Appendix 1

Provisional Translation
from Japanese Original

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The Standards for Marketing Approval of Cold Remedies

1. Scope of Cold Remedies

The scope of either medicines subject to these standards covers all oral medicines intended for use in treating cold symptoms (Kampo medicine* formulas are not covered).

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for cold remedies are as follows. For either medicines 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. The types of active ingredients that may be combined are shown in Table 1.
b. At least 1 of the active ingredients from Group 1 or 2 in Column I of Table 1 must be included. However, in the case of formulas consisting of crude drugs only, Earthworm (Lumbricus) from Column XVI of Table 1 should be combined instead of them.
c. Active ingredients from different columns of Table 1 may be combined with each other, unless otherwise stipulated.
d. Active ingredients from Column VIII of Table 1 may be combined only in formulas that contain active ingredients from Column II of the table.
e. Up to 3 of the active ingredients from Group 1 in Column I of Table 1 can be combined.
f. When the active ingredients from Column II, III, IV, V, VI, VIII, IX, or X or the Kampo medicine formulas from Column XVII of Table 1 are combined, one ingredient can be used from each Column. However, the active ingredients from Groups 2 and 3 in Column VI of Table 1 may be combined at the same time.
g. When the active ingredients from Group 2 in Column I of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 1 or 3 in the same column.
h. When the active ingredients from Group 2 from Column I of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column III, Group 3 in Column VI, from Column VII, Column XIII or Column XIV, Earthworm from Column XVII or the Kampo medicine formulas from Column XVII.
i. When the active ingredients from Group 3 in Column I of Table 1 are combined, they should be combined simultaneously with acetaminophen from Group 1 in the same column, and should not be combined simultaneously with other active ingredients from the same column.
j. When the active ingredients from Group 3 in Column I of Table 1 are combined,

they should not be combined simultaneously with the active ingredients from Group 3 in Column II, Group 2 in Column III, from Column VI, Column XIII or the active ingredients from Column XIV, Earthworm from Column XVI, or the Kampo medicine formulas from Column XVII.

k. When the active ingredients from Group 2 in Column II of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Column XIV or the Kampo medicine formulas from Column XVII.
l. When the active ingredients from Group 3 in Column II of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 3 in Column I or from Column XIV or the Kampo medicine formulas from Column XVII.
m. When the active ingredients from Group 2 in Column III of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column I, Group 3 in Column I, from Column IV, Column VIII, Column IX, Column XIII, Column XIV or Column XV, or Kakkontokakikyo from Column XVII.
n. When the active ingredients from Group 2 in Column VI of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 3 in Column I, from Column VIII, Column XIII, Column XIV or the Kampo medicine formulas from Column XVII.
o. When the active ingredients from Group 3 in Column VI of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column I, Group 3 in Column I, from Column VIII, Column XIII, Column XIV or the Kampo medicine formulas from Column XVII.
p. When the active ingredients from Column VII of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column I or from Column VIII or the Kampo medicine formulas from Column XVII.
q. When the active ingredients from Column VIII of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column III, Group 2 and Group 3 in Column VI, from Column VII, Column XIII or Column XIV or the Kampo medicine formulas from Column XVII.
r. When the active ingredients from Column IX of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column III, from Column XIII or Column XIV or the Kampo medicine formulas from Column XVII.
s. Combinations of glycyrrhizinic acid and its salts from Column IX of Table 1 and Glycyrrhiza from Column XV are not acceptable.
t. Combinations of Ephedra herb or Kampo medicine formulas containing Ephedra herb or their extracts and the active ingredients from Group V of Table 1 are not acceptable.
u. Combinations between the Kampo medicine formulas from Column XVII of Table 1 and the active ingredients from Column XIII, XIV, XV or XVI are not acceptable.
v. Apart from Kososan formula, Kampo medicine or non-Kampo crude drug medicines must be in the extract form when used in combinations.
w. The crude drugs used in the Kampo medicine formulas from Column XVII of Table 1 and their combination ratios must be as specified in Table 2.

