REGULATORY CONTROL OF GENERIC MEDICINES IN MALAYSIA

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National Pharmaceutical Control Bureau
Ministry of Health Malaysia

WHO Collaborating Centre For Regulatory Control of Pharmaceuticals

Member of Pharmaceutical Inspection Cooperation Scheme

MS ISO 9002 REG. No : AR 1171

PRESENTATION OUTLINE

- INTRODUCTION
  - Legal Requirement
  - Why register?
  - Definition
- REGISTRATION REQUIREMENTS
  - Product registration criteria (How do we ensure QSE?)
  - Registration procedures
- POST-MARKET SURVEILLANCE (PMS) ACTIVITIES
- INNOVATOR VS. GENERICS

LEGAL REQUIREMENT

The Control of Drugs and Cosmetic Regulations 1984 was promulgated under the Sale of Drugs Act 1952 (Revised 1989)

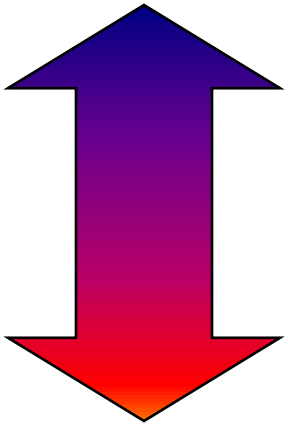
- **Subregulation 7(1)**
  - **No person shall manufacture, sell, supply, import or possess or administer any product unless,**
  - **The product is a registered product ;**
  - **The person holds the appropriate licence issued under this regulation.**

- **Subregulation 8(1)**
  - **The Authority may, on application made in such manner or form as it may require, register any product subject to such conditions as it may impose.**

WHY REGISTER?

- To ensure that products available on the market are efficacious, of quality and safe for human use.

- Safety
- Quality
- Efficacy



DEFINITION : GENERIC PRODUCTS

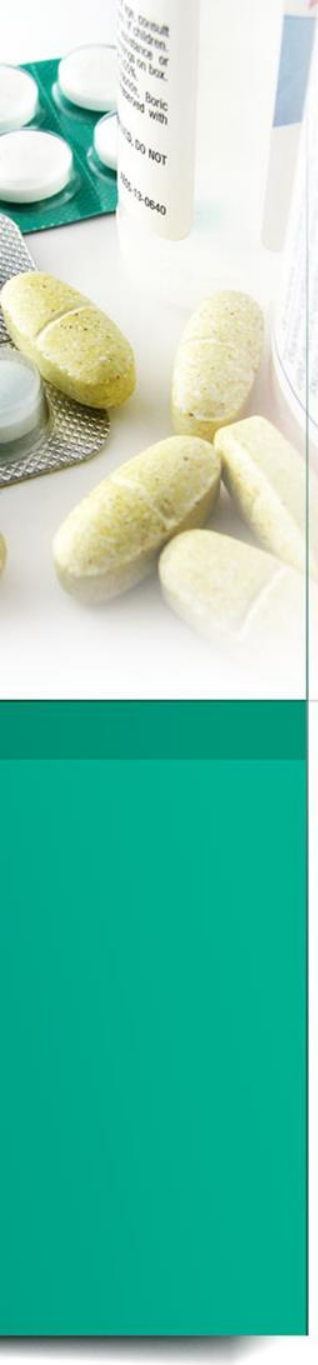
- A product that is essentially similar to a currently registered product in Malaysia.
- The term generic is not applicable to biological & biotechnology products.

DEFINITION : GENERIC PRODUCTS

- Active ingredient previously approved.
- Product information previously approved.
- Route of administration, strength and dosage form equal to those of previously approved product.

DEFINITION : GENERIC PRODUCTS

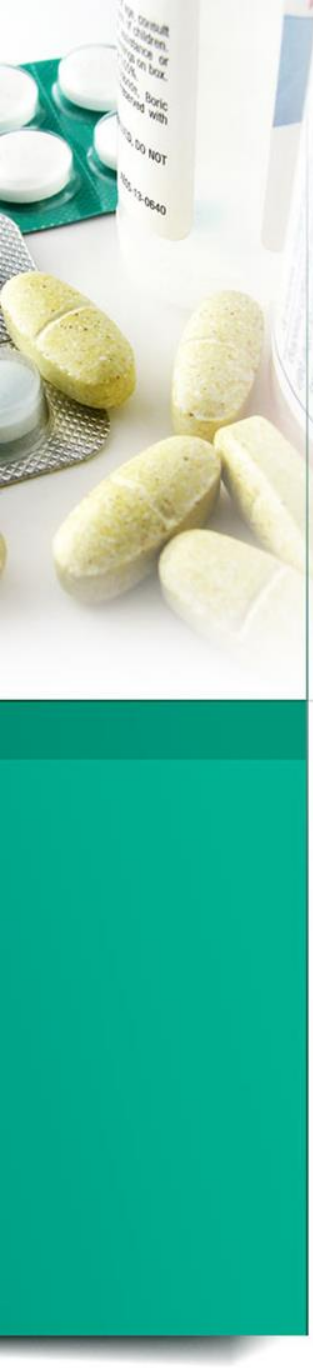
- Usually intended to be interchangeable with the innovator product.
- Manufactured without a licence from innovator company.
- Marketed after expiry of patent or other exclusivity rights.
- Marketed either under the approved non-proprietary name or under a brand name (proprietary name)



