Appendix 3

Provisional Translation
from Japanese Original

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The Standards for Marketing Approval of Antitussives and Expectorants

1. Scope of Antitussives and Expectorants

The scope of remedies subject to these standards covers oral remedies (including troches and drops) intended for use as antitussives and expectorants.
However, remedies based on Kampo medicine* formulas and non-Kampo crude drug remedies consisting of crude drug only are not covered.
*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for antitussives and expectorants are as follows.
For remedies 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. Table 1 lists the active ingredients that may be used.
The types of active ingredients that may be used in troches and drops are limited to those marked by in Table 1. The active ingredients from Column X should only be combined for troches and drops.
b. One ingredient from Columns I, II, III, XII, or XIII of Table 1 must be included. However, cases where only the active ingredients from Groups 2 and 3 in Column VI of the same table are combined simultaneously are excluded.
c. Active ingredients from different columns of Table 1 may be combined with each other, unless otherwise stipulated.
d. Active ingredients from Group IX of Table 1 may be combined only in remedies that contain active ingredients from Column I or VIII in this table.
e. In Columns I to III and Columns V to X of Table 1, only 1 ingredient from each group may be used.
However, cases where only the active ingredients from Groups 2 and 3 in Column VI of the same table are combined simultaneously are excluded.
f. Active ingredients from Column XII of Table 1 should not be combined simultaneously with the active ingredients from Column II or V of the same table.
g. Active ingredients from Group 2 in Column I of Table 1 should not be combined simultaneously with the active ingredients from Columns III, IV, V, XII, XIII, or XIV.
h. Active ingredients from Column IV of Table 1 should not be combined simultaneously with the active ingredients from Group 2 in Column I, or from Columns V, XII, or XIII.
i. Active ingredients from Group 2 in Column VI of Table 1 should not be combined simultaneously with the active ingredients from Column V, XII, or XIII of the same table.
j. Active ingredients from Group 3 in Column VI of Table 1 should not be

combined simultaneously with the active ingredients from Column V, XII, or XIII of the same table.

k. Active ingredients from Group 2 in Column VIII of Table 1 should not be combined simultaneously with the active ingredients from Column V or XIII of the same table.

(2) Quantities of Active Ingredients

a. The maximum single dose and maximum daily dose of each active ingredient in Table 1 should be the doses specified in the same table, unless otherwise specified.
b. When the active ingredients from Column IX are combined with those from Column II, V, or XII of Table 1 are combined, the maximum single and daily doses of the ingredients in Column IX should be half of the amounts specified in Table 1.
c. When 2 or more of the active ingredients from Columns II and V of Table 1 are combined or when 2 or more of the active ingredients from Column XII, XIII, or XIV are combined, the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should not exceed 1.
d. The lower limit of the combined amounts of each active ingredient in Table 1 should be half of the maximum single or daily dose, unless otherwise specified. However, for the active ingredients from Column IX, the limit should be 1/5th.
e. When the active ingredients from Group 2, Column VI of Table 1 are combined simultaneously with only the active ingredients from Group 3 in the same column, the single dose should be 4 mg and the daily dose should be limited to 12 mg.
f. The single dose of the active ingredients from Group 3 in Column VI of Table 1 should be limited to 250 mg and the daily dose should be limited to 750 mg.
g. The single dose of the active ingredients from Group 2 in Column VIII of Table 1 should be 0.334 mg as clemastine and the daily dose should be limited to 1 mg as clemastine.
h. In the case of troches and drops containing Group I ingredients from Column X of Table 1 and having a dosage regimen for children, the coefficients given in Table 2 should not be used to calculate the combined amount of the ingredients from Column X.
i. In the case of troches and drops to be taken 5 to 6 times per day, the lower limits of the combined amounts of each active ingredient should be half of the maximum daily dose.
j. When the active ingredients from Column II of Table 1 are combined simultaneously with the active ingredients from Column V, the lower limits of the combined amounts should be as follows.

- When the active ingredients from Column II of Table 1 are indicated for "cough," "cough associated with wheezing (wheezy, whistling)," or "sputum," the lower limit of the amounts of the ingredients in Column V should be 1/5th of the maximum single and daily doses.
- When other ingredients with an indication of "coughing" are combined, the lower limits of the amounts of ingredients from both Column II and V should be 1/5th of the respective maximum single and daily doses.
  However, in the case of proportional combinations, lower limits should be such that the sum of the values obtained by dividing the amount of each active ingredient by its maximum daily dose equals half.
- When the active ingredients from Column V of Table 1 are indicated for "cough associated with wheezing (wheezy, whistling)" or "sputum," the lower limit of the amounts of the ingredients in Column II should be 1/5th of the maximum single and daily doses.

k. When used in combinations, the lower limit of the daily amounts of the active ingredients from Column XI of Table 1 is 1/5 of the maximum daily dose.
l. The lower limits of the amounts of crude drugs should be 1/10th of the maximum daily dose. However, when the indications approved for a particular crude drug are claimed, the lower limit should be half of the maximum daily dose.

