Drug Regulation in Thailand

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Pre-marketing control

Bureau of Drug Control

Thai Food and Drug Administration (Thai FDA)

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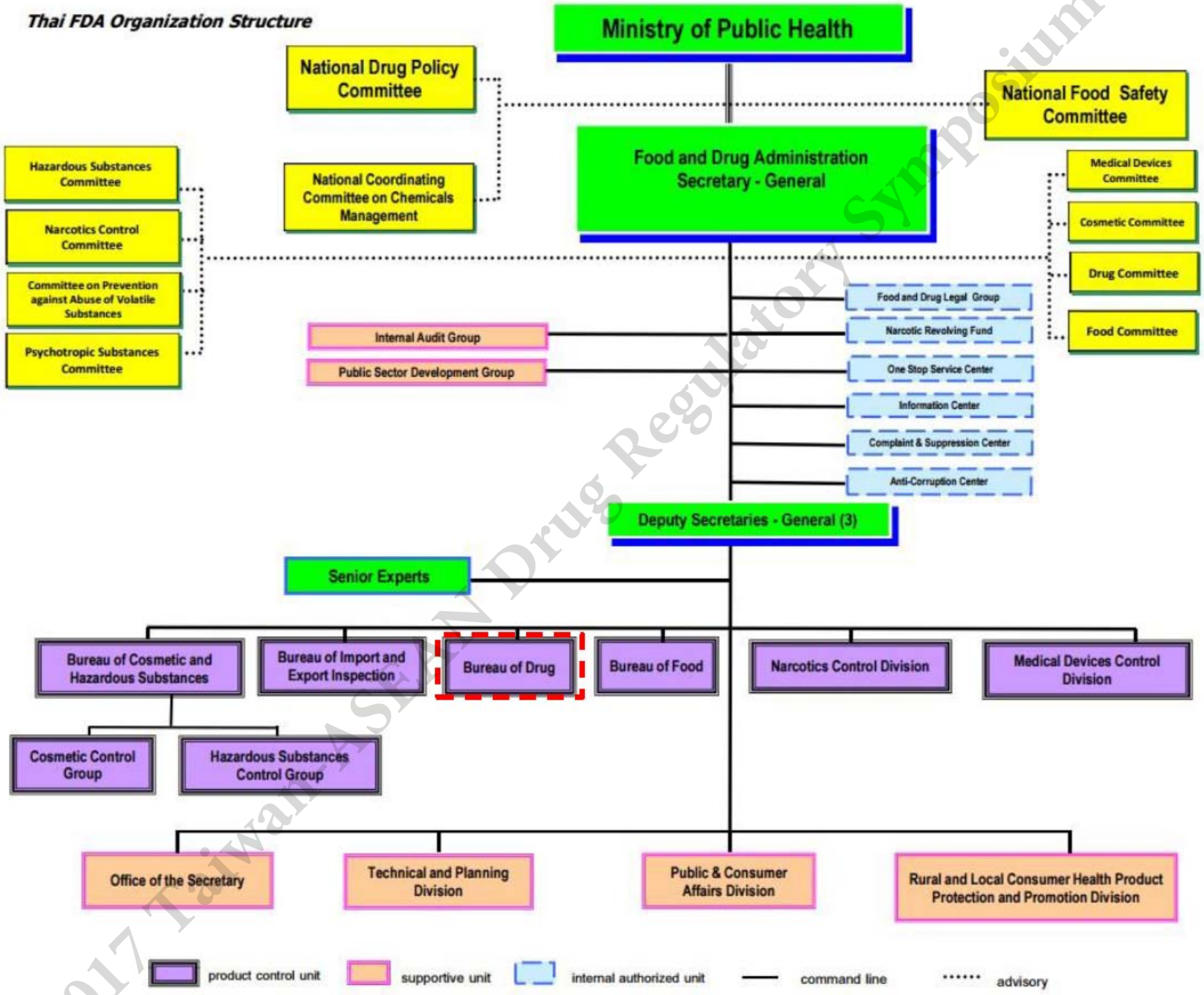
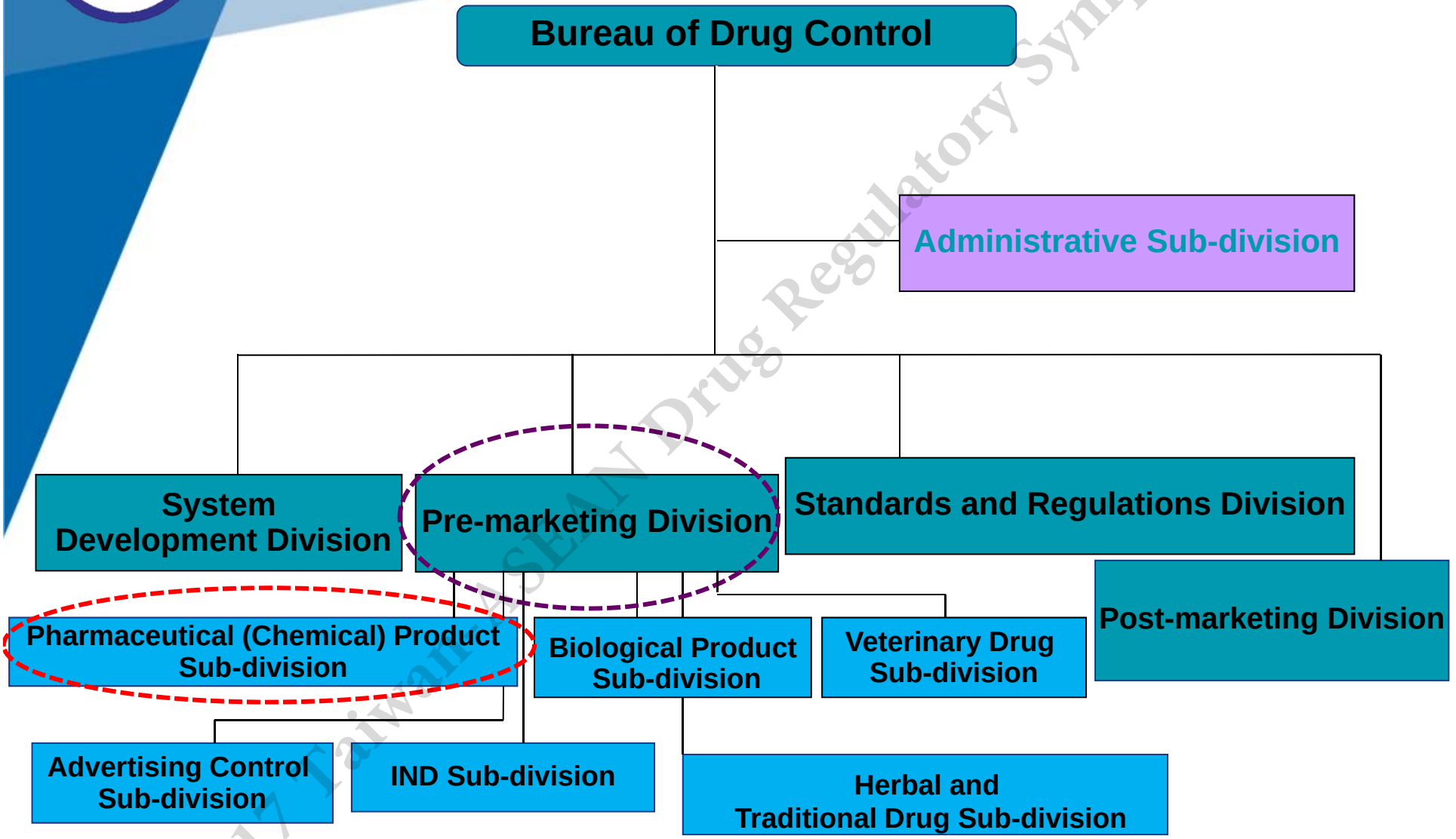
Outline

