By Ravi Varahalu and Jairam Masetti

This article, the second in a two-part series on the Southeast Asian Regulatory Environment for Pharmaceuticals, examines the regulatory landscape in Brunei, Vietnam, Laos, Myanmar (Burma) and Cambodia (Table 1). Part one, published in December 2014, examined the larger ASEAN markets of Singapore, Malaysia, Indonesia, Philippines and Thailand.¹

Since 2010, drug companies have dealt with one set of regulatory requirements for all 10 member countries in the Association of Southeast Asian Nations (ASEAN): Singapore, Malaysia, Indonesia, Philippines, Thailand, Vietnam, Brunei, Myanmar, Cambodia and Laos. The ASEAN-mandated filing of the ASEAN Common Technology Dossier (ACTD) has helped pharmaceutical companies easily navigate the ASEAN markets; however, in recent years, ASEAN health authorities have been re-organized and some significant regulatory changes have taken place.

ASEAN Background

The ASEAN Pharmaceutical Product Working Group (PPWG) continually works to harmonize the efforts of the ASEAN member countries to complement and facilitate the ASEAN Free Trade Area (AFTA) objective, which is to eliminate technical barriers to trade posed by these regulations, without compromising drug quality, safety or efficacy. PPWG envisioned the same regulatory requirements applying for all ASEAN member countries; however, significant efforts still are required to reach this objective (Table 2).

The ACTD is similar to the International Conference on Harmonization (ICH) CTD with some notable differences² (Table 3).
Table 1. Southeast Asian Pharmaceutical Markets

<table>
<thead>
<tr>
<th>Countries</th>
<th>Brunei</th>
<th>Vietnam</th>
<th>Laos</th>
<th>Myanmar</th>
<th>Cambodia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 2014</td>
<td>423,205</td>
<td>92,547,959</td>
<td>6,894,098</td>
<td>53,718,958</td>
<td>15,408,270</td>
</tr>
<tr>
<td>Average GDP Growth (%) (2011–2015)</td>
<td>2.3%</td>
<td>6.49%</td>
<td>7.3%</td>
<td>6.50%</td>
<td>7.20%</td>
</tr>
<tr>
<td>Pharma Market</td>
<td>$100 million USD in 2013</td>
<td>$2,775 million USD</td>
<td>$170 million USD in 2012 to $190 million USD in 2013</td>
<td>$350 million USD in 2013 to $390 million USD in 2014</td>
<td>$210 million USD</td>
</tr>
<tr>
<td>Compound Annual Growth Rate</td>
<td>5.4 %</td>
<td>16%</td>
<td>8%</td>
<td>12%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Table 2: Regulatory Agencies, Approval Times and Fees

<table>
<thead>
<tr>
<th>Countries</th>
<th>Health Authority</th>
<th>Marketing Authorization Application (MAA) Approval Timelines</th>
<th>Fees</th>
</tr>
</thead>
</table>
| Brunei | Ministry of Health through the Department of Pharmaceutical Services (DPS) | • 12 to 14 Months | • Processing fee $150 USD Payable at the point of submission of the application for a medicinal product registration  
• Annual Product License fee $37 USD Payable from second year onward |
| Vietnam | Ministry of Health (MOH) and the Drug Administration of Vietnam (DAV) | New Drug Application:  
• Vaccines, biological medicines and chemical medicines (NCEs): 18-24 months from the date of submission of the dossier  
Generic Drug:  
• Generics: 14-22 months from the date of submission of the dossier | • Government Filing fee $220-300 USD (depending on whether the medicinal products have data confidentiality requirements or bioequivalent dossier and/or clinical dossier requirements) |
| Laos | Food and Drug Department (FDD) Ministry of Health | • 8 to 12 months | • Modern drug produced within the country: $30 USD/per product per dose  
• Modern drug imported: $100 USD/per product per dose  
• Traditional drug produced within country: $15 USD/per product per dose  
• Traditional drug imported: $50 USD/per product per dose |
Brunei Darussalam

Brunei Darussalam’s Ministry of Health (MOH), through the Department of Pharmaceutical Services (DPS), oversees the registration system of all medicinal products for human use in the country. Medicinal products in Brunei Darussalam are regulated under the Medicines Order of 2007, Medicines (Licensing, Standard Provision and Fees) Regulations of 2010, Medicines (Labeling) Regulations of 2010 and the Poisons Act of 1956.172

**Registration Procedures**

DPS mainly is responsible for executing the control of drugs. Registration of pharmaceutical products requires submission of a detailed monograph pertaining to pharmacology, pharmacokinetics (PK), toxicology, biopharmaceutics, clinical pharmacology, clinical efficacy, safety and any other supporting documents, such as clinical trial data or comparative studies.

