Report on the Deliberation Results

June 9, 2015

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

[Brand name]	Botox for Injection 50 Units Botox for Injection 100 Units
[Non-proprietary name]	Botulinum Toxin Type A (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	July 25, 2014

[Results of deliberation]
In the meeting held on June 5, 2015, the First Committee on New Drugs concluded that the partial changes for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is 4 years.

[Conditions for approval]
The applicant is required to:

1. Develop and appropriately implement a risk management plan;
2. Take necessary measures to ensure that the product is used only by qualified physicians who have completed a training course on the product, fully understand the safety and efficacy of the product, and have sufficient knowledge and experience of the injection technique for the product;
3. Take necessary measures to ensure that the unused product is deactivated and discarded safely and reliably, for example, to ensure that the pharmacy department is requested to dispose of it, and to keep its record; and
4. Conduct a post-marketing drug use-results survey in all patients treated with the product as a rule until data from a specific number of patients have been accumulated, in order to identify the characteristics of patients treated with the product, since the number of patients with strabismus was very limited in the Japanese clinical studies, and at the same time, collect the safety and efficacy data of the product without delay and take measures necessary for the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

May 19, 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]	Botox for Injection 50 Units Botox for Injection 100 Units
[Non-proprietary name]	Botulinum Toxin Type A
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	July 25, 2014
[Dosage form/Strength]	Powder for reconstitution prior to injection: One vial contains 50 or 100 units of botulinum toxin type A.
[Application classification]	Prescription drug, (4) Drug with a new indication, (6) Drug with new dosages
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug III

Review Results

May 19, 2015

[Brand name]	Botox for Injection 50 Units Botox for Injection 100 Units
[Non-proprietary name]	Botulinum Toxin Type A
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	July 25, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of strabismus 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 indications and dosage and administration as shown below, with the following conditions.

[Indications] Blepharospasm, hemifacial spasm, cervical dystonia, upper limb spasticity, lower limb spasticity, talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy, severe primary axillary hyperhidrosis, and strabismus

(The underline denotes the text added in this application.)

[Dosage and administration]

Blepharospasm

The usual initial adult dosage of botulinum toxin type A (Botox) is 1.25 to 2.5 units/site, injected intramuscularly into 6 sites of the orbicularis oculi muscle per eye. In patients who have undergone resection of the orbicularis oculi muscle, the target injection sites should be carefully identified by electromyography. The treatment effect usually lasts for 3 to 4 months. Botox treatment should be repeated if symptoms relapse, but not within 2 months of the previous dose. For subsequent injection sessions, the dose may be increased up to 2-fold the initial dose. However, the dose used for the subsequent injection should be decreased as appropriate in the event of adverse drug reactions such as lagophthalmos and eyelid ptosis presumably due to exaggerated muscle-paralyzing effect, the pharmacological action of Botox. The cumulative dose of Botox treatment in 1 month should not exceed 45 units.

Hemifacial spasm

The usual adult dosage of botulinum toxin type A (Botox), injected intramuscularly into the spastic muscle,* is shown below. In the case of multiple spastic muscles, Botox should be injected into each muscle in divided doses.

- The initial dose is 10 units in total.
- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 20 units in total) may be administered.
- Botox treatment may be repeated if symptoms relapse, at a dose of up to 30 units, but not within 2 months of the previous dose.

* Spastic muscle: orbicularis oculi muscle, corrugator muscle, frontalis muscle, orbicularis oris muscle, greater zygomatic muscle, lesser zygomatic muscle, risorius muscle, platysma muscle, mentalis muscle, etc.

Cervical dystonia

The usual adult dosage of botulinum toxin type A (Botox), injected intramuscularly into the tonic muscle,* is shown below. In the case of multiple tonic muscles, Botox should be injected into each muscle in divided doses.

- The initial dose is 30 to 60 units in total.
- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 180 units in total) may be administered.
- Botox treatment may be repeated if symptoms relapse, at a dose of up to 240 units in total, but not within 2 months of the previous dose.

* Tonic muscles: sternocleidomastoid muscle, trapezius muscle, splenius muscle, scalenus muscle, anterior edge of the trapezius muscle, levator scapulae, paraspinal muscle, platysma muscle, etc.

Upper limb spasticity

The usual adult dosage of botulinum toxin type A (Botox) is 240 units in total injected intramuscularly in divided doses into each of the tonic muscles.* The maximum single dose is 240 units, but the dose should be decreased to the minimum dose required as appropriate, depending on the type and number of tonic muscles to be treated. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

* Tonic muscles: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis, flexor pollicis longus, adductor pollicis, etc.

Lower limb spasticity

The usual adult dosage of botulinum toxin type A (Botox) is 300 units in total injected intramuscularly in divided doses into each of the tonic muscles.* The maximum single dose is 300 units, but the dose should be decreased to the minimum dose required as appropriate, depending on the type and number of tonic muscles to be treated. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

* Tonic muscles: gastrocnemius muscle (medial head, lateral head), soleus muscle, tibialis posterior muscle, etc.

Talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy

The usual dosage of botulinum toxin type A (Botox) for children ≥2 years of age is 4 units/kg injected intramuscularly into 2 sites each of the medial/lateral head of the affected gastrocnemius muscle. When injected into both legs, the dose of 4 units/kg is divided to each leg. If the patients have an inadequate response to the initial dose, Botox may be injected into the muscles such as the soleus muscle and tibialis posterior muscle. The dose may be adjusted according to the symptoms. The total single dose should not exceed 200 units. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

Severe primary axillary hyperhidrosis

The usual adult dosage of botulinum toxin type A (Botox) is 50 units per axilla injected intracutaneously into multiple (10-15) sites, 1 to 2

cm apart. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 4 months of the previous dose.

Strabismus

The usual dosage of botulinum toxin type A (Botox) for adults and children ≥12 years of age, injected intramuscularly into an extraocular muscle, is shown below.

- Initial dose
  - (1) Vertical strabismus: 1.25 to 2.5 units into the superior or inferior rectus muscle
  - (2) Horizontal strabismus of <20 prism diopters: 1.25 to 2.5 units into the medial or lateral rectus muscle
  - (3) Horizontal strabismus of 20 to 50 prism diopters: 2.5 to 5.0 units into the medial or lateral rectus muscle
  - (4) Abducens nerve palsy persisting ≥1 month: 1.25 to 2.5 units into the medial rectus muscle
- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 2-fold the initial dose) may be administered.
- Retreatment with Botox is allowed if the response to the previous dose has worn off, at a dose up to 2-fold a previous single dose, but not within 3 months of the previous dose.
- A single dose per muscle should not exceed 10 units.

(The underline denotes the text added in this application.)

[Conditions for approval] The applicant is required to:

1. Develop and appropriately implement a risk management plan;
2. Take necessary measures to ensure the product is used only by qualified physicians who have completed a training course on the product, fully understand the safety and efficacy of the product, and have sufficient knowledge and experience of the injecting technique of the product;
3. Take necessary measures to ensure that the unused product is deactivated and discarded safely and reliably in the clinical setting, for example, to ensure the pharmacy department is requested to dispose of it, and to keep its record; and
4. Conduct a post-marketing drug use-results survey in all patients treated with the product as a rule until data from a specific number of patients have been accumulated, in order to identify the characteristics of patients treated with the product, since the number of patients with strabismus were very limited in the Japanese clinical studies, and at the same time, collect the safety and efficacy data of the product without delay and take measures necessary for the proper use of the product.

Review Report (1)

March 19, 2015

I. Product Submitted for Registration

[Brand name] Botox for injection 50 Units
Botox for injection 100 Units

[Non-proprietary name] Botulinum Toxin Type A

[Applicant] GlaxoSmithKline K.K.

[Date of application] July 25, 2014

[Dosage form/Strength] Powder for reconstitution prior to injection: One vial contains 50 or 100 units of Botulinum Toxin Type A.

[Proposed indications] Blepharospasm, hemifacial spasm, cervical dystonia, upper limb spasticity, lower limb spasticity, talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy, severe primary axillary hyperhidrosis, and strabismus

(The underline denotes the text added in this application.)

[Proposed dosage and administration]

Blepharospasm

The usual initial adult dosage of botulinum toxin type A (Botox) is 1.25 to 2.5 units/site injected intramuscularly into 6 sites of the orbicularis oculi muscle per eye. In patients who have undergone resection of the orbicularis oculi muscle, the target injection sites should be carefully identified by electromyography. The treatment effect usually lasts for 3 to 4 months. Botox treatment should be repeated if symptoms relapse, but not within 2 months after the previous dose. For subsequent injection sessions, the dose may be increased up to 2-fold the initial dose. However, the dose used for the subsequent injection should be decreased as appropriate in the event of adverse drug reactions such as lagophthalmos and eyelid ptosis presumably due to exaggerated muscle-paralyzing effect, the pharmacological action of Botox. The cumulative dose of Botox treatment in 1 month should not exceed 45 units.

Hemifacial spasm

The usual adult dosage of botulinum toxin type A (Botox), injected intramuscularly into the spastic muscle, is shown below.* In the case of multiple spastic muscles, Botox should be injected into each muscle in divided doses.

- The initial dose is 10 units in total.
- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 20 units in total) may be administered.
- Botox treatment may be repeated if symptoms relapse, at a dose of up to 30 units, but not within 2 months after the previous dose.

* Spastic muscle: orbicularis oculi muscle, corrugator muscle, frontalis muscle, orbicularis oris muscle, greater zygomatic muscle, lesser zygomatic muscle, risorius muscle, platysma muscle, mentalis muscle, etc.

Cervical dystonia

The usual adult dosage of botulinum toxin type A (Botox), injected intramuscularly into the tonic muscle, is shown below.* In the case of multiple tonic muscles, Botox should be injected into each muscle in divided doses.

- The initial dose is 30 to 60 units in total.

- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 180 units in total) may be administered.
- Botox treatment may be repeated if symptoms relapse, at a dose of up to 240 units in total, but not within 2 months after the previous dose.

* Tonic muscles: sternocleidomastoid muscle, trapezius muscle, splenius muscle, scalenus muscle, anterior edge of the trapezius muscle, levator scapulae, paraspinal muscle, platysma muscle, etc.

Upper limb spasticity

The usual adult dosage of botulinum toxin type A (Botox) is 240 units in total injected intramuscularly in divided doses into each of the tonic muscles.* The maximum single dose is 240 units, but the dose should be decreased to the minimum dose required as appropriate, depending on the type and number of tonic muscles to be treated. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

* Tonic muscles: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis, flexor pollicis longus, adductor pollicis, etc.

Lower limb spasticity

The usual adult dosage of botulinum toxin type A (Botox) is 300 units in total injected intramuscularly in divided doses into each of the tonic muscles.* The maximum single dose is 300 units, but the dose should be decreased to the minimum dose required as appropriate, depending on the type and number of tonic muscles to be treated. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

* Tonic muscles: gastrocnemius muscle (medial head, lateral head), soleus muscle, tibialis posterior muscle, etc.

Talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy

The usual dosage of botulinum toxin type A (Botox) for children ≥2 years of age is 4 units/kg injected intramuscularly into 2 sites each of the medial/lateral head of the affected gastrocnemius muscle. When injected into both legs, the dose of 4 units/kg is divided to each leg. If the patients have an inadequate response after the initial dose, Botox may be injected into the muscles such as the soleus muscle, tibialis posterior muscle. The dose may be adjusted according to the symptoms. The total single dose should not exceed 200 units. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

Severe primary axillary hyperhidrosis

The usual adult dosage of botulinum toxin type A (Botox) is 50 units per axilla injected intracutaneously into multiple (10-15) sites, 1 to 2 cm apart. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 4 months of the previous dose.

Strabismus

The usual dosage of botulinum toxin type A (Botox) for adults and children ≥12 years of age, injected intramuscularly into an extraocular muscle, is shown below.

- Initial dose
  (1) Vertical strabismus: 1.25 to 2.5 units into any one of extraocular muscles
  (2) Horizontal strabismus of <20 prism diopters: 1.25 to 2.5 units into any one of extraocular muscles
  (3) Horizontal strabismus of 20 to 50 prism diopters: 2.5 to 5.0 units into any one of extraocular muscles
  (4) Abducens nerve palsy persisting ≥1 month: 1.25 to 2.5 units into the medial rectus muscle
- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 2-fold the initial dose) may be administered.
- Retreatment with Botox is allowed if the response to the previous dose has worn off, at a dose up to 2-fold a previous single dose, but not within 3 months of the previous dose.
- A single dose per muscle should not exceed 25 units.

(The underline denotes the text added in this application.)

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.