- Organization of Bureau of Drug Control
- Laws and Regulations concerning Drug Registration
- Drug Registration and Approval
  - Definition of New Drugs and Generic Drugs
  - ASEAN Harmonization and Requirements for New Drugs Registration
  - New Drugs Review Process
    - Standard review
    - Priority review
    - Abridged review
    - Conditional Approval and Unconditional Approval of New Drugs



The Organization Chart of Bureau of Drug Control



Roles and Responsibilities

The main role of the Thai FDA is to protect consumers health, especially, to ensure safety, quality and efficacy of health products within its remit. These include *foods, drugs, psychotropic substances, narcotics, medical devices, volatile substances, cosmetics and hazardous substances* available in the country. This has to be implemented in accordance with national legislation and international agreements.

Regulation of Drugs

Current Laws and Regulations :

- **Drug Act B.E. 2510 (1967)**
- **Drug Act (2nd Revision) B.E. 2518 (1975)**
- **Drug Act (3rd Revision) B.E. 2522 (1979)**
- **Drug Act (4th Revision) B.E. 2527 (1984)**
- **Drug Act (5th Revision) B.E. 2530 (1987)**
- **Ministerial Regulation on Drug Registration B.E. 2555 (2012)**

Pre-Marketing : Licensing

The drug Act requires that persons who wish to sell, produce or import drugs into Thailand have to obtain a license from the Thai FDA

- **License to manufacture**
- **License to sell**
- **License to import**

Pre-Marketing : Registration

- **Registration process is to ensure efficacy, safety and quality of drugs freely sold in the Kingdom**
- **Only the authorized licensees can apply for drug registration**
- **Upon receipt of Drug Registration Certificate, the drug can be lawfully marketed**
- **The granted certificate is valid to the validity of its authorized licensee**

Pre-Marketing : Advertising Control

- **Drug Advertisements and other promotional materials need to embody truth and accuracy**
- **Advertisements of any kinds must be approved by Thai FDA before being disseminated**