(2) Quantities of Active Ingredients

a. The maximum daily dose of each of the active ingredients is that specified in Table 1, unless otherwise specified. However, when the active ingredients from Column V or XIII in Table 1 are combined with the ingredients in Column X, 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 2/3rd.

b. When 2 or more of the active ingredients from Group 1 in Column I of Table 1 are combined or when 2 or more of the active ingredients from Column XIII, XIV, or XV 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.
c. When the active ingredients from Group 1 in Column I of Table 1 are combined with Earthworm, Kakkonto formula, Maoto formula, or Kakkontokakikyo, the sum of the values obtained by dividing the amounts of the active ingredients or the formulations combined by their respective maximum daily doses should not exceed 1.
d. When used in combinations, the amounts of the Kampo medicine formulas from Column XVII of Table 1 must not be less than 1/5th and not more than half of the maximum daily dose.
e. The lower limit of the amounts of each of the active ingredients should be half of the maximum daily dose, unless otherwise specified.
f. When 2 or more of the active ingredients from Group 1 in Column I of Table 1 are combined, the lower limit of the amounts should be 1/5th of the maximum daily dose for each active ingredient, and the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should be not less than half.
g. When used in combinations, the lower limit of the amounts of the active ingredients from Columns X and XII of Table 1 is 1/5th of the maximum daily dose.
h. When used in combinations, the lower limit of the amounts of glycyrrhizinic acid and its salts from columns IX of Table 1 and the active ingredients from Columns XIII, XIV, XV, and XVI is 1/10th of the respective maximum daily doses. However, in the case of combination with Earthworm as described in (1) b, the maximum daily dose from Column XVI should be combined.
i. In cases where indications for treatment of coughing and sputum are based only on the active ingredients from Columns XIII, XIV, or XV of Table 1, when used in combinations, the lower limits of the active ingredients from Columns XIII, XIV, or XV should be half of the respective maximum daily doses.
   However, in cases where 2 or more of the crude drugs from Column XV are combined, the lower limit should be 1/5th of the respective maximum daily doses, and the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily dose should be not less than half.
j. The daily dose of the active ingredients from Group 2 in Column I of Table 1 should be limited to 450 mg.
k. The daily dose of the active ingredients from Group 3 in Column I of Table 1 should be limited to 300 mg, and the amount of acetaminophen from Column 1 in the same column, which is combined simultaneously, should be limited to 450 mg.
l. The daily dose of the active ingredients from Group 2 in Column II of Table 1 should be limited to 1 mg as clemastine.
m. The daily dose of the active ingredients from Group 3 in Column II of Table 1 should be limited to 4 mg.
n. The daily dose of the active ingredients from Group 2 in Column III of Table 1 should be limited to 30 mg.
o. The daily dose of the active ingredients from Group 3 in Column VI of Table 1 should be limited to 750 mg.

(3) Dosage Forms

The dosage forms are tablets, capsules, pills, granules, powders, and syrups.

(4) Dosage and Administration

a. Except for syrups, cold remedies are to be taken by oral administration 3 times a day within 30 minute after a meal. Syrups are to be taken, in principle, after every meal. However, if required, they can also be taken before going to bed. If it is absolutely necessary, they can be taken approximately every 4 hours up to a maximum of 6 times a day.
b. For hard capsules, 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.
c. For tablets 6 mm in diameter or less, dosage for children under 3 years of age is not approved.
d. For other dosage forms, dosage for infants under 3 months of age is not approved.
e. For children under the age of 15 years, the maximum daily doses acceptable are the values obtained by multiplying the amount of the active ingredient given in 2 (2) by the coefficients for each age group in Table 3, unless otherwise specified. The maximum single dose of syrups is calculated by using the range of coefficients, and dissolving or suspending 1/6th of the calculated value in water to make less than 10 mL in each case.
f. For formulas containing aspirin, aspirin aluminum, and sasapyrine from Group 1 in Column I, the active ingredients from Group 2 in Column 1, promethazine methylenedisalicylate from Group 1 in Column II, or the active ingredients from Group 3 in Column II, dosage for children under 15 years of age is not approved.
g. For formulas containing the active ingredients from Group 3 in Column VI, dosage for children under 8 years of age is not approved.
h. For formulas containing the active ingredients from Group 3 in Column I or Group 2 in Column II or tranexamic acid from Column IX, dosage for children under 5 years of age is not approved.
i. For formulas containing the active ingredients from Group 2 in Column III, dosage for children under 3 years of age is not approved.
j. For formulas containing tranexamic acid from Column IX of Table 1 with dosage for children under 15 years of age, 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) in Table 1 by the coefficient corresponding to the respective age group in Table 3.