The application was submitted to add a new indication and new dosage and administration. The mechanism of action of Botulinum Toxin Type A on strabismus, the indication to be added with this application, is considered to decrease imbalance of the tension in the extraocular muscles, the muscles responsible for controlling ocular alignment, through muscle relaxant effect mediated by the suppression of acetylcholine release at the neuromuscular junctions around the injection site (Kimura H et al, *Journal of the eye*, 2001; 18: 1137-1140). It is identical to the mechanism of action for the previously approved indications. Therefore, no new pharmacology studies were conducted and no "Non-clinical data" were submitted.

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

Strabismus is an ophthalmological disorder caused by ocular misalignment resulting in the failure of both eyes to look in the same direction. Strabismus causes not only functional problems such as abnormal binocular vision, diplopia, abnormal head posture, and asthenopia, but also problems in facial appearance such as inability to make normal eye contact with other people, which are a handicap in social life (Maruo T et al. *Textbook of Orthoptics*. Bunkodo, Co., Ltd.; 2006:294-300, Matsuo O et al. *Pathophysiology 13, Ocular disorders*. Japan Medical Journal, Co., Ltd.; 2009:148-153). In infants, whose visions are still developing, strabismus may interfere with the normal development of binocular vision and in visual acuity, leading to abnormalities in binocular vision and visual acuity, i.e., amblyopia (Maruo T et al. *Textbook of Orthoptics*. Bunkodo, Co., Ltd.; 2006:294-300).

Botulinum Toxin Type A, the active ingredient of Botox for injection 50 Units and Botox for injection 100 Units (hereinafter collectively referred to as Botox), is a neurotoxin that exhibits a muscle relaxant effect by inhibiting the release of a neurotransmitter acetylcholine. Botox was approved in October 1996 for the indication of blepharospasm, followed by approval for additional indications for hemifacial spasm in January 2000, for cervical dystonia in June 2001, for talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy in February 2009, for upper and lower limb spasticity in October 2010, and for severe primary axillary hyperhidrosis in November 2012.

As of May 2014, Botox is approved in 87 countries or regions for various indications including strabismus, blepharospasm, hemifacial spasm, cervical dystonia, spasms, overactive bladder, facial feature lines, and hyperhidrosis. The indication for strabismus, the one proposed in the present application, is approved in 39 countries or regions including the US, France, Canada, and Australia.

In Japan, a clinical study was initiated by Allergan Japan K.K. in [redacted], but development was discontinued because of the failure to demonstrate dose-response relationship.[1)] Subsequently, "The Study Group on Unapproved and Off-label Drugs of High Medical Need" concluded that botulinum toxin was a drug of high medical need. On December 13, 2010, the applicant was requested to develop botulinum toxin product (HPB/RDD Notification No. 1213-1, PFSB/ELD Notification No. 1213-1). In response to the request, the applicant started a clinical study in [redacted]. The applicant has now submitted the application for a partial change approval claiming the efficacy and safety of botulinum toxin for strabismus has been confirmed.

In Japan, distigmine bromide is approved for the indication for the treatment of accommodative esotropia, but no drug is approved for the correction of the angle of strabismus.

2. Clinical data

2.A Summary of the submitted data

As the efficacy and safety evaluation data, the results from the Japanese phase III study (5.3.5.1.1, Study LOC116246) in patients ≥12 years of age with horizontal strabismus were submitted. As the reference data, the results from a foreign clinical study (Reference 5.3.5.2.1, Scott study) were submitted.

2.A.(1) Japanese phase III study (5.3.5.1.1, Study LOC116246 [May 2012 to June 2014])

Patients ≥12 years of age with horizontal strabismus[2)] (target sample size, 40: 10 patients with baseline strabismus angle in the primary position of ≥10 and <20 prism diopters [PD]; 30 patients with ≥20 and <50 PD, 10 patients each per group)[3)] were subjected to a no-treatment-controlled, randomized, evaluator-masked, parallel group, comparative study (the first treatment phase) and an open-label, uncontrolled study (the second treatment phase in patients receiving readministration) in order to investigate the efficacy and safety of Botox in a single-dose administration and in multiple-dose administration.

At the start of the first treatment phase, subjects in the Botox group were to receive Botox at a single site in the medial or lateral rectus muscle[4)] of the affected eye (≥10 and <20 PD cohort, 1.25 or 2.5 units; ≥20 and <50 PD cohort, 2.5 or 5.0 units), whereas patients in the no-treatment group were not to receive the study drug. If, at Week 4 of the first treatment phase, patients met the criteria for additional dosing,[5)] the patients were to receive Botox at the same dose as or 2-fold the initial dose,[6)] whichever was selected.

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1) The audit by the sponsor revealed serious GCP violations in the data of the clinical study, precluding the reliability of the data. Therefore, the data of the study are not included in the clinical data package for the present application.

2) The main inclusion criteria were as follows:
- Patients with paralytic strabismus or comitant strabismus
  Patients with paralytic strabismus had to have paralysis lasting for ≥3 months and had to have the disease only in one eye.
- Patients with horizontal deviation of the eye from the primary position (esotropia or exotropia)
- Strabismus patients with absolute strabismus angle in the primary eye position of ≥10 and <50 PD both for near and distance vision

3) The target sample size was 66 patients (36 patients with baseline strabismus angle in the primary position of ≥10 and <20 PD [12 patients per group]; 30 patients with ≥20 and <50 PD [10 patients per group]) when the study started. However, because of the difficulty in recruiting the target sample size of ≥10 and <20 PD, the sample size was changed from 36 to 10 during the study.

4) Among patients with comitant strabismus, patients with strabismus in both eyes were to receive the study drug only in one eye, and the study drug was to be injected to the same muscle throughout the study period.

5) An additional dose was to be administered if the subjects met all of the following criteria, except for when strabismus was overcorrected, from esotropia to exotropia of ≥10 PD (absolute value) or vice versa, by Week 4 of the first treatment phase.
- The absolute strabismus angle in the primary position ≥10 PD in subjects with ≥10 and <20 PD at the start of the first treatment phase, ≥20 PD in subjects with ≥20 and <50 PD at the start of the first treatment phase
- Subjects requested additional dosing.
- There were no safety problems in the additional dosing, as judged by the investigator (or subinvestigator).

6) Subjects in the no-treatment group were to receive either the high or low dose of Botox.

Subjects who met the criteria for readministration[7)] during the period from Week 12 to Week 24 after the last dose in the first treatment phase (or after the start of the first treatment phase in subjects in the no-treatment group) were to proceed to the second treatment phase, and subjects who did not meet the criteria were to undergo additional 24-week follow-up. During the second treatment phase, the study drug was to be readministered, at the same dose as or 2-fold the previous dose, whichever was selected, to a single site in the medial or lateral rectus muscle[4)] of the affected eye, and subjects were to be followed up for 24 weeks.

All of the 41 randomized subjects in the first treatment phase (≥10 and <20 PD cohort, 10 subjects [3 subjects in the no-treatment group, 4 subjects in the Botox 1.25 unit group, 3 subjects in the Botox 2.5 unit group]; ≥20 and <50 PD cohort, 31 subjects [10 subjects each in the no-treatment group and in the Botox 2.5 unit group, 11 subjects in the Botox 5.0 unit group]) were included in the safety analysis set and in the efficacy analysis set (full analysis set [FAS] 1). During the first treatment phase, the study was discontinued in 3 subjects for reasons of an adverse event (1 subject in the Botox 2.5 unit group in the ≥10 and <20 PD cohort), protocol deviations (1 subject on the Botox 5.0 unit group in the ≥20 and <50 PD cohort), and meeting discontinuation criteria (1 subject in the Botox 5.0 unit group in the ≥20 and <50 PD cohort). In the second treatment phase, all of the 15 treated subjects (5 subjects in the ≥10 and <20 PD cohort, 10 subjects in the ≥20 and <50 PD cohort) were included in the safety analysis set and in the efficacy analysis set. During the second treatment phase, only 1 subject in the ≥20 and <50 PD cohort discontinued the study (consent withdrawal).

The change in the strabismus angle in the primary position (mean of strabismus angles at near and distance vision) from baseline at Week 4 of the first treatment phase, the primary endpoint, was as shown in Table 1. In the ≥20 and <50 PD cohort, a statistically significant difference in the change was observed between the no-treatment group and each of Botox groups ($P = 0.031$ in the Botox 2.5 unit group, $P = 0.005$ in the Botox 5.0 unit group; analysis of variance [ANOVA] with the treatment group as the factor. Fisher's least significant difference method was used for the adjustment for multiplicity of testing). In the ≥10 and <20 PD cohort, the change in the strabismus angle from baseline was greater in each Botox group than in the no-treatment group, but the difference was not statistically significant ($P = 0.091$ in the Botox 1.25 unit group, $P = 0.338$ in the Botox 2.5 unit group; ANOVA with the treatment group as the factor. Fisher's least significant difference method was used for the adjustment for multiplicity of testing).

Table 1. Change in strabismus angle from baseline at Week 4 of the first treatment phase (FAS1, OC [observed cases])

Baseline strabismus angle	Treatment group	Strabismus angle		Change from baseline[a)]	Comparison with the no-treatment group[b)]	
		Baseline	Week 4		Between-group difference [95% confidence interval (CI)]	*P* value
≥10 and <20 PD	No-treatment	16.17 ± 2.754 (3)	18.50 ± 7.794 (3)	2.33 ± 6.602		
	Botox 1.25 units	15.00 ± 1.414 (4)	7.50 ± 6.137 (4)	-7.50 ± 7.141	-9.83 [-21.81, 2.14]	0.091
	Botox 2.5 units	15.17 ± 2.930 (3)	12.00 ± 1.414 (2)	-3.75 ± 2.475	-6.08 [-20.39, 8.23]	0.338
≥20 and <50 PD	No-treatment	33.75 ± 8.760 (10)	33.20 ± 9.855 (10)	-0.55 ± 2.291		
	Botox 2.5 units	30.55 ± 6.166 (10)	17.15 ± 17.645 (10)	-13.40 ± 15.105	-12.85 [-24.46, -1.24]	0.031
	Botox 5.0 units	35.27 ± 9.152 (11)	18.00 ± 18.126 (11)	-17.27 ± 15.476	-16.72 [-28.06, -5.38]	0.005

Mean ± standard deviation (SD) (Number of subjects evaluated)

a) The protocol had specified that the efficacy in this study was evaluated in FAS1. However, since the protocol had also stipulated that the missing data of the primary analysis was performed in observed cases, the change in the strabismus angle from baseline at Week 4 of the first treatment phase was evaluated in the FAS1 population that excluded 1 subject in whom the study was discontinued before Week 4 of the first treatment phase (the Botox 2.5 unit group in the ≥10 and <20 PD cohort).

b) ANOVA with the treatment group as the factor; Fisher's least significant difference method was used for the adjustment for multiplicity of testing.

7) Subjects who met all of the following criteria were to receive readministration, except for when strabismus overcorrected, from esotropia to exotropia of ≥10 PD (absolute value) or vice versa, during the first treatment phase.

- The absolute strabismus angle in the primary position ≥10 PD in subjects with ≥10 and <20 PD at the start of the first treatment phase, ≥20 PD in subjects with ≥20 and <50 PD at the start of the first treatment phase. In addition, the rate of change was <50% when compared with the strabismus angle at the maximum change.
- After the previous dose, ≥12 weeks have passed.
- Subjects requested the readministration.
- There were no safety problems in readministration, as judged by the investigator (or subinvestigator).

The incidences of adverse events (including laboratory abnormalities) observed by Week 4 of the first treatment phase were 0% (0 of 3 subjects) in the no-treatment group, 0% (0 of 4 subjects) in the Botox 1.25 unit group, and 100.0% (3 of 3 subjects) in the Botox 2.5 unit group in the ≥10 and <20 PD cohort; and 10.0% (1 of 10 subjects) in the no-treatment group, 40.0% (4 of 10 subjects) in the Botox 2.5 unit group, and 36.4% (4 of 11 subjects) in the Botox 5.0 unit group in the ≥20 and <50 PD cohort. The incidences of adverse events were 29.3% (12 of 41 subjects) after Week 4 of the first treatment phase and 40.0% (6 of 15 subjects) in the second treatment phase. No death occurred. A serious adverse event was observed in 1 subject (strabismus[8)]) in the Botox 2.5 unit group in the ≥10 and <20 PD cohort before Week 4 of the first treatment period, and its causal relationship to the study drug could not be ruled out.

The incidences of adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out were as shown in Table 2.

