The Approval Standards for OTC Drugs in JAPAN

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Outline

1. What are OTC drugs in Japan ?

2. The Approval Standards for OTC drugs in Japan
   - What are the Approval Standards?
   - Background and benefit of the standards

3. Manufacturing Approval Standards for Antipyretic Analgesics
   - Active ingredients
   - Dosage form
   - Dosage and administration
   - Indications

OTC drugs (Over-the-counter drugs)

- Drugs other than prescription drugs that are intended for use at the discretion of general consumers by direct purchase in a pharmacy or a drug store under guidance by pharmacists or other medical personnel.

- In Japan, OTC drugs include Switch OTC drugs and Direct OTC drugs.
  - ✓ **Switch OTC drugs (Switch from Rx to OTC drugs)**

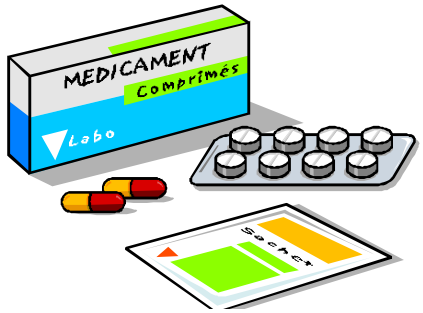
    Drugs with active ingredients which have never been used as active ingredients in any approved OTC drugs.
  - ✓ **Direct OTC drugs**

    Drugs with active ingredients which have never been used as active ingredients in any approved prescription drugs.

Characteristics of OTC drugs

OTC drugs should:

- Be assured the quality, efficacy, and safety
- Provide information to customers in order to allow them to choose drugs without prescription at their own discretion
- Consider lifestyles and healthcare needs of consumers
- Comply with the latest standards and knowledge in the sciences of medicine and pharmacy (including public health, nutrition, and related areas)



Approval Standards for OTC drugs

- The Approval Standards are guidelines and criteria for drugs such as active ingredients, daily maximum dose, combinations allowed, dosage and administration, and indications in each therapeutic classes. They are similar to OTC Monograph in the USA, but require review and GMP inspection.
- If the application products conform to the standards, the Minister of Health, Labour and Welfare delegate approval authority to prefectural governors.

Background of establishment of Approval Standards

- In 1969, MHLW (Ministry of Health, Labour and Welfare) indicated a policy to promote the efficacy and acceleration of OTC drug reviews, and manufacturing approval standards for cold remedies was established in 1970.

