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Review of Monographed OTC in Asia Pacific

Dr. Noppadon (Nhum) Adjimatera

South East Asia (SEA) Regulatory & Medical Affairs Director,
RB, SEA, Thailand

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Drug registration procedure in Asia Pacific

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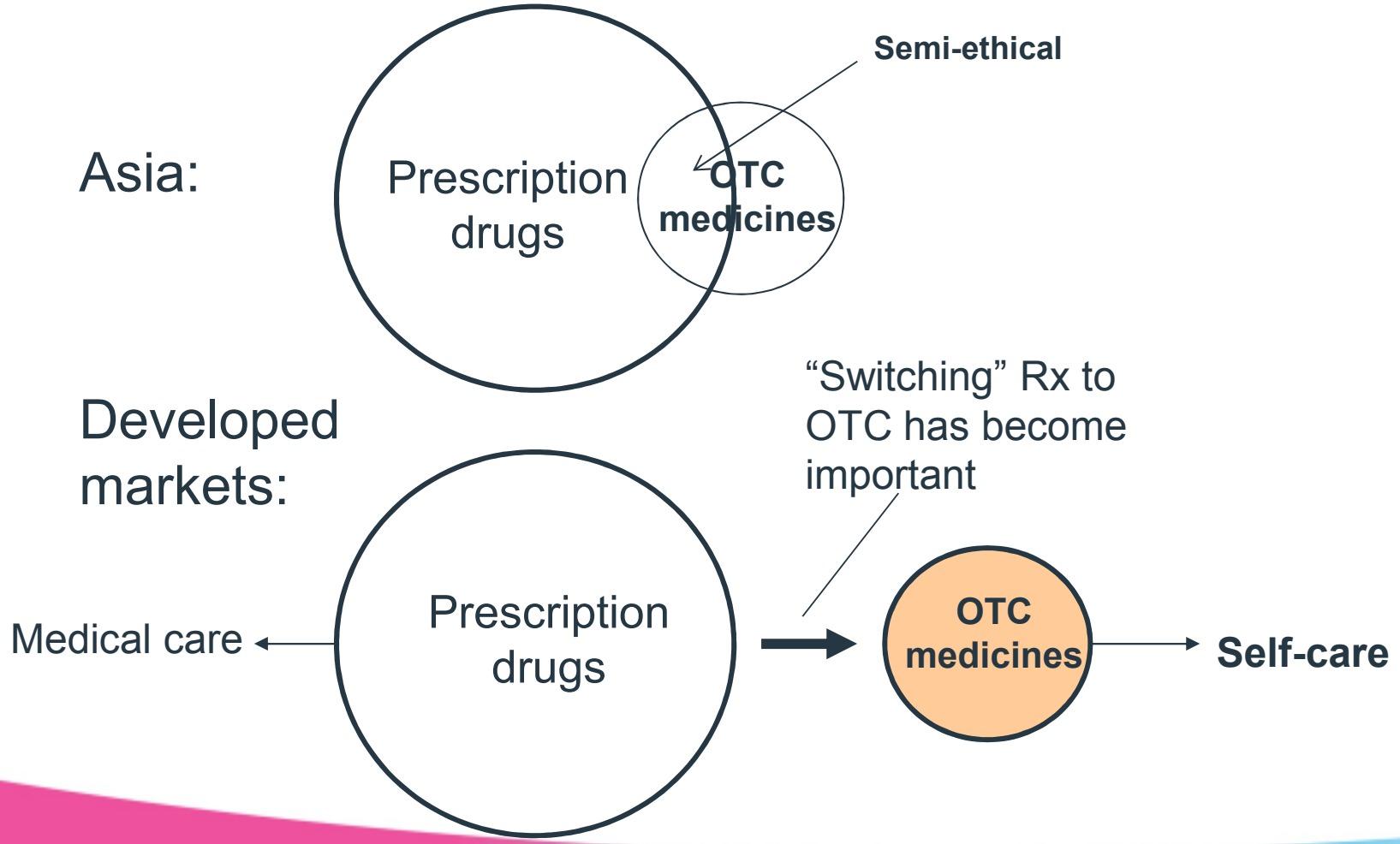
OTC Regulations are usually covered under the Rx regulatory framework



