount of skin penetration of histamine in skin-scratch testing suggest that the scratch method has a safety profile comparable to that of the prick method.

PMDA asked the applicant to explain why histamine dihydrochloride can be used in children with the same dosing regimen as in adults.

The applicant's response:

Children and adults showed similar reactions in SPTs with histamine dihydrochloride 10 mg/mL, although children had smaller reactions than adults (Ménardo JL *et al*., *J Allergy Clin Immunol.* 1985;75:646-51). In a study evaluating histamine dihydrochloride 9 mg/mL, similar reaction was observed in the group aged ≥6 and <9 years as compared with a group of adults aged ≥51 and <60 years (Skassa-Brociek W *et al*., *J Allergy Clin Immunol.* 1987;80:711-6). These data suggest that histamine dihydrochloride can elicit sufficient reaction as a positive control for skin testing in children as seen in adults. In postmarketing settings outside Japan, only one case of hypersensitivity in a patient aged <17 years was spontaneously reported for safety data of children. Although the proportion of children in the population receiving histamine dihydrochloride is unknown, SPTs are medically necessary in children, and histamine dihydrochloride 10 mg/mL is used also in children in clinical practice outside Japan (Palosuo K *et al*., *J Allergy Clin Immunol*. 2001;108:634-8; Roberts G *et al*., *J Allergy Clin Immunol*. 2005;115:1291-6; Peters RL *et al*., *J Allergy Clin Immunol*. 2014;133:485-91; and Blumchen K *et al*., *J Allergy Clin Immunol*. 2014;134:390-8). In Europe, there is no difference in the dosing regimen between children and adults in the SPC of Soluprick or the position paper of the Global Allergy and Asthma European Network and the Allergic Rhinitis and its Impact on Asthma (Bousquet J *et al*., *Allergy*. 2012;67:18-24). In Japan, the Food Allergy Guidelines and the Latex Allergy Guidelines state that "a positive control (histamine dihydrochloride 10 mg/mL) should be used," and histamine dihydrochloride is currently used in children at the same dosing regimen as in adults in clinical practice. As described above, histamine dihydrochloride 10 mg/mL used as a positive control in SPTs can elicit sufficient reaction also in children, and its safety profile does not seem to significantly differ between children and adults. Thus, the product can be used in children with the same dosing regimen as in adults.

PMDA's view on pediatric dosing regimen:
The concentration of the active ingredient (10 mg/mL histamine) in the product is appropriate, for the following reasons: (1) In overseas countries, Soluprick (10 mg/mL histamine dihydrochloride) has been used as a positive control in SPTs with no problems with its efficacy or safety since its approval in 1985. (2) In Japan, the Latex Allergy Guidelines and the Food Allergy Guidelines recommend the use of histamine dihydrochloride 10 mg/mL solution as a positive control in SPTs, and a histamine dihydrochloride solution 10 mg/mL, prepared from a reagent, is used in clinical practice. (3) The efficacy and safety of the product (histamine dihydrochloride 10 mg/mL) were demonstrated in Japanese subjects in the phase III clinical study. Given the applicant's explanation, the efficacy and safety of the product in skin-scratch testing are considered to be comparable to those in skin-prick testing, and the product is considered to have adequate efficacy and acceptable safety in children at the same dosing regimen as in adults. Therefore, PMDA concluded that the dosage and administration should be described as shown below and that the criterion for positive response used in the Japanese phase III study (i.e., "a wheal diameter of ≥3 mm at 15 minutes after administration of the product is considered to be a positive response,") should be included in the Precautions for Dosage and Administration section of the package insert.

Dosage and administration

The product is used as a positive control for allergen screening. The surface of the skin is pricked (prick method) or scratched (scratch method) without drawing blood, and a drop of the product is applied to the site of the prick or scratch.

4.(iii).B.(4) Indication

As the efficacy and safety of the product have been demonstrated by the phase III study and other data, PMDA concluded that the indication of the product should be described as follows:

Indication

Positive control in skin testing with allergen scratch extracts to evaluate skin reactions

4.(iii).B.(5) Clinical positioning

The applicant's explanation on the clinical positioning of the product:

Skin testing is used to diagnose immunoglobulin E (IgE)-mediated type 1 allergies (e.g., asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy) (Japanese Society of Allergology, Comprehensive Guidelines on Allergy 2013, Kyowa Kikaku, 2013). The Japanese guidelines for allergic rhinitis (Committee of the Practical Guideline for the Management of Allergic Rhinitis, Perennial Rhinitis and Pollinosis, Practical Guideline for the Management of Allergic Rhinitis in Japan 2013, Life Science. 2013) state that allergic rhinitis should be diagnosed through comprehensive assessment based on various tests performed after an interview with the patient about his/her symptoms in detail. Since it is known that skin test results may be affected by some factors, for example, an intake of an oral antihistamine before the test, the product is intended to be used as a positive control to enhance the reliability of the test results. The use of the product as a positive control in skin testing enables accurate results. Therefore, it is recommended to use the product as a positive control in all subjects who receive skin testing. The diagnostic procedures for food allergies (described in the Food Allergy Guidelines) and the Latex Allergy Guidelines recommend that histamine dihydrochloride should be used as a positive control in all patients who receive skin testing when antibody tests and skin tests are performed to identify the causal allergens of specific IgE antibody-dependent reactions after detailed history-taking and observation. While skin tests are easy and convenient and are widely used to diagnose various allergies in clinical practice, histamine dihydrochloride as a diagnostic drug in skin testing is not available in Japan. In the current circumstances, a reagent for research purposes is used as a substitute for a diagnostic drug, or skin tests are performed without a positive control. The product is expected to improve such circumstances and to contribute to the wide use of precise and accurate skin testing. In conclusion, the product is considered necessary for all patients receiving skin testing.

PMDA's response:

The clinical position of histamine dihydrochloride solution has been established as a positive control in skin testing for the diagnosis of type 1 allergies. The efficacy and safety of the product have been demonstrated with the dosing regimen defined in the phase III study and recommended by other sources. Based on the above, PMDA concluded that it is clinically significant to make the product, which assures the reliability of skin test results, available in clinical practice.

4.(iii).B.(6) Post-marketing investigations

PMDA considers that at present, no additional pharmacovigilance or risk minimization activities are necessary in the risk management plan for this application because there are no safety concerns, in light of the following facts: (1) No particular safety problems have been identified in the clinical study results. (2) Sufficient data are available from clinical experience of histamine as a positive control in clinical practice in and outside Japan. (3) The degree of systemic exposure to histamine following administration of the product is limited. (4) The bioactivity of histamine is well known.

4.(iii).B.(7) Brand name

PMDA asked the applicant to change the proposed brand name with the reference to the section "Change of brand names of allergen preparations" in "Review Report by the Working Group on Safety of Drugs and Medical Devices" (Document No. 3, the 14th meeting of the Working Group on Safety of Drugs and Medical Devices, http://www.mhlw.go.jp/shingi/2007/11/dl/s1105-2c.pdf). The applicant answered that they changed the brand name to "Allergen Scratch Extract Positive control "TORII" Histamine Dihydrochloride" accordingly. PMDA concluded that the newly proposed name was acceptable.

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 inspections and assessment are currently under way, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently under way, and the results and PMDA's conclusion will be reported in the Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of the product as a positive control solution in skin testing with allergen scratch extracts has been demonstrated and its safety is acceptable in view of the benefits expected from the use of the product.

This application may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 20, 2015

I. Product Submitted for Registration

[Brand name]	Allergen Scratch Extract Positive control "TORII" Histamine Dihydrochloride
[Non-proprietary name]	Histamine dihydrochloride
[Applicant]	Japan Tobacco Inc.
[Date of application]	December 22, 2014

II. Content of the Review

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

(1) Efficacy

PMDA concluded that the efficacy of the product has been demonstrated given the following facts:

- Histamine is widely known to be a main allergen that induces immediate allergic reactions.
- Soluprick Positive control (the overseas brand name of Allergen Scratch Extract Positive control "TORII" Histamine Dihydrochloride) has long been used as a positive control in skin-prick tests (SPTs) to identify allergens outside Japan.
- The use of histamine dihydrochloride is recommended in both the Japanese and foreign guidelines. Histamine dihydrochloride solution prepared from the reagent has been used in the Japanese clinical practice.
- The expected efficacy results were obtained from the Japanese phase III clinical study.

The above conclusion by PMDA was supported by the expert advisors.

(2) Safety

PMDA concluded that the product has no clinically significant problems with its safety in light of the following facts:

- Only non-serious adverse events were reported in association with the product in the postmarketing setting outside Japan.
- No adverse events were reported in subjects in the Japanese phase III clinical study.
- Trace amount of histamine administered in SPTs is unlikely to cause adverse reactions.

The above conclusion by PMDA was supported by the expert advisors.