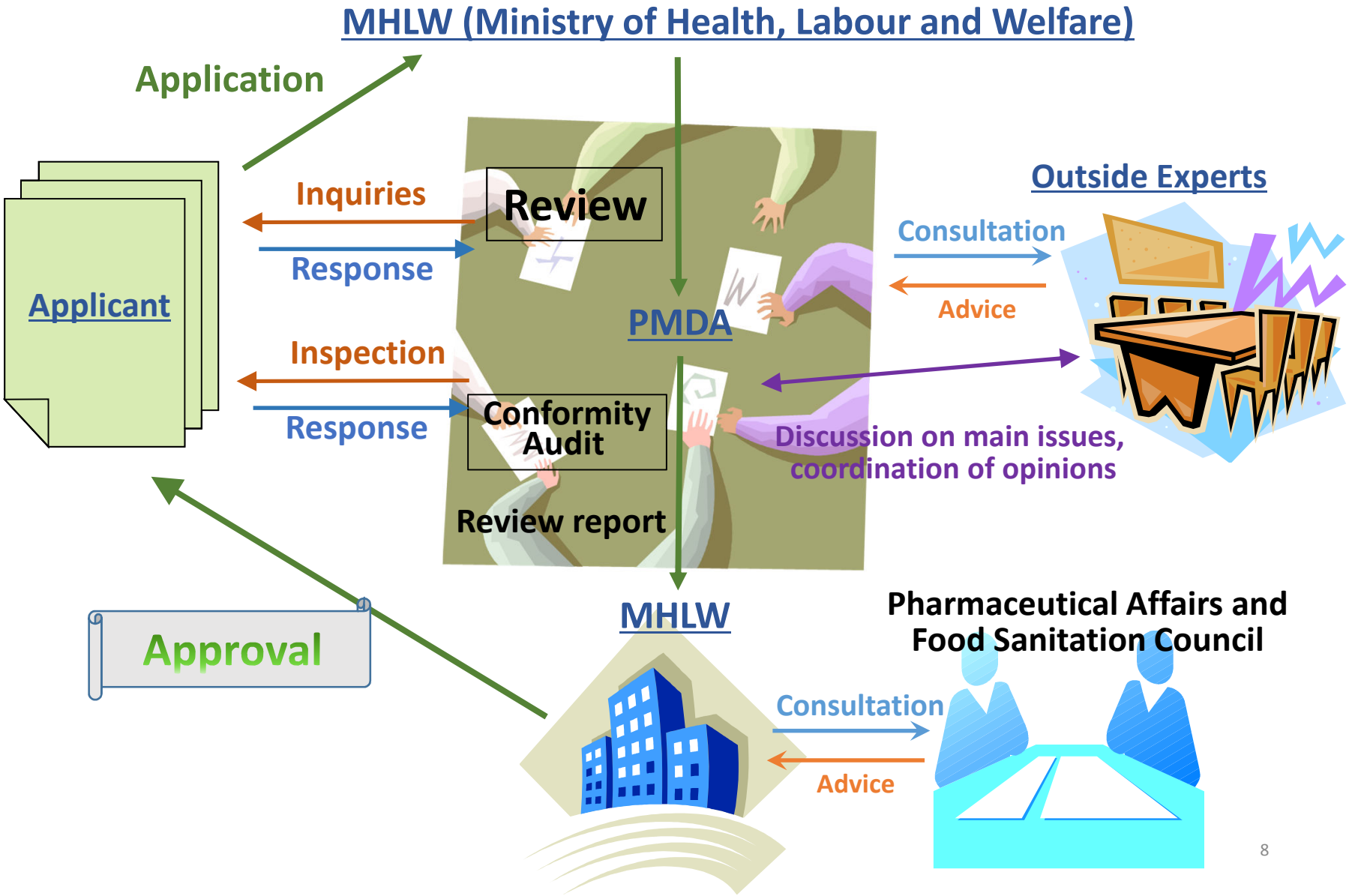
- The standards are updated as necessary.
  In 2015, the standards for cold remedies, antipyretic analgesics, antitussives and expectorants and oral preparations for rhinitis were updated.

- Currently, 15 therapeutic classes are listed.