Drug registration procedure in Asia Pacific

Example of ASEAN

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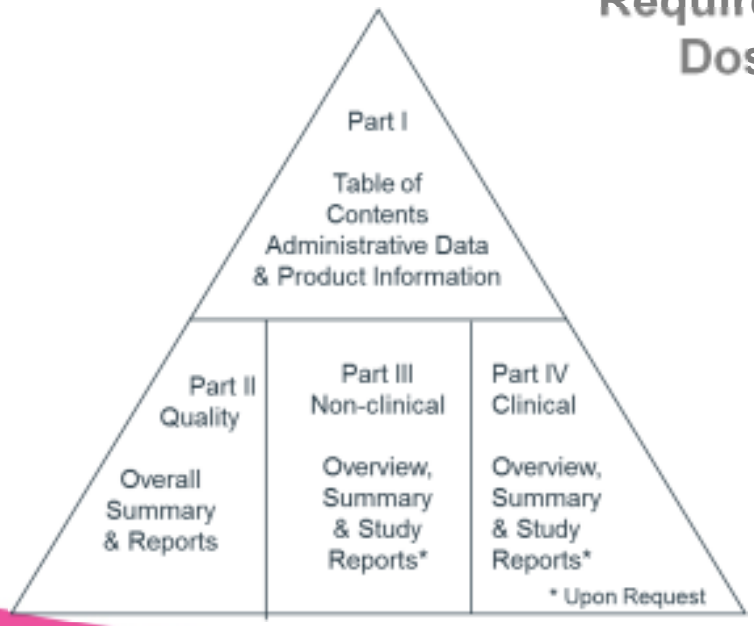
OTC

- **Registration Submission - full application**
- **Typically get waived on Non-clinical & Clinical module**

R_x

- **Registration Submission – full application**

Required Registration Dossier (ACTD)



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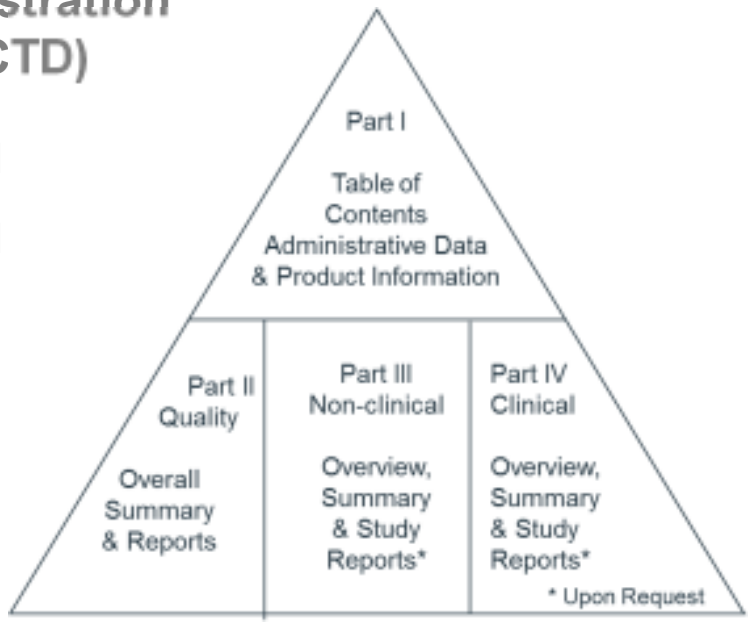

Different type of drug registration procedure

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Full review

Full dossier (NDA)

Q E S

- Novel medicine (NCE. Combinationn, delivery system)
- Full dossier on Quality, Efficacy, Safety (including clinical studies)

Full dossier (Generics)

Q E

- Generic medicines (similar to registered products in countries)
- Full dossier on Quality
- Efficacy is typically exempted with Bio-equivalence study
- Safety is typically exempted

Abbreviated Dossier

Q

- Well-established generic medicines
- Selected section in Quality
- Efficacy and Safety section is exempted