Table 2. Incidences of adverse events for which a causal relationship to the study drug could not be ruled out

	By Week 4 of the first treatment phase						After Week 4 of the first treatment phase	Second treatment phase
	≥10 and <20 PD			≥20 and <50 PD				
	No-treatment	1.25 units	2.5 units	No-treatment	2.5 units	5 units		
Number of subjects examined	3	4	3	10	10	11	41	15
Adverse events for which a causal relationship to the study drug could not be ruled out	0	0	66.7 (2)	0	30.0 (3)	18.2 (2)	7.3 (3)	6.7 (1)
Eyelid ptosis	0	0	0	0	20.0 (2)	18.2 (2)	4.9 (2)	6.7 (1)
Strabismus	0	0	33.3 (1)	0	0	9.1 (1)	0	0
Diplopia	0	0	0	0	0	9.1 (1)	2.4 (1)	0
Conjunctival hyperaemia	0	0	33.3 (1)	0	0	0	0	0
Therapeutic response increased	0	0	0	0	10.0 (1)	0	0	0
Eye movement disorder	0	0	0	0	0	0	2.4 (1)	0
Ophthalmoplegia	0	0	0	0	0	0	0	6.7 (1)

Incidence (%) (Number of subjects with events)

No clinically significant changes were observed in vital signs (blood pressure, pulse rate), electrocardiogram, visual acuity, or slit-lamp examination.

Based on the above, the applicant explained that Botox was superior to no-treatment for Japanese patients with horizontal strabismus of ≥20 and <50 PD, that Botox was suggested to be effective in patients with strabismus angle of ≥10 and <20 PD as well, and that no significant safety problems were noted.

2.B Outline of the review by PMDA

2.B.(1) Clinical positioning of Botox

PMDA asked the applicant to explain the clinical positioning of Botox in the treatment of strabismus.

The applicant's explanation:
Strabismus may be treated by non-invasive or surgical methods. Non-invasive methods include correction of refractive error, prism adaptation, and optometric training. Although non-invasive methods are used in some types of accommodative esotropia, it is not indicated for patients with a large strabismus angle (Ohba M et al. *Journal of the eye*. 2002:19;1557-1564). In patients who have an inadequate response to or are ineligible for non-invasive methods, the only alternative treatments available are surgical therapies such as a muscle weakening or strengthening operation, but reoperation becomes necessary in 10% to 30% of the treated patients (Matsuo O ed. *Pathophysiology 13, Ocular disorders*. Japan Medical Journal, Co., Ltd.; 2009:148-153, Iwashige H et al. *Journal of Japanese Ophthalmological Society.* 1986;90:54-62). In contrast, botulinum toxin is included in the guidelines

8) The initial dose was injected into the medial rectus muscle instead of lateral rectus muscle by mistake, causing aggravation of strabismus. Therefore, lateral rectus recession was performed.

and textbooks available in the US and the UK as a treatment option for strabismus.[9)] Botox can be administered into the extraocular muscle transconjunctivally, making the therapy far less invasive than surgical operation and allowing administration on an outpatient basis. After the initial dose, the patient is monitored and, based on the treatment effect, Botox is readministered. It is thus possible to treat the patient while checking for the effect of Botox to correct the ocular alignment. The effect of Botox is reversible, seldom causing persistent adverse drug reactions. In addition, the procedure is easy, less invasive, and allows multiple-dose administration. For these reasons, botulinum toxin is described as a standard treatment in Japanese textbooks.[10)] The results of interviews with Japanese and non-Japanese experts of strabismus on the clinical positioning of Botox suggest (i) that non-invasive therapy, surgical operation, or Botox is selected according to the conditions of individual patients and, in general, non-invasive therapy and surgical operation is used in preference to Botox, (ii) but that Botox will be used for patients reluctant to undergo surgery, inoperable patients, patients with overcorrection or undercorrection after strabotomy, and patients who require only temporary treatment effect during the early phase of paralytic strabismus or because of unstable strabismus angle due to thyroid ophthalmopathy, etc. Botox thus provides a new treatment option for strabismus treatment in Japan.

PMDA' view:
Taking account of the submitted clinical data, Japanese and foreign textbooks, etc., Botox is qualified as a treatment option for strabismus. It is important to select an appropriate treatment method according to patient conditions, upon accurate understanding of the benefit of Botox compared to other treatment methods and the potential risk of Botox such as effect on distant sites and on the respiratory function as well as production of neutralizing antibody. Methods for promoting proper use of Botox will be discussed in "2.B.(8) Post-marketing investigations."

2.B.(2) Efficacy of Botox

2.B.(2).1) Change in the target sample size in Japanese phase III study (5.3.5.1.1, Study LOC116246)

In the Japanese phase III study, the target sample size for strabismus angle of ≥10 and <20 PD cohort was changed. PMDA asked the applicant to explain the reason for the change and the interpretation of the study results.

The applicant's explanation:
In the initial protocol for the Japanese phase III study, the target sample size in the ≥10 and <20 PD cohort was set at 36 in order to achieve a statistical power of ≥82% in the comparison between the no-treatment group versus the Botox 1.25 or 2.5 unit group. As it turned out, a sufficient number of patients could not be enrolled as planned, for the following reasons: (a) Most of strabismus patients had a history of surgical operation of strabismus, with many of them falling under the exclusion criteria, (b) subjects had to make 4 return visits during the period from treatment with Botox to Week 4 post-dose, making it difficult for business people and students to participate in the study, (c) since the effect of Botox is reversible, patients without surgical history tend to prefer surgical treatment to the treatment with Botox, and (d) patients with strabismus angle of ≥10 and <20 PD tend not to want treatment or visit the ophthalmologist because they do not feel any particular inconvenience in daily life and the extent of their cosmetic problems is minor. In [redacted], in order to facilitate subject enrollment, the study period was prolonged by 7 months, the exclusion criteria were changed to allow, with some conditions, enrolling patients who had undergone surgical operation for strabismus, the total number of office visits was decreased, and additional institutions were included in the study facilities. Despite these changes, patients in the ≥10 and <20 PD cohort could not be recruited in a sufficient number because of the limited number of treatable patients, for the following reasons: (a) They do not dare to participate in the study for treatment because the strabismus has little effect on their daily life, (b) frequent office visits

9) American Academy of Ophthalmology. *Esotropia and exotropia_Preferred practice pattern.* 2012, American Optometric Association. *Strabismus: Esotropia and Exotropia_Optometric clinical practice guideline*. 2011, Taylor RH. *Guidelines for the management of strabismus in childhood*. The Royal College of Ophthalmologists; 2012, Moore AP et al eds. *Handbook of botulinum toxin treatment*. Second edition. Wily-Blackwell; 2003:383-403, Jankovic J et al eds. *Therapy with botulinum toxin*. Marcel Dekker; 1994:371-376, Pratt-Johnson JA eds. *Management of strabismus and amblyopia*. 2nd ed. Thieme; 2001:169-186

10) Ohno S eds. *Standard textbook of ophthalmology*. Igaku-Shoin Ltd.; 2010:288-298, Maruo T et al. *Atlas of Strabismus and Amblyopia*. 3rd ed. Kanehara & Co., Ltd.; 1998:218-219, Maruo T et al. *Strabismus and ocular motility abnormalities*. Bunkodo Co., Ltd.; 2002:204-210, Maruo T et al. *Textbook of Orthoptics.* Bunkodo Co., Ltd.; 2006:404-405, Matsuo O eds. *Pathophysiology 13, Ocular disorders*. Japan Medical Journal, Co., Ltd.; 2009:148-153

are difficult because of school attendance and office work, and (c) patients without ophthalmological complaints do not visit the ophthalmologist, strabismus with <20 PD does not cause any particular cosmetic problem, and wearing prismatic spectacles is useful for correcting diplopia caused by small-angle strabismus. Based on the above, the target sample size in the ≥10 and <20 PD cohort was changed from 36 to 10 for the purpose of feasibility.

As is evident in Table 1, which shows the change in the strabismus angle from baseline at Week 4 of the first treatment phase in the ≥10 and <20 PD cohort in the Japanese phase III study, although neither the Botox 1.25 nor 2.5 unit group was superior to the no-treatment group, each Botox group tended to be recovering compared to the no-treatment group. Investigation of the change over time in the strabismus angle in individual subjects showed that strabismus improved in all subjects in the Botox groups except for 1 subject in whom the study was discontinued because of injection at a wrong site.[8)] Of these subjects, the strabismus angle at Week 4 of the first treatment phase improved to <10 PD in 33.3% (2 of 6 subjects).

Thus, accurate statistical evaluation of efficacy in the ≥10 and <20 PD cohort is difficult because of the change in the target sample size after the start of the Japanese phase III study. Nevertheless, Botox is expected to be effective in patients with horizontal strabismus of ≥10 and <20 PD.

PMDA's view:
Prior to the planning of the study, a detailed survey should have been performed on the patient population, study feasibility, needs for Botox in strabismus treatment in Japan (in particular, needs in patients with strabismus angle of ≥10 and <20 PD), and the study should have been designed accordingly, reflecting the survey results appropriately. However, given the characteristics of the patient population with strabismus angle of ≥10 and <20 PD and the scarce need for Botox in the treatment of strabismus in Japan, PMDA understands the difficulty of enrolling patients in the ≥10 and <20 PD cohort without significant delay compared with the enrollment of patients in the ≥20 and <50 PD cohort. It was inevitable that patients enrolled in the ≥10 and <20 PD cohort did not reach the number as originally planned. With this proviso, and despite the difficulty in drawing any clear conclusion from the results of the Japanese phase III study, Botox is expected to be effective in patients with horizontal strabismus of ≥10 and <20 PD as well, by taking account of the following: (i) Botox was demonstrated to be effective in patients with horizontal strabismus of ≥20 and <50 PD, and (ii) in the ≥10 and <20 PD cohort in the Japanese phase III study, strabismus angle decreased little in the no-treatment group (Table 1) but improved in all subjects in each Botox group, except for 1 subject who received injection at a wrong site.[8)] The efficacy of Botox in patients with horizontal strabismus of ≥10 and <20 PD should continue to be investigated in the post-marketing surveillance.

2.B.(2).2 Factors affecting the efficacy of Botox
PMDA asked the applicant to explain the factors affecting the efficacy of Botox.

The applicant's explanation:
Table 3 shows the results of subgroup analysis, by patient characteristic, on the change in the strabismus angle from baseline at Week 4 of the first treatment phase in the Japanese phase III study (5.3.5.1.1, Study LOC116246). Strabismus angle decreased in each Botox group in all subgroups, although the number of evaluable subjects was particularly small in the ≥10 and <20 PD cohort.

Table 3. Change in the strabismus angle from baseline at Week 4 of the first treatment phase, by patient characteristic, in the Japanese phase III study (5.3.5.1.1, Study LOC116246) (FAS1, OC)