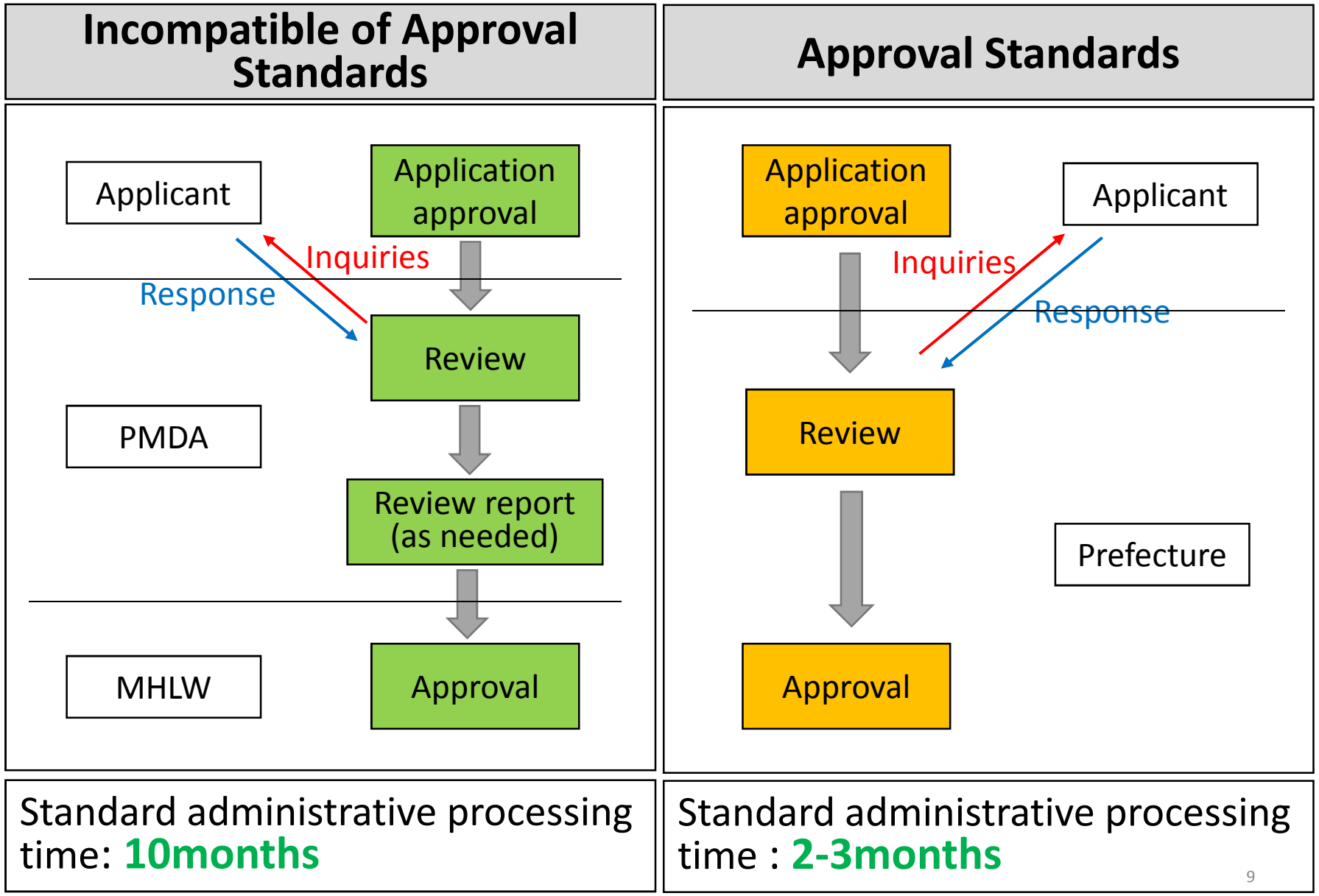
Therapeutic Classes for Approval Standards

Therapeutic class	Establish	Last update	Number of ingredients
Cold remedies	1970	2015	126
Antipyretic Analgesics	1972	2015	52
Antitussives and Expectorants	1976	2015	120
Gastrointestinal Medicines	1980	1986	256
Laxatives	1982	1998	128
Antivertigo Medicines	1984	—	49
Ophthalmic Medicines	1986	—	56
Vitamin Preparations	1988	1995	68
Enemas	1988	—	3
Anthelmintics	1989	1995	27
Nasal Drops for Rhinitis	1991	2012	20
Oral Preparations for Rhinitis	1993	2015	47
Antihemorrhoids (External Preparations)	1995	—	70
Athlete’s Foot and Ringworm Remedies	1998	—	74
Antipruritic and Anti-inflammatory Drugs	2012	—	43
Total			1139

Process of review and conformity audit for OTC drugs (outline)



Review of OTC drugs under Approval Standards

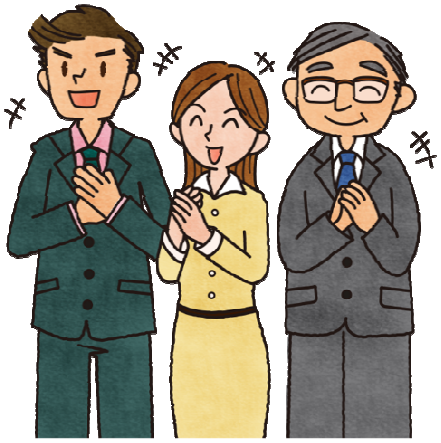


Benefit of Approval Standards

Health authority

- reduce total review time
- PMDA can focus on review of new OTC drugs (e.g., Switch OTC drugs, Direct OTC drugs, etc.).

Industry



- decrease review time.
- easy to predict the approval time

Public

- ensuring transparency of reviews
- lighten the national burden (e.g., time, medical expenses, etc.).

Manufacturing Approval Standards for Antipyretic Analgesics

- The scope of preparations subject to these standards covers oral medicines intended for the relief of pain or fever (formulations based on KANPO preparations and those containing entirely of crude drugs are not covered).

- The Approval Standards indicate types and quantities of active ingredients, dosage form, dosage and administration and indications.