(5) Indications

Relief of various symptoms of a common cold: running nose, stuffy nose, sneezing, sore throat, cough, phlegm (sputum), chills (feeling cold due to fever), fever, headache, joint pain, and muscle pain.

However, when any single type of the active ingredients listed in the right column of the following table is not included, the indications in the left column of the table cannot be claimed.

Left column	Right column
Runny nose, stuffy nose, sneezing	Ingredients from Column II of Table 1
Cough	Ingredients from Columns III, IV, V, XIII, or XIV of Table 1
Phlegm (sputum)	Tipepidine citrate or tipepidine hibenzate from Column III of Table 1 or the ingredients from Columns V, VI, VII, XIII, or XV

(6) Packaging Units

For syrups, the maximum volume of the containers is a 2-day supply at the maximum daily dosage for children aged 6 years.

Table 1

Active ingredients and Maximum Daily Doses

Category		Name of active ingredient	Maximum daily dose (mg)
Column I	Group 1	Aspirin Aspirin aluminum Acetaminophen Ethenzamide Sasapyrine Salicylamide Lactylphenetidine	1500 2000 900 1500 1500 3000 600
	Group 2	Ibuprofen	450
	Group 3	Isopropylantipyrine	300
Column II	Group 1	Isothipendyl hydrochloride Difeterol hydrochloride Tripelenamine hydrochloride Thonzylamine hydrochloride Fenethazine hydrochloride Methodilazine hydrochloride Chlorpheniramine maleate d-Chlorpheniramine maleate Carbinoxamine diphenyldisulfonate Diphenylpyraline hydrochloride Diphenylpyraline teoclate Diphenhydramine hydrochloride Diphenhydramine salicylate Alimemazine tartrate Diphenhydramine tannate Triprolidine hydrochloride Mebhydrolin napadisilate Promethazine methylenedisalicylate Carbinoxamine maleate Difeterol phosphate	7 90 100 50 50 8 7.5 3.5 7.5 4 4.5 75 75 5 75 4 150 40 7.5 90
	Group 2	Clemastine fumarate	1 [as clemastine]
	Group 3	Mequitazine	4
Column III	Group 1	Alloclamide hydrochloride Tipepidine citrate Cloperastine hydrochloride Chloperastine phendizoate Codeine phosphate Dihydrocodeine phosphate Dibunate sodium Tipepidine hibenzate Dextromethorphan hydrobromide Dextromethorphan phenolphthalinate Carbetapentane citrate	75 60 48 84 48 24 90 75 48 72 48
	Group 2	Dimemorfan phosphate	30
Column IV		Noscapine Noscapine hydrochloride	48 48

Column V		dl-Methylephedrine hydrochloride dl- Methylephedrine saccharinate	60 60
Column VI	Group 1	Guaifenesin Potassium guaiacolsulfonate Potassium cresolsulphonate	250 250 250 (135)
	Group 2	Bromhexine hydrochloride	12 (8)
	Group 3	L-carbocysteine	750
Column VII		Ethyl L-cysteine hydrochloride	300
Column VIII		Belladonna total alkaloid Isopropamide iodide extract	0.3 (0.12) 6 (1.5)
Column IX		Glycyrrhizinic acid and its salts Tranexamic acid	39 [as glycyrrhizinic acid] 750 (280)
Column X		Caffeine and sodium benzoate Caffeine hydrate Anhydrous caffeine	300 150 150
Column XI		Vitamin B_1, its derivatives, and their salts Vitamin B_2, its derivatives, and their salts Vitamin C, its derivatives, and their salts Hesperidin, its derivatives, and their salts	25 (1) 12 (2) 500 (50) 90 (18)