Post-Marketing

- **Marketed products regularly sampled for testing at the drug analysis Laboratory of the Department of Medical Sciences**
- **Inspection of manufacturing sites and pharmacy stores**
- **GMP Clearance of Overseas Pharmaceutical Manufacturers – PIC/S**

Pharmaceutical (Chemical) Product Sub-division

New Drugs

Generic Drugs

Definition “New Drugs”

- New Chemical Entities (NCE)
- New Indication (NI)
- New Combination (NCO)
- New Delivery System (ND)
- New Route of Administration (NR)
- New Dosage Form (NDOS)
- New Strength (NS)

Definition “Generic Drugs”

- **Same active ingredient(s)**
- **Same dosage form**
- **Same strength**
- **Same route of administration**
- **Same conditions of use**

Compared to reference drugs (New Drugs in Thailand which registered after 1991)

Drug Registration Process

2 main steps

Step 1

The permission to import/manufacture drug samples

Step 2

Application for product registration approval

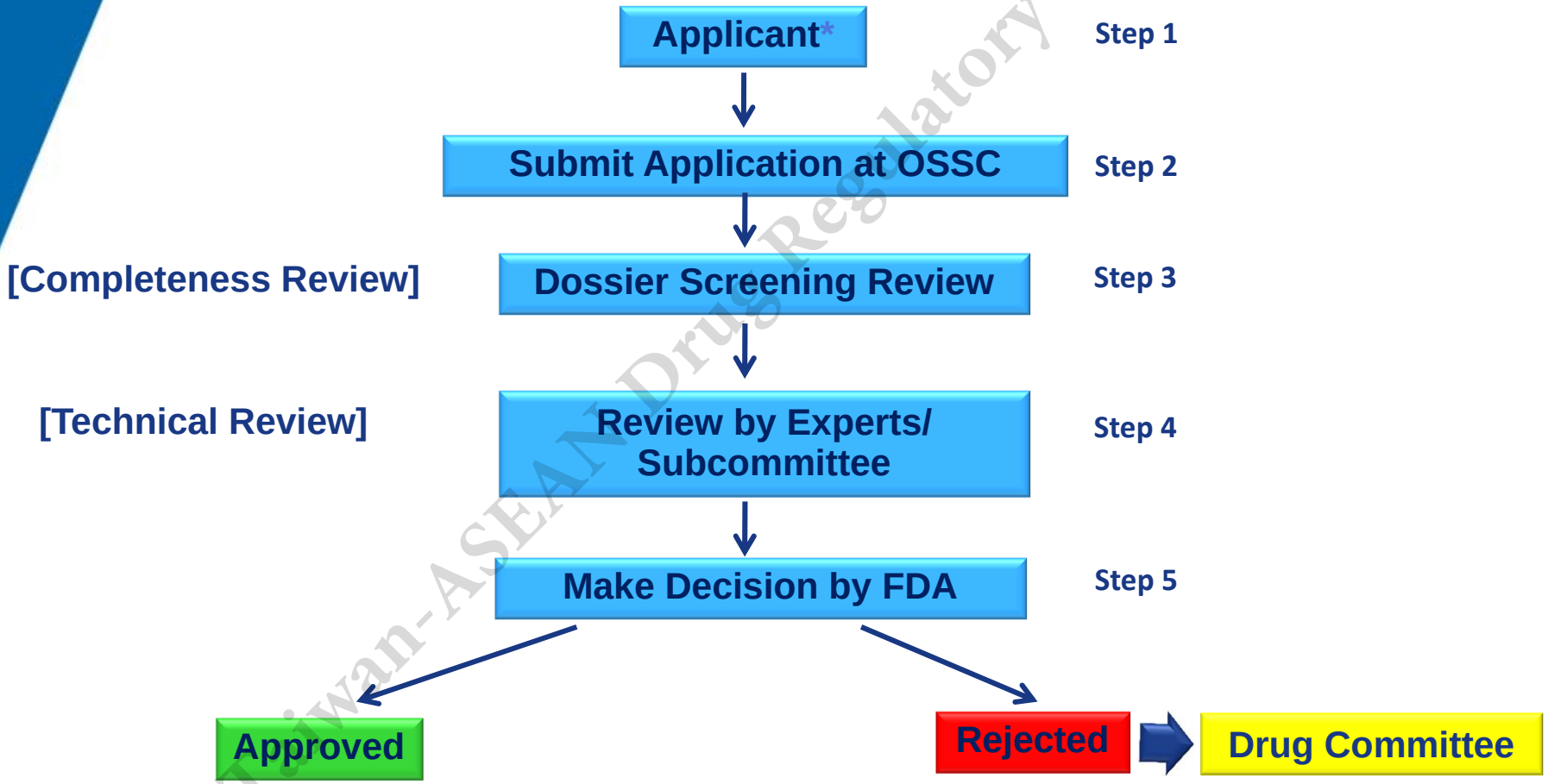
The permission to import/manufacture drug samples

Documents:

1. Application form (Por Yor 8/Nor Yor 8/Yor Bor 8)*
   - Manufacturer/Importer Name and Address
   - License to manufacture/import Number
   - Product Name and Description
   - Drug Formula (active ingredient(s) only)
   - Packaging
   - Quantity of drug sample to manufacture/import
2. Labels
3. Leaflets

*Por Yor 8 = Manufacturer drug product
Nor Yor 8 = Importer drug product
Yor Bor 8 = Manufacturer Thai Traditional drug

Flowchart of Drug Review Process



*Applicant: Persons licensed to produce/import drugs

From step 1 to step 2

Since July 2015 - Licensing Facilitation Act B.E. 2558 (2015)

Applicants

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Prepare Dossier
(ASEAN HARMONIZATION)

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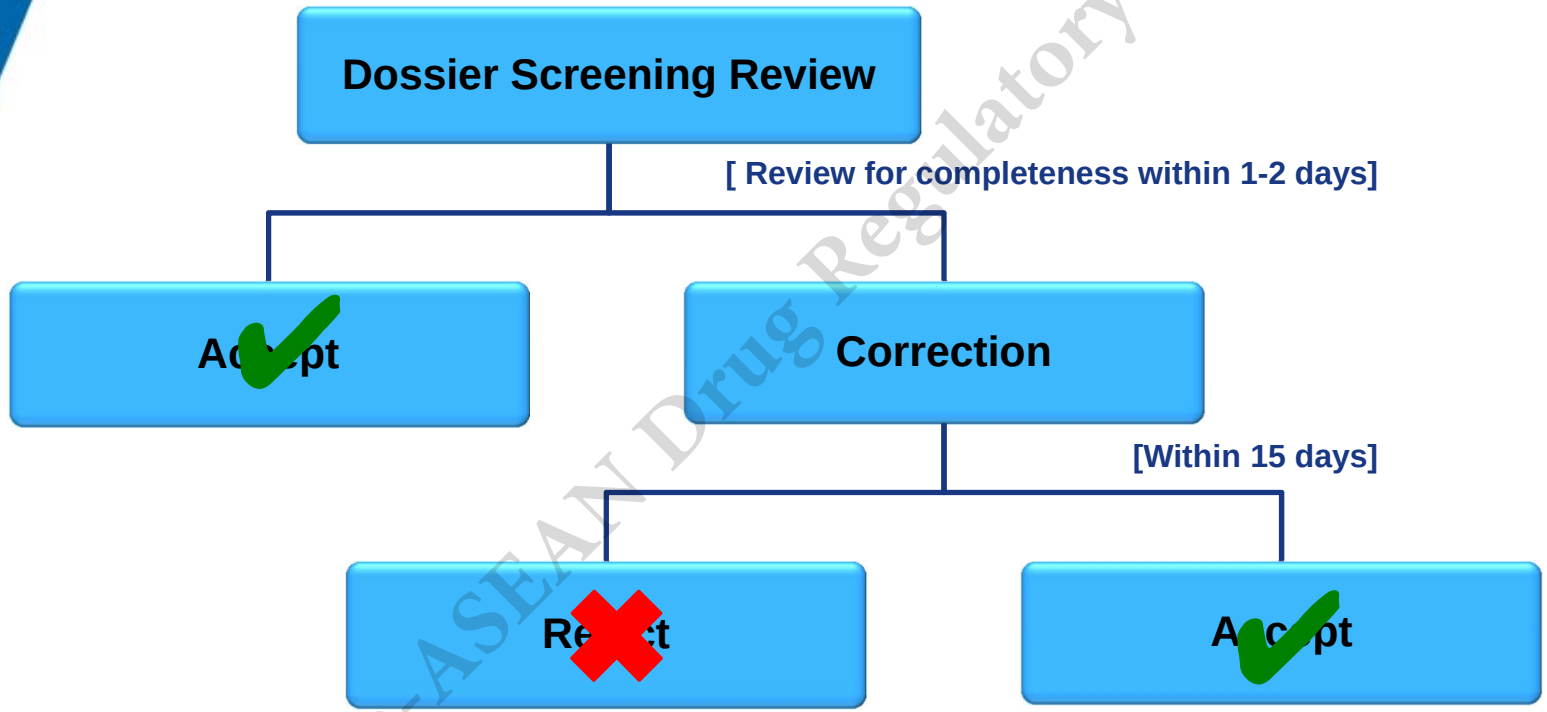
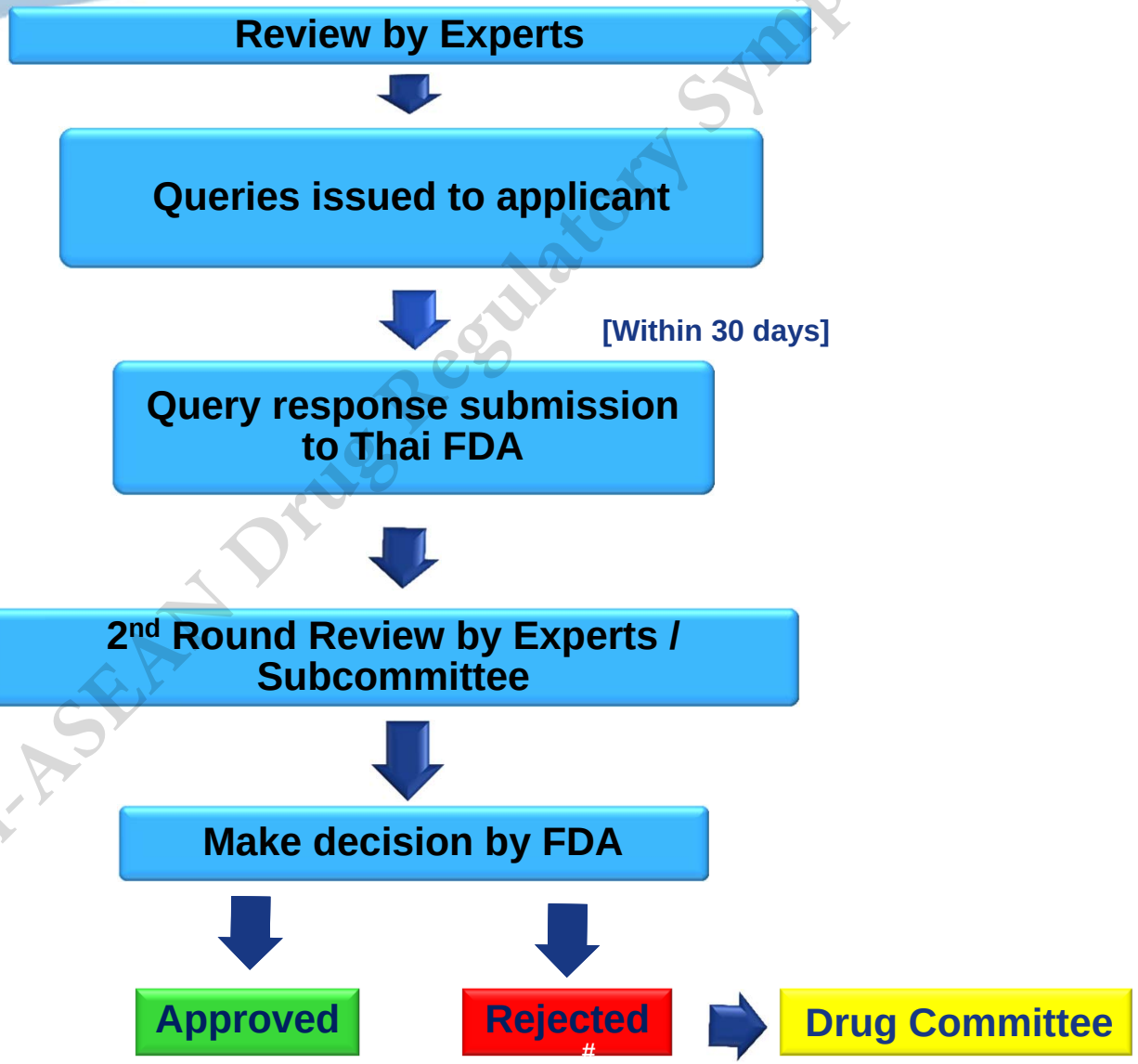
Submit Application at OSSC

