Appendix 5

Provisional Translation
from Japanese Original

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The Standards for Marketing Approval of Gastrointestinal Medicines

1. Scope of Gastrointestinal Medicines

The scope of preparations subject to these standards covers all medicines for oral use formulated with the intent of relieving symptoms of gastrointestinal diseases (evacuants and Kampo medicine* formulas are not covered).

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for gastrointestinal 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) The types of active ingredients that may be used are shown in Table 1.

(b) Preparations mainly containing active ingredients from Column I, II, III, or IV can be mutually combined with other active ingredients from Columns I, II, III, and IV as well as the active ingredients from Columns V (limited to those with a "□" mark in Groups 3, 4, and 5), VII, and VIII.

However, notwithstanding the above rules, preparations having their main active ingredients only from Column I cannot include the following active ingredients: those in Group 2 of Column IV or those with a "□" mark in Group 5 of Column V. Preparations mainly containing active ingredients only from Column IV cannot include the active ingredients from Column VII.

(c) Preparations mainly containing active ingredients from Column V of Table 1 can include the active ingredients from Column I, II, III, IV, or VI (limited to Scopolia Extract in Group 1 and ingredients in Group 4).

(d) Preparations mainly containing active ingredients from Column VI of Table 1 can include the active ingredients from Column I (except Group 3), II, III, or V (limited to Groups 3 and 4).

However, preparations mainly containing active ingredients from Group 1 of Column VI cannot include the active ingredients from Column II (limited to Nux Vomica Extract in Group 1 or ingredients in Group 3). When the active ingredients from Column VI (except for Group 4) are used in combination, they should be limited to 1 type from each group.

(e) When the active ingredients from Column VII (except for Group 9) of Table 1 are used in combination, they should be limited to 1 type from each group.

(f) The active ingredients from Column I (excluding Group 3) and Group 2 of Column II cannot be combined in the same preparation.

(g) When the same active ingredient appears in at least 2 columns of Table 1, it

should not be duplicated in the formula.

(h) Berberine chloride and berberine tannate in Group 1 of Column V must not be combined with Coptis Rhizome or Phellodendron Bark in Group 1 of Column II or Group 5 of Column V of Table 1. Glycyrrhizinic acid, its salts, and glycyrrhiza extracts in Group 3 of Column VII cannot be combined with Glycyrrhiza in Group 9 of Column VII.

(i) The vitamins given in the Appendix may be combined with the active ingredients listed in Table 1 as long as there is good reason for their combination and the effect is mild.

(2) Quantities of Active Ingredients

(a) The maximum daily doses of the active ingredients listed in Table 1 (except for those in Group 1 of Column III and Group 1 of Column IV) should correspond to data in Table 1. The maximum single dose should be 1/3rd of the maximum daily dose.

(b) When not less than 2 active ingredients in Group 1 or Group 2 of Column I listed in Table 1 are combined, the sum of the values obtained by dividing the amount of each active ingredient by its respective maximum daily dose should not exceed 2.

(c) When at least 2 active ingredients in Group 2 or Group 3 of Column II are combined, or when at least 2 active ingredients in Group 2 of Column III or at least 2 active ingredients in Group 1, 2, 3, or 4 of Column V of Table 1 are included, the sum of the values obtained by dividing the amount of each active ingredient by its respective maximum daily dose should not exceed 1 for any group.

(d) When the crude drugs marked with "*" in Group 1 of Column II in Table 1 are combined in preparations for which the main active ingredient comes from Column I, the daily dose of the crude drug concerned should not be more than 1/10th of the maximum daily dose shown in Table 1.

(e) When preparations whose main active ingredients are from Groups 1 and 2 of Column I and which are tested for acid-neutralizing capacity or pH by the methods specified elsewhere, the acid-neutralizing capacity of the daily dose of the preparation should not be less than 150 mL when expressed as the amount of 0.1N hydrochloric acid consumed, and the pH of the preparation should not be less than 3.5.
The acid-neutralizing capacity of a single dose of the preparation should be not less than 50 mL.

(f) In preparations mainly containing active ingredients from Group 1 of Column III of Table 1, the digestive activity of the digestive enzymes included in a single dose of the preparation should not be less than the minimum daily unit for at least 1 of the following: starch saccharifying activity, starch dextrinizing activity, starch liquefying activity, protein digesting activity, fat digesting activity, fibrin saccharifying activity, or fibrin disintegrating activity specified in Group 1 of Column III.
The minimum unit for a single dose shall be 1/3rd of the minimum daily unit.

(g) For preparations mainly containing active ingredients from Group 1 of Column IV in Table 1, the minimum daily dose of the active ingredient concerned should be the amount shown in Table 1, and the minimum single dose should be 1/3rd of the minimum daily dose.