		≥10 and <20 PD			≥20 and <50 PD		
		Treatment group	Change from baseline	Difference from the no-treatment group [95% CI]	Treatment group	Change from baseline	Difference from the no-treatment group [95% CI]
Sex	Men	No treatment	2.33 ± 6.602 (3)		No treatment	-0.17 ± 0.289 (3)	
		1.25	-2.00 (1)	-4.33 [-37.13, 28.47]	2.5	-20.80 ± 18.431 (5)	-20.63 [-44.95, 3.68]
		2.5	-5.50 (1)	-7.83 [-40.63, 24.97]	5.0	-22.75 ± 15.218 (6)	-22.58 [-46.12, 0.96]
	Women	No treatment	- (0)		No treatment	-0.71 ± 2.782 (7)	
		1.25	-9.33 ± 7.506 (3)	-	2.5	-6.00 ± 6.062 (5)	-5.29 [-16.08, 5.51]
		2.5	-2.00 (1)	-	5.0	-10.70 ± 14.503 (5)	-9.99 [-20.78, 0.81]
Age	≤18 years old	No treatment	- (0)		No treatment	-1.67 ± 2.887 (3)	
		1.25	-9.33 ± 7.506 (3)	-	2.5	-10.50 ± 14.849 (2)	-8.83 [-34.66, 17.00]
		2.5	-2.00 (1)	-	5.0	- (0)	-
	≥19 years old	No treatment	2.33 ± 6.602 (3)		No treatment	-0.07 ± 2.050 (7)	
		1.25	-2.00 (1)	-4.33 [-37.13, 28.47]	2.5	-14.13 ± 16.088 (8)	-14.05 [-28.58, 0.47]
		2.5	-5.50 (1)	-7.83 [-40.63, 24.97]	5.0	-17.27 ± 15.476 (11)	-17.20 [-30.77, -3.63]
Body weight[a)]	<56.4 kg	No treatment	9.50 (1)		No treatment	-0.06 ± 1.898 (8)	
		1.25	-9.33 ± 7.506 (3)	-18.83 [-56.12, 18.46]	2.5	-6.88 ± 6.625 (4)	-6.81 [-15.43, 1.81]
		2.5	- (0)	-	5.0	-17.38 ± 11.477 (4)	-17.31 [-25.93, -8.69]
	≥56.4 kg	No treatment	-1.25 ± 3.182 (2)		No treatment	-2.50 ± 3.536 (2)	
		1.25	-2.00 (1)	-0.75 [-15.77, 14.27]	2.5	-17.75 ± 18.099 (6)	-15.25 [-46.28, 15.78]
		2.5	-3.75 ± 2.475 (2)	-2.50 [-14.76, 9.76]	5.0	-17.21 ± 18.257 (7)	-14.71 [-45.18, 15.75]
Age of onset[a) b)]	<34.0 years old	No treatment	9.50 (1)		No treatment	-0.50 ± 2.729 (5)	
		1.25	-7.50 ± 7.141 (4)	-17.00 [-42.41, 8.41]	2.5	-18.75 ± 23.757 (4)	-18.25 [-38.94, 2.44]
		2.5	-2.00 (1)	-11.50 [-43.64, 20.64]	5.0	-18.90 ± 10.449 (5)	-18.40 [-37.91, 1.11]
	≥34.0 years old	No treatment	-1.25 ± 3.182 (2)		No treatment	-0.60 ± 2.074 (5)	
		1.25	- (0)	-	2.5	-9.83 ± 5.820 (6)	-9.23 [-25.22, 6.75]
		2.5	- (0)	-	5.0	-15.92 ± 19.668 (6)	-15.32 [-31.30, 0.67]
Disease duration[a) b)]	<3.2 years	No treatment	-1.25 ± 3.182 (2)		No treatment	-2.50 ± 3.536 (2)	
		1.25	-7.00 ± 8.660 (3)	-5.75 [-26.97, 15.47]	2.5	-10.60 ± 8.003 (5)	-8.10 [-31.60, 15.40]
		2.5	- (0)	-	5.0	-11.64 ± 15.929 (7)	-9.14 [-31.66, 13.38]
	≥3.2 years	No treatment	9.50 (1)		No treatment	-0.06 ± 1.898 (8)	
		1.25	-9.00 (1)	-18.50	2.5	-16.20 ± 20.729 (5)	-16.14 [-30.78, -1.50]
		2.5	-2.00 (1)	-11.50	5.0	-27.13 ± 9.357 (4)	-27.06 [-42.79, -11.34]
Type of eye movement disorder	Paralytic	No treatment	- (0)		No treatment	- (0)	
		1.25	-17.00 (1)	-	2.5	-13.50 (1)	-
		2.5	- (0)	-	5.0	-22.75 ± 8.421 (4)	-
	Comitant	No treatment	2.33 ± 6.602 (3)		No treatment	-0.55 ± 2.291 (10)	
		1.25	-4.33 ± 4.041 (3)	-6.67 [-17.20, 3.87]	2.5	-13.39 ± 16.021 (9)	-12.84 [-25.52, -0.16]
		2.5	-3.75 ± 2.475 (2)	-6.08 [-17.86, 5.69]	5.0	-14.14 ± 18.229 (7)	-13.59 [-27.19, 0.01]
Direction of deviation of eye position	Esotropia	No treatment	9.50 (1)		No treatment	-1.50 ± 2.236 (5)	
		1.25	-17.00 (1)	-26.50	2.5	-21.50 ± 21.806 (4)	-20.00 [-37.98, -2.02]
		2.5	-2.00 (1)	-11.50	5.0	-25.08 ± 8.587 (6)	-23.58 [-39.81, -7.36]
	Exotropia	No treatment	-1.25 ± 3.182 (2)		No treatment	0.40 ± 2.133 (5)	
		1.25	-4.33 ± 4.041 (3)	-3.08 [-14.06, 7.89]	2.5	-8.00 ± 6.156 (6)	-8.40 [-22.11, 5.31]
		2.5	-5.50 (1)	-4.25 [-18.97, 10.47]	5.0	-7.90 ± 17.473 (5)	-8.30 [-22.62, 6.02]

Mean ± SD (Number of subjects evaluated); no treatment, no-treatment group; 1.25, Botox 1.25 unit group; 2.5, Botox 2.5 unit group; 5.0, Botox 5.0 unit group

a) Stratified by median value

b) Onset age and disease duration were unknown in 1 subject. The change in strabismus angle in this subject was -5.50 PD.

PMDA's view:

Only a small number of subjects were evaluated in the Japanese phase III study, posing limitations to the accuracy of the evaluation. Nevertheless, the presented study data do not suggest any significant effect of patient characteristics investigated on the efficacy of Botox, requiring no particular measures at present. Information on the effect of patient characteristics on the efficacy of Botox should continue to be collected in the post-marketing surveillance.

2.B.(3) Safety of Botox

2.B.(3).1) Safety profiles of Botox in patients treated for strabismus compared with those in patients treated for approved indications

PMDA asked the applicant to explain whether or not there were differences in the incidences of adverse events in the Japanese clinical study for strabismus and the Japanese studies for approved indications.

The applicant's explanation:
The incidences of the major adverse events observed in the Japanese phase III study (5.3.5.1.1, Study LOC116246) for strabismus were as shown in Table 4. Compared with the Japanese clinical studies for approved indications, the incidences of eye-related adverse events such as eyelid ptosis, conjunctival haemorrhage, diplopia, and strabismus, etc., were higher, whereas other adverse events did not show any significant difference.

Table 4. Incidences of major adverse events in Japanese phase III study (5.3.5.1.1, Study LOC116246)

	By Week 4 of the first treatment phase						After Week 4 of the first treatment phase	The second treatment phase
	≥10 and <20 PD			≥20 and <50 PD				
	No treatment	1.25 units	2.5 units	No treatment	2.5 units	5 units		
Number of subjects evaluated	3	4	3	10	10	11	41	15
Adverse events	0	0	100.0 (3)	10.0 (1)	40.0 (4)	36.4 (4)	29.3 (12)	40.0 (6)
Eyelid ptosis	0	0	0	0	20.0 (2)	18.2 (2)	4.9 (2)	6.7 (1)
Conjunctival haemorrhage	0	0	33.3 (1)	0	0	9.1 (1)	0	0
Strabismus	0	0	33.3 (1)	0	0	9.1 (1)	0	0
Diplopia	0	0	0	0	0	9.1 (1)	2.4 (1)	0
Conjunctival hyperaemia	0	0	33.3 (1)	0	10.0 (1)	0	0	0
Nasopharyngitis	0	0	0	10.0 (1)	0	0	4.9 (2)	6.7 (1)
Bronchitis	0	0	0	0	0	0	4.9 (2)	0
Gastroenteritis	0	0	0	0	0	0	2.4 (1)	6.7 (1)

Incidence (%) (Number of subjects with events)

Based on the study data presented, PMDA considers that the safety risk of Botox in patients with strabismus does not exceed that in patients treated for the approved indications except for eye-related adverse events. Eye-related adverse events and effects on distant sites, as individual factors in light of the safety profile of Botox, are discussed in the following sections.

2.B.(3).2) Eye-related adverse events

PMDA asked the applicant to explain the incidence of eye-related adverse events in strabismus patients.

The applicant's explanation:
The incidences of eye-related adverse events[11)] in the Japanese phase III study (5.3.5.1.1, Study LOC116246) were as shown in Table 5. All events were mild or moderate. The only serious adverse event was strabismus in 1 subject[8)] which was caused by injection at the wrong site and resulted in study discontinuation. The outcomes were recovered/resolved or recovering/resolving for all adverse events except for eye movement disorder in 1 subject, which also tended to resolve.

Table 5. Incidences of eye-related adverse events in Japanese phase III study (5.3.5.1.1, Study LOC116246)

	By Week 4 of the first treatment phase						After Week 4 of the first treatment phase	The second treatment phase
	≥10 and <20 PD			≥20 and <50 PD				
	No treatment	1.25 units	2.5 units	No treatment	2.5 units	5 units		
Number of subjects evaluated	3	4	3	10	10	11	41	15
Adverse events	0	0	100.0 (3)	0	30.0 (3)	27.3 (3)	12.2 (5)	26.7 (4)
Eyelid ptosis	0	0	0	0	20.0 (2)	18.2 (2)	4.9 (2)	6.7 (1)
Conjunctival haemorrhage	0	0	33.3 (1)	0	0	9.1 (1)	0	0
Strabismus	0	0	33.3 (1)	0	0	9.1 (1)	0	0
Diplopia	0	0	0	0	0	9.1 (1)	2.4 (1)	0
Conjunctival hyperaemia	0	0	33.3 (1)	0	10.0 (1)	0	0	0
Dry eye	0	0	0	0	0	0	2.4 (1)	0
Eye movement disorder	0	0	0	0	0	0	2.4 (1)	0
Punctate keratitis	0	0	0	0	0	0	2.4 (1)	0
Conjunctival deposit	0	0	0	0	0	0	0	6.7 (1)
Conjunctivitis allergic	0	0	0	0	0	0	0	6.7 (1)
Corneal erosion	0	0	0	0	0	0	0	6.7 (1)
Ophthalmoplegia	0	0	0	0	0	0	0	6.7 (1)

Incidence (%) (Number of subjects with events)

11) Events classified as "Eye disorders" in system organ class of MedDRA

The applicant also explained that, in the safety database of Allergan Inc., US (10,645,943-14,923,963 patient-years during the period from January 1, 1990 to December 31, 2013),[12] a total of 62 eye-related adverse events[11] were reported in patients who used Botox for the treatment of strabismus or strabismus congenital (eyelid ptosis [21 events], strabismus [8 events], diplopia [5 events], eye movement disorder [5 events], extraocular muscle paresis [3 events], episcleritis [2 events], ophthalmoplegia [2 events], vision blurred [2 events]), most of which were events known to occur at or around the site of the injection of Botox for the treatment of blepharospasm or hemifacial spasm.

PMDA asked the applicant to explain the risk of overcorrection caused by the treatment with Botox.

The applicant's explanation:
In the Japanese phase III study, no overcorrection[13] occurred in subjects in the ≥10 and <20 PD cohort, whereas in the ≥20 and <50 PD cohort, overcorrecton[13] occurred in 10.0% (1 of 10 subjects) in the Botox 2.5 unit group and in 27.3% (3 of 11 subjects) in the Botox 5.0 unit group by Week 4 of the first treatment phase. Overcorrection of strabismus angle by more than 10 PD (absolute value) occurred only in 1 subject in the Botox 2.5 unit group. In this subject, the strabismus angle at 1 week after dosing was -40.0 PD but resolved almost to the orthophoric position, at -0.5 PD, at 8 weeks after dosing. Thus, because of the reversibility of the effect of Botox, the overcorrection wears off spontaneously over time, posing little risk.

PMDA's view:
Judging from the clinical study data, eye-related adverse events such as eyelid ptosis are the risks unique to strabismus patients treated with Botox. However, a serious adverse event or adverse event leading to study discontinuation was observed in only 1 subject.[8] Given the low severity and the favorable outcome, eye-related adverse events are unlikely to pose clinically significant problems in strabismus patients. Overcorrection occurred in some subjects in the Japanese phase III study (5.3.5.1.1, Study LOC116246), but was not clinically significant in most of the cases, suggesting that overcorrection associated with Botox is unlikely to pose clinically significant problems. Information on the eye-related risks caused by Botox should be provided to healthcare professionals in the clinical setting using materials for them, and continue to be investigated in the post-marketing surveillance.

2.B.(3).3) Effects on distant sites

PMDA asked the applicant to explain the incidences of adverse events related to distant spread of the toxin effect in strabismus patients.

The applicant's explanation:
Table 6 shows the incidences of adverse events related to distant spread of the toxin effect[14] in the Japanese phase III study (5.3.5.1.1, Study LOC116246). No adverse events occurred beyond proximity of the injection site [for eye disorder-related adverse events, see "2.B.(3).2) Eye-related adverse events"].

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12) Includes all adverse events collected by Allergan Inc., US from spontaneous reports all over the world including Japan, as well as serious adverse events in clinical studies. The number of patients exposed to Botox was estimated separately for US, Europe, and other countries and regions, and the number of the exposed patients in other countries or regions was estimated based on the minimum and maximum number of vials used per single dose. Therefore, the estimated number of exposed patients is expressed in range. The percentage of patients with strabismus among patients who used Botox is estimated to be 0.3% based on the survey using the clinical database of the US (Truven Health MarketScan).

13) Overcorrection was defined as "percentage change in strabismus angle from baseline <-100%".