DEFINITION : GENERIC PRODUCTS

Types of generic applications

- Generic Pharmaceutical Products
  - Full Evaluation
    - Scheduled Poison
    - OTC / Non Scheduled Poison **
  - Abridged Evaluation
    - OTC / Non Scheduled Poison *categories

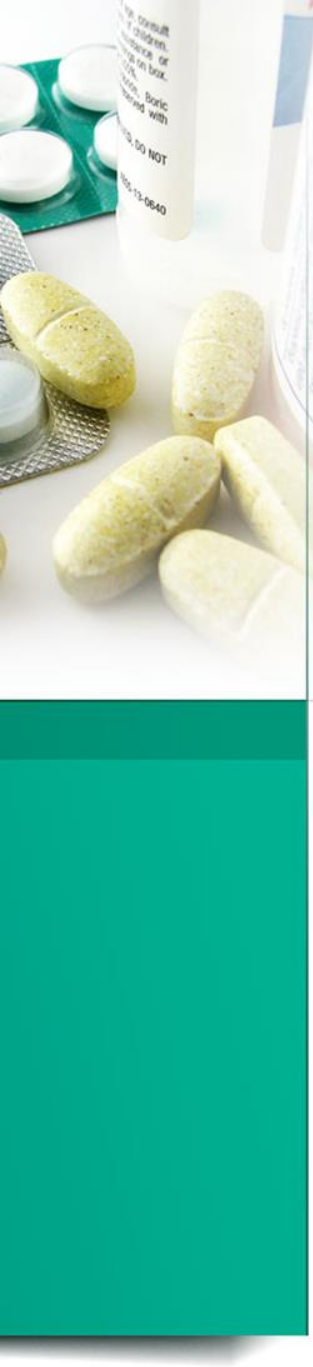


DEFINITION : GENERIC PRODUCTS

- **Scheduled Poison(s) Products**
  - Pharmaceutical products which contain scheduled poison(s) as defined in the First Schedule under POISON ACT 1952.
  - E.g. Atenolol, Ibuprofen, Lisinopril, Cimetidine, Dextromethorphan, etc.

DEFINITION : GENERIC PRODUCTS

- **Non-Scheduled Poison(s) Products (Over-the-Counter (OTC))**
  - Pharmaceutical products which do not contain scheduled poison(s), other than health supplements or natural medicines or cosmetics.
  - E.g. Paracetamol, Simethicone, Aspirin, Clotrimazole, etc.

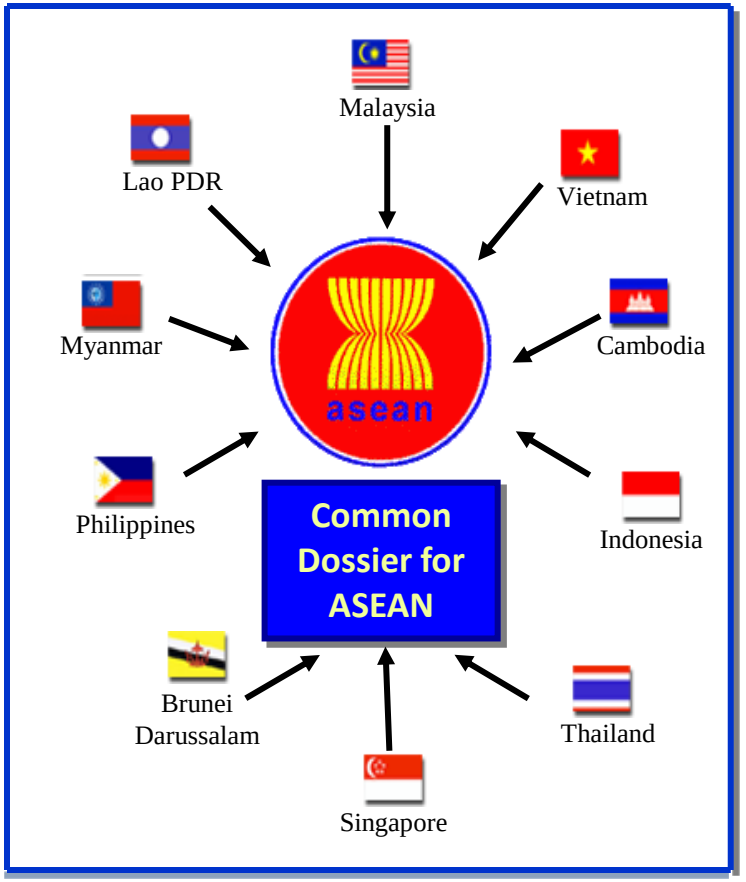


DEFINITION : GENERIC PRODUCTS

- **Non-Scheduled Poison(s) Products (Over-the-Counter (OTC))**
  - Includes, but not limited to the following :
    - Antiseptics / skin disinfectants;
    - Locally-acting lozenges / pastilles;
    - Topical analgesics / counter-irritants;
    - Topical nasal decongestants;
    - Emollient / demulcent / skin protectants;
    - Keratolytics;
    - Anti-dandruff;
    - Oral care;
    - Anti-acne;
    - Medicated plasters / patch / pad; and
    - Topical antibacterial

With the advent of globalisation, efforts are currently undertaken towards ASEAN Harmonisation process.