(3) Dosage Form

The dosage forms should be capsules, granules, pills, fine granules, powders, electuaries, tablets, infusions, decoctions, or liquids for oral use (limited to mildly

acting preparations mainly containing ingredients from Column I or II).

(4) Dosage and Administration

(a) In principle, dosage and administration should be 3 times a day.
Oral liquids mainly containing ingredients from Column I or II, or preparations mainly containing ingredients from Column V or VI listed in Table 1 can be taken 1 to 3 times a day, and if they are taken not less than 2 times a day, the interval between doses must not be less than 4 hours.

(b) For infusions and decoctions, the method of preparation at the time of use should be indicated.

(c) The time of administration (such as before or after meals, between meals) and the administration interval should be indicated.

(d) Dosage in infants less than 3 months of age is not approved.

(e) For capsules, pills, or tablets larger than 6 mm in diameter, dosage in children less than 5 years of age is not approved.

(f) For pills or tablets smaller than 6 mm in diameter, dosage in children less than 3 years of age is not approved.

(g) The maximum daily dose for children less than 15 years of age should be obtained by multiplying the maximum daily doses listed in Table 1 by the values given in the coefficient column for the corresponding age ranges stated in Table 2.

(h) The minimum daily doses specified in (2) (e) and (2) (f) should be multiplied by the values given in the coefficient column for the corresponding age ranges in Table 2 to obtain the minimum daily dose for children less than 15 years of age. However, the minimum daily doses specified in (2) (g) should be applied irrespective of age.

(5) Indications

(a) The range of indications for preparations mainly containing active ingredients from the columns of Table 1 (except Columns VII and VIII) is shown in Table 3. When active ingredients from at least 2 of Columns I, II, III, and IV are used as the main ingredients, the indications should cover all of those in the columns concerned.
The indications in Column III of Table 3 can be claimed for preparations whose main active ingredients are from Group 1 in Column III, only if the minimum daily units of at least 1 of the following are achieved: starch saccharifying activity, starch dextrinizing activity, starch liquefying activity, protein digestive activity, and fat digestive activity.

(b) For preparations claiming the indications mentioned in Column V or VI of Table 3, the indications listed in the other columns of the same table should not be claimed.

(c) Notwithstanding the above standards, the indications in Column I of Table 3 cannot be claimed in cases where Nux Vomica Extract in Group 1 of Column II is included in preparations containing active ingredients from Column I in Table 1.
In addition, the indications in Column I of Table 3 cannot be claimed for preparations containing active ingredients only from Group 3 of Column I in Table 1.

(Table 1)

Classification		Active ingredient	Maximum daily dose
Column I	Group 1	Dried aluminum hydroxide gel	3 g
		Magnesium aluminosilicate	4 g
		Magnesium silicate	6 g
		Synthetic aluminum silicate	10 g
		Synthetic hydrotalcite	4 g
		Magnesium oxide	1 g
		Magnesium hydroxide-aluminum hydroxide co-precipitate	4 g
		Aluminum hydroxide gel	30 mL (1.2 g as aluminum oxide)
		Aluminum hydroxide-sodium bicarbonate co-precipitate	2 g
		Dried mixed aluminum hydroxide and magnesium carbonate gel	3 g
		Aluminum hydroxide-magnesium carbonate-calcium carbonate co-precipitate	4 g
		Magnesium hydroxide	2.4 g
		Sodium bicarbonate	5 g
		Magnesium carbonate	2 g
		Precipitated calcium carbonate	3 g
		Magnesium aluminometasilicate	4 g
		Anhydrous dibasic calcium phosphate	2.4 g
		Dibasic calcium phosphate	3 g
		Cuttlefish Bone	3 g
		Abalone Shell	3 g
		Oyster Shell	3 g
	Group 2	Aminoacetic acid	0.9 g
		Dihydroxyaluminum aminoacetate	3 g
	Group 3	Scopolia Extract	30 mg