Step 2

Since July 2015 - Licensing Facilitation Act, B.E. 2558 (2015)



From step 4 to step 5



Application for product approval registration

Product Registration

To ensure quality, efficacy and safety of the products

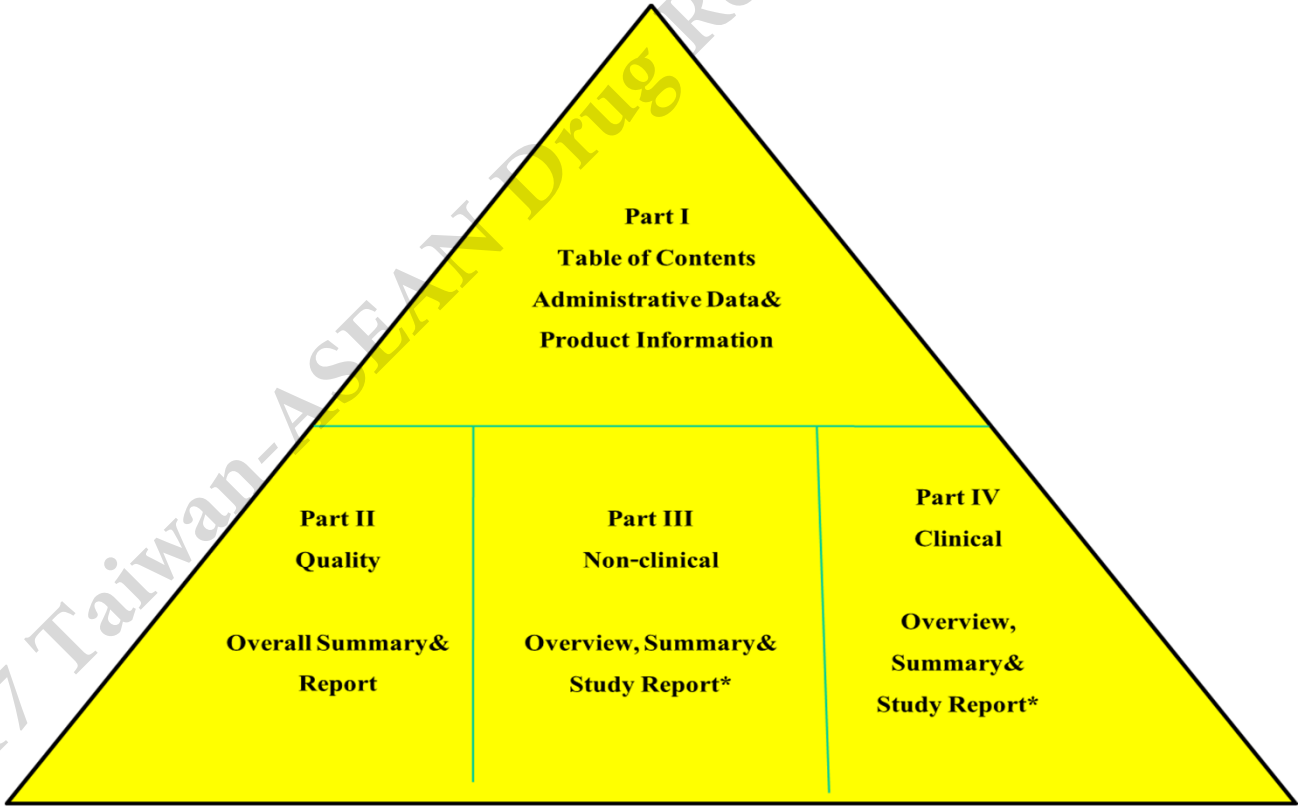
- New Drugs
- Generic Drugs

- ASEAN harmonization on pharmaceutical registration
  - ACTD, ACTR
- Fast track or priority review for life-threatening medicines and medicines in urgent need for public health problems
- Abridged evaluation of new drugs using reference drug regulatory authority assessment (~30% reduction of timelines)
- Safety Monitoring Program for New Drugs

ASEAN Harmonization On Pharmaceutical Registration

- ASEAN Common Technical Requirement (ACTR)
- ASEAN Common Technical Dossier (ACTD)

Thailand has fully implemented ASEAN harmonized products in pharmaceutical registration since 2009



ASEAN HARMONIZATION ON PHARMACEUTICAL REGISTRATION

FDA Notification 2008: Implementation of ASEAN Harmonized Product on Pharmaceutical Registration

Date started: 1Jan 2009

- **Manual/Guidance on New Drug Registration (ASEAN Harmonization)**
- **Requirements and Documents to be submitted for New Drug Registration (ASEAN Harmonization)**
- **Manual/Guidance on Generic Drugs Registration (ASEAN Harmonization)**

4 Technical Guidelines

(1) Analytical Validation Guideline

(2) BA/BE Studies Guideline

(3) Process Validation Guideline

(4) Stability Study

New Drugs Registration (ASEAN Harmonization)

ASEAN Common Technical Dossier (ACTD)

Documents to be submitted 4 Parts

Part 1: Administrative Data and Product Information

Part 2: Quality Document

Part 3: Nonclinical Document

Part 4: Clinical Document

Part 1: Administrative Data and Product Information

3 Sections:

Section A: Introduction

Section B: Overall Table of Contents

Section C: Documents required for registration

- Application form(Yor1)
- Certifications: License to manufacture/import, GMP Certificate, Certificate of Pharmaceutical Product (CPP)/Certificate of Free Sales (CFS)
- Labeling
- Product Information:
  - Package Insert (PI)
  - Summary of Product Characteristics (SPC): required for NCE
  - Patient Information Leaflet (PIL)
- Por Yor 8/Nor Yor 8
- Photograph of drug product
- Comparative data between new drug and existing drugs

Part 2: Quality Document

ACTD 4 Sections:

- Section A: Table of Contents
- Section B: Quality Overall Summary: Drug Substance, Drug Product
- Section C: Body of Data: Drug Substance, Drug Product
- Section D: Key Literature References

ACTR:

Drug Substance

- General Information
- Manufacture
- Characterization
- Control of Drug Substance
- Reference Standards
- Container Closure System
- Stability

Drug Product

- Description/Composition
- Pharmaceutical development
- Manufacture
- Control of excipients
- Control of Finished Product
- Reference Standards
- Container Closure System
- Stability
- Interchangeability