- Pharmaceutical Product Working Group – ASEAN Consultative Committee for Standards and Quality (**PPWG-ACCSQ**)
- Objective : to develop harmonization schemes of pharmaceutical regulations of the ASEAN member countries to complement and facilitate the objective of AFTA, particularly the elimination of technical barriers to trade posed by regulations, however without compromising product quality, efficacy and safety.
- **ASEAN Common Technical Dossier/Requirements (ACTD/ACTR)**
- ASEAN Technical Documents – Process Validation, Analytical Validation, Stability, BA/BE

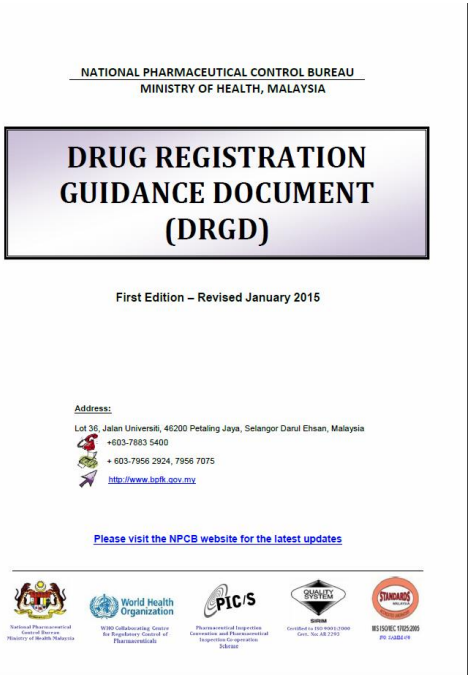


ASEAN COMMON TECHNICAL DOSSIER/REQUIREMENTS (ACTD/ACTR)

- **Adopted and adapted from ICH Requirements.**
- **Implemented since July 2003.**

ASEAN COMMON TECHNICAL DOSSIER/REQUIREMENTS (ACTD/ACTR)

- **Available guidelines**
  - **Drug Registration Guidance Document (DRGD)**
  - **ASEAN Guidelines on Process Validation**
  - **ASEAN Guidelines for the Conduct of BA/BE Studies**
  - **ASEAN Guidelines for Drug Product Stability Study**
  - **ASEAN Guidance on ACTD**


NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH, MALAYSIA

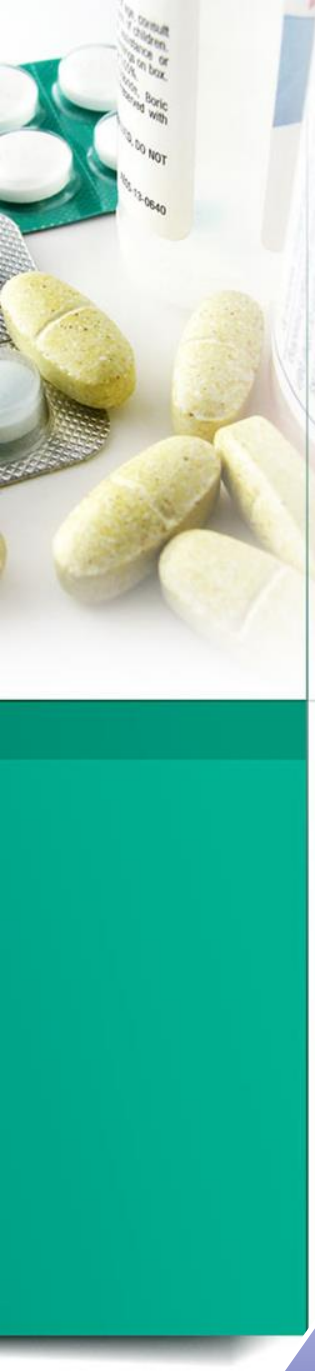
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)