Classification		Active ingredient	Maximum daily dose (g)		Classification		Active ingredient	Maximum daily dose (g)	
			Extract (converted to crude drug amount)	Powder				Extract (converted to crude drug amount)	Powder
Column II	Group 1	Aniseed	3	1	Column II	Group 1	Citrus Unshiu Peel	5	3
		Aloe	–	0.15			*Capsicum	–	0.1
		Fennel	3	1			Bitter Orange Peel	5	3
		Turmeric	6	2			Animal bile (including Bear Bile)	–	0.5
		Lindera Root	5	1			Picrasma Wood	5	0.5
		Isodon Herb	10	3			Nutmeg	3	1
		Scutellaria Root	6	3			Ginseng	6	3
		Phellodendron Bark	3	3			Mentha Herb (including peppermint)	3	1
		Coptis Rhizome	3	1.5			Long pepper	2	0.5
		Processed Garlic Bulb	–	0.2			Atractylodes Rhizome	5	2
		Zedoary	3	3			Hop Strobile	3	1
		Pogostemon Herb	8	3			Nux Vomica Extract	–	0.03
		Calamus Root	6	2			Menyanthes trifolia herb	4	1.3
		Processed Ginger	3	1					
		Orange Fruit	5	2			Saussurea Root	3	1
		Immature Orange	5	2			Bitter Cardamon	3	1
		Cinnamon Bark	5	1			Japanese Gentian	1.5	0.5
		Gentian	1.5	0.5			Alpinia Officinarum Rhizome	3	1
		Red Ginseng	6	3					
		Magnolia Bark	5	1.5			Fennel Oil	0.08	
		Euodia Fruit	3	1			Cinnamon Oil	0.03	
		*Pepper	5	1.5			Ginger Oil	0.03	
		Calumba	5	1.5			Cardamon Oil	0.03	
		Condurango	9	3			Clove Oil	0.02	
		*Japanese Zanthoxylum Peel	3	1			Bitter Orange Peel Oil	0.03	
		Resurrection Lily Rhizome	6	2			Mentha Oil	0.03	
		Perilla Fruit	6	3			Lemon Oil	0.03	
		Amomum Seed	3	1			*l*-Menthol	0.18	
		Ginger	3	1			*dl*-Menthol	0.18	

		Cardamon	3	1		Group 2	Betaine hydrochloride	0.6
		Immature Citrus Unshiu Peel	5	3			L-Glutamic acid hydrochloride	1.8
		Acorus Gramineus Rhizome	6	2				
		Centaury Herb	2	0.7				
		Swertia Herb	1.5	0.05		Group 3	Carnitine chloride	0.6
		Atractylodes Lancea Rhizome	5	2			Bethanechol chloride	0.045
		Perilla Herb	2	1				
		Star Anise	3	1				
		Rhubarb	0.2	0.1		Group 4	Dried yeast	10
		Panax Japonicus Rhizome	6	3				
		Clove	2	0.5				

Classification		Active ingredient	Minimum daily unit[Note 1)]	
Column III	Group 1	Starch digestive enzymes	Starch saccharifying activity:	250 units
			Starch dextrinizing activity:	210 units
			Starch liquefying activity:	360 units
		Protein digestive enzymes	Proteolytic activity:	1,500 units
		Fat digestive enzymes	Fat digestive activity:	100 units
		Fibrin digestive enzymes	Fibrin saccharifying activity:	13 units
			Fibrin disintegrating activity:	25 units

Group 2	Active ingredient	Maximum daily dose (g)
	Ursodesoxycholic acid	0.06
	Oxycholanates	0.15
	Cholic acid	0.9
	Bile powder	1.5
	Bile extract (powder)	0.5
	Dehydrocholic acid	0.5
	Animal bile (including Bear Bile)	0.5

Note 1) Methods for measuring the digestive activity of each digestive enzyme are specified separately.

		Active ingredient	Minimum daily dose	
Column IV	Group 1	Live bacteria for intestinal regulation	1×10^6	
	Group 2		Maximum daily dose (g)	
			Extract (converted to crude drug amount)	Powder
		Mallotus Bark	5	1.5
		Gambir	–	2
		Processed Mume	10	3
		Cassia Seed	10	3
		Geranium Herb	10	3

Classification		Active ingredient	Maximum daily dose (g)	
Column V	Group 1	Acrinol	0.3	
		Berberine chloride	0.3	
		Guaiacol	0.6	
		Creosote	0.5	
		Phenyl salicylate	1	
		Guaiacol carbonate	1.2	
		Berberine tannate	0.3	
	Group 2	Bismuth subsalicylate	3	
		Bismuth subnitrate	2	
		Bismuth subcarbonate	3	
		Bismuth subgallate	2	
		Tannic acid	1.2	
		Albumin tannate	4	
		Methylene thymol tannin	2	
	Group 3	Kaolin	10	
		Natural aluminum silicate	10	
		Aluminum hydroxynaphthoate	0.9	
		Pectin	0.6	
		Medicinal carbon	5	
	Group 4	Precipitated calcium carbonate	3	
		Calcium lactate	5	
		Dibasic calcium phosphate	3	
			Extract (g) (converted to crude drug amount)	Powder (g)
	Group 5	□ Gambir	-	2
		□ Processed Mume	10	3
		Phellodendron Bark	9	3
		Coptis Rhizome	3	1.5
		Sophora Root	3	1.5
		□ Geranium Herb	10	3
		Rhus Javanica Nutgall	-	3
		□ Crataegus Fruit Swertia	8	3
		Herb Myrica Rubra	-	0.9
		Bark	5	2