Minimal or No review

Monograph Partial & Full

Q ✓ E ✓ S ✓

- Well-established generic medicines
- Pre-determined quality / efficacy / safety standard to comply
- Quality section is limited
- Efficacy /Safety section is exempted
- Minimal review or none

Q Quality section
E Efficacy section
S Safety section

Monograph system

“Recipe book” covering acceptable ingredients, doses, formulations and labelling

- No submission or Agency assessment / approval required provided compliance with the monograph
- Company required to hold all technical information on file to prove compliance
- For specific Active ingredient, dictates:
  - Dosage strength(s)
  - Dosage form(s)
  - Claims/Indications
  - Directions
  - Warnings/Labelling requirements

Different monograph system & process

Partial Monograph

Thailand*, Japan*, Taiwan*,, Korea*

- Typically with pre-determined efficacy & safety section
- Partial pre-determined quality section
- Mfger need to submit further quality section (and/or efficacy/ safety section)

Minimal review

Full Monograph

USA, Singapore*, Australia/NZ

- Typically with pre-determined quality, efficacy & safety section
- No dossier from Mfger is requirerd

Minimal or No review

* For some medicinal class, actives, therapeutic category

Comparison of Full review vs. Monograph

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How are they different?

Full approval system

- Pre-approval required
- Clinical studies may be needed
- Possible marketing exclusivity
- Product-based
- Product-specific labeling
- Dosage specific
- Approved MA is the license to market

Monograph system

- No pre-approval
- Clinical studies not needed
- No marketing exclusivity
- Ingredient-based
- Class labeling
- Dosage ranges/forms
- Monograph is open to anyone

How are they the same?

- Standards for Quality, Safety and Efficacy
- Manufacturing and GMP inspections
- Labelling requirements
- Advertising regulations

Pros & Cons of Monograph System

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PROS

- Speed to market
- Certainty/predictability
- New flavour variants/ certain forms possible without Clinical data

CONS

- Lose point of differentiation vs. competition
- Fixed dosage, indications, labelling & harmonisation of pack claims
- Loss of claims unique to specific local markets - end up with lowest common denominator
- Opens up market to generic competition (own-label can copy us and get to market more quickly)
- Still need to meet same GMP, Quality and Safety requirements
- Risk of major Safety/Efficacy review of OTC ingredients
- Likely to take many years to develop/implement

US Regulatory System for OTC medicines

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Two regulatory pathways:

- New Drug Application (NDA)
  - FDA “approves” marketing
  - Product-specific
- OTC Drug Monograph
  - FDA “allows” marketing (pre-approval not required)
  - Active ingredient/Product category-specific
  - Monograph developed by the OTC Drug Review

Example of OTC Monographs:
Antacid

Full Monograph

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Product Category	Regulatory Route	Monograph Status/ Date of NDA OTC Approval	Active Ingredients	BRAND EXAMPLES
Acid reducers - Antacids	OTC Monograph Single Ingredients	FM (June 4, 1974)	aluminum-based antacids, bicarbonate-based antacids, bismuth-based antacids, calcium (carbonate or phosphate), citrate ion as citric acid or salt, glycine, magnesium-based antacids, milk solids dried, phosphate-based antacids, potassium-based antacids, sodium-based antacids, silicates, tartaric acid or its salts	PEPTO-BISMOL ORIGINAL bismuth subsalicylate
				TUMS, PEPTO-BISMOL CHILDREN'S calcium carbonate
				PHILLIPS ORIGINAL magnesium hydroxide
	OTC Monograph Combinations	FM (June 4, 1974)	combinations of antacids	ALKA SELTZER ANTACID RELIEF citric acid/sodium bicarbonate/ potassium bicarbonate
				MYLANTA aluminum hydroxide / magnesium hydroxide
				ROLAIDS calcium carbonate/magnesium hydroxide
				GAVISCON aluminum hydroxide/magnesium carbonate
			combinations with any nonantacid laxative	
			combinations with analgesics	See *A. Internal Analgesics*
			combinations with anti-flatulents	MAALOX CHILDREN'S calcium carbonate /simethicone
				MAALOX, GELUSIL aluminum hydroxide/magnesium hydroxide/simethicone

FDA

US Monograph structure
Example: *Antacid*

Full Monograph

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PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