14) Events classified as any one of the following preferred terms of MedDRA: bradycardia, accommodation disorder, diplopia, extraocular muscle paresis, eyelid function disorder, eyelid ptosis, pupillary reflex impaired, vision blurred, constipation, dry mouth, dysphagia, ileus paralytic, botulism, muscular weakness, urinary retention, pelvic floor muscle weakness, bulbar palsy, cranial nerve palsies multiple, cranial nerve paralysis, dysarthria, 7th nerve paralysis, facial paresis, hyporeflexia, hypotonia, paralysis, paralysis flaccid, paresis cranial nerve, peripheral nerve palsy, peripheral paralysis, speech disorder, vocal cord paralysis, vocal cord paresis, aspiration, diaphragmatic paralysis, dysphonia, dyspnoea, pneumonia aspiration, respiratory arrest, respiratory depression, and respiratory failure

Table 6. Incidences of adverse events related to distant spread of effect in Japanese phase III study (5.3.5.1.1, Study LOC116246)

	By Week 4 of the first treatment phase						After Week 4 of the first treatment phase	The second treatment phase
	≥10 and <20 PD			≥20 and <50 PD				
	No-treatment	1.25 units	2.5 units	No-treatment	2.5 units	5 units		
Number of subjects evaluated	3	4	3	10	10	11	41	15
Adverse events related to distant spread of effect	0	0	0	0	20.0 (2)	18.2 (2)	7.3 (3)	6.7 (1)
Eyelid ptosis	0	0	0	0	20.0 (2)	18.2 (2)	4.9 (2)	6.7 (1)
Diplopia	0	0	0	0	0	9.1 (1)	2.4 (1)	0

Incidence (%) (Number of subjects with events)

The applicant also explained that, in the safety database of Allergan Inc., US (10,645,943-14,923,963 patient-years during the period from January 1, 1990 to December 31, 2013),[12)] there were no adverse events related to distant spread of the toxin effect reported in strabismus patients, which suggested that the risk of adverse events at distant sites is minor in strabismus patients, requiring no further caution statement in the package insert.

PMDA's view:
Judging from the clinical study results presented, the risk of effect at distant sites in strabismus patients is unlikely to exceed the risk observed in patients treated for approved indications. However, because of the extremely small number of subjects evaluated in the Japanese phase III study, the risk of effects at distant sites should continue to be investigated in the post-marketing surveillance.

2.B.(4) Efficacy and safety in multiple-dose administration

PMDA asked the applicant to explain the efficacy and safety of Botox in multiple-dose administration.

The applicant's explanation:
Table 7 shows the maximum deviation change,[15)] the net change, and the maximum % deviation change[16)] in strabismus angle in the first and second treatment phases of the Japanese phase III study (5.3.5.1.1, Study LOC116246). No decrease was observed in the maximum change, the maximum rate of change, or the final change in strabismus angle in the second treatment phase compared with the first treatment phase, suggesting that multiple-dose administration is unlikely to cause decrease in the extent or duration of the efficacy.

15) Maximum deviation change (PD) = strabismus angle at maximum change after each dose – strabismus angle before the first treatment phase
In subjects with exotropia, the observed value was multiplied by -1. In subjects with esotropia, the observed value was used as is.

16) Maximum % deviation change = maximum change in strabismus angle/strabismus angle before the first treatment phase × 100
In subjects with exotropia, the observed value was multiplied by -1. In subjects with esotropia, the observed value was used as is.

Table 7. Maximum change, final change, and maximum rate of change in strabismus angle in Japanese phase III study (5.3.5.1.1, Study LOC116246)

≥10 and <20 PD		No-treatment → Botox	Botox 1.25 units	Botox 2.5 units	Total
Up to Week 48 after the last dose in the first treatment phase	Number of subjects evaluated	3	4	3	10
	Maximum deviation change	-9.50 ± 2.179	-8.88 ± 6.434	5.83 ± 22.115	-4.65 ± 13.265
	Maximum % deviation change	-58.30 ± 3.936	-57.80 ± 37.767	47.17 ± 151.828	-26.46 ± 90.460
	Net change	-0.50 ± 4.924	-1.25 ± 11.266	9.17 ± 19.107	2.10 ± 12.358
Up to Week 24 after the last dose in the second treatment phase	Number of subjects evaluated	2	1	2	5
	Maximum deviation change	-5.75 ± 8.132	-3.00	-8.75 ± 2.475	-6.40 ± 4.891
	Maximum % deviation change	-32.85 ± 46.457	-21.40	-55.30 ± 2.121	-39.54 ± 27.740
	Net change	-4.00 ± 9.192	-2.00	0.50 ± 0.707	-1.80 ± 5.131
≥20 and <50 PD		No-treatment → Botox	Botox 2.5 units	Botox 5.0 units	Total
Up to Week 48 after the last dose in the first treatment phase	Number of subjects evaluated	10	10	11	31
	Maximum deviation change	-13.00 ± 6.142	-18.70 ± 18.642	-27.45 ± 14.794	-19.97 ± 15.027
	Maximum % deviation change	-42.31 ± 22.361	-64.24 ± 62.742	-80.47 ± 38.877	-62.93 ± 45.716
	Net change	-2.50 ± 3.993	-6.70 ± 7.387	-11.18 ± 12.007	-6.94 ± 9.077
Up to Week 24 after the last dose in the second treatment phase	Number of subjects evaluated	6	3	1	10
	Maximum deviation change	-18.33 ± 12.424	-12.33 ± 2.021	-9.50	-15.65 ± 9.967
	Maximum % deviation change	-52.37 ± 31.892	-44.67 ± 21.426	-42.20	-49.04 ± 26.192
	Net change	-6.83 ± 7.387	-2.33 ± 4.752	-4.50	-5.25 ± 6.317

Mean ± SD

In the Japanese phase III study, the incidence of adverse events was 43.9% (18 of 41 subjects) in the first treatment phase and 40.0% (6 of 15 subjects) in the second treatment phase, showing no difference between the phases. The severity was mild in 26.8% (11 of 41 subjects) and moderate in 17.1% (7 of 41 subjects) in the first treatment phase, and mild in 26.7% (4 of 15 subjects) and moderate in 13.3% (2 of 15 subjects) in the second treatment phase, showing no significant difference. Among subjects who proceeded to the second treatment phase, only 1 subject experienced the same adverse event as in the first treatment phase (nasopharyngitis). This subject belonged to the no-treatment group in the first treatment phase and, as a result, nasopharyngitis during this phase occurred without administration of Botox. Thus the safety risk did not tend to increase by multiple-dose administration of Botox.

PMDA's view:
Based on the clinical study data presented, multiple-dose administration of Botox is unlikely to decrease the efficacy or increase the risk. However, because of the extremely small number of subjects evaluated in the Japanese phase III study, the efficacy and safety of multiple-dose administration of Botox should continue to be investigated in the post-marketing surveillance.

2.B.(5) Efficacy and safety in patients positive for neutralizing antibody

PMDA asked the applicant to explain the efficacy and safety of Botox in patients positive for neutralizing antibody.

The applicant's explanation:
In the Japanese phase III study (5.3.5.1.1, Study LOC116246), test for neutralizing antibody was performed at the screening and at the end of the study. As a result, neutralizing antibody-positive subjects were not detected at either time point. In the meta-analysis of 16 Japanese and foreign clinical studies of Botox, neutralizing antibody was detected in 0.49% (11 of 2240 subjects), and loss of treatment effect due to the production of the neutralizing antibody was observed in only 3 subjects (Naumann M et al. *Movement Disorders*. 2010;25:2211-2218). Based on the above results, neutralizing antibody is unlikely to be produced provided that Botox is used appropriately for the treatment of strabismus. As a precautionary measure, however, a caution statement on neutralizing antibody production will be included in the package insert, as is the case for the approved indications.

PMDA's view:
Given the extremely small number of subjects evaluated in the Japanese clinical study on strabismus, it is appropriate to raise caution to neutralizing antibody as is the case with the approved indications,

because the possibility of decreases in the efficacy caused by neutralizing antibody production cannot be clearly excluded. The effects of the neutralizing antibody on the efficacy and safety of Botox should continue to be investigated in the post-marketing surveillance.

2.B.(6) Indication

PMDA asked the applicant to explain the rationale for proposing "strabismus" as an indication despite the fact that the Japanese phase III study (5.3.5.1.1, Study LOC116246) was conducted only in patients with horizontal strabismus.

The applicant's explanation:

Strabismus is classified in various ways: horizontal strabismus (esotropia, exotropia) and vertical strabismus (hypertropia, hypotropia) according to the direction of the ocular misalignment; or comitant strabismus and paralytic strabismus (noncomitant strabismus) according to the presence or absence of eye movement disorder (Maruo T et al. *Textbook of Orthoptics*. Bunkodo, Co., Ltd.; 2006:294-300, Matsuo O et al. *Pathophysiology 13, Ocular disorders*. Japan Medical Journal, Co., Ltd.; 2009:148-153). There were very few patients with vertical strabismus (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Patient Survey 2011, Table 97 [total number of patients by disease and injury], 2011), precluding the conduct of a clinical study on this patient group. Injection of Botox to any one of the tonic extraocular muscles relaxes the muscle, thereby improving the balance of extraocular muscles and allowing the eye to approach the primary position. Since the mechanism is common both to horizontal strabismus and vertical strabismus, Botox with the demonstrated efficacy for horizontal strabismus is expected to be equally effective for vertical strabismus. In addition, in a foreign clinical study (Reference 5.3.5.2.1, Scott study), Botox decreased the strabismus angle in patients with vertical strabismus to the same extent as observed in patients with horizontal strabismus. Furthermore, Botox has been used in patients with vertical strabismus in and out of Japan over many years.[17)] In the Japanese phase III study, the change in strabismus angle in patients with comitant strabismus and in patients with paralytic strabismus was as shown in Table 3. Thus, strabismus was improved in both subgroups although the effect on paralytic strabismus was evaluated in only a small number of patients enrolled. In the Japanese phase III study, patients with the following disorders were excluded: Old paralytic strabismus, strabismus exceeding 50 PD, restrictive strabismus, Duane's syndrome associated with weakening of lateral rectus muscle, strabismus secondary to past retrodisplacement of antagonist muscle, and strabismus caused by thyroid ophthalmopathy. As for old paralytic strabismus, Botox is not expected to be effective because a long time has passed after the disease onset, resulting in a severe contracture of the antagonist muscle. The disease is generally treated by surgical operation. To raise caution, it will be described in the package insert that Botox is ineffective for this type of strabismus. Regarding strabismus exceeding 50 PD, restrictive strabismus, Duane's syndrome associated with weakening of lateral rectus muscle, and strabismus secondary to past retrodisplacement of antagonist muscle, the latest Company Core Data Sheet (CCDS) states that the efficacy in these diseases has not been established. This information will also be provided in the package insert to raise caution. As regards strabismus caused by thyroid ophthalmopathy, patients with the disease were excluded from the Japanese phase III study because the disease may possibly be cured by the treatment of the primary disease. However, there are reports which state that Botox is effective for this type of strabismus as well,[18)] suggesting that any specific caution regarding this type of strabismus is unnecessary.

Based on the above, the applicant considers it appropriate to have proposed that the indications of Botox include "strabismus," with a caution statement in the package insert regarding the following diseases: old paralytic strabismus, strabismus exceeding 50 PD, restrictive strabismus, Duane's syndrome associated with weakening of lateral rectus muscle, and strabismus secondary to past retrodisplacement of antagonist muscles.

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17) Dunn WJ et al. *Ophthalmology*. 1986;93:470-475, Iwashige H et al. *Japanese Review of Clinical Ophthalmology*. 1987;81:951-961, McNeer KW. *J Pediatr Ophthalmol Strabismus*. 1989;26:162-164, McNeer KW. *J Pediatr Ophthalmol Strabismus*. 1990;27:3-9, Scott AB. *Arch Ophthalmol*. 1990;108:509-510, Petitto VB et al. *Ophthalmology*. 1991;98:509-513, Lennerstrand G et al. *Acta Ophthalmol Scand*. 1998;76:27-37, Kikkawa DO et al. *Am J Ophthalmol*. 2003;135:427-431, Stiglmayer N et al. *Coll Antropol*. 2005;29:41-46, Merino PS et al. *Eur J Ophthalmol*. 2014;24:147-152, Brin MF et al. eds. *Scientific and Therapeutic Aspects of Botulinum Toxin*. Lippincott Williams & Wilkins; 2002:189-195, Moore AP et al. eds. *Handbook of botulinum toxin treatment*. Wiley-Blackwell; 2003:383-403

18) Ohba M et al. *Journal of the eye*. 2002;19:1557-1564, Kimura H. *Journal of the eye*. 1995;12:415-422, Dunn WJ et al. *Ophthalmology*. 1986;93:470-475

PMDA's view:
Although the efficacy and safety of Botox were investigated only in patients with horizontal strabismus in the Japanese phase III study, the mechanism of action of Botox is common to horizontal and vertical strabismus. In addition, given the limited number of patients with vertical strabismus, precluding the conduct of an appropriate comparative study, it is considered acceptable to propose that the indications of Botox include "strabismus," instead of limiting it only to "horizontal strabismus." Regarding old paralytic strabismus, Botox is unlikely to be effective given the pathology of the disease. As for strabismus exceeding 50 PD, restrictive strabismus, Duane's syndrome associated with weakening of lateral rectus muscle, and strabismus secondary to past retrodisplacement of antagonist muscle, patients with these types of strabismus were excluded from the Japanese phase III study, and the efficacy of Botox is not established in the CCDS. Taking account of these, it is appropriate to provide a caution statement in the package insert regarding these types of strabismus. The description will be finalized based on the review at the Expert Discussion. As regards strabismus caused by thyroid ophthalmopathy, although patients with this type of strabismus were excluded from the Japanese phase III study, there are reports that suggest the efficacy of Botox for this type of strabismus. Taking account of these, it is unnecessary to provide a caution statement in the package insert, but the fact that patients with this type of strabismus were excluded from the Japanese phase III study should be provided to healthcare professionals in the clinical setting via materials for proper use. Information on the efficacy and safety of Botox in patients with different types of strabismus should be collected in the post-marketing surveillance.