Classification		Active ingredient	Maximum daily dose	
Column VI	Group 1	Oxyphencyclimine hydrochloride	7 mg	
		Dicyclomine hydrochloride	30 mg	
		Methixene hydrochloride	8.75 mg	
		Scopolamine hydrobromide	0.3 mg	
		Atropine methylbromide	6 mg	
		Anisotropine methylbromide	30 mg	
		Scopolamine methylbromide	4.8 mg	
		l-Hyoscyamine methylbromide	2.25 mg	
		Methylbenactyzium bromide	30 mg	
		Belladonna extract	60 mg	
		Isopropamide iodide	7.5 mg	
		Diphenylpiperidinomethyldioxolane iodide	60 mg	
		Scopolia Extract	60 mg	
		Scopolia Rhizome (Total) Alkaloid citrates	1 mg	
	Group 2	Papaverine hydrochloride	90 mg	
	Group 3	Ethyl aminobenzoate	0.6 g	
			Extract (g) (converted to crude drug amount)	Powder (g)
	Group 4	Corydalis Tuber	5	1.5
		Glycyrrhiza	5	1.5
		Magnolia Bark	5	1.5
		Peony Root	5	2

Classification		Active ingredient	Maximum daily dose (g)	
Column VII	Group 1	Sodium azulene sulfonate	0.006	
	Group 2	Aldioxa	0.3	
	Group 3	Glycyrrhizinic acid, its salts, and glycyrrhiza extracts	(as glycyrrhizinic acid) 0.2	
	Group 4	L-Glutamine	2	
	Group 5	Potassium copper chlorophyllin Sodium copper chlorophyllin	0.2 0.2	
	Group 6	Histidine monohydrochloride	0.18	
	Group 7	Pepsin decomposition products of pig stomach wall Acid hydrolysis products of pig stomach wall	0.3 0.3	
	Group 8	Methylmethioninesulfonium chloride	0.15	
	Group 9		Extract (g) (converted to crude drug amount)	Powder (g)
		Mallotus Bark	5	1.5
		Corydalis Tuber	5	1.5
		Glycyrrhiza	5	1.5

Column VIII	Dimethylpolysiloxane	0.18 g

(Table 2) Age coefficients

Age	Coefficients
15 years of age or over	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

(Table 3)

Main ingredient	Indications
Column I	Hyperacidity, heartburn, feeling of discomfort in the stomach, feeling of fullness in the stomach, constricted feeling in the stomach (stomach heaviness), heaviness in the stomach, heaviness in the chest, belching (burping), nausea (retching, stomach retching, retching due to hangovers and overdrinking, sick feeling, and feeling of sickness), vomiting, excessive drinking (overdrinking), and stomachache
Column II	Loss of appetite (anorexia), feeling of fullness in the stomach and abdomen, indigestion, weak stomach, excessive eating (overeating), excessive drinking (overdrinking), heartburn, constricted feeling in the stomach (stomach heaviness), heaviness in the chest, nausea (retching, stomach retching, retching due to hangovers and overdrinking, sick feeling, and feeling of sickness), and vomiting
Column III	For promoting digestion, indigestion, loss of appetite (anorexia), excessive eating (overeating), constricted feeling in the stomach (stomach heaviness), heaviness in the chest, and feeling of fullness in the stomach and abdomen due to indigestion
Column IV	Intestinal regulation (regulation of stool), feeling of fullness in the abdomen, soft stool, and constipation
Column V	Diarrhea, diarrhea due to indigestion, food poisoning, vomiting and purging, water poisoning, loose bowels, soft stool, and diarrhea accompanied by abdominal pain[Note 1)]
Column VI	Stomachache, abdominal pain, gripping pain (colic, spasms), hyperacidity, and heartburn

Note 1) Only when scopolia extract in Group 1 of Column VI is included.

(Appendix)

1. Vitamins that can be included in preparations mainly containing active ingredients from Column II or III are indicated below, together with their maximum daily doses.

Ingredient	Maximum daily dose
Vitamin B_1, its derivatives, and their salts	25 mg

2. Vitamins that can be included in preparations mainly containing active ingredients from Column IV are listed below, together with their maximum daily doses.

Ingredient	Maximum daily dose
Nicotinamide	5 mg
Calcium panthothenate Biotin	30 mg
Vitamin B_1, its derivatives, and their salts	25 μg
Vitamin B_2, its derivatives, and their salts	25 mg
Vitamin B_6, its derivatives, and their salts	12 mg
Vitamin C, its derivatives, and their salts	50 mg
	500 mg

However, the combination of biotin and nicotinamide is permitted only when including live lactic acid bacteria or lactic acid producing bacteria for intestinal regulation.

3. Vitamins that can be included in preparations mainly containing active ingredients from Column V are listed below, together with their maximum daily doses.

Ingredient	Maximum daily dose
Vitamin B_1, its derivatives, and their salts Vitamin B_2, its derivatives, and their salts	25 mg 12 mg