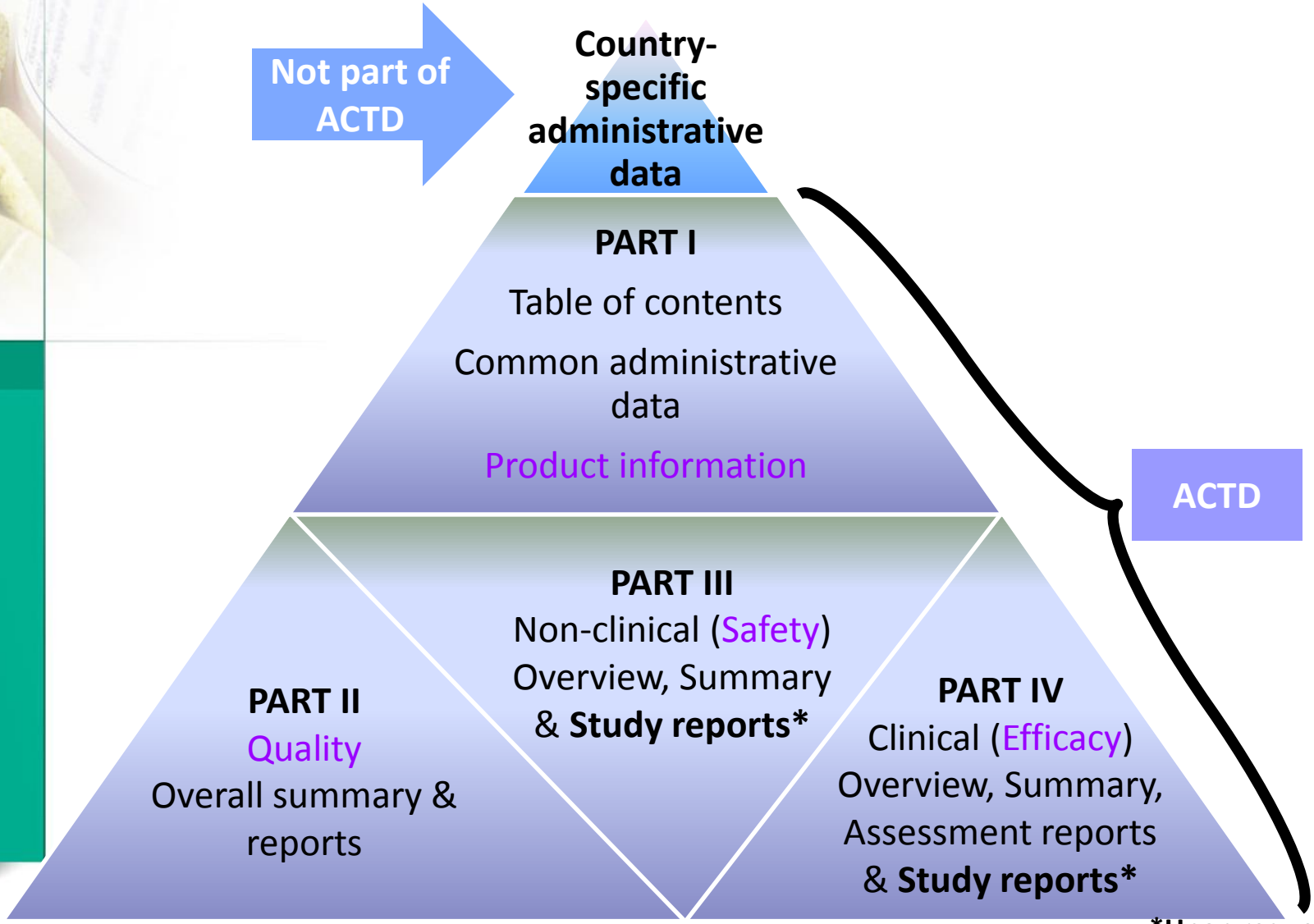
First Edition – Revised January 2015

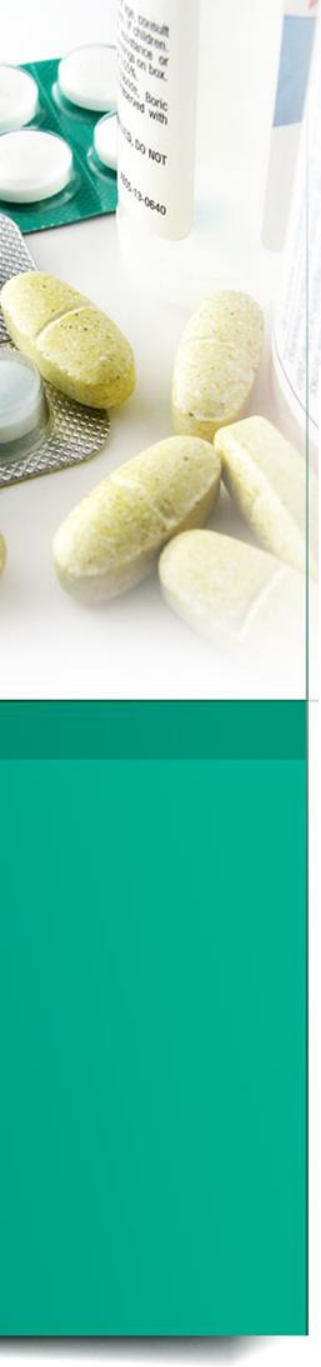
Address:
Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor Darul Ehsan, Malaysia
+603-7883 5400
+ 603-7956 2924, 7956 7075
http://www.bpfk.gov.my

Please visit the NPCB website for the latest updates

ORGANISATION OF APPLICATION DOSSIER (ACTD)







THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PART I : Administrative Data & Product Information	
Section A	**Product Particulars** Product name, name & strength of active ingredient(s), product description, indication, dosage, contraindication, warning & precautions, storage condition & shelf life
Section B	**Product Formula**
Section C	**Particulars of Packing**
Section D	**Label & Package Insert**
Section E	**Supplementary Documentation** Letter of Authorisation, Certificate of Pharmaceutical Product, CFS, GMP

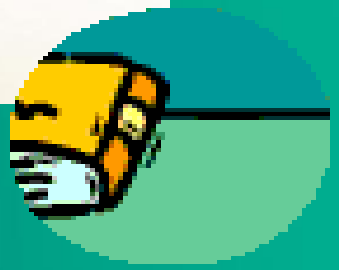
THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PART II : Quality b) Part P – Drug Product	
P1	**Description & Composition**
P2	**Pharmaceutical Development** Justification of overages, selection of preservative, formula development summary
P3	**Manufacturer** Batch Manufacturing Formula, Manufacturing & Packaging Process, Control of Critical Steps & Intermediates, Process Validation
P4	**Control of Excipients** Specifications
P5	**Control of Finished Product** Specification, Certificate of Analysis (CoAs)
P8	**Stability** Real time & accelerated stability report
P9	**Product Interchangeability / Equivalent Evidence** BE Report – applicable only for listed generic oral solid immediate release dosage form Bioavailabiliy Report – applicable for all modified-release/extended-release/sustained release product

THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PART II : Quality a) Part S – Drug Substance	
General Information	Nomenclature Structure General properties
Manufacturer	
Control of Drug Substance	Specification Certificate of Analysis (CoAs)

PRODUCT REGISTRATION CRITERIA (HOW DO WE ENSURE QSE?)



SAFETY

- Non Permitted/Prohibited/Restricted Ingredients, e.g. :
  - Phenylpropanolamine (PPPA), Sibutramine, Terfenadine, Penicillin for topical use, Amaranth, Tartrazine, Cyclamates, Methylene chloride (solvent for film-coating in locally manufactured product)

- Product Information (SPECIAL REQUIREMENTS) - label / warning / precautions / drug interactions / adverse effects
  - E.g. i) Amiodarone (PI – boxed statement)

This product is to be used only by a registered medical practitioner with experience in cardiology.

ii) Fibrates (PI – under 'Drug Interactions')

'Concurrent use of lovastatin (or other HMG-CoA reductase inhibitors)may cause severe myositis and myoglobinuria.'

QUALITY

- Certificate of Pharmaceutical Product (CPP) : GMP Certificate & Certificate of Free Sale
  - GMP inspection : Basic GMP Requirement
    - Premise, Location and facilities, Equipment and quality control
    - Testing procedures and Standard Operating Procedures
    - Products security, Manufacturing records and recall procedures
    - Self Inspection
- Product Testing :
    - Product Specifications: Compendial /Non-compendial
    - Microbial Limit Test

- With effect from 1st July 2012, all pharmaceutical products should be manufactured in PIC/S or ICH countries. Applicant can provide valid GMP certificate/documents if the facilities have been inspected by any regulatory authorities from PIC/S or ICH countries and from ASEAN country through ASEAN Sectoral Mutual Recognition Arrangement for GMP.

- However, if the applicant is unable to provide any evidence of GMP compliance to PIC/S standards as above, application to request for GMP site inspection can be submitted to Centre for Compliance and Licensing (GMP) of National Pharmaceutical Control Bureau (NPCB).

EFFICACY

- **Bioequivalence Studies**
  - **Generics**
  - ‘A pharmaceutical product usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of the patent or other exclusivity rights’

Pharmaceutical products

Quality

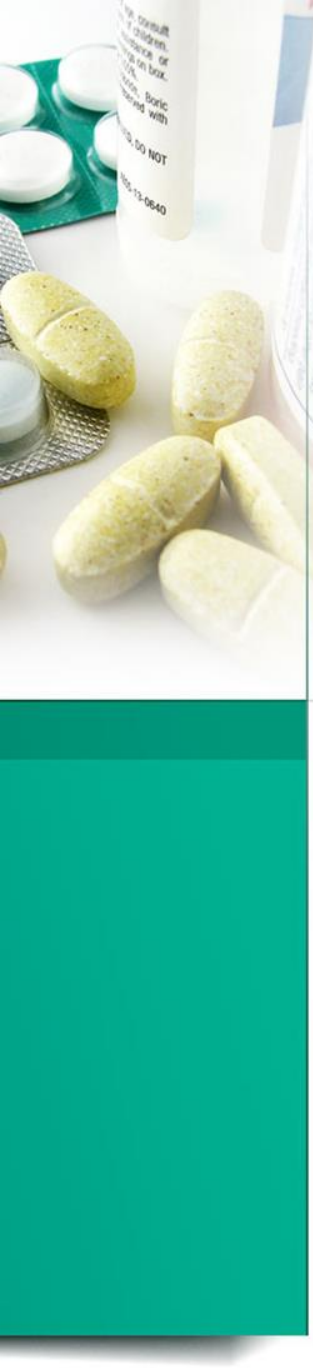
- Certification – CPP, GMP
- GMP inspection
- Product formulation
- Mfg. process & PV
- QC (IPQC, FPQC)
- Storage & stability study