The product registration application is divided into three types:

- **innovator product (NCE/biotech)**
  - Applies to new medicinal product containing:
    - a new chemical/biological entity

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**Table 3. Additional Document Requirements**

<table>
<thead>
<tr>
<th>Countries</th>
<th>Samples</th>
<th>Certificate of Pharmaceutical Products (CoPP)</th>
<th>Manufacturing License</th>
<th>Good Manufacturing Practices (GMP) Certificate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunei</td>
<td>NR</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Vietnam</td>
<td>R</td>
<td>R/L</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Laos</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Myanmar</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Cambodia</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

R: Required  
NR: Not Required
A new combination of existing chemical/biological entity(ies)
o existing chemical/biological entity(ies) in a new dosage form
do existing chemical or biological entity(ies) for use by a different route of
administration

- **generic product**
  Applies to any medicinal product similar to a currently registered product in
  Brunei Darussalam. The term generic is not applicable to biological and
  biotechnological products.

- **application for registration of medicinal products via the abridged route**
  Applies to any medicinal product classified as General Sale List (GSL) medicine
  (for certain categories only) and registered in at least one benchmark country.
  Products include antiseptics/skin disinfectants; lozenges/pastilles; health
  supplements; topical analgesics/counter-irritants; emollients/demulcents;
  keratolytic; topical nasal decongestants, etc. This list is not exhaustive.)

**Dossier Requirements**

All applications for medicinal product registration in Brunei must comply with ACTD and
ASEAN Common Technical Requirements (ACTR). The application dossier has four
parts:

- Part I: Administrative Data and Product Information
- Part II: Quality
- Part III: Nonclinical
- Part IV: Clinical Documents

The data requirements are based on the following criteria (**Table 4**):

**Table 4: Data Requirements for Different Product Categories**

<table>
<thead>
<tr>
<th>Application Type</th>
<th>Data requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovator product registered for less than 5 years in at least one benchmark country</td>
<td>Parts I, II, III and IV</td>
</tr>
<tr>
<td>Innovator product registered for less than 5 years in at least one benchmark country containing existing chemical/biological entity(ies) in a new dosage form</td>
<td>Parts I, II and PK data</td>
</tr>
<tr>
<td>Innovator product registered for more than 5 years in three benchmark countries</td>
<td>Parts I and II</td>
</tr>
<tr>
<td>Generic product</td>
<td>Parts I and II</td>
</tr>
<tr>
<td>Abridged application</td>
<td>Part I only</td>
</tr>
</tbody>
</table>

**Registration Timelines**

- The submitted application will be reviewed and validated for completeness within
  10 working days.
- The Drug Registration Unit (DRU) may request further information and additional
  supporting documents from the applicant through a screening query letter.
  Applicants should respond within 60 calendar days from the date of the letter.
  Once all required documents are submitted, they will be reviewed for
  completeness.
- The application will not proceed for evaluation if there has been no response
  after 60 days. DRU will issue a non-acceptance letter and the documents
  will be returned.

If the applicant still wishes to pursue product registration, a new application would have
to be submitted (**Figure 1**).
Southeast Asia Regulatory Landscape for Pharmaceuticals (Part 2)

Vietnam

The Drug Administration of Vietnam (DAV), under the MOH, is the country’s primary drug regulatory authority. Regulations often can be unclear, and they frequently are implemented on a case-by-case basis. These uncertainties can pose a barrier to market entry for foreign pharmaceutical companies. Additionally, drug approval times often vary and long delays are typical.

Registration Procedures

Only the following entities are permitted to register pharmaceutical products in Vietnam:
- domestic pharmaceutical manufacturers
- foreign-invested companies licensed to manufacture pharmaceuticals in Vietnam
- domestic entities that are permitted to trade in pharmaceuticals
- foreign entities that hold trading licenses (Figure 2)
Figure 2: Medicinal Product Registration Procedures

1. Trader fills in application form
2. Trader submits application form to Ministry of Health
3. Application for Registration
   - Ministry of Health checks and evaluates application
   - If not approved, Trader is informed of rejection
   - If approved, Trader sends sample
4. Ministry of Health notifies Trader and requests sample
   - If not approved, Ministry of Health carries out tests
   - If rejected, Ministry of Health informs Trader of rejection
   - If approved, Ministry of Health issues Certificates
   - Certificate
   - Trader proceeds with normal import

Supporting Documents
- Importation Plan
A product registration application must include the following:
- Good Manufacturing Practice (GMP) certificate for the manufacturing facility in the country of origin
- Free-sale certificate issued in the country of origin (The product sold in Vietnam must have the same specifications as the one sold in the country of origin.)
- product information, including drug interactions, use indications, dosage, overdose management, storage conditions and shelf life
- a detailed description regarding the manufacturing process, as well as in-process quality control procedures
- stability data (in real time) from three batches
- quality specifications, including the relevant analytical methods for finished products, raw materials and excipients
- three samples of the product, including Certificates of Analysis, active ingredients and excipients
- packaging materials, including Vietnamese language inserts

Most of these materials may be submitted in English.