2.B.(7) Dosage and administration

2.B.(7).1) Dosage and administration in Japanese phase III study (5.3.5.1.1, Study LOC116246)

PMDA asked the applicant to provide the rationale for the dosage and administration in the Japanese phase III study.

The applicant's explanation:
In the US, the application for Botox was submitted by Oculinum Inc., US (currently Allergan Inc., US) based on the results of Scott study (5.3.5.2.1), which retrospectively collected the efficacy and safety data in patients receiving Botox for the treatment of strabismus during the period from 1977 through 1984. As a result, Botox was approved for the indication of strabismus, but the detailed rationales for the dosage and administration in the US are unclear. In the Japanese phase III study, the following initial doses were selected by referring to the dosage regimen in the US: 1.25 or 2.5 units in patients with ≥10 and <20 PD and 2.5 or 5.0 units in patients with ≥20 and <50 PD. It is reported that the maximum effect of Botox is reached at 1 to 2 weeks after dosing in most patients and 4 weeks after dosing in some patients (Iwashige H et al. *Journal of Japanese Ophthalmological Society.* 1986;90:1366-1374). Based on this finding, the time to the additional dosing was set at 4 weeks in order for its necessity to be judged after the effect of the initial dose has fully been achieved. If subjects met the criteria for the additional dosing,[5)] the subjects were to receive Botox at the same dose as or 2-fold the initial dose. Since the efficacy of Botox is considered to last approximately 3 months, if subjects met the readministration criteria[7)] during the period from Week 12 to Week 24 after the last dose in the first treatment phase, the subjects were to receive Botox at the same dose as or 2-fold the previous dose. In the Japanese phase III study, pediatric patients aged ≥12 years were also included in subjects. Binocularity has fully developed approximately by the age of 6 years (Maruo T et al. *Textbook of Orthoptics*. Bunkodo, Co., Ltd.; 2006:176-183), which suggests that it is appropriate to regard strabismus in children ≥12 years of age, beyond the critical age for binocularity, as identical to that in adults. Pediatric patients were therefore treated with the same dosage and administration as those for adult patients.

2.B.(7).2) Initial dose

(a) Initial dose in patients with horizontal strabismus

PMDA asked the applicant to explain the rationale for the proposed initial dose in patients with horizontal strabismus.

The applicant's explanation:
Table 1 shows the efficacy of Botox in each dose group in the Japanese phase III study (5.3.5.1.1, Study LOC116246). The results showed that no significant difference in the efficacy was observed between the low dose and the high dose,[19] neither in the ≥10 and <20 PD cohort nor in the ≥20 and <50 PD cohort. In the ≥20 and <50 PD cohort, baseline strabismus angle was ≥40 PD in 2 subjects in the Botox 2.5 unit group and in 5 subjects in the Botox 5.0 unit group. Both subjects in the Botox 2.5 unit group showed improvement of only approximately -2.5 PD, whereas 2 subjects in the Botox 5.0 unit group achieved strabismus angle of <20 PD, precluding the necessity for additional dosing.[5] Two of the remaining 3 subjects also achieved improvement of -15 and -16 PD. In the Japanese phase III study, all subjects in the no-treatment group received additional dosing. The high dose was selected for the additional dosing in 1 subject in the ≥10 and <20 PD cohort and in 2 subjects in the ≥20 and <50 PD cohort. Strabismus angle before the additional dosing in these subjects was relatively large, i.e., 27.5 PD in the subject in the ≥10 and <20 PD cohort and 45.0 and 37.5 PD in the subjects in the ≥20 and <50 PD cohort, which suggested that a high initial dose is needed in patients with a large strabismus angle. A detailed survey of Japanese and foreign textbooks, guidelines, and published articles showed that the initial dose of Botox in patients with horizontal strabismus was 0.5 to 5.0 units in Japan and 0.25 to 50.0 units in foreign countries.[20] Regarding the criteria for the initial dose, there was a report proposing the usual dose within the ranges from 2.5 to 7.5 units, which should be calculated according to the age, body weight, type of strabismus, and extent of strabismus angle (Iwashige H. *Journal of the eye*. 1991;8:1885-1891). The applicant interviewed 10 Japanese experts on strabismus about the necessity of the high initial dose,[19] to which 6 experts expressed the opinion that the high dose[19] is necessary for patients with a large strabismus angle. According to the results of the interview, the percentage of patients requiring a high initial dose[19] was 70% to 100% in patients with <20 PD (2.5 units) and 10% to 80% in patients with ≥20 and <50 PD (5.0 units).

Based on the above, the applicant considers it appropriate to select 1.25 to 2.5 units as the initial dose in patients with horizontal strabismus with <20 PD and at 2.5 to 5.0 units in patients with ≥20 and <50 PD.

(b) Initial dose in patients with vertical strabismus and patients with abducens nerve palsy
PMDA asked the applicant to explain the rationale for the proposed initial dose in patients with vertical strabismus and patients with abducens nerve palsy.

The applicant's explanation:
The efficacy and safety of the initial dose of Botox in Japanese patients with vertical strabismus were not investigated. In patients with horizontal strabismus, however, Botox was shown to be effective in the Japanese phase III study conducted using the dosage and administration similar to those in the US, and the mechanism of action of Botox is considered to be common between patients with vertical strabismus and patients with horizontal strabismus. Therefore, the applicant considers it appropriate to select 1.25 to 2.5 units as the initial dose for patients with vertical strabismus as is the case in the US. Next, the applicant interviewed 10 Japanese experts of strabismus about the necessity of starting the treatment at the high dose (2.5 units) in patients with vertical strabismus. Six experts were of the opinion that the high initial dose is necessary, particularly in patients with a large strabismus angle. The results of the interview showed that 5% to 100% of patients required the high initial dose (2.5 units).

As for patients with abducens nerve palsy, it is recommended to determine the timing of the initial dose at ≥1 month after the onset because the disease often remits spontaneously, and to start the treatment at a relatively low dose (1.25-2.5 units) (Scott AB. *Vol VII Module 12: Botulinum toxin treatment of strabismus*. American Academy of Ophthalmology, 1989:1-11). It is reported that the rate of spontaneous remission in patients with paralytic strabismus is 13% to 80% with oculomotor nerve

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19) Low dose: 1.25 units in the ≥10 and <20 PD cohort; 2.5 units in the ≥20 and <50 PD cohort
High dose: 2.5 units in the ≥10 and <20 PD cohort; 5.0 units in the ≥20 and <50 PD cohort

20) Iwashige H et al. *Journal of Japanese Ophthalmological Society*. 1986;90:1366-1374, Iwashige H et al. *Journal of Japanese Ophthalmological Society*. 1995;99:232-237, Iwashige H et al. *Journal of the eye*. 1991;8;1885-1891, Abbasoglu OE et al. *Eye*. 1996;10:385-391, Carruthers JDA et al. *Arch Ophthalmol*. 1990;108:1432-1435, Flanders M et al. *Can J Ophthalmol*. 1987;22:212-217, Gammon JA et al. *J Ophthalmic Nurs Technol*. 1986;5:51-57, Moore AP et al. editors. *Handbook of botulinum toxin treatment*. Second edition. Wily-Blackwell; 2003:383-403, Brin MF et al. eds. *Scientific and Therapeutic Aspects of Botulinum Toxin.* Lippincott Williams & Wilkins; 2002:189-195

paralysis, 14% to 82.1% with trochlear nerve paralysis, and 32% to 82.6% with abducens nerve palsy, and that the recuperation period is 42 days to 3.3 months for oculomotor nerve paralysis, 52 days to 3 months for trochlear nerve paralysis, and 45 days to 2.7 months for abducens nerve palsy.[21)] Thus, there is no significant difference either in the rate of spontaneous remission or in the recuperation period among different types of paralytic strabismus. Whereas the site of injection is limited to the medial rectus muscle in patients with abducens nerve palsy, the muscle to be treated in patients with oculomotor or trochlear nerve paralysis has to be selected according to the disease conditions, precluding the setting of any specific dose for patients with oculomotor or trochlear nerve paralysis. In the Japanese phase III study, patients with paralytic strabismus were enrolled only if the paralysis had persisted for ≥3 months in order to exclude patients who were likely to achieve spontaneous remission. However, there is a report recommending the use of Botox at an early phase to prevent the contracture of the antagonist muscles that may occur while the patient waits for the recovery from the paralysis (Kimura H. *Journal of the eye*. 1995;12:415-422). The proposed dosage and administration are set to allow administration of Botox for persistent abducens nerve palsy of ≥1 month. The applicant interviewed 10 Japanese experts of strabismus regarding the necessity of starting the treatment at a high dose in patients with abducens nerve palsy. Seven experts were of the opinion that a high initial dose is necessary in patients with a large strabismus angle or with mobility limitation. The results of the interview showed that a high initial dose (2.5 units) was required in 10% to 100% of patients.

Based on the above, the applicant considers it appropriate to select 1.25 to 2.5 units as the initial dose in patients with vertical strabismus or with abducens nerve palsy persisting ≥1 month.

2.B.(7).3) Additional dose and dosing interval

PMDA asked the applicant to explain the rationale for the proposed additional dose and the time to additional dose.

The applicant's explanation:
In the Japanese phase III study (5.3.5.1.1, Study LOC116246), 21.4% (6 of 28 subjects) in the Botox group received an additional dosing. In 2 of these subjects, strabismus angle improved to <10 PD at 4 weeks after the additional dosing. The only adverse event observed among these 6 subjects within 4 weeks after the additional dosing was dental caries in 1 subject in the Botox 2.5 unit group in the ≥10 and <20 PD cohort, who received the additional dosing at the same dose. The time to additional dosing or the readministration interval and doses thereof, described in Japanese and foreign textbooks and published literature, are 1 to 50 weeks and 1.25 to 25 units, respectively, in patients with horizontal strabismus; 2 to 4 months and 2.5 to 15 units, respectively, in patients with vertical strabismus; and 1 to 5 months and 0.75 to 7.75 units, respectively, in patients with abducens nerve palsy.[22)] Based on the above, the applicant considers it appropriate to set the maximum additional dose at 2-fold the initial dose when no adequate response is obtained after the initial dose, as is the case in the US, and to set the time to additional dosing at ≥4 weeks.

2.B.(7).4) Dose and interval of readministration

PMDA asked the applicant to explain the rationale for the proposed dose and readministration interval.