Safety

- Free from banned ingredients
- Product info. : warning labels / precautions / drug interactions / AEs
- Conditional registration

Efficacy

- Same A/I, amt. of A/I, route of administration, indications, etc.
- BE/BA studies



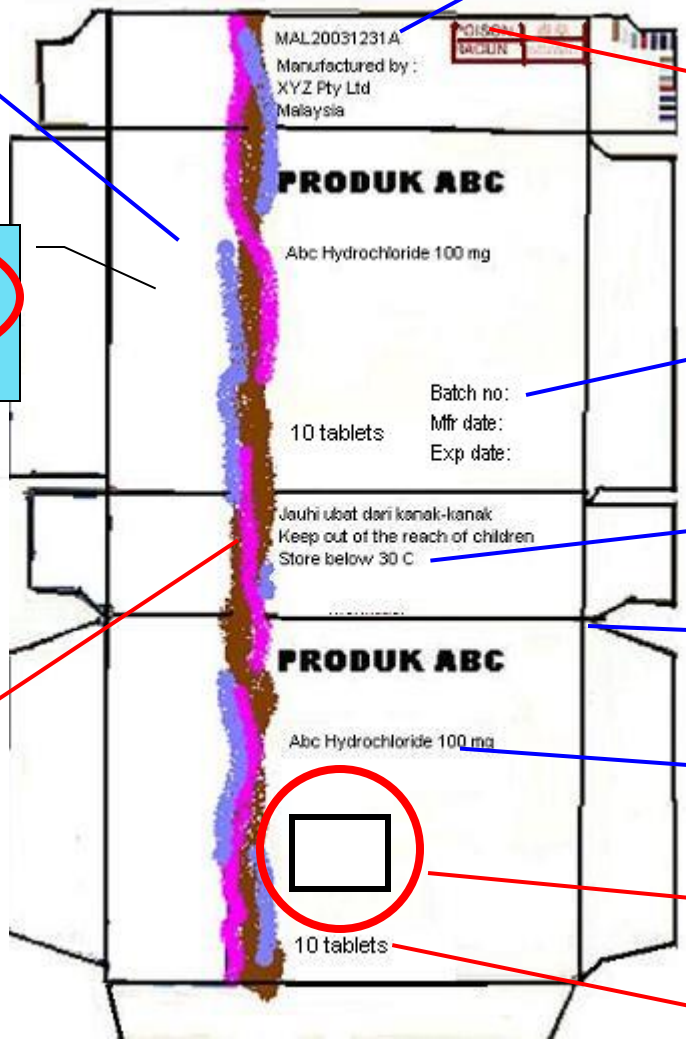
GENERICS

Bypasses the expense and time required to demonstrate the drugs efficacy and safety through clinical trials

BUT

Still needs to conform to the same standard of quality, safety and efficacy required of the innovator's product.

LABELING REQUIREMENTS



Product Registration No.

Route of administration

"Controlled Medicine" / Ubat Terkawal (for scheduled poisons only)*

To declare source of ingredient derived from animal origin(for active, excipient and/or capsule shell)

Batch No.
Manufacturing date
Expiry date

Storage condition

*Statement 'Keep Medicines Out Of Reach Of Children' in Bahasa Malaysia & English

If applicable:
Warnings, name & content of alcohol & *preservatives

Product Name

Active ingredient(s) and strength(s)

Security label (hologram)

Dosage form & pack size

IMPLEMENTATION OF BA/BE REQUIREMENTS IN MALAYSIA

- Implemented by the Drug Control Authority since September 1999(in phases)
- Compulsory for ALL generic products (containing scheduled poison) in the form of immediate release, oral solid dosage forms starting from 1.1.2012
  - as an additional requirement for the registration of generic products in 'oral solid immediate release' dosage forms

IMPLEMENTATION OF BA/BE REQUIREMENTS IN MALAYSIA

- As a mechanism to ensure that generics are therapeutically equivalent to the innovator product and are clinically interchangeable