Part 3 : Nonclinical Document
ACTR

1. Pharmacology

-Primary Pharmacodynamics

-Secondary Pharmacodynamics

-Safety Pharmacology

-Pharmacodynamics Drug Interactions

2. Pharmacokinetics

-Absorption

-Distribution

-Metabolism

-Excretion

-Pharmacokinetics Drug Interactions

-Other Pharmacokinetics Studies

3. Toxicology

- Single dose toxicity
- Repeat dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Local tolerance
- Other toxicity studies, if available

Part 4 : Clinical Document
ACTR

1. Bioavailability (BA) and Bioequivalence (BE) Studies
2. Studies Pertinent to Pharmacoknetics using Human Biomaterials:
   - Plasma Protein Binding Studies
   - Hepatic Metabolism and Drug Interaction Studies
   - Studies using Other Human Biomaterials
3. Human Pharmacokinetic (PK) Studies:
   - Heathy Subject PK and Initial Tolerability Studies
   - Patient PK and Initial Tolerability Studies
   - Intrinsic Factor PK Studies
   - Extrinsic Factor PK Studies
   - Population PK Studies
4. Human Pharmacodynamic (PD) Studies
   - Healthy Subject PD and PK/PD studies
   - Patients PD and PK/PD studies
5. Efficacy and Safety
   - Controlled Clinical Studies Pertinent to the Claimed Indication
   - Uncontrolled Clinical Studies
6. Post Marketing Data (if available)
7. References

General considerations in New Drugs Review

- Trial design and conduct
- Reliability of studies and submitted documents
- GLP and GCP compliance
- Efficacy; relevance endpoints
- Safety; seriousness of adverse reactions, drop-outs
- Significant difference in ethnic factors?
- Risk-benefit assessment
  - Benefit outweighs risk
  - Identified risks can be controlled
- Ensure product quality and their reproducibility

New Drugs VS Generic Drugs Review Process

New Drugs Requirements	Generic Drug Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Quality Controls	3. Quality Controls
4. Labeling	4. Labeling
5. Nonclinical Studies (animal)	5. Bioequivalence
6. Clinical Studies	

Thai FDA Notification
Abridged Evaluation of New Drugs

- Thai FDA Notification on New Drugs using Reference Drug Regulatory Authority Assessment was issued in July 2015
- It has come into effect since October 1, 2015
- 3 channels for new drugs registration
    - Standard review
    - Priority review
    - Abridged review

Abridged Evaluation of New Drugs

- **Reducing the number of experts to evaluate new drugs dossiers**
- **Using the assessment report of benchmark / reference agencies as part of the evaluation**

Priority Review

- A fast track or priority review channel for life-threatening medicines and medicines in urgent need for public health problems
  - HIV/AIDS drugs, anticancer, anti-TB, anti-malarial drugs
- Pharmaceutical products of which R&D is in Thailand

Conditions

Drugs which have been approved by one of the following benchmark / reference agencies and being sold in the country

- **US FDA**
- **EMA, EU (Centralized System)**
- **MHRA, UK**
- **Swiss Medic**
- **TGA, Australia**
- **Health Canada**
- **PMDA, Japan**

Conditions

- The application must be submitted within two years from the approval date of benchmark/reference agency
- The same pharmaceutical products and the proposed indications, dosage regimens, patient groups and/or directions for use must be the same as those approved by the reference agency
- Full assessment report of benchmark/reference agency and all list of questions and answers during the assessment process together with post-approval variations and related documents in English must be submitted

Conditions

- **The product's manufacturing and quality must be the same as that currently approved by the reference agency and must comply with Thai FDA regulation and requirements**

- **The pharmaceutical product including its indications, dosage regimens, directions for use and patient populations has not been rejected or withdrawn, approved through appeal process or pending deferral by a drug regulatory agency**

New Drugs Evaluation (Standard VS Abridged evaluation)

- 6 Experts for 1 New Drug Application (Standard)
  - 2 Experts for quality part (Manu 1, QC 1)
  - 2 Experts for nonclinical part
  - 2 Experts for clinical part
- 4 Experts for 1 New Drug Application (Abridged)
  - 2 Experts for quality part (Manu 1, QC 1)
  - 1 Experts for nonclinical part
  - 1 Experts for clinical part
- Subcommittee on New Drugs Evaluation

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Evaluation process

- Generally, review by experts and internal reviewers
- Propose to New Drug Subcommittee for consideration if
  - Expert opinions are not unanimous
  - Not approved
  - Drugs that may cause social or other problems or may have high potential for misuse/abuse
  - Pending for phase III clinical trials