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21) Kobashi R et al. *Jpn J Ophthal*. 1996;40:502-510, Iwasaki Y et al. *Journal of Japanese Ophthalmological Society*. 1993;97:845-850, Fujii M et al. *Japanese Review of Clinical Ophthalmology*. 2001;95:750-753, Mimura O et al. *Japanese Review of Clinical Ophthalmology*. 2007;101:178-181

22) Carruthers JDA et al. *Arch Ophthalmol*. 1990;108:1432-1435, Dengis CA et al. *Exp Brain Res*. 1998;119:475-482, Dunn WJ et al. *Ophthalmology*. 1986;93:470-475, Flanders M et al. *Can J Ophthalmol*. 1987;22:212-217, Gammon JA et al. *J Pediatr Ophthalmol Strabismus*. 1985;22:221-226, Han SH et al. *J Pediatr Ophthalmol Strabismus*. 2001;38:68-71, Holmes JM et al. *J AAPOS*. 2001;5:370-376, Hunter DG et al. *J Pediatr Ophthalmol Strabismus*. 1996;33:241-246, Kikkawa DO et al. *Am J Ophthalmol*. 2003;135:427-431, Kraft SP et al. *Am Orthopt J*. 1989;39:89-97, Moore AP et al. editors. *Handbook of botulinum toxin treatment*. Second edition. Wily-Blackwell; 2003:383-403, Lennerstrand G et al. *Acta Ophthalmol Scand*. 1998;76:27-37, McNeer KW. *J Pediatr Ophthalmol Strabismus*. 1990;27:3-9, McNeer KW. *J Pediatr Ophthalmol Strabismus*. 1989;26:162-164, Merino PS et al. *Eur J Ophthalmol*. 2014;24:147-152, Metz HS et al. *Am J Ophthalmol*. 1991;112:381-384, Metz HS et al. *Graefes Arch Clin Exp Ophthalmol*. 1988;226:141-144, Murray ADN. *Aust N Z J Ophthalmol*. 1989;17:239-245, Petitto VB et al. *Ophthalmology*. 1991;98:509-513, Repka MX et al. *J Pediatr Ophthalmol Strabismus*. 1994;31:79-83, Scott AB et al. *Ophthalmology*. 1985;92:676-683, Scott AB. *Arch Ophthalmol*. 1990;108:509-510, Brin MF et al. eds. *Scientific and Therapeutic Aspects of Botulinum Toxin*. Lippincott Williams & Wilkins; 2002:189-195, Stiglmayer N et al. *Coll Antropol*. 2005;29:41-46, Wagner RS et al. *J Pediatr Ophthalmol Strabismus*. 1989;26:106-108, Wutthiphans S et al. *J Med Assoc Thai*. 2008;91:S86-91, Iwashige H et al. *Journal of Japanese Ophthalmological Society*. 1986;90:1366-1374, Iwashige H et al. *Journal of Japanese Ophthalmological Society*. 1995;99:232-237, Iwashige H et al. *Japanese Review of Clinical Ophthalmology*. 1987;81:951-961, Ohba M et al. *Journal of Japanese Ophthalmological Society*. 1999;103:112-118

The applicant's explanation:
Table 7 shows the efficacy of readministration in the Japanese phase III study (5.3.5.1.1, Study LOC116246). Data suggested that administration at the same dose as or 2-fold the previous dose provided efficacy similar to that observed in the initial dose, with no clinically significant safety problems. The interval to readministration[23)] (mean ± SD) in the Japanese phase III study was 117 ± 24 days in the ≥10 and <20 PD cohort and 137 ± 29 days in the ≥20 and <50 PD cohort. Table 8 shows the duration of the efficacy.[24)] The short duration of efficacy in the ≥10 and <20 PD cohort during the second treatment phase was due to the large variability in data associated with the small number of subjects evaluated (5 subjects). Accordingly, the applicant considers it appropriate to set the maximum dose of readministration at 2-fold the previous dose and the readministration interval at >3 months.

Table 8. Duration of the efficacy in Japanese phase III study (5.3.5.1.1, Study LOC116246)

	≥10 and <20 PD		≥20 and <50 PD	
	First treatment phase	Second treatment phase	First treatment phase	Second treatment phase
Number of subjects evaluated	10	5	31	10
Duration of efficacy (days)	86.0 [6.0, 189.0]	63.0 [56.0, NA]	88.0 [58.0, 140.0]	83.5 [6.0, 115.0]

Median [95% CI]; NA, Not available

2.B.(7).5) Maximum dose

PMDA asked the applicant to explain the rationale for the proposed maximum dose of 25 units.

The applicant's explanation:
In the foreign clinical study (5.3.5.2.1, Scott study), the mean dose of Botox was 3.62 to 6.83 units, with the maximum dose being 125.0 units. The maximum dose in the US was set at 25 units based on the results of this study, but the detailed rationale is unclear. In the Japanese phase III study (5.3.5.1.1, Study LOC116246), the initial dose was set at 1.25 to 5.0 units, and twice the previous dose was allowed in the additional dosing and the readministration, from which it was possible to administer 20.0 units of Botox at the maximum but, as it turned out, the maximum dose actually used was 5.0 units.

The applicant interviewed 10 Japanese experts on strabismus regarding the necessity of using doses exceeding 5 units. Six experts were of the opinion that a dose exceeding 5 units is necessary, with the maximum dose required being 10 units according to 4 experts and 15 units according to 2 experts. Patients requiring doses exceeding 5 units included patients with strabismus caused by thyroid ophthalmopathy, patients with paralytic strabismus associated with strong contracture, or patients with a large strabismus angle, who accounted for 1% to 20% of target patients for the treatment with Botox. Thyroid ophthalmopathy during the active phase is treated with immunosuppressive therapy (Wiersinga WM et al. *Trends Endocrinol Metab*. 2002;13:280-287) and, after more than 6 months have passed after transition to the inactive phase, a surgical operation is performed (Bartalena L et al. *Eur J Endocrinol*. 2008;158:273-285). Response rate to immunosuppressive therapy is approximately 80% (Bartalena L et al. *Eur J Endocrinol*. 2008;158:273-285), with some patients failing to respond to the therapy or showing relapse. In these patients, Botox is the only treatment available before surgical treatment becomes feasible. Patients with strabismus associated with endocrine disorder such as thyroid ophthalmopathy need a higher dose than patients with ordinary comitant strabismus possibly because of the hypertrophy and fibrosis/contracture of extraocular muscles affecting the efficacy of Botox (Scott AB. *Doc Ophthalmol*. 1984;58:141-145, Dunn WJ et al. *Ophthalmology*. 1986;93:470-475). In 3 published articles on the efficacy and safety of Botox in patients with strabismus caused by endocrine disorder,[25)] the maximum doses used were 5, 15, and 20 units. In patients with paralytic strabismus associated with strong contracture or patients with a large strabismus angle, surgical operation is performed in preference to drug therapies. However, patients unresponsive to the surgical treatment often have scarring/adhesion

23) Time from the previous dosing (the last dose in the first treatment phase) to the readministration

24) The duration of efficacy was defined as "time from the last dose in the first or second treatment phase up to the time point when the % change in strabismus angle in the primary position decreased to <50% for the first time compared with the maximum change in strabismus angle."

25) Dunn WJ et al. *Ophthalmology*. 1986;93:470-475, Kikkawa DO et al. *Am J Ophthalmol*. 2003;135:427-431, Stiglmayer N et al. *Coll Antropol*. 2005;29:41-46

of muscles in the previously operated eye, which makes it difficult to predict the effect of the surgery, possibly requiring the third surgery (Iwashige H. *Japanese Journal of ophthalmic surgery*. 1992;5:181-184, Kimura A. *Journal of the eye*. 2010;27:1659-1664).

In foreign clinical studies, 23.4% of subjects (531 of 2273 subjects) received Botox >0.14 units/kg (children aged ≤10 years) or ≥5.0 units (adults), but no clinically significant safety problems were observed. In Japanese or foreign published literature,[26)] up to 25 units of Botox per dose has been administered, without any clinically significant safety problems. The safety database of Allergan Inc., US (10,645,943-14,923,963 patient-years during the period from January 1, 1990 to December 31, 2013)[12)] showed that adverse events reported in patients receiving >5 units of Botox were eyelid ptosis (4 patients) and off-label use, strabismus, and strabismus congenital (3 patients each). The only serious adverse event observed was strabismus (3 patients), but serious strabismus was observed in 4 patients at doses of ≤5 units of Botox as well.

Based on the above, the maximum dose was set at 25 units in the proposed dosage and administration. However, given the facts that the efficacy and safety of Botox at >5.0 units was not investigated in the Japanese phase III study and that none of the strabismus experts interviewed expressed the opinion that a dose of 25 units is necessary, the applicant considers it unnecessary to set the maximum dose at 25 units. Instead, the applicant considers it appropriate to set the maximum dose at 10 units, for the following reasons: (i) Botox at doses exceeding 5 units is needed in patient populations such as patients with strabismus caused by thyroid ophthalmopathy, patients with paralytic strabismus associated with strong contracture, or patients with a large strabismus angle, and no other treatment options are available for these patients, (ii) since the approval of Botox with the maximum dose of 25 units in the US, Botox has been used in patients with strabismus across the world, and (iii) the foreign post-marketing safety information shows no events specific to high doses, and the incidences of serious adverse events are not dose-dependent. The maximum permitted dose of 10 units meets the requirement for these patient groups.

PMDA's view:
The clinical study data presented suggest that there are no major problems with the initial dose, additional dose, the time to additional dosing, the dose at the readministration, or the readministration interval in patients with horizontal strabismus. Although the initial dose was not investigated in Japanese patients with vertical strabismus, taking account of the facts that Botox acts by the same mechanism of action on horizontal and vertical strabismus and that Botox is shown to be effective in Japanese patients with horizontal strabismus at the same dose as in the US patients, it is acceptable to set the same initial dose in patients with vertical strabismus as in the US patients. In the Japanese phase III study, patients with abducens nerve palsy were treated with the same dosage regimen as patients with horizontal strabismus were. Since it is reported that abducens nerve palsy often remits spontaneously, there are no major problems with the proposed initial dose in patients with abducens nerve palsy persisting ≥1 month. As for the maximum dose of Botox, it is unnecessary to set the maximum dose at 25 units in Japan, for the following reasons: (i) Although it is allowed to administer up to 25 units of Botox in foreign countries, the detailed justification for the dose is unclear, (ii) Botox at 25.0 units was not administered to any of the subjects in the Japanese phase III study, and (iii) strabismus experts interviewed did not support the necessity of dose increase to 25 units. Instead, although the maximum dose of Botox used in the Japanese phase III study was 5.0 units, there is clinical significance to allow dose increase to 10 units as a treatment option if no adequate response is obtained at 5 units, taking account of the facts that (a) it is likely that there are patients who require Botox at a dose exceeding 5 units, such as patients with strabismus caused by thyroid ophthalmopathy or patients with paralytic strabismus associated with strong contracture (these patient groups were excluded in the Japanese phase III study) and that (b) treatment options are limited in these patients.

[26)] Abbasoglu OE et al. *Eye*. 1996;10:385-391, Carruthers JDA et al. *Arch Ophthalmol*. 1990;108:1432-1435, Flanders M et al. *Can J Ophthalmol*. 1987;22:212-217, Gammon JA et al. *J Ophthalmic Nurs Technol*. 1986;5:51-57, Iwashige H et al. *Journal of Japanese Ophthalmological Society*. 1986;90:1366-1374, Iwashige H et al. *Journal of Japanese Ophthalmological Society*. 1995;99:232-237, Iwashige H et al. *Journal of the eye*. 1991;8:1885-1891

Based on the above, PMDA considers that the dosage and administration of Botox for the treatment for strabismus should be set as shown below. The final decision on dosage and administration will be made, taking account of comments raised in the Expert Discussion.

[Dosage and administration] (The underline denotes the text altered from the proposed dosage and administration)
The usual dose of botulinum toxin type A (Botox) for adults and children ≥12 years of age, injected intramuscularly into an extraocular muscle, is shown below.

- Initial dose
  (1) Vertical strabismus: 1.25 to 2.5 units into any one of extraocular muscles
  (2) Horizontal strabismus of <20 prism diopters: 1.25 to 2.5 units into any one of extraocular muscles
  (3) Horizontal strabismus of 20 to 50 prism diopters: 2.5 to 5.0 units into any one of extraocular muscles
  (4) Abducens nerve palsy persisting ≥1 month: 1.25 to 2.5 units into the medial rectus muscle
- The patients should be monitored for 4 weeks after the initial dose. If patients have an inadequate response to treatment, additional injections (up to 2-fold the initial dose) may be administered.
- Retreatment with Botox is allowed if the response to the previous dose has worn off, at a dose up to 2-fold a previous single dose, but not within 3 months of the previous dose.
- A single dose per muscle should not exceed <u>10</u> units.

2.B.(8) Post-marketing investigations
PMDA's view:
Taking account of the results of the Japanese clinical study in patients with horizontal strabismus and from the safety information obtained in routine clinical use in approved indications, it is necessary to investigate the following matters in the post-marketing surveillance: occurrences of hypersensitivity reaction, eye disorder, convulsive seizure, production of neutralizing antibody, dysphagia in patients with cervical dystonia, action at distant sites, and fall; safety in patients with neuromyopathy; and interactions with agents with muscle relaxation. In the post-marketing surveillance, information should be collected also on patient characteristics affecting the efficacy and safety of Botox and on the incidences of eye disorders commonly found with strabismus such as eyelid ptosis.

The active ingredient of Botox is botulinum toxin, and use of Botox for strabismus requires the procedure specific to this indication. It is necessary to take appropriate measures so that Botox is used only by physicians who fully understand the safety and efficacy of the product, have detailed anatomical knowledge, and have thorough knowledge and experience of the procedure of electromyography and injecting Botox. Also, it is necessary to take appropriate measures to ensure that the unused product is deactivated and discarded safely and reliably.

The applicant explained the plan to conduct a post-marketing surveillance on Botox whereby all strabismus patients treated with Botox (target sample size, 300) will be monitored for up to 1 year.

The appropriateness of these approaches will be finalized, taking account of comments raised in the Expert Discussion.