Column XII	Glycine Magnesium silicate Synthetic aluminum silicate Synthetic hydrotalcite Magnesium oxide Dihyrdoxyaluminum and aminoacetate (aluminum glycinate) Aluminum hydroxide gel (as dried aluminum hydroxide gel) Dried aluminum hydroxide gel Aluminum hydroxide-Sodium hydrogen carbonate coprecipitate Aluminum hydroxide-Magnesium carbonate mixed dried gel Aluminum hydroxide-Magnesium carbonate-Calcium carbonate coprecipitate Magnesium hydroxide-Aluminum potassium sulfate coprecipitation product Magnesium carbonate Magnesium aluminometasilicate	900 3000 3000 4000 500 1500 1000 1000 900 3000 1500 1800 2000 1500

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

Crude drugs and Kampo medicine formulas

Classification	Name of crude drug or Kampo medicine formula	Maximum daily dose (g)	
		Extract (converted to the amount of crude drug or preparation)	Powder
Column XIII	Ephedra Herb	4	–
Column XIV	Nandina Fruit	10	–
Column XV	Cherry Bark	4	–
	Polygala Root	5	–
	Glycyrrhiza	5	1.5
	Platycodon Root	4	2
	Plantago Seed	5	–
	Plantago Herb	10	–
	Lycoris Radiata Bulb	0.8	–
	Senega	4	1.5
	Fritillaria Bulb	2.5	1.5

Classification	Name of crude drug or Kampo medicine formula	Maximum daily dose (g)	
		Extract (converted to the amount of crude drug or preparation)	Powder
Column XVI	Fennel	3	–
	Phellodendron Bark	3	3
	Coptis Rhizome	3	1.5
	Zedoary	3	3
	German Chamomile Flower	10	–
	Cinnamon Bark	5	1
	Gentian	0.5	0.5
	Oriental Bezoar	–	0.02
	Animal gall (including Bear Bile)	0.5	0.5
	Adenophora Root	5	2.5
	Ginger	3	1
	Atractylodes Lancea Rhizome	5	2
	Clove	2	0.5
	Citrus Unshiu Peel	5	3
	Atractylodes Rhizome	5	2
	Earthworm (Lumbricus)	3	2
	Panax Japonicus Rhizome	6	3
	Ginseng	6	3
Column XVII	Kakkonto	25	–
	Kakkontokakikyo	29	–
	Keishito	15	–
	Kososan	11	6
	Saikokeishito	24	–
	Shosaikoto	24	–
	Shoseiryuto	24	–
	Bakumondoto	30	–
	Hangekovokuto	16	–
	Maoto	13	–

(Note) Powder combinations will not be accepted where no maximum daily dose is given in the powder column.

Table 2

Name of Kampo medicine formula		Kakkonto	Kakkontokakikyo	Keishito	Kososan	Saikokeishito	Shosaikoto	Shoseiryuto	Bakumondoto	Hangekovokuto	Maoto
Component crude drugs and combination ratios	Scutellaria Root					2	3				
	Pueraria Root	8	8								
	Glycyrrhiza	2	2	2	1	2	2	2	2		2
	Platycodon root		4								
	Apricot Kernel										4
	Cinnamon Bark	3	3	4		3		3			3
	Cyperus Rhizome				4						
	Brown Rice								10		
	Magnolia Bark									3	
	Schisandra Fruit							3			
	Bupleurum Root					5	7				
	Asiasarum Root							3			
	Peony Root	3	3	4		3		3			
	Ginger	1	1	1	1	1	1	2		1	
	Perilla Herb				2					2	
	Jujube	4	4	4		2	3		3		
	Citrus Unshiu Peel				3						
	Ginseng					2	3		2		
	Ophiopogon Tuber								8		
	Pinellia Tuber					4	5	5	5	5	
	Poria Sclerotium									5	
	Ephedra Herb	4	4					3			4

Table 3

Age coefficients

Age group	Coefficient
15 years of age and over	1
11 to under 15 years of age	2/3
7 to under 11 years of age	1/2
3 to under 7 years of age	1/3
1 to under 3 years of age	1/4
6 months to under 1 year of age	1/5
3 months to under 6 months of age	1/6