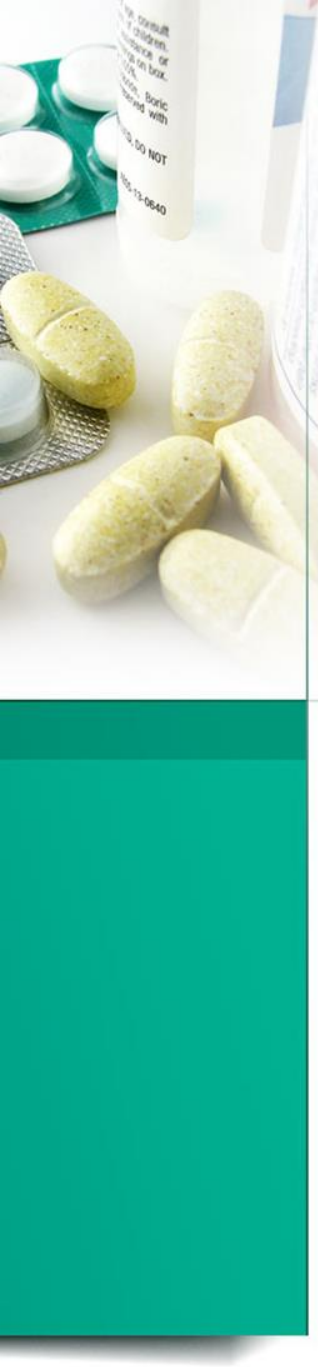
Two pharmaceutical products are bioequivalent if they **are pharmaceutically equivalent and their bioavailabilities (rate and extend of availability) after administration in the same molar dose are similar to such a degree that their effects can be expected to be essentially the same.

BA/BE report: **applicable for all modified release/extended release/sustained release product

ONLINE SUBMISSION

- Starting from July 2003 – QUEST.
- All categories of product.
- Secured online transactions : registration, variations, re-registration, etc.
- Evaluation – additional data required via e-communication.
- Approval – certification.
- Rejection – appeal.

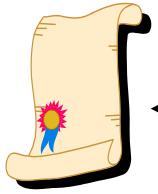
OVERVIEW OF QUEST SYSTEM



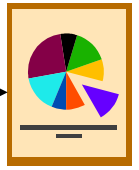
BPFK Review Team

Applicant

Database



Certificates



Statistical Data

Stakeholder

EVALUATION (ONLINE)

- Full evaluation consist of :
  - Part I : Sections A, B, C, D & E
  - Part II : Part P (Drug Product)
    Part S (Drug Substance)

- Abridged evaluation consist of :
  - Part I only : Section A, B, C, D, E & F

FLOWCHART OF GENERAL ONLINE REGISTRATION PROCESS

* Evaluation based on ACTD format & ACTR
- Labeling, PI, PIL
* Verification of GMP status/CPP

Applicant – submit application via QUEST

Evaluation of application dossier

Evaluation Committee *(within NPCB)*

Drug Control Authority
(decision making body – meets monthly)

Reassessment

More information needed

Registered

Issue Product Registration Number (validity : 5 years)

Rejected

Appeal to Minister of Health

REGISTRATION CONDITIONS

- Registration no: MAL07021234A
- Product registration is for a period of 5 years
- Updating of product information / amendments / variations is allowed through proper application - any changes that would affect the quality, safety and efficacy of product will not be allowed
- Renewal of registration is required for maintenance on the register (to be notified by holder within 6 months before registration expires)

REGISTRATION CONDITIONS

- Post Market Surveillance, Adverse Drug Reaction Monitoring and investigation on complaints AT ALL TIME.

- The DCA wishes that all medical practitioners, health professionals, consumers and the public report any complaints regarding the quality of medicines particularly if they experience adverse reactions or any other problems with these medicines.

- DCA will not hesitate to suspend, cancel, recall unsafe or substandard products from the market.

POST-MARKET SURVEILLANCE (PMS) ACTIVITIES

OBJECTIVES OF CENTRE FOR POST-REGISTRATION OF PRODUCTS

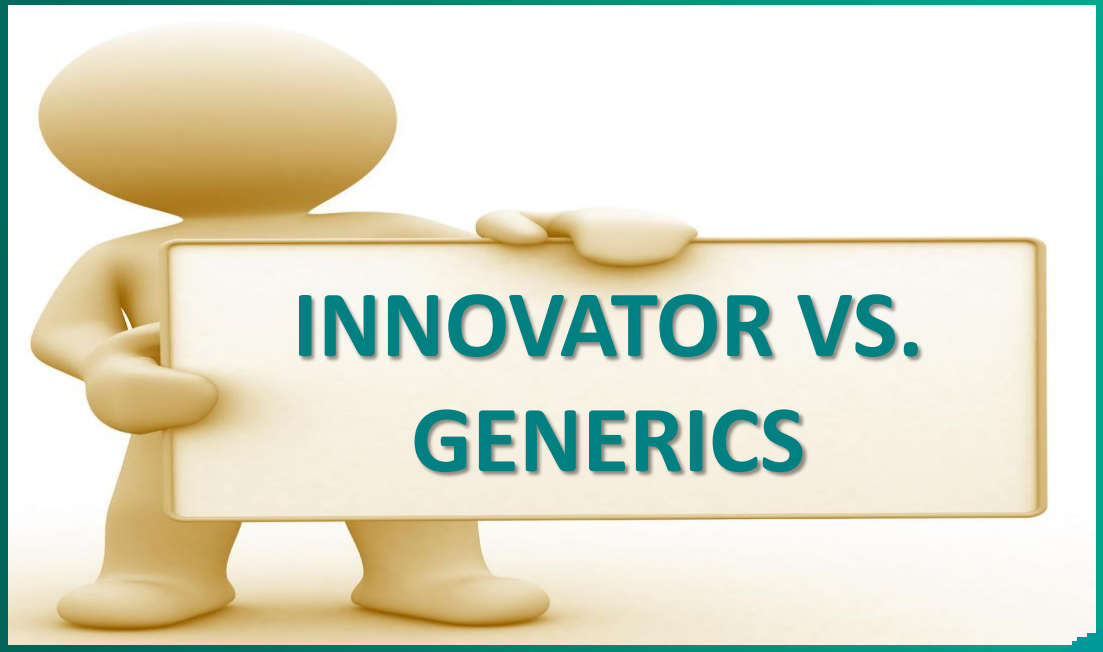
- Ensure that drugs registered for use in Malaysia comply in terms of quality, efficacy and safety.