Registration Timelines

The drug registration applicant must submit a marketing authorization application dossier to DAV. Marketing authorization will be granted within one year from the date of receiving a complete and valid application, unless DAV considers the application to be inadequate or incomplete. In that case, an official letter clearly stating the supplementary requirements necessary or reason for refusal will be issued.

Marketing authorization is valid for a maximum of five years from the signed date. In special cases, MOH will consider and issue separate regulations. For example, in the case of NCEs, the marketing authorization is valid for one or two years. The drug registration applicant can submit a re-registration dossier within six months before and after a circulation registration number expires (Table 5).

Table 5. Time required in Vietnam for new and generic drugs registration

<table>
<thead>
<tr>
<th>Type of Review</th>
<th>Process of New Drug Registration</th>
<th>Process of New Generic Drug Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>• Vaccines, biological medicines and chemical medicines (NCEs): 18-24 months from the date of submission of the dossier</td>
<td>• Generics: 12-14 months from the date of submission of the dossier</td>
</tr>
</tbody>
</table>

Laos

Drugs and medical products sold in the Laos must be registered with MOH. MOH is required to issue a certificate stating the drug conforms to legal health standards.

Registration Procedures

Before registration, MOH must inspect and analyze drugs and medical products to determine whether they conform to established safety and efficacy standards. To apply for drug registration, the applicants must be legally permitted to manufacture and import modern drugs or traditional medicines for the purpose of selling in Laos. Foreign manufacturers that do not have a local entity are required to engage a local representative or licensed local company to import modern drugs or traditional medicines into Laos.

Drug registration committees appointed by MOH decide whether a drug can be registered in Laos. The consideration period is within 180 days. The Food and Drug Department (FDD) issues a drug registration number and certificate for any approved drug, authorizing the license holder to either manufacture or import.
Any new drug being imported into Laos or produced for the treatment of serious diseases, i.e., HIV/AIDS, hepatitis, cancer, cardiovascular disease, will be given priority provided it already is available in one of the EU Member States, the US, Australia or Japan. Additional required documents can be provided upon request, e.g., toxicology, pharmacology, PK, bio-availability and clinical trials (Figure 3).

Figure 3: Drug Registration Procedures

![Drug Registration Procedures Diagram]
**Registration Timelines**

Medicinal product registration in Laos normally takes approximately six months once FDD confirms the application and receives all supporting documents. In the case of drug samples, permission to import has to be granted before the drug registration certificate is issued. The drug company should supply the reference substances for analysis when needed.

For approved drugs, product owners (i.e., manufacturers, importers or exporters) must print the registration number on the labels, boxes, containers, blisters, vials, etc. For imported drugs, a Lao version leaflet must be produced if there is no possibility of printing the Lao content on the label (Table 6).

**Table 6. Time required in Laos for new and generic drugs registration**

<table>
<thead>
<tr>
<th>Type of Review</th>
<th>Process of New Drug Registration</th>
<th>Process of New Generic Drug Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>• 12 Months</td>
<td>• 6 Months</td>
</tr>
</tbody>
</table>

**Myanmar**

The Myanmar (Burma) government enacted the National Drug Law (ND Law) in 1992. The basic purpose of the ND Law is to control and regulate the manufacture, import, export, storage, distribution and sale of drugs systematically. A drug registration application must be submitted to the Department of Health, Food and Drug Administration (FDA) using an original prescribed form (Form 1 Registration).

**Registration Procedures**

Applications for a medicinal product must be submitted in person by an authorized representative of the drug’s owner. No other means will be accepted. If the producer is a foreign company, the applicant must be a resident representative of the foreign company. An authorization letter must be submitted by the foreign manufacturer to the local party, who then will serve as the contact person.

Drug registration must be initiated by the applicant by entering a drug or list of drugs in a registry book at Drug Control Section 1 (DCS1), part of FDA. DCS1 then will issue a letter of intimation for remittance of assessment fees, which amount to $100 USD plus fees for laboratory analysis, depending on the drug category. After obtaining the letter, the applicant must remit the assessment fees to account No 91892 at Myanmar Foreign Trade Bank (MFTB).

