Appendix 6

Provisional Translation
from Japanese Original

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The Standards for Marketing Approval of Laxatives

1. Scope of Laxatives

The scope of preparations subject to these standards covers oral medicines intended for the relief of the symptoms of constipation or the elimination of intestinal contents (except for preparations covered by the Standards for Marketing Approval of gastrointestinal medicines and Kampo medicine* formulas.

* Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for laxatives are as follows.

For preparations not conforming to these standards, concerning the 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 in laxatives are shown in Tables 1 and 2.

(b) At least 1 of the active ingredients in Table 1 must be used.

(c) Preparations mainly containing the active ingredients from Group I, II, III, or IV in Column A of Table 1 may be made by mutual combination of the active ingredients in these 4 groups, and may also include the active ingredients in Table 2.

(d) When active ingredients from Group I, Group II, or Group III in Column A of Table 1 are combined, only 1 ingredient from each group should be used. When active ingredients from Group IV are used, up to 4 active ingredients from this group may be included. However, when active ingredients from 2 or more groups, among Groups I, II, III, and IV, are combined, up to 4 active ingredients from Column A of Table 1 (except Group V) may be combined.

(e) The following combinations are not permitted among the active ingredients of Group IV in Column A of Table 1: Aloes with aloin, Cascara sagrada bark with casanthranol, Pharbitis seeds with Pharbitis seed resin, Senna or Senna fruit with sennoside or sennosides A and B, and Jalap tuber with Jalap resin.

(f) For preparations mainly containing the active ingredients from Group V of Column A in Table 1, combinations with the other active ingredients in these standards are not permitted.

(g) When the active ingredients from Column B of Table 1 are used as a main ingredient, only 1 active ingredient can be used in a preparation and none of the other active ingredients covered by these standards should be combined.

(h) When the active ingredients from Column I or II of Table 2 are combined, up to 4 active ingredients in the same column may be used.
When active ingredients in both Columns I and II of Table 2 are combined, up

to 5 of the active ingredients from the whole table may be used.

(i) Other than the active ingredients in Tables 1 and 2, vitamins in the Appendix may be included if there is a sound basis for their combination and the effect is mild.

(2) Quantities of Active Ingredients

(a) The maximum single and daily doses of the active ingredients from Column A of Table 1 are as indicated in the table.

(b) The maximum single doses of the active ingredients from Column B of Table 1 are as indicated in the table.

(c) The maximum daily dose of each of the active ingredients from Column I (except live bacteria for intestinal regulation) and Column II of Table 2 are as given in the table. The maximum single dose should be 1/3rd of the maximum daily dose.

(d) When 2 or more of the active ingredients from Column A of Table 1 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 2.

(e) When 2 or more of the active ingredients from either Column I or Column II of Table 2 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 2 in each column.

(f) The minimum daily dose of live bacteria for intestinal regulation from Column I of Table 2 is as given in the same group, and the minimum single dose should be 1/3rd of the minimum daily dose.

(3) Dosage Forms

The dosage forms are capsules, granules, pills, fine granules, powders, lingual tablets (limited to preparations mainly containing the active ingredients from Group V of Column A of Table 1), tablets, infusions, decoctions, chocolate preparations and liquids for oral use (limited to syrups and preparations mainly containing the active ingredients from Group I of Column A or those from Column B of Table 1).

(4) Dosage and Administration

(a) Preparations should, in principle, be taken by oral administration 1 to 3 times daily, and the administration times and intervals must be clearly indicated. When the preparation is taken twice a day or more, the interval between doses must be not less than 4 hours. However, preparations mainly containing the active ingredients from Column B of Table 1 should be taken not more than once a day, to be taken when required.

(b) For preparations mainly containing the active ingredients from Column A of Table 1, the dosage range for different degrees of constipation must be indicated.
Since there are individual differences with respect to the degree of constipation, it must be stated that the minimum dose should be taken initially and then the dose should be gradually increased (or decreased) depending on the condition of relief.

(c) In principle, dosage for children under 3 years of age is not permitted.

(d) Regardless of the rules described in (a), (b), or (c), preparations mainly containing the active ingredients from Group V of Column A in Table 1 will be approved only for small children and infants. Entries for dosage and

administration should be made in accordance with Table 5.

(e) In the case of infusions and decoctions, the method of preparation at the time of use should be clearly indicated.

(f) For capsules, and pills and tablets larger than 6 mm in diameter, dosage for children under 5 years of age is not approved.

(g) The maximum single and daily doses for those under 15 years of age are the values obtained by multiplying the coefficients corresponding to the respective age groups in Table 3 by the maximum single and daily doses shown in Tables 1 and 2.
However, the minimum daily dose of live bacteria for intestinal regulation from Column I of Table 2 should be applied irrespective of age.

(5) Indications

(a) The indications for preparations mainly containing the active ingredients from Column A of Table 1 are shown from Column I of Table 4. However, the indications for preparations mainly containing the active ingredients from Group V of Column A in Table 1 are as specified in Table 5.

(b) The indications for preparations mainly containing the active ingredients from Column B of Table 1 are as specified from Column II of Table 4.

(6) Packaging Units

The maximum volume of syrup containers is a 2-day supply at the maximum daily dose for adults (15 years of age and over).

