ASEAN: Pharmaceutical Registration Overview and Product Life Cycle

Atthachai Homhuan, Ph.D.
Manager, Regulatory Affairs
3D: Discovery-Development-Delivery

Pharmaceutical Innovation Cycle

- Discovery
  - Lead identification/optimization
  - Basic research

- Development
  - New/improved tools
  - Preclinical and clinical development

- Delivery
  - Getting products to patients

From R&D to Access of Medicine

Discovery → Lab/Animal test → Clinical Studies → New Drug Approval

Manufacturing/QC → Product → Physician → Access of Medicine
What Are Clinical Trials?

**CLINICAL STUDIES**

- Research studies involving **people**

- Try to answer scientific questions and find **better ways** to prevent, diagnose, or treat disease
Overview of Clinical Trials - On the Rise in ASEAN

<table>
<thead>
<tr>
<th>Country</th>
<th>Legislation on Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>No specific legislation</td>
</tr>
<tr>
<td>Malaysia</td>
<td>No specific legislation</td>
</tr>
<tr>
<td>Philippines</td>
<td>Rules &amp; Regulations on Registration, Including Approval &amp; Conduct of Clinical Trials and Lot or Batch Release, etc. Administrative Order No. 47-a</td>
</tr>
<tr>
<td>Singapore</td>
<td>Medicines (Clinical Trials) Regulations (2000)</td>
</tr>
<tr>
<td>Thailand</td>
<td>No specific legislation</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Regulation on Clinical Trials (2012)</td>
</tr>
</tbody>
</table>
Participating Parties in Clinical Trial

- Patients/ Healthy Volunteer
- Clinical Investigator and Team
- Sponsor
- Institution
- Community
- Ethical Review Board
- Regulatory authorities

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Legal Aspects/ Issues in Clinical Trials

- Protection of Subjects/ Patients
- Conflict of Interest
- Intellectual Property (IP) Rights
- Negotiation of the Agreements
From R&D to Access of Medicine
What are Branded (Patented)/Generic Drug Products?

- After patent expiration
- Freedom to operate search
- Patent Infringement Analysis

Active pharmaceutical Ingredient (API) + Excipients = Branded

Excipients = Generic
Pharmaceutical Equivalents

Patented drug

Possible Differences
- Drug particle size
- Excipients (type, amount)
- Manufacturing equipment or process
- Site of manufacture etc.

Generics

Could lead to differences in product performance *in vivo* *(human body)*
Model of Oral Dosage Form Performance

Dosage Form Performance

Drug in Solution

Gut Wall

Drug Concentration Measurement

Blood

Site of Action

Therapeutic Effect

BA/BE

Drug Molecules

Dosage Forms

Clinical Measurement
Bioequivalence: a key measurement

The Thai FDA prefers the BE study conducted by accredited laboratory in Thailand
Technical Requirements for the Registration of Patented Drug VS Generics

**Patented Drugs**
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Bioavailability
8. Clinical Studies

**Generics**
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

**Quality**

**Safety and Efficacy**
Marketing Authorization File Dossier: ACTD Requirements

- Certificate of Rx Prod. (Cert. Free Sale)
  - GMP Cert.
  - Applicant information

- Labeling requirements (countries specific)
  - Trade name clearance
  - Patent status

*to be provided upon request
ASEAN Technical Guidelines

- Conduct bioavailability (BA)/ bioequivalence (BE) studies
- Manufacturing process validation
- Validation of analytical procedures
- Stability studies of drug product
- Other international guidelines e.g. ICH, WHO, Pharmacopoeia

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Meeting with the FDA and Handling Official Actions

Meeting Preparation

- Be persuasive, but open and honest
- Focus on Q&A
  Avoid broad, open-ended questions
  Be specific and answerable
- Do not speculate
- Caution: do not stress commercial concerns over science
# IP Legislation and Drug Registration

<table>
<thead>
<tr>
<th>Country</th>
<th>IP Legislation</th>
<th>Data Exclusivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indonesia</strong></td>
<td>IP laws in place, USTR Priority Watch</td>
<td>No specific legislation, but protection as a trade secret</td>
</tr>
<tr>
<td><strong>Malaysia</strong></td>
<td>Improvement on IP protection</td>
<td>No specific legislation, but protection of undisclosed information based on common law practice</td>
</tr>
<tr>
<td><strong>Philippines</strong></td>
<td>IP protection, but ineffective enforcement of IPR</td>
<td>No specific legislation</td>
</tr>
<tr>
<td><strong>Singapore</strong></td>
<td>Strong IP protection and legal enforcement</td>
<td>Five years from the filing date of the originator’s pharmaceutical product, for text data</td>
</tr>
<tr>
<td><strong>Thailand</strong></td>
<td>IP laws in place – USTR Priority Watch List</td>
<td>Five years from the date of recordation of clinical data (physical protection)</td>
</tr>
<tr>
<td><strong>Vietnam</strong></td>
<td>IP laws in place; some weaknesses remain</td>
<td>Agreement between the USA and Vietnam – five years from marketing authorization</td>
</tr>
</tbody>
</table>
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ASEAN GMP Accreditation

- In 2005, ASEAN Mutual recognition Agreement (MRA) on GMP Inspection
- Accept the conclusions of GMP Inspections of manufacturers carried out by other party’s inspection service.
GMP Conformity Assessment of an oversea manufacture

- Pharmaceutical Inspection Co-operation Scheme (PICS)
- Singapore (20,000-30,000 USD) with certificate validity of two years
- Thailand: Quality System Dossier Evaluation with certificate validity of three years
- Import and export of pharmaceuticals VS GMP
ASEAN Variation Guideline for drug product

• Variations to valid MA license, keeping history of all variations made

• Changes in pharmaceutical industry are inevitable due to many reasons including changing needs, new findings, and continuous improvement

• Regulations require that all changes be evaluated carefully and follow the proper regulatory path for implementation

• Failure to comply with regulatory requirements for post-approval changes can potentially lead to “misbranded or adulterated” status for a given product
Type of post Approval Changes

1. **Major Variation (MaV 1-16)**
   - Changes that may affect significantly and/or directly the aspects of quality, safety and efficacy
   - If application fulfills the requirements as per described in guideline, the DRA shall issue an approval for the proposed change

2. **Minor Variation (MiV)**
   - Minor Variation with prior-approval (MiV-PA 1-35)
   - Minor Variation with notification (MiV 1-10)

*DO & TELL*
Conclusion

• Regulatory Affairs and drug registration can be considered every interaction a company can have with a regulatory authority

• The company should consider the entire life cycle of a product, from conception to marketing, and eventual recall or removal

• The compliance action is the key element for the company and thus the drug registration and RA related works are the multidisciplinary work between legal and sciences.
Contact Information

- Dr. Atthachai Homhuan
- Telephone: +66 2653 5610
- E-mail: Atthachai.H@Tilleke.com
- www.tilleke.com