(3) Dosage Forms

The dosage forms are tablets, capsules, pills, granules, powders, troches, drops, and oral solutions (with the exception of elixirs; hereinafter the same should apply), and syrups.

(4) Dosage and Administration

a. The dosage is "3 to 4 times a day," and the timing of doses or intervals between doses must also be indicated.
However, as for troches, drops, and oral solutions, and syrups, the dosage may be up to 6 doses per day. For dosages of 5 to 6 doses a day, troches and drops should be taken at intervals of at least 2 hours and oral solutions and syrups at intervals of about 4 hours, in principle.
b. The dosage for troches and drops should be allowed to dissolve slowly in the mouth without chewing.
c. For hard capsules, troches, syrups, and soft capsules larger than 6 mm in diameter, pills, and tablets, dosage for children under 5 years of age is not approved. Even for capsules smaller than 6 mm in diameter, dosage for children under 3 years of age is not approved.
d. Dosages for infants under 3 months of age are not approved.
e. For remedies containing promethazine hydrochloride or promethazine methylene disalycilate from Group 1 in Column VIII of Table 1, dosage for children under 15 years of age is not approved.
f. For remedies containing the active ingredients from Group 3 in Column VI of Table 1, dosage for children under 8 years of age is not approved.
g. For remedies containing the active ingredients from Column IV of Table 1 or the active ingredients from Group 2 in Column VIII, dosage for children under 5 years of age is not approved.
h. For remedies containing the active ingredients from Group 2 in Column I of Table 1, dosage for children under 3 years of age is not approved.
i. The maximum daily dose for children under 15 years of age is the amount obtained by multiplying the maximum daily dose in Table 1 by the coefficient corresponding to the respective age group in Table 2, unless otherwise specified.
j. The maximum single dose of the active ingredients in oral solutions and syrups is 1/6th of the maximum daily dose (for children under 15 years of age, the maximum daily dose according to i. above), and the maximum single dose is 10 mL, unless otherwise specified.
k. For remedies containing the active ingredients from Group 2, Column I of Table 1 with dosage for children under 15 years of age, the maximum single dose is 10 mg and the maximum daily dose is 30 mg. The maximum daily dose for children under 15 years of age is the amount obtained by multiplying the maximum daily dose (30 mg) by the coefficient corresponding to the respective age group in Table 2.
l. For remedies containing the active ingredients from Column IV of Table 1 with dosage for children under 15 years of age, the maximum single dose is 140 mg and the maximum daily dose is 420 mg. The maximum daily dose for

children under 15 years of age is the amount obtained by multiplying the maximum daily dose (420 mg) by the coefficient corresponding to the respective age group in Table 2.

(5) Indications

a. The indications include “cough, cough associated with wheezing (wheezy, whistling), and sputum.”
However, for indications in the left column of the following table to be claimed, at least 1 of the ingredients from the corresponding right column must be included.
b. When the active ingredients from Column IV of Table 1 are combined, the indications are “cough or sputum associated with sore throat.” However, they should be combined concomitantly with any ingredient with indications of “cough” and “sputum” from the left column of the next table.
c. When only the active ingredients from Group 2 and Group 3 in Column VI of Table 1 are combined concomitantly, the indications are “sputum and cough with sputum”.
d. For troches and drops, in addition to the above indications, the following may also be given: hoarse voice due to throat inflammation, rough throat, throat discomfort, sore throat, and swollen throat.

Left column	Right column
Cough	Ingredients from Columns I, II, III, XII, or XIII of Table 1
Cough associated with wheezing (wheezy, whistling)	Ingredients from Column II, V, or XII in Table 1, except for cases in which an ingredient from Column I of Table 1 is also combined.
Phlegm (sputum)	Tipepidine citrate or tipepidine hibenzate from Group 1 in Column I of Table 1 or the ingredients from Columns II, V, VI, VII, XII, or XIV
Cough associated with sore throat and sputum	Ingredients from Column IV of Table 1, only when combined concomitantly with any ingredient with indications of “cough” and “sputum.”
Sputum and cough with sputum	Only when combined concomitantly with only the ingredients from Group 2 and Group 3 in Column VI of Table 1.

(6) Packaging Units

The maximum volume of containers for oral solutions and syrups is a 4-day supply at the maximum daily dose for adults (15 years of age and older).