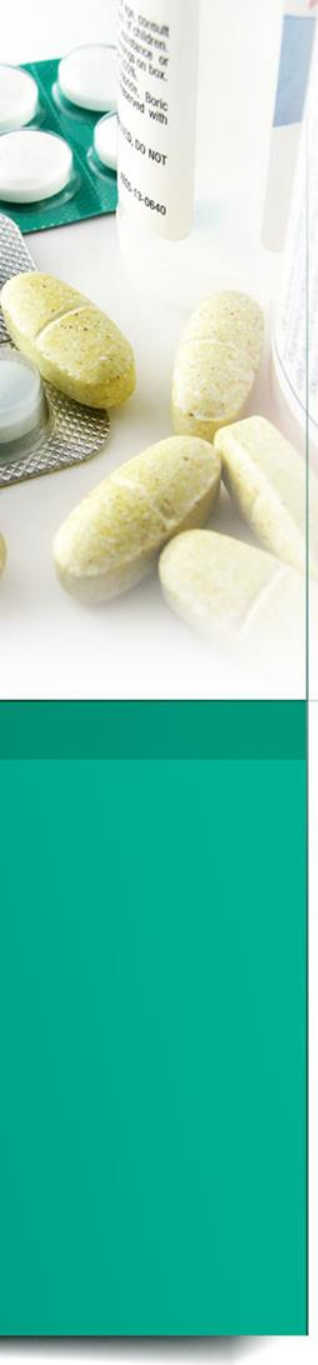
- Ensure that product labeling (inserts, labels, indications and claims) of registered products are as approved by Drug Control Authority.

- Monitor the safety profile of marketed drugs in order to
  - ❑Take the necessary actions to minimize risks to consumers
  - ❑Reevaluate the risks-benefits ratio of marketed products

POST-REGISTRATION

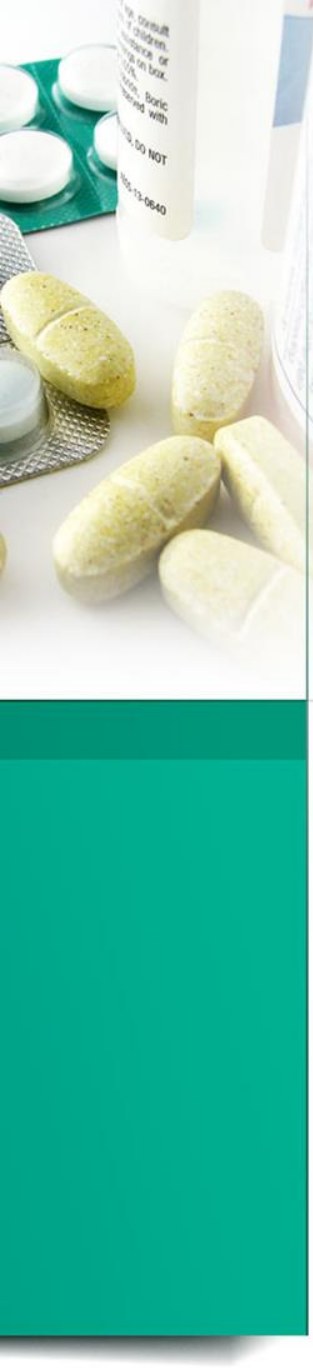
- Routine surveillance
  - Market Sampling
  - Laboratory Analysis
  - Label Monitoring
- Investigations of product complaints
  - Quality defects
  - Safety & efficacy issues
- Safety profile monitoring of products
  - Adverse Drug Reactions (ADR) Monitoring
  - Review of Periodic Safety Update Reports (PSUR)





REQURIEMENTS : INNOVATOR VS. GENERICS

Criteria	Innovator	Generic
Registration by DCA	Yes	Yes
Procedures	Online/Manual	Online
Processing Fee	RM4000-RM5000	RM 2200-RM3000
Requirements	Quality , Safety Efficacy (Animal and Clinical Study)	Quality , Safety Efficacy (BE Study)
Processing Time	245 w.d	210 w.d



REQURIEMENTS : INNOVATOR VS. GENERICS

Criteria	Innovator	Generic
Validity of registration	5 years	5 years
PMS & ADR monitoring	Yes	Yes
GMP Facilities	Yes	Yes
Finished Product QC	Yes	Yes
Stability Data	Yes	Yes