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

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application. 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 application (5.3.5.1.1, Study LOC116246). 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 submitted data, the efficacy of Botox in the treatment of patient with strabismus has been demonstrated and its safety is acceptable in view of its observed benefits. Botox provides a new treatment option for the treatment of strabismus, and is of clinical significance. Also, it is necessary to further discuss the indications and the dosage and administration of Botox in the Expert Discussion.

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

Review Report (2)

May 19, 2015

I. Product Submitted for Registration

[Brand name]	Botox for injection 50, 100 units
[Non-proprietary name]	Botulinum Toxin Type A
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	July 25, 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).

In the Expert Discussion, the conclusions of PMDA described in the Review Report (1) were supported, and the following items were subjected to additional discussions, based on which necessary measures were taken.

(1) Dosage and administration

PMDA's conclusion that the maximum dose of Botox should be 10 units was supported by the Expert Discussion. Therefore, PMDA instructed the applicant to clearly indicate the muscles for Botox injection with the following modifications to the Dosage and Administration section, to which the applicant responded appropriately.

[Dosage and administration] (The underline denotes the text altered from the proposed dosage and administration)
The usual dose of botulinum toxin type A (Botox) for adults and children ≥12 years of age, injected intramuscularly into an extraocular muscle is shown below.

- Initial dose
  (1) Vertical strabismus: 1.25 to 2.5 units into the superior or inferior rectus muscle
  (2) Horizontal strabismus of <20 prism diopters: 1.25 to 2.5 units into the medial or lateral rectus muscle
  (3) Horizontal strabismus of 20 to 50 prism diopters: 2.5 to 5.0 units into the medial or lateral rectus muscle
  (4) Abducens nerve palsy persisting ≥1 month: 1.25 to 2.5 units into the medial rectus muscle
- The patients should be monitored for 4 weeks after the initial dose. If patients have an inadequate response to treatment, additional injections (up to 2-fold the initial dose) may be administered.
- Retreatment with Botox is allowed if the response to the previous dose has worn off, at a dose up to 2-fold a previous single dose, but not within 3 months of the previous dose.
- A single dose per muscle should not exceed 10 units.

(2) Risk management plan (draft)

The following comment was raised by the expert advisors at the Expert Discussion: since injection of Botox to the extraocular muscle using electromyography requires detailed anatomical knowledge and injection technique, physicians who use Botox should not only attend the training course on Botox as is the case for approved indications, but also be certified as ophthalmology specialists. Based on the above comment, PMDA asked the applicant to explain the measures to be taken for the proper use of Botox.

The applicant's explanation:
In order to ensure that Botox is used by physicians with specialized knowledge and experience, physicians who want to use Botox will be required not only to attend the training course but also to be certified as ophthalmology specialists. Given the high-level skills required for the injection, the training course will be provided only as a live demonstration unlike the training course for approved indications. In the training course, there will be an explanation of the outline of strabismus, evaluation method, various treatment methods, anatomy of each target muscle, dosage and administration, precautions for injection (including the demonstration using videos), the results of the Japanese clinical study, and the safety information. Also, joint seminars will be held in collaboration with related academic societies to familiarize physicians with the procedure of electromyography and with diagnosis/treatment of strabismus and to provide information on the safety and proper use of botulinum toxin. In addition, distribution of botulinum toxin to clinics in charge of treating target patients, as well as the deactivation and disposal of unused product, will be controlled appropriately, as is the case for the approved indications.

PMDA accepted the above response of the applicant. Also, taking account of the results of the review in "2.B.(8) Post-marketing investigations" of the Review Report (1) and of the comments raised by the expert advisors at the Expert Discussion, PMDA concluded, regarding the current draft risk management plan for Botox, that it is appropriate to perform safety and efficacy evaluations as listed in Table 9 and to perform additional pharmacovigilance activities and risk minimization actions as shown in Table 10.

Table 9. Safety and efficacy investigations in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Hypersensitivity reaction • Administration in patients with neuromyopathy • Production of neutralizing antibody • Dysphagia in patients with cervical dystonia • Effect on distant muscles • Eye disorder • Convulsive seizure	• Interactions with muscle relaxing agents • Interactions with other botulinum toxin preparations administered simultaneously or every several months • Fall	• None
Efficacy specifications		
• Efficacy in routine clinical use		

Table 10. Outline of additional pharmacovigilance activities and risk minimization actions in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization actions
• Early post-marketing phase vigilance (strabismus) • All case use-results survey (strabismus)	• Ensuring use by physicians with specialized knowledge and experience • Distribution management • Control of deactivation/disposal • Preparation and supply of information materials for healthcare professionals • Preparation and supply of information materials for patients • Providing information obtained during the early post-marketing phase vigilance (strabismus)

Based on the above, PMDA instructed the applicant to conduct a post-marketing surveillance to investigate these items.[27)]

The applicant explained the plan for a use-results survey on strabismus patients as outlined in Table 11.

27) "Dysphagia in patients with cervical dystonia" and "fall" are excluded because they are included in the risks to be evaluated in patients with cervical dystonia and lower limb spasticity and in patients ≥2 years of age with infantile cerebral palsy, respectively.

Table 11. Outline of use-results survey plan (draft)

Objective	To collect and evaluate the safety and efficacy information in strabismus patients in routine clinical use of Botox
Survey method	All case survey method
Patient population	All patients with diagnosis of strabismus who have received Botox for the first time for the treatment of strabismus
Observation period	Up to 1 year
Planned sample size	300
Main investigation items	• Patient characteristics (age, sex, direction of deviation, type of strabismus, age of onset, etiology, strabismus angle, complication, etc.) • Administration conditions of Botox (dose, reasons for dose change/discontinuation/termination, etc.) • Prior treatment for strabismus and concomitant therapies • Incidence of adverse events • Whether or not tests for pulmonary function or antibody were performed, and results if any • Strabismus angle in the primary position, overall efficacy evaluation

PMDA accepted the above plan of the applicant, and concluded that Botox may be approved with the following conditions.

[Conditions for approval]
The applicant is required to:
1. Develop and appropriately implement a risk management plan;
2. Take necessary measures to ensure that the product is used only by physicians who have attended a training course on the product, fully understand the safety and efficacy of the product, and have sufficient knowledge and experience of the procedure of injecting the product;
3. Take necessary measures to ensure that the unused product is deactivated and discarded safely and reliably in the clinical setting, for example, to ensure the pharmacy department is requested to dispose of it, and to keep its record; and
4. Conduct a post-marketing drug use-results survey in all patients treated with the product as a rule until data from a specific number of patients have been accumulated in order to identify the characteristics of patients treated with the product, since the number of patients with strabismus was very limited in the Japanese clinical studies, and at the same time, collect the safety and efficacy data of the product without delay and take measures necessary for the proper use of the product.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying indications and dosage and administration as shown below with the following conditions for approval. Since this is an application of a drug with new indications/new dosages, the re-examination period on indications and dosages and administration pertaining to this application is 4 years.

[Indications] Blepharospasm, hemifacial spasm, cervical dystonia, upper limb spasticity, lower limb spasticity, talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy, severe primary axillary hyperhidrosis, and strabismus

(The underline denotes the text added in this application.)

[Dosage and administration] Blepharospasm

The usual initial adult dosage of botulinum toxin type A (Botox) is 1.25 to 2.5 units/site injected intramuscularly into 6 sites of the orbicularis oculi muscle per eye. In patients who have undergone resection of the orbicularis oculi muscle, the target injection sites should be carefully identified by electromyography. The treatment effect usually lasts for 3 to 4 months. Botox treatment should be repeated if symptoms relapse, but not within 2 months of the previous dose. For subsequent injection sessions, the dose may be increased up to 2-fold the initial dose. However, the dose used for the subsequent injection should be decreased as appropriate in the event of adverse

drug reactions such as lagophthalmos and eyelid ptosis presumably due to exaggerated muscle-paralyzing effect, the pharmacological action of Botox. The cumulative dose of Botox treatment in 1 month should not exceed 45 units.

Hemifacial spasm

The usual adult dosage of botulinum toxin type A (Botox), injected intramuscularly into the spastic muscle, is shown below.* In the case of multiple spastic muscles, Botox should be injected into each muscle in divided doses.

- The initial dose is 10 units in total.
- The patients should be monitored for 4 weeks after the initial dose. If patients have an inadequate response to treatment, additional injections (up to 20 units in total) may be administered.
- Botox treatment may be repeated if symptoms relapse, at a dose of up to 30 units, but not within 2 months of the previous dose.

* Spastic muscle: orbicularis oculi muscle, corrugator muscle, frontalis muscle, orbicularis oris muscle, greater zygomatic muscle, lesser zygomatic muscle, risorius muscle, platysma muscle, mentalis muscle, etc.

Cervical dystonia

The usual adult dosage of botulinum toxin type A (Botox), injected intramuscularly into the tonic muscle,* is shown below. In the case of multiple tonic muscles, Botox should be injected into each muscle in divided doses.

- The initial dose is 30 to 60 units in total.
- The patients should be monitored for 4 weeks after the initial dose. If patients have an inadequate response to treatment, additional injections (up to 180 units) may be administered.
- Botox treatment may be repeated if symptoms relapse, at a dose of up to 240 units, but not within 2 months of the previous dose.

* Tonic muscles: sternocleidomastoid muscle, trapezius muscle, splenius muscle, scalenus muscle, anterior edge of the trapezius muscle, levator scapulae, paraspinal muscle, platysma muscle, etc.

Upper limb spasticity

The usual adult dosage of botulinum toxin type A (Botox) is 240 units in total injected intramuscularly in divided doses into each of the tonic muscles.* The maximum single dose is 240 units, but the dose should be decreased to the minimum dose required as appropriate, depending on the type and number of tonic muscles to be treated. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

* Tonic muscles: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis, flexor pollicis longus, adductor pollicis, etc.

Lower limb spasticity

The usual adult dosage of botulinum toxin type A (Botox) is 300 units in total injected intramuscularly in divided doses into each of the tonic muscles.* The maximum single dose is 300 units, but the dose should be decreased to the minimum dose required as appropriate, depending on the type and number of tonic muscles to be treated. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

* Tonic muscles: gastrocnemius muscle (medial head, lateral head),

soleus muscle, tibialis posterior muscle, etc.

Talipes equinus associated with lower limb spasticity in patients ≥2 years of age with infantile cerebral palsy

The usual dosage of botulinum toxin type A (Botox) for children ≥2 years of age is 4 units/kg injected intramuscularly into 2 sites each of the medial/lateral head of the affected gastrocnemius muscle. When injected into both legs, the dose of 4 units/kg is divided to each leg. If patients have an inadequate response after the initial dose, Botox may be injected into the muscles such as the musculus soleus, tibialis posterior muscle. The dose may be adjusted according to the symptoms. The total single dose should not exceed 200 units. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 3 months of the previous dose.

Severe primary axillary hyperhidrosis

The usual adult dosage of botulinum toxin type A (Botox) is 50 units per axilla injected intracutaneously into multiple (10-15) sites, 1 to 2 cm apart. Retreatment with Botox is allowed if the effect of the previous dose has worn off, but not within 4 months of the previous dose.

Strabismus

The usual dosage of botulinum toxin type A (Botox) for adults and children ≥12 years of age, injected intramuscularly into an extraocular muscle, is shown below.

- Initial dose

(1) Vertical strabismus: 1.25 to 2.5 units into the superior or inferior rectus muscle

(2) Horizontal strabismus of <20 prism diopters: 1.25 to 2.5 units into the medial or lateral rectus muscle

(3) Horizontal strabismus of 20 to 50 prism diopters: 2.5 to 5.0 units into the medial or lateral rectus muscle

(4) Abducens nerve palsy persisting ≥1 month: 1.25 to 2.5 units into the medial rectus muscle

- The patients should be monitored for 4 weeks after the initial dose. If the patients have an inadequate response to treatment, additional injections (up to 2-fold the initial dose) may be administered.
- Retreatment with Botox is allowed if the response to the previous dose has worn off, at a dose up to 2-fold a previous single dose, but not within 3 months of the previous dose.
- A single dose per muscle should not exceed 10 units.

(The underline denotes the text added in this application)

[Conditions for approval] The applicant is required to:

1. Develop and appropriately implement a risk management plan;
2. Take necessary measures to ensure that the product is used only by qualified physicians who have attended a training course on the product, fully understand the safety and efficacy of the product, and have sufficient knowledge and experience of the procedure of injecting the product;
3. Take necessary measures to ensure that the unused product is deactivated and discarded safely and reliably, for example to ensure the pharmacy department is requested to dispose of it, and to keep its record; and
4. Conduct a post-marketing drug use-results survey in all patients treated with the product as a rule until data from a specific number of patients have been accumulated, in order to identify the characteristics of patients treated with the product, since the number of patients with strabismus was very limited in the Japanese clinical studies, and at the same time, collect the safety and efficacy data of the product without delay and take measures necessary for the proper use of the product.