Subpart A—GENERAL PROVISIONS
- Definition of Antacid

Subpart B—ACTIVE INGREDIENTS
- Antacid active ingredients
- Listing of specific active ingredients
- Combination with non-antacid active ingredients

Subpart C—TESTING PROCEDURES
- Determination of percent contribution of active ingredients
- Test modifications

Subpart D—LABELING
- Labeling of antacid products
- Professional labeling

(Ref: http://www.ecfr.gov/cgi-bin/text-idx?SID=94812fdcc1679e122faa92123018e088&tpl=/ecfrbrowse/Title21/21cfr331_main_02.tpl)

FDA

Example of FDA monograph: Antacid

Full Monograph

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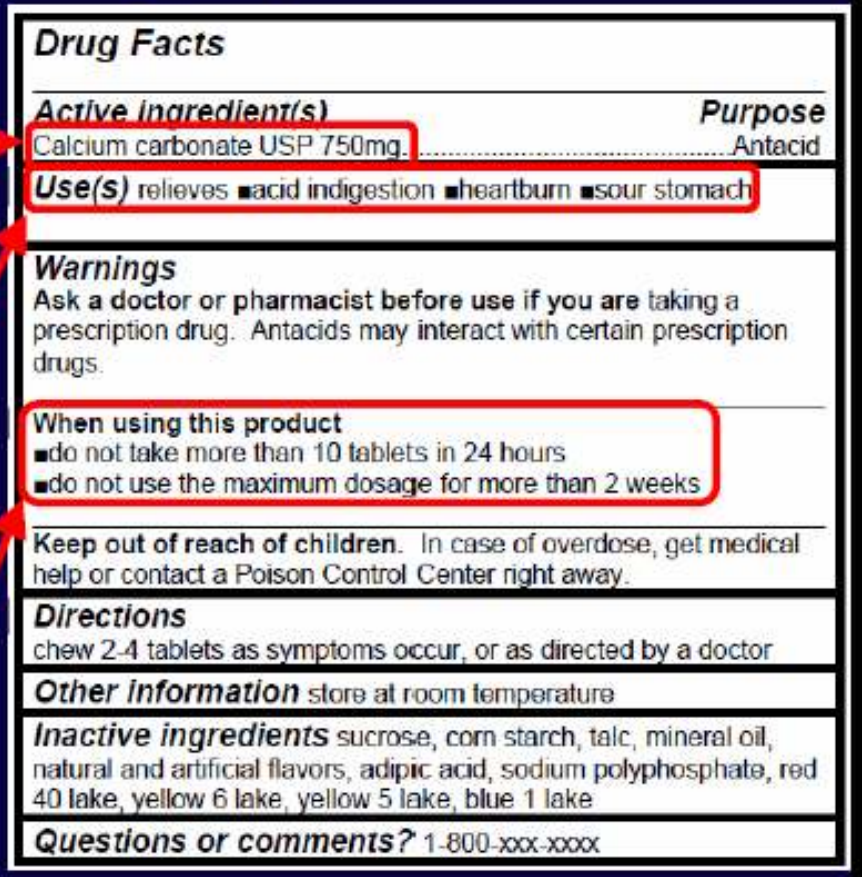
§331.10 *Active ingredients*...Calcium, as carbonate or phosphate; maximum daily dosage limit 160mEq. calcium (e.g., 8 grams calcium carbonate)

§331.30(b) *Indications*...''For the relief of'' (optional, any or all of the following:) ''heartburn,'' ''sour stomach,''and/or ''acid indigestion''

§331.30(c) *Warnings*...''Do not take more than (maximum recommended daily dosage) in a 24–hour period, or use the maximum dosage of this product for more than 2 weeks,



Drug Facts

Active ingredient(s) — **Purpose**
Calcium carbonate USP 750mg. ..... Antacid

Use(s) relieves ▪acid indigestion ▪heartburn ▪sour stomach

Warnings
Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.