(3) Dosage and administration

PMDA concluded that the concentration of the active ingredient, histamine dihydrochloride 10 mg/mL, is appropriate, for the following reasons:

- Histamine dihydrochloride 10 mg/mL has been used as a positive control in SPTs without compromising efficacy or safety in clinical practice in and outside Japan.
- The efficacy and safety of the product (histamine dihydrochloride 10 mg/mL) have been demonstrated in Japanese subjects in the Japanese phase III clinical study.

The above conclusion by PMDA was supported by the expert advisors.

Although only skin-prick tests were performed in the Japanese phase III clinical study, there is a report showing that skin-prick tests and skin-scratch tests both yield stable results when performed by well-trained and experienced personnel. Both tests are currently used in clinical practice, and the amount of histamine absorbed by the tissues during skin-scratch tests is as small as that in skin-prick tests. These findings suggest that there are no significant problems in the efficacy and safety of the product in skin-scratch testing, and PMDA thus concluded that the product can be used in both skin-prick and skin-scratch testing. With regard to use in children, PMDA concluded that the product can be used in children because reports show that histamine dihydrochloride in children elicited a similar reaction to that in adults; no particular safety concerns in children have been raised from the overseas postmarketing data; and healthcare practitioners actually use histamine dihydrochloride solution (prepared from the reagent) as a positive control in SPTs in children. These PMDA's conclusions on the concentration and pediatric use of the product were supported by the expert advisors.

Based on the above discussion, PMDA concluded that the instructions in the Dosage and Administration section of the package insert should be described as proposed by the applicant. This conclusion was supported by the expert advisors.

[Dosage and administration]
Diagnostic use
The product is used as a positive control for allergen screening. The surface of the skin is pricked (prick method) or scratched (scratch method) without drawing blood, and a drop of the product is applied to the site of the prick or scratch.

Given the description in the SPC in Europe and other data, PMDA concluded that the positive response should be defined as a wheal diameter of ≥3 mm at 15 minutes after skin-prick testing, and that this definition should be included in the Precautions for Dosage and Administration section of the package insert. However, the expert advisors commented that the package insert should not specify the numerical value (i.e., ≥3 mm) as a standard or guide for the positive response, because skin reactions to substances with a pharmacologically equivalent potency may vary greatly depending on the skin conditions, and therefore diagnosis may not be made based on the absolute wheal diameter produced by a suspect

substance, but rather on the relative wheal diameter compared with the control wheal diameter produced by the product, a positive control.

Based on the above discussion, PMDA asked the applicant to include the following statement in the precautions for dosage and administration of the package insert. The applicant agreed.

Precautions for Dosage and Administration
A wheal with a diameter of ≥3 mm usually develops at 15 minutes after the administration of the product.

(4) Indication
As the efficacy and safety of the product have been demonstrated in the Japanese phase III clinical study and other data, PMDA concluded that the indication of "positive control to evaluate skin reactions to allergen scratch extracts" is appropriate, as with the indication of the approved negative control product. This conclusion was supported by the expert advisors. However, the applicant commented that the indication should reflect the fact that the product is required also for skin testing on substances other than the approved allergen scratch extracts (e.g., foods). Based on the discussion, PMDA concluded that the product should be approved for the following indication.

Indication
Diagnostic use
Positive control to evaluate skin reactions to allergens

(5) Clinical positioning
Based on the guidelines in and outside Japan, the clinical position of histamine dihydrochloride solution has been established as a positive control used in skin testing for the diagnosis of type 1 allergies. The efficacy and safety of the product as a positive control solution have been confirmed by the results from the Japanese phase III study and other data. In light of the above, PMDA concluded that it is clinically significant to make the product, which is effective in assuring the reliability of skin test results, available in clinical practice. The PMDA's conclusion was supported by the expert advisors.

(6) Risk management plan (draft)
PMDA concluded that at present, no additional pharmacovigilance or risk minimization activities are necessary in the risk management plan for this application, and the PMDA's conclusion was supported by the expert advisors. The applicant plans to conduct a postmarketing surveillance to collect data on the clinical use of the product.

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 were conducted for the data

submitted in the new drug 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. As a result, 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 for the data submitted in the new drug 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. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below. Since the product is a drug with a new indication, the re-examination period is 4 years. The drug substance is classified as a poisonous drug. The drug product is not classified as a poisonous drug, a powerful product, a biological product, or a specified biological product.

[Indication]	Diagnostic use Positive control to evaluate skin reactions to allergens
[Dosage and administration]	Diagnostic use The product is used as a positive control for allergen screening. The surface of the skin is pricked (prick method) or scratched (scratch method) without drawing blood, and a drop of the product is applied to the site of the prick or scratch.