If the application is to register drugs manufactured outside Myanmar, FDA will issue an “Approval for Importation of Drug Samples.” The approval holder must comply with the conditions stipulated in the approval and the regulations of the commerce and customs departments.

The registration evaluation process will begin after all application requirements have been met, including registration assessment fees, the complete set of documents and a sufficient quantity of drug samples.

Once these steps are completed, FDA has two weeks from receipt of documents to accept the dossier. FDA would issue the preview for the complete dossier, and return the incomplete dossier to the concerned party.

When FDA accepts a dossier, it issues an acknowledgement of receipt. After previewing the documentation, if the information provided is inadequate, FDA will request further information. If all documentation is in order, the registration evaluation process will proceed at FDA’s primary laboratory.

If primary laboratory analysis results support approval, FDA’s General Affairs Section (GAS) issues a letter of intimation to remit registration fees of $200 USD for each drug approved.

Finally, the drug registration certificate is issued (Table 7).
Southeast Asia Regulatory Landscape for Pharmaceuticals (Part 2)

Cambodia

The Cambodia Food and Drug Department in MOH is the government agency responsible for pharmaceutical control in the country. The Food and Drug Department has five bureaus:

1. Registration and Cosmetics Bureau
2. Essential Drugs Bureau
3. Pharmaceutical Trade Bureau
4. Drug Regulation Bureau
5. Food Safety Bureau

The Registration and Cosmetics Bureau is responsible for registering all drugs and specific cosmetics coming into the country. Registration is the main mechanism for controlling the country’s pharmaceutical product quality. Registration involves evaluating documents using the following criteria:

- administrative-application, summary of product info, GMP, Certificate of Pharmaceutical Product (CPP)
- qualitative and quantitative formulation, manufacturing process, certificate of analysis of ingredients, control procedures of ingredients, stability, bioavailability and bioequivalence
- preclinical-pharmacokinetics, toxicology
- clinical trials

Registration Procedures

Cambodia’s drug registration process is limited and its laboratory facilities have low capacity to test quality so registration is based on documentation and work from other countries. Local pharmaceutical manufacturing facilities must comply with GMPs (refer to Pharmaceutical Inspection Co-operation Scheme (PIC/S)), and undergo training by MOH.

Facilities established overseas need to submit full documentation, including the plant master file, plant layout, latest GMP assessment report and latest GMP certificate as well as other documents for consideration for certifying overseas manufacturing facilities.

Pharmaceutical product application files (innovative drugs and generic drugs) must be submitted following ACTR and ACTD (Table 8).

Table 7: Time required as per review types for new and generic drugs registration

<table>
<thead>
<tr>
<th>Type of Review</th>
<th>Process of New Drug Registration</th>
<th>Process of New Generic Drug Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>• 1 Year for new chemical entities</td>
<td>• FDA 3 months to approve the registration of common drugs • 6-9 Months for less common drugs</td>
</tr>
</tbody>
</table>

Table 8: Time required as per review types for new and generic drugs registration

<table>
<thead>
<tr>
<th>Type of Review</th>
<th>Process of New Drug Registration</th>
<th>Process of New Generic Drug Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>• 1 Year for new chemical entities</td>
<td>• 6-9 Months for Generic Drug</td>
</tr>
</tbody>
</table>

Conclusion

The objectives and aspirations of ASEAN countries have evolved over time, and significant progress has been made in harmonizing the regulations. However, it is essential that all member countries, working groups and committees adapt to the changing requirements, ensure the free flow of trade and support AFTA’s objectives.
One of the key challenges for ASEAN in harmonizing standards and conformance is the lack of well-established structures in some of the countries as discussed in this article.

Some of the bigger stakeholders in the region have set ambitious goals for moving toward accepting electronic submissions (eACTD). Instead, the goal should be enhancing the entire region’s infrastructure and having one single platform for all countries to accept applications similar to Common European Submission Platform (CESP) in Europe. However, it looks like only few larger countries in the ASEAN region have implemented the required IT platform leaving the smaller players using paper submissions.

Considering the differences, industry must understand and define clear regulatory strategy by looking at the target countries, different patent terms and extensions, data requirements and registration timelines, as these attributes can have a major impact on product marketing plans.

References

About the Authors

Ravi Varahalu is a regulatory professional with nearly 12 years of industry experience in pharmaceutical companies, including American Remedies, GSK and MakroCare. He specializes in designing market expansion strategies, addressing regulatory challenges and assisting pharmaceutical companies in registering their products in emerging markets. Varahalu can be reached at ravi.varahalu@makrocare.com.

Jairam Masetti is a research professional with nearly nine years of experience in the analytics spaces with in life science domain. He specializes in analyzing big data. Masetti can be reached at jairam.masetti@makrocare.com.