Appendix 8

Provisional Translation
from Japanese Original

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The Standards for Marketing Approval of Ophthalmic Medicines

1. Scope of Ophthalmic Medicines

The scope of preparations subject to these standards covers medicines to be applied to the mucous membrane of the eyes to treat symptoms of eye diseases and those to be used when inserting contact lenses.

2. Approval Standards

The approval standards for ophthalmic medicines are as follows.

For preparations not conforming to these standards, efficacy and safety data and reasons justifying the combination should be submitted; the preparation in question will be reviewed based on these data.

(1) Types of Active Ingredients

(a) Active ingredients that may be used in ophthalmic medicines are listed in Table I.

(b) At least 1 active ingredient from Column A, B, C, or D; Group 1, 2, or 3 of Column E; Column F, G, or H; Group 1 of Column I; or Column J in Table I must be used.

(c) Preparations mainly containing the active ingredients in Column A, B, C, or D; Group 1, 2, or 3 of Column E; or Group 1 of Column F (hereinafter referred to as "ordinary eye drops") in Table I may be formulated through the mutual combination of any of the active ingredients in these columns and groups, and may also include the active ingredients in Group 4, 5, or 6 of Column E or those in Group 2 or 3 of Column F in Table I.

(d) Preparations mainly containing active ingredients in Column G (hereinafter referred to as "antibacterial eye drops") in Table I may include up to 3 active ingredients from Column A, B, C, D, E, or F.

(e) Preparations mainly containing active ingredients in Groups 2 or 3 of Column F or those in Column H of Table I (hereinafter referred to as "artificial tears") may be formulated through the mutual combination of any of the active ingredients in Group 2 or 3 of Column F or those in Column H, and may also include the active ingredients in Group 1 of Column F or those in Column I.

(f) Preparations mainly containing active ingredients in Group 1 of Column I (hereinafter referred to as "contact lens insertion preparations") of Table I may also include active ingredients in Column F or H or those in Group 2 of Column I.

(g) Preparations mainly containing active ingredients in Column C, D, H, or J, listed in Table I, are used for washing the eyes and are referred to as "eyewashes." Those mainly containing active ingredients from Column C or D may be formulated by combining any of the active ingredients from Column C or D, and may also include active ingredients from Column E or F. Preparations mainly containing active ingredients from Column H or J of

Table I can include only 1 active ingredient from Column H or J, and no other active ingredients mentioned in these standards should be used.

(h) When the active ingredients from Column A, D, or G of Table I are combined, only 1 ingredient from each column may be used.

(i) When the active ingredients from Column C, E, or F of Table I are combined, up to 3 ingredients from each column may be used, but only 1 from each group is permitted.

(2) Quantities of Active Ingredients

(a) The maximum concentrations of the active ingredients from Column A, B, C, D, E, F, or G; Group 1 of Column I; or Column J should be those given in mentioned in Table I. However, in the case of eyewashes, the maximum concentrations of the active ingredients in Columns C, D, E, and F should be 1/10th of the maximum concentrations mentioned in Table I.

(b) When 2 or more of the active ingredients from any 1 of Column C, E, or F of Table I are combined, the sum of the values obtained by dividing the concentration of each active ingredient by its respective maximum concentration should not exceed 2. However, in the case of eyewashes, the maximum concentration stipulated in (2) (a) shall apply.

(c) In the case of ordinary eye drops, when only 1 active ingredient from Column A, B, C, or D; Group 1, 2, or 3 of Column E; or Group 1 of Column F of Table I is included, the minimum concentration of the ingredients should be half of the maximum concentration. When 2 or more of these active ingredients are combined, the minimum concentration of each shall be 1/5 of the maximum concentration.

(d) In the case of antibacterial eye drops, when active ingredients in Column G of Table I are included, the minimum concentration of these active ingredients should be half of the maximum concentration. When active ingredients from Column A, B, C, or D; Group 1, 2, or 3 of Column E; or Group 1 of Column F are included, their minimum concentrations should be 1/5 of the maximum concentration.

(e) In the case of artificial tears, when active ingredients listed in Column F or Group 1 of Column I in Table I are used, their minimum concentrations should be 1/10th the maximum concentration. pH values must be in the range of 5.5 to 8.0, and specific osmotic pressures (specific osmotic pressures with respect to physiological saline) must be in the range of 0.85 to 1.55 when pH and osmotic pressures are measured by the methods specified elsewhere.

(f) For contact lens insertion preparations, when 1 active ingredient from Group 1 of Column I in Table I is used, the minimum concentration should be half of the maximum concentration. When 2 active ingredients are included, their minimum concentrations should be 1/5th of the maximum concentration. When active ingredients in Column F are combined, their minimum concentrations should be 1/10th of the maximum concentration.

(g) In the case of eyewashes, when active ingredients from Column C, D, or J of Table I are combined, the minimum concentration should be 1/5th of the maximum concentration specified in (2) (a). When active ingredients in Column E or F are used, the minimum concentration should be 1/10th of the maximum concentration specified in (2) (a). pH values must be in the range of 5.5 to 8.0, and specific osmotic pressures (specific osmotic pressure with respect to physiological saline) must be in the range of 0.60 to 1.55 when pH and osmotic pressures are measured by the methods specified elsewhere.