When using this product
▪do not take more than 10 tablets in 24 hours
▪do not use the maximum dosage for more than 2 weeks

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
chew 2-4 tablets as symptoms occur, or as directed by a doctor

Other information store at room temperature

Inactive ingredients sucrose, corn starch, talc, mineral oil, natural and artificial flavors, adipic acid, sodium polyphosphate, red 40 lake, yellow 6 lake, yellow 5 lake, blue 1 lake

Questions or comments? 1-800-xxx-xxxx

Monograph system in Asia Pacific for OTC products

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- Australia – N2 application (monograph)
- Japan – Drugs of Approval Standards established (14 Categories)
- Thailand – Household remedy medicines
- Singapore – Quasi-medicine (Listing)

Australia OTC monograph

Full Monograph

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- ‘N2’ application (or 'Monograph') is introduced by TGA in 2013, with initial 3 OTC monographs: **Aspirin, Paracetamol, Ibuprofen** (as single active)
- N2 applications have an evaluation target by the agency of **105 days**
- Applications only contain abbreviated data packages

Structure of Australia OTC monograph

- Active substance
- Indications
- Labelling
- Dosage forms and strengths
- Directions for use
- Quality requirements

Australian Government
Department of Health
Therapeutic Goods Administration

NOTE: The use of the Monograph is optional as registrations can continue via existing routes

Example: Aus OTC Monograph for Ibuprofen

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Active substance: only applies to medicines containing ibuprofen (CAS no. 15687-27-1) and excludes preparations containing any salts and derivatives of ibuprofen.

Indications: Temporary relief of pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular, aches and pains, arthritis, osteoarthritis, rheumatic pain, period pain, fibrositis, neuralgia, sore throat, tennis elbow, and colds and flu. Reduces fever. For paediatric formulations, in addition to any of the indications above that are appropriate to the age group, the following indications would be acceptable: relief of pain associated with teething, earache and/or immunisation.

Dosage form & strength:

Active substance	Dosage strengths	Dosage forms (excludes modified release dosage forms)
Ibuprofen	200 mg	Coated tablets
	200 mg	Orally disintegrating tablets
	20 mg/mL (100 mg/5 mL)	Suspension, liquids
	40 mg/mL (200 mg/5 mL)	Suspension, liquids

Posology:

Dosage form and strength	Age	Single dose	Dose interval	Maximum daily dose
200 mg tablet	7 -12 years	1 tablet	Every 6-8 hours when necessary	4 tablets in 24 hours
200 mg tablet	Adults and children 12 years and over	1 – 2 tablets	Every 4-6 hours when necessary	6 tablets in 24 hours

http://www.tga.gov.au/pdf/otc-argom-otc-n2-monographs-ibuprofen.pdf

Australian Government
Department of Health
Therapeutic Goods Administration

Japan: Approval drug standard

Partial Monograph

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- PMDA issue the standards:
  - Active ingredients
  - Dosage
  - Indication, etc.
- The approval standard is based on the well-established efficacy and safety profiles.
- PMDA authority to grant approval transferred to the prefecture governor
- Example of Approval drug standard (& year of issue)

Cold remedies (1970)
Antipyretics analgesics (1972)
Antitussives/ expectorants (1976)
GI drugs (1980)
Purgatives (1982)
Nasal drops for rhinitis (1991)
Oral drugs for rhinitis (1993)
Topical anti-hemorrhoidals (1995)
Drugs for athlete's foot and ringworm (1998)
Ophthalmic drugs (1986)
Vitamin preparations (1988)
Enemas (1988)
Anthelmintics (1989)
Anti-vertigo drugs (1984)

Thailand Monograph Example

Household remedy

Partial Monograph

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- Monograph system is used only for Household Remedy, that manufacturer must follow, which are:-
  - actives
  - dosage form
  - Indication
  - usage instruction
  - labeling detail
  - pack size
- Deviation from monograph is not permitted.
- Manufacturer must submit dossier and get exemption on clinical and safety information

Example of monograph
Antiseptic Liquid

(๑๒.๗) น้ำยาฆ่าเชื้อโรคคลอโรไซลีนอล
ในสูตรตำรับประกอบด้วย

Chloroxylenol	ร้อยละ ๔.๘	โดยน้ำหนักต่อปริมาตร
Isopropyl Alcohol Solution	ร้อยละ ๑๒	โดยปริมาตร