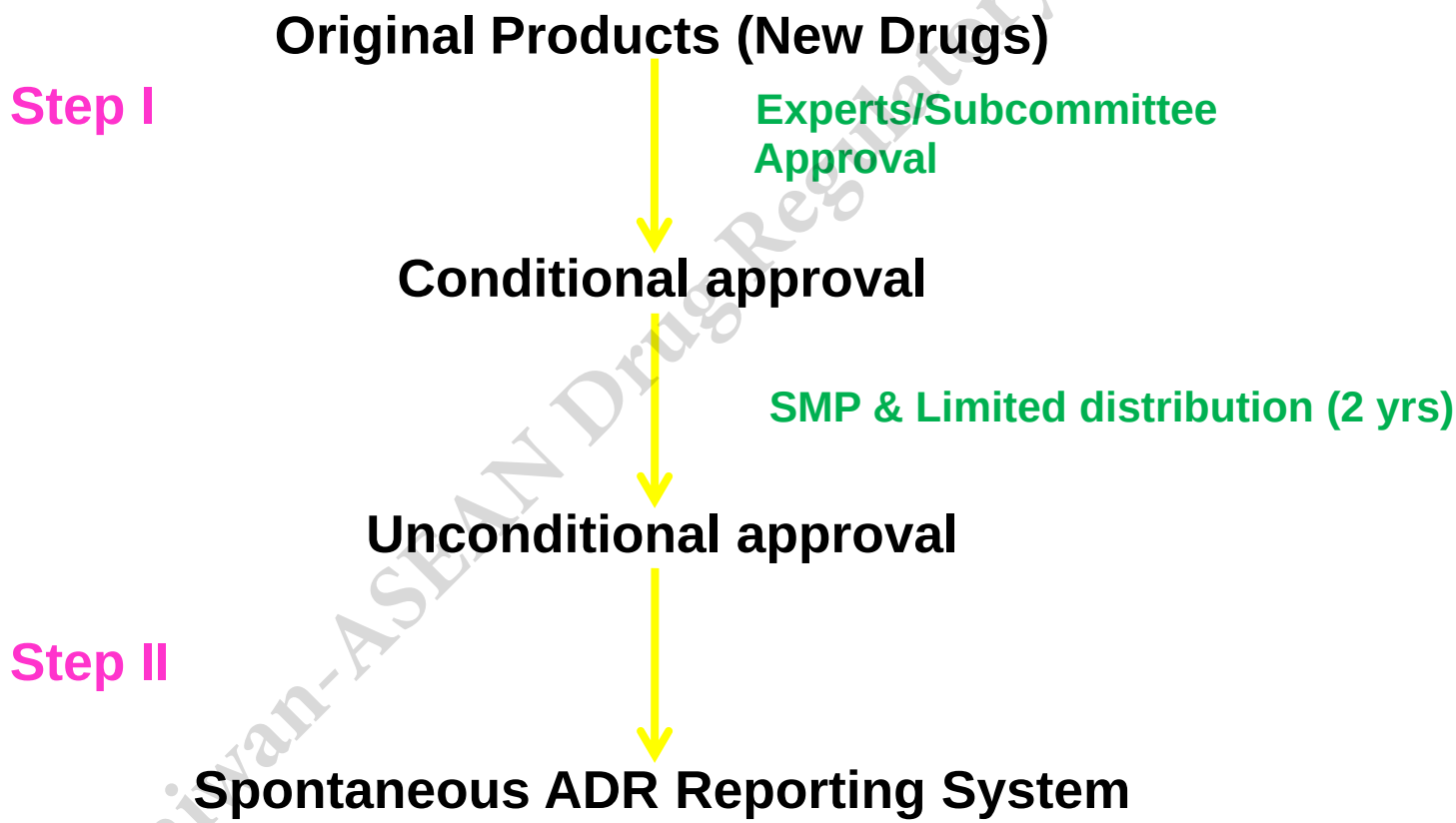
Timelines for Drug Registration

Type of Drugs	Working day (Working Days)	Abridged Evaluation (Working Days)
NCEs and other New drugs	280	200
Priority Review NCEs and other New drugs	220	150
Generic drugs	155	-

Safety Monitoring Program (SMP)

- To confirm the drug safety in Thai patients
- To generate earlier safety signals and gather more safety information of New drugs before granting and unconditional approval
- To more rigorously control the usage of New drugs
- To more rigorously control the usage of New drugs
- To encourage physicians, pharmacist and other health professionals to have more concerns on the safety of New drugs and their usage

Safety Monitoring Program (SMP)



Conditional Approval

- **Safety Monitoring Program (SMP) will be conducted for approximately 2 years**
- **Drug packages must bear labeling to show conditional approval status:**
  - **Triangle shows monitoring status**

  - **Specially control drug – ยาควบคุมพิเศษ**
  - **Registration No. (NC) – 1C 5/52 (NC)**
  - **Limited distribution only through medical institutes or hospitals – ใช้เฉพาะสถานพยาบาล/ใช้เฉพาะโรงพยาบาล**

Unconditional Approval

Labeling:

- Not to show triangle mark
- Can be distributed through normal market channels and categorized as
  - Specially control drug – ยาควบคุมพิเศษ
  - Dangerous drug – ยาอันตราย
- Registration No.(N) – 1C 5/52 (N)

คุ้มครอง ห่วงใย ใส่ใจคุณภาพ

สำนักงานคณะกรรมการอาหารและยา
Food and Drug Administration

Thank you for your attention