(h) Unless otherwise specified, when active ingredients in Groups 4, 5, and 6 of Column E, or Groups 2 and 3 of Column F in Table I are combined, the minimum concentration should be 1/10th of the maximum concentration.

(3) Dosage Form

The dosage form shall be ophthalmic solutions (eye drops and eyewashes).

(4) Dosage and Administration

(a) Ordinary eye drops, antibacterial eye drops, and artificial tears are to be administered 3 to 6 times a day.
(b) For contact lens insertion preparations, the detailed method of use should be stated.
(c) Eyewashes are to be used 3 to 6 times a day to wash the eyes.

(5) Indications

(a) The range of indications for ordinary eye drops is shown in Table II-1. However, for indications in the upper column of the following table to be claimed, at least 1 of the ingredients from the columns listed in the corresponding lower column must be included.

Upper column	Lower column
Conjunctival congestion	Columns A, C, and D
Inflammation of eyes (snow blindness), blepharitis (inflammation of the eyelids), and itchy eyes due to ultraviolet light and other rays	Columns C and D and Group 1 of Column E

(b) The range of indications for antibacterial eye drops is shown in Table II-2.
(c) The range of indications for artificial tears is shown in Table II-3.
However, "treatment of feeling of discomfort when inserting soft contact lenses" cannot be claimed when the effect is brought about due to the effect of ingredients on the lenses, such as adsorption on the lenses.
(d) The range of indications for contact lens insertion preparations is shown in Table II-4.
However, "ease of insertion of soft contact lenses" cannot be claimed when the effect is brought about due to the effect of ingredients on the lenses, such as adsorption on the lenses.
(e) The range of indications for eyewashes is shown in Table II-5.

(6) Packaging Units

(a) The maximum volume of containers for ordinary eye drops, antibacterial eye drops, and artificial tears is 20 mL.
(b) The maximum volume of containers for contact lens insertion preparations is 100 mL.
(c) The maximum volume of containers for eyewashes is 500 mL.

Table I

Column	Group	Active ingredient	Maximum concentration (%)
A		Epinephrine	0.003
		Epinephrine hydrochloride	0.003 (as epinephrine)
		Ephedrine hydrochloride	0.1
		Terahydrozoline hydrochloride	0.05
		Naphazoline hydrochloride	0.003
		Naphazoline nitrate	0.003
		Phenylephrine hydrochloride	0.1
		dl-Methylephedrine hydrochloride	0.1
B		Neostigimine methylsulfate	0.005
C	1	ε-Aminocaproic acid	5
	2	Allantoin	0.3
	3	Berberine chloride	0.025
		Berberine sulfate	0.025
	4	Sodium azulene sulfonate	0.02
	5	Dipotassium glycyrrhizinate	0.25
	6	Zinc sulfate	0.25
		Zinc lactate	0.25
	7	Lysozyme chloride	0.5 (potency)
D		Diphenhydramine hydrochloride	0.05
		Chlorpheniramine maleate	0.03
E	1	Sodium flavine adenine dinucleotide	0.05
	2	Cyanocobalamin	0.02
	3	Retinol acetate	50,000 units/100 mL
		Retinol palmitate	50,000 units/100 mL
	4	Pyridoxine hydrochloride	0.1
	5	Panthenol	0.1
		Calcium pantothenate	0.1
		Sodium pantothenate	0.1
	6	Tocopherol acetate	0.05
F	1	Potassium L-aspartate	1
		Magnesium L-aspartate	1
		Mixture of magnesium L-aspartate and potassium L-aspartate (equal mixture)	2
	2	Aminoethyl sulfonic acid	1
	3	Sodium chondroitin sulfate	0.5

G		Sulfamethoxazole	4
		Sodium sulfamethoxazole	4
		Sulfisoxazole	4
		Sodium sulfisomidine	5
H		Potassium chloride	–
		Calcium chloride	–
		Sodium chloride	–
		Sodium bicarbonate	–
		Sodium carbonate	–
		Dried sodium carbonate	–
		Magnesium sulfate	–
		Sodium hydrogen phosphate	–
		Monobasic sodium phosphate	–
		Monobasic potassium phosphate	–
I	1	Polyvinyl alcohol	2
		Polyvinylpyrrolidone	2.5
	2	Hydroxyethl cellulose	–
		Hydroxypropylmethyl cellulose	–
		Glucose	–
		Methylcellulose	–
J		Alkylpolyaminoethylglycine	0.1
		Boric acid	2

Table II

1 (general ophthalmic drops)	Eyestrain, redness of the conjunctiva, prevention of eye troubles（after swimming, or to wash out sweat or dust etc.）, ophthalmia by ultraviolet rays etc. (snow blindness etc.), blepharitis (running eye), foreign-body feeling by contact lenses, itchy eyes, blurred vision (eye mucus)
2 (antibiotic ophthalmic drops）	Conjunctivitis (pink-eye), chalazia, blepharitis (running eye), itchy eyes
3 (Artificial tears)	Eyestrain, prevention of dry-eyes, foreign-body feeling by contact lenses, blurred vision (eye mucus)
4 (eye-lotions for contact lenses)	Help to wear hard contact lenses or soft contact lenses
5 (eye washes)	Irrigation of eyes, prevention of eye troubles (after swimming, or to wash out sweat or dust etc.)