Table 1

Classification		Active ingredients	Maximum single dose (g)		Maximum daily dose (g)	
Column A	Group I	Magnesium oxide	0.7 (2)		2	
		Magnesium hydroxide	0.7 (2.1)		2.1	
		Magnesium carbonate	2.7		8	
		Sodium sulfate	5		15	
		Magnesium sulfate	5		15	
	Group II	Carboxymethylcellulose calcium	2		6	
		Carboxymethylcellulose sodium	2		6	
		Plantago ovata coating (Ispaghula husk)	3.5		10.5	
	Group III	Sodium dioctyl-sulfosuccinate	0.067 (0.12)		0.2	
	Group IV	Aloin	0.02		0.06	
		Sulfur	0.5		1.5	
		Casanthranol	0.067 (0.1)		0.2	
		Sennoside (as sennosides A and B)	0.016 (0.024)		0.048	
		Sennosides A and B	0.016 (0.024)		0.048	
		Bisacodyl	0.007 (0.015)		0.02	
			Powder (g)	Extract (g) (converted to crude drug amount)	Powder (g)	Extract (g) (converted to crude drug amount)
		Aloes	0.25 (0.38)	0.25 (0.38)	0.75	0.75
		Rose fruit	0.67	1.7	2	5
		Cascara sagrada bark	–	1 (1.5)	–	3
		Pharbitis seed	0.1	–	0.3	–
		Pharbitis seed resin	0.05	–	0.15	–
		Senna	0.5 (0.75)	2 (3)	1.5	6
		Senna fruit	0.5 (0.75)	–	1.5	–
		Rhubarb	1 (1.5)	1.4 (2)	3	4
		Frangula bark	–	1 (1.5)	–	3
		Jalap root	0.1	–	0.3	–
		Jalap resin	0.05	–	0.15	–
	Group V	Malt extract	As per Table 5			
Column B		Aromatic castor oil	20 mL		–	
		Castor oil	20 mL		–	

(Note) Figures in parentheses are the maximum single dose applicable when the dosage is once or twice a day.

Table 2

Classification	Active ingredient	Maximum daily dose (g)	
Column I	Ursodeoxycholic acid	0.06	
	Oxycolanate	0.15	
	Dried yeast	10	
	Cholic acid	0.9	
	Dimethylpolysiloxane	0.18	
	Live bacteria for intestinal regulation	1×10^6 (*)	
	Sodium bicarbonate	3	
	Dehydrocholic acid	0.5	
		Powder (g)	Extract (g) (converted to crude drug amount)
	Linseed	2	–
	Japanese valerian	2	–
	Glycyrrhiza	1.5	5
	Cassia seed	3	10
	Smilax rhizome	1.5	5
	Gardenia fruit	1	3
	Rehmannia root	1.5	5
	Peony root	2	5
	Houttuynia herb	5	15
	Cimicifuga rhizome	1	3
	Cnidium rhizome	1.5	5
	Jujube	1.5	5
	Bile extract (powder)	0.5	
	Japanese angelica root	1.5	5
	Animal bile	0.5	–
	Moutan bark	1.3	4
	Hemp fruit	5	–
	Coix seed	6	20

(*) Minimum daily dose

Classification	Active ingredient	Maximum daily dose (g)	
		Powder (g)	Extract (g) (converted to crude drug amount)
Column II	Fennel	0.5	1.5
	Plectranthus herb	1.5	5
	Scutellaria root	1.5	3
	Phellodendron Bark	1.5	1.5
	Coptis Rhizome	0.75	1.5
	Zeodary	1.5	1.5
	Calamus Root	1	3
	Immature orange	1	2.5
	Cinnamon Bark	0.5	2.5
	Gentian	0.25	0.75
	Magnolia bark	0.75	2.5
	Condurango	1.5	4.5
	Resurrection Lily Rhizome	1	3
	Ginger	0.5	1.5
	Swertia herb	0.025	0.75
	Atractylodes Lancea Rhizome	1	2.5
	Perilla Herb	0.5	1
	Citrus Unshiu Peel	1.5	2.5
	Bitter orange peel	1.5	2.5
	Ginseng	1.5	3
	Mentha herb	0.5	1.5
	Mentha oil	0.015	
	Atractylodes rhizome	1	2.5
	Nux vomica extract	0.015	
	dl-Menthol	0.09	
	l-Menthol	0.09	
	Saussurea root	0.5	1.5
	Japanese gentian	0.25	0.75

Table 3 Age coefficient

Age	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

Table 4

	Indications
Column I	○ Constipation ○ Relief of the following symptoms due to constipation: dull headache, hot flush, skin roughness, eruption, loss of appetite (anorexia), fullness in the abdomen, abnormal fermentation in the intestines, and hemorrhoids
Column II	○ Rapid excretion of intestinal contents (food poisoning, etc.)

Table 5

Dosage and administration (maximum single dose)	Indications
1 to under 3 years of age: 15 g/dose 6 months to under 1 year of age: 9 g/dose Under 6 months of age: 9 g/dose Take orally up to 3 times a day in each case	Constipation in infants and small children

Appendix

Ingredients	Maximum daily dose
Vitamin B_1, its derivatives, and their salts	25 mg
Vitamin B_6	50 mg
Nicotinamide	5 mg
Calcium panthothenate	30 mg

(Note) Nicotinamide is to be combined only when lactic acid bacteria or lactic acid producing bacteria are used as live bacteria for intestinal regulation.