REGULATORY CONTROL OF GENERIC MEDICINES IN MALAYSIA

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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
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

- 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
REGISTRATION REQUIREMENTS
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
ORGANISATION OF APPLICATION DOSSIER (ACTD)

PART I
Table of contents
Common administrative data
Product information

PART II
Quality
Overall summary & reports

PART III
Non-clinical (Safety)
Overview, Summary & Study reports*

PART IV
Clinical (Efficacy)
Overview, Summary, Assessment reports & Study reports*

*Upon request

Not part of ACTD
Country-specific administrative data
THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PART I : Administrative Data & Product Information

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section A</td>
<td><strong>Product Particulars</strong>&lt;br&gt;Product name, name &amp; strength of active ingredient(s), product description, indication, dosage, contraindication, warning &amp; precautions, storage condition &amp; shelf life</td>
</tr>
<tr>
<td>Section B</td>
<td><strong>Product Formula</strong></td>
</tr>
<tr>
<td>Section C</td>
<td><strong>Particulars of Packing</strong></td>
</tr>
<tr>
<td>Section D</td>
<td><strong>Label &amp; Package Insert</strong></td>
</tr>
<tr>
<td>Section E</td>
<td><strong>Supplementary Documentation</strong>&lt;br&gt;Letter of Authorisation, Certificate of Pharmaceutical Product, CFS, GMP</td>
</tr>
</tbody>
</table>
## PART II : Quality
### b) Part P – Drug Product

<table>
<thead>
<tr>
<th>P1</th>
<th>Description &amp; Composition</th>
</tr>
</thead>
</table>
| 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  
Bioavailability Report – applicable for all modified-release/extended-release/sustained release product |
**PART II : Quality**
a) Part S – Drug Substance

| General Information | Nomenclature  
|                     | Structure    
|                     | General properties |
| Manufacturer        | 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 1\textsuperscript{st} 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’
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

Pharmaceutical products
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.

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

Storage condition

Product Name

Active ingredient(s) and strength(s)

Batch No. Manufacturing date Expiry date

Security label (hologram)

Dosage form & pack size

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

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

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

Route of administration

Batch no:
Mfr date:
Exp date:

10 tablets

PRODUK ABC

Abc Hydrochloride 100 mg

Jouhi ubat dari kanak-kanak
Keep out of the reach of children
Store below 30 C

PRODUK ABC

Abc Hydrochloride 100 mg

10 tablets
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 extent 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**
REGISTRATION PROCEDURES
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
- Stakeholder
- Statistical Data
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 CONDITION
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)
INNOVATOR VS. GENERICS
## REQUIREMENTS: INNOVATOR VS. GENERICS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Innovator</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration by DCA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Procedures</td>
<td>Online/Manual</td>
<td>Online</td>
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<tr>
<td>Processing Fee</td>
<td>RM4000-RM5000</td>
<td>RM2200-RM3000</td>
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<tr>
<td>Requirements</td>
<td>Quality, Safety, Efficacy (Animal and Clinical Study)</td>
<td>Quality, Safety, Efficacy (BE Study)</td>
</tr>
<tr>
<td>Processing Time</td>
<td>245 w.d</td>
<td>210 w.d</td>
</tr>
</tbody>
</table>
## REQUIREMENTS: INNOVATOR VS. GENERICS

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<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validity of registration</td>
<td>5 years</td>
<td>5 years</td>
</tr>
<tr>
<td>PMS &amp; ADR monitoring</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>GMP Facilities</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Finished Product QC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stability Data</td>
<td>Yes</td>
<td>Yes</td>
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</table>
Thank You...