Active ingredients listed in the Approval Standards

Classification		Active Ingredient	Maximum single dose (mg)	Maximum daily dose (mg)
Column I	Group 1	Acetaminophen	300	900
		Lactylphenetidin	200	600
	Group 2	Aspirin	750	1500
		Aspirin aluminum	1000	2000
		Ethenzamide	500	1500
		Sasapyrine	500	1500
		Salicylamide	1000	3000
		Sodium salicylate	1000	3000
	Group 3	Ibuprofen	200	450
	Group 4	isopropylantipyrine	150	450
Column II		Allylisopropylacetylurea	60	180
		Bromovalerylurea	200	600
Column III		Tranexamic acid	250	750
Column IV		Caffeine and sodium benzoate	150	300
		Caffeine hydrate	120	250
		Anhydrous caffeine	120	250

Active ingredients listed in the Approval Standards

Classification	Active Ingredient	Maximum daily dose (mg)
Column V	Vitamin B_1, its derivatives, and their salts	25
	Vitamin B_2, its derivatives, and their salts	12
	Vitamin C, its derivatives, and their salts	500
	Hesperidine, its derivatives, and their salts	90
Column VI	Glycine	900
	Magnesium silicate	3000
	Synthetic aluminum silicate	3000
	Synthetic hydrotalcite	4000
	Magnesium oxide	500
	Dihydroxyaluminum aminoacetate	1500
	Aluminum hydroxide gel (as dried aluminum hydroxide gel)	1000
	Dried aluminum hydroxide gel	1000
	Aluminum hydroxide-sodium bicarbonate co-precipitate	900
	Dried mixed aluminum hydroxide and magnesium carbonate gel	3000
	Aluminum hydroxide-calcium carbonate-magnesium carbonate co-precipitate	1500

Active ingredients listed in the Approval Standards

Classification	Active Ingredient	Maximum daily dose (mg)
Column VI	Magnesium hydroxide-aluminum potassium sulfate co-precipitate	1800
	Magnesium carbonate	2000
	Magnesium Aluminometasilicate	1500

(Crude drugs)

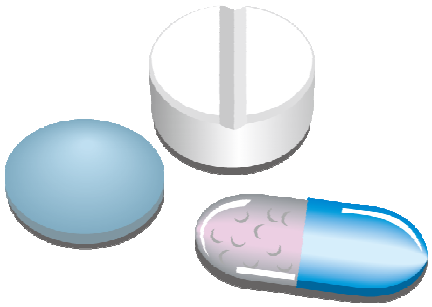
Classification	Active ingredient	Maximum daily dose (g)	
		Extract	Powder
Column VII	Lumbricus	3	2
Column VIII	Japanese valerian	6	2
	Glycyrrhiza	5	1.5
	Cinnamon bark	5	1
	Peony root	5	2
	Mountain bark	6	2
Column IX	Zanthoxylum fruit	2	1
	Ginger	3	1
	Citrus unshiu peel	5	3

Active ingredients

- At least 1 active ingredient in Column1; Groups 1, 2 or 3 listed in previous slide must be used.
- Other rules of combination and quantity are described for each classifications.

Dosage Form

- The dosage forms should be tablets, capsules, pills, granules, and powders.



Dosage and Administration

- Once a day administration

  Take the medicine not more than once a day. If possible, avoid taking the medicine on an empty stomach.

- Twice a day administration

  Take the medicine not more than twice a day with an interval of at least 6 hours between doses. If possible, avoid taking the medicine on an empty stomach.

- Three times a day administration

  Take the medicine not more than 3 times a day with an interval of at least 4 hours between doses. If possible, avoid taking the medicine on an empty stomach.

- Other rules are described in the standards.

Indications

- The indications should be within the following scope.

1. Relief of headache, toothache, pain after tooth extraction, sore throat, earache, joint pain, neuralgia, lumbago, muscular pain, pain due to stiff shoulders, contusion pain, bone fracture pain, sprain pain, painful menses (menstrual pain), and traumatic pain.

2. Relief of chills and fever

Summary

- The Approval Standards play a key role in review of OTC drugs, and provide benefits for health authority, industry and public.

- The Approval Standards are updated as necessary, since 1970 when standards for cold remedies were established.
- Currently, 15 therapeutic classes are listed in the standards.

Thank you for your attention!

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