Table 1

Active Ingredients and Maximum Single and Daily Doses

Category		Name of active ingredient	Maximum single dose (mg)	Maximum daily dose (mg)
Column I	Group1	Alloclamide hydrochloride	25	75
		Tipepidine citrate Cloperastine	20	60
		hydrochloride Chloperastine	20	60
		phendizoate Codeine phosphate	35	105
		Dihydrocodeine phosphate	20	60
		Dibunate sodium Tipepidine	10	30
		hibenzate	30	90
		Dextromethorphan hydrobromide	25	75
		△Dextromethorphan	20	60
		phenolphthalinate	30	90
		Carbetapentane citrate	20	60
	Group2	Dimemorfan phosphate	15 (10)	60 (30)
Column II		Trimethoquinol hydrochloride	2	6
		△ *dl*-Methylephedrine hydrochloride	25	75
		l-Methylephedrine hydrochloride	25	75
		Methoxyphenamine hydrochloride	50	150
Column III		△Noscapine	20	60
		Noscapine hydrochloride	20	60
Column IV		Tranexamic acid	250 (70)	750 (280)
Column V		Aminophylline	100	300
		Diprophylline	100	300
		Theophylline	200	600
		Proxyphylline	70	210
Column VI	Group 1	Foeniculated ammonia spirit (as 1 ingredient)	2mL	-
		Ammonium chloride	300	900
		△Guaifenesin	100	300
		△Potassium guaiacolsulfonate	90	270
		△Potassium cresolsulphonate	90	270
		l-Menthol	-	90
	Group 2	Bromhexine hydrochloride	4 (2)	12 (8)
	Group 3	L-carbocysteine	250	750
Column VII		Ethyl L-cysteine hydrochloride	100	300
		Methyl L-cysteine hydrochloride	100	300

Column VIII	Group1	Alimemazine tartrate	2.5	7.5
		Isothipendyl hydrochloride	4	12
		Iproheptine hydrochloride	50	150
		Difeterol hydrochloride	30	90
		Tripelenamine hydrochloride	25	75
		Thonzylamine hydrochloride	20	60
		Fenethazine hydrochloride	30	90
		Chlorpheniramine maleate	4	12
		d-Chlorpheniramine maleate	2	6
		Carbinoxamine diphenyldisulfonate	4	12
		Diphenylpyraline hydrochloride	2	6
		Diphenylpyraline teoclate	3	9
		Diphenhydramine hydrochloride	30	90
		Diphenhydramine salicylate	40	120
		Diphenhydramine tannate	50	150
		Fenethazine tannate Triprolidine hydrochloride Promethazine	45	135
		hydrochloride Promethazine methylene disalycilate	2	6
		Carbinoxamine maleate	5	15
		Difeterol phosphate	6	18
			4	12
			30	90
	Group2	Clemastine fumarate	0.334 [as clemastine]	1 [as clemastine]
Column IX		Caffeine and sodium benzoate	100	300
		Caffeine hydrate	100	300
		Anhydrous caffeine	100	300
Column X		△Chlorhexidine hydrochloride	5	-
		△Cetylpyridinium chloride	1	-
		△Dequalinium chloride	0.25	-
Column XI		Glycine Magnesium silicate		900
		Synthetic aluminum silicate Synthetic hydrotalcite Magnesium oxide		3000
		Dihyrdoxyaluminum and aminoacetate		3000
		Aluminum hydroxide gel (as dried aluminum hydroxide gel)		4000
		Dried aluminum hydroxide gel		500
		Aluminum hydroxide-Sodium hydrogen carbonate coprecipitate		1500
		Aluminum hydroxide-Magnesium carbonate mixed dried gel		1000
		Aluminum hydroxide-Magnesium carbonate-Calcium carbonate coprecipitate		1000
		Magnesium hydroxide-Aluminum potassium sulfate coprecipitation product		900
		Magnesium carbonate		3000
		Magnesium aluminometasilicate		1500
				1800
				2000
				1500

(Crude drugs)

Category	Name of crude drug or Kampo medicine formula	Maximum daily dose (g)	
		Extract (converted to the crude drug amount)	Powder
Column XII	Ephedra Herb	4	-
Column XIII	Nandina Fruit	10	-
Column XIV	Cherry Bark Polygala	4	-
	Root Glycyrrhiza	5	-
	Platycodon Root	5	1.5
	Apricot Kernel	4	2
	Plantago Seed Plantago	4	-
	Herb Lycoris Radiata	5	-
	Bulb Senega	10	-
	Ipecac Fritillaria	0.8	-
	Bulb	4	1.5
		0.05	0.05
		2.5	1.5
Column XV	Gambir	-	2
	Fennel	3	-
	Scutellaria Root	6	3
	Trichosanthes Seed	2	-
	Cinnamon Bark	5	1
	Oriental Bezoar	-	0.02
	Schisandra Fruit	5	-
	Asiasarum Root Aster	3	-
	Root	5	-
	Musk Adenophora	-	0.01
	Root Ginger	5	2.5
	Mulberry Bark Perilla	3	1
	Herb	5	-
	Panax Japonicus Rhizome	2	-
	Citrus Unshiu Peel Ginseng	6	3
	Ophiopogon Tuber	5	3
	Pinellia Tuber	6	3
		10	-
		5	-

(Note) A numerical value within parentheses is the lower limit of amounts for combination.

Table 2

Range of Age Coefficients

Age	Coefficient
15 years of age and older	1
11 to under 15 years of age	2/3
8 to under 11 years of age	1/2
5 to under 8 years of age	1/3
3 to under 5 years of age	1/4
1 to under 3 years of age	1/5
3 months to under 1 year of age	1/10