สรรพคุณ ใช้ทำความสะอาดรอบบาดแผล
วิธีใช้ ห้ามใส่แผลโดยตรง
เจือจางน้ำยา ๑ ส่วนกับน้ำ ๑๙ ส่วน ใช้เช็ดทำความสะอาดรอบบาดแผล
คำเตือน ห้ามรับประทาน
การเก็บรักษา ปิดฝาให้สนิท
ขนาดบรรจุ ขวดละไม่เกิน ๔๕๐ มิลลิลิตร

สำนักงานคณะกรรมการอาหารและยา
Food and Drug Administration

Singapore example

"Quasi-medicinal product"

Partial Monograph

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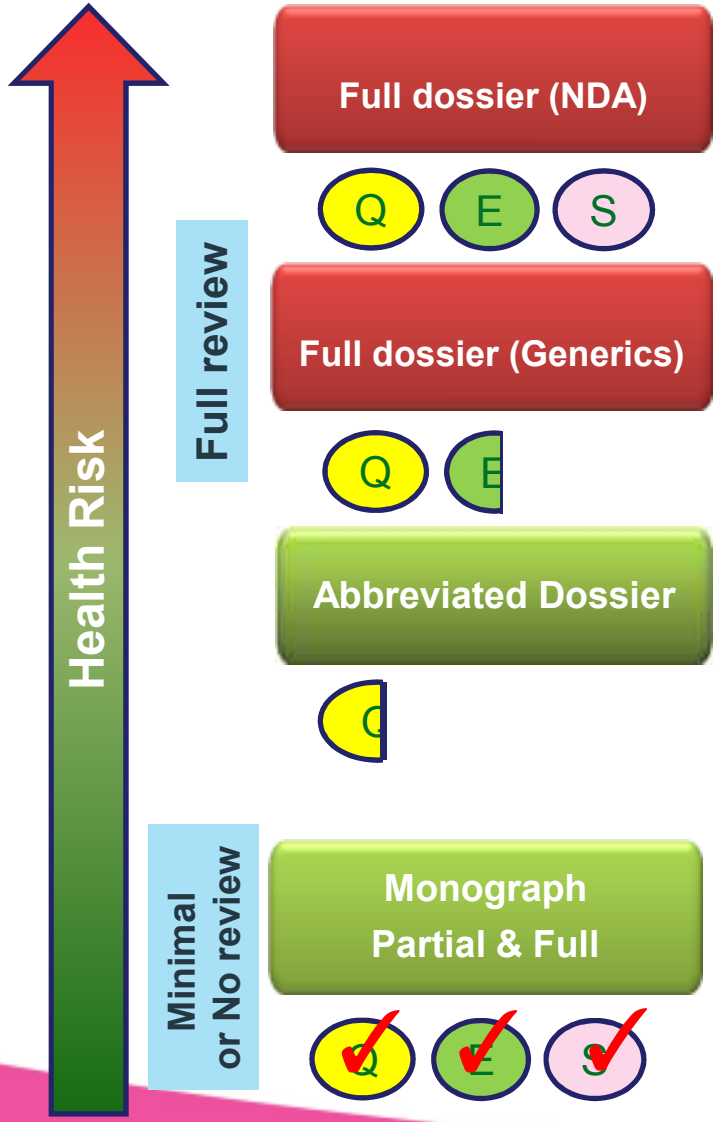
- Listed product will not require registration & dossier
- Product can be marketed if complied with basic GMP/labeling and permitted indications/actives
- Example of Quasi-medicine product
  - Acne treatment, except etretinate or 13-cisretinoic acid
  - medicated soap;
  - sweets for relieving cough and throat irritations;
  - medicated plasters;
  - medicated oil and balm (e.g. containing methyl salicylate etc.)

HSA Health Sciences Authority

Summary



- OTC drug registration should be based on their low health risk, and allow the abbreviated application
- Monograph system (partial and full) helps increase efficiency in drug approval, as it get pre-approval component for quality, safety and efficacy aspects, and minimize the review by health authority.
- Monograph system should be used with caution, as it might create the level field and lack of differentiation points.

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Thank you

ขอบคุณครับ