



## REGULATORY REQUIREMENTS FOR THE REGISTRATION OF GENERIC SOLID ORALS IN USA, SINGAPORE, MALAYSIA, AND THAILAND

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### ABSTRACT

The availability of generic medication is an important issue in the ASEAN region. The regulatory requirements of various countries vary from each other. Therefore it is challenging for the companies to develop a single drug which can be simultaneously submitted in various countries for approval. The role of regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in circulation in their country. It not only includes the process of regulating and monitoring the drugs but also the process of manufacturing, distribution, and promotion. The regulatory environment has similar characteristics but drug registration requirements and processes differ among the countries. One of the primary challenges for regulatory is to ensure that the pharmaceutical products are developed as per the regulatory requirement of that country. This process involves the assessment of critical parameters during product development. Regulatory requirements and generic drug registration for USA and ASEAN regions is made at the end of the section. In ASEAN region documentation can be filed in the ACTD format. In US region documentation can be filled in the CTD/eCTD format.

**Keywords:** ASEAN, ACTD, ICH CTD, Documentation, Regulatory Authority.

### INTRODUCTION

The solid oral dosage form segment is the largest segment within the U.S. solid oral dosage forms market making up approximately 45.1% of this market<sup>11</sup>. This segment is expected to grow from \$4.8 billion in 2011 to \$5.9 billion by 2016 at a 4.1% compound annual growth rate (CAGR). Generics are expected to be a growth driver for this segment, with patents expiring for several drugs and companies looking to manage their portfolios and manufacturing capacity. A generic drug is a drug defined as "a drug product that is comparable to brand or reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use". According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamic properties<sup>1</sup>.

The ASEAN<sup>2</sup> (Association of Southeast Asian Nations) group of nations, [namely Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia] is an eye catcher for most pharmaceutical companies due to the growing population and attractive pharmaceutical market growth.

ASEAN established the CTD so it is called as ASEAN Common Technical Document (ACTD) and the ASEAN Common Technical Requirements (ACTR) to create harmonized requirements and a common format for all submissions of dossiers in the ASEAN countries. The ACTR are a set of written requirements or guidelines intended to provide guidance to applicants in order to be able to prepare application dossiers in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities (DRAs).

#### Dossier Format –ASEAN CTD

As mentioned before, the ASEAN countries established the ACTD as their format for submissions. It is a standard derived from the ICH CTD. The ASEAN CTD is a guideline of the agreed upon common format for the preparation of a well-structured ACTD application that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use.

The ACTD is similar to the ICH CTD. The ICH CTD is divided into 5 modules whereas the ACTD contains of 4 parts. The reason for doing this is the fact that the ASEAN countries normally receive a reference application, which is a dossier which was already approved in other countries in the world (mostly EU and USA) and make the evaluation of the parts mainly based on the overviews and summaries. Based on this, the need for detailed documentation is in most of the ASEAN countries is less compared to the ICH countries, e.g. most study reports are not required to be submitted. The Module 1 of the CTD containing the regional registration

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and administrative information is still presented as Part I of the ACTD. The Module 2 of the CTD does not exist itself for the ACTD. The Quality Overall Summary (QOS) and the overview and summaries of the non-clinical and clinical documentation (similar like the documents in ICH Module 2) are included at the beginning of these Parts. Part II of the ACTD contains the pharmaceutical-chemical-biological documentation (the quality information), which corresponds to the ICH Module 3. The non-Clinical information is presented as Part III of the ACTD (equivalent to ICH Module 4) and the clinical documentation is contained in Part IV of the ACTD (to be consistent with ICH Module 5). The differences between ICH-CTD and ACTD are presented in the attached comparison pyramid.

### MARKETING A DRUG PRODUCT IN USA<sup>3</sup>

To enter into the US market, the product will need to get the approval from the US Food and Drug Administration (FDA). The applicant files a market application with FDA. After reviewing the application, FDA will decide whether to grant the product approval. Selling the product without the approval would make you a felony under the US Federal Food, Drug and Cosmetic Act. The FDA has approved following pathways:

1. The Abbreviated New Drug Application (ANDA),
2. Over-the-Counter (OTC) Monograph
3. The New Drug Application (NDA).

### Generic Drug Product Registration Requirements in US

1. The eCTD is mandatory for the submission of the drug applications (NDA/ANDA).
2. US FDA guidance (CFR) documents and FDA sections (e.g. 505 (b) for NDA and 505(j) for ANDA) are followed for the preparation of the dossier for the drug approval applications.
3. The applications are different e.g.
  - For new drug- NDA
  - For generic drug – ANDA
  - For biological application – BLA
4. The application is directly submit to the FDA by the applicant or through any approved contact agent for whom a certification is provided to the agency according to the GDEA 1992.
5. Administrative information is different i.e. cover letter, forms (356h), application information, field copy certification, debarment certification, financial certification, Patent information and exclusivity.
6. The paper size for the submission is Letter size (8.5x11 inches) with font size 12 in times new roman format. The tables and figures have small font size i.e. 8 to 10.
7. Package inserts are provided for drug product in labeling.
8. Proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided.
9. The information about the clinical investigators is provided in the Module 5 and in financial disclosure Statement section of this module.

10. Request for waiver of *in-vivo* BE studies is provided in the module 1.
11. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.
12. The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA of US is provided.
13. Risk management Plans section is for the post marketing surveillance and controlling the adverse effects of the drugs by proper management. This is the part of Clinical Trial Phase IV.
14. The executed batch records for manufacturing and packaging are provided in Module 3.2.R for only single batch.
15. The declaration is given for the residual solvents limits used or present in the drug substance and excipients according to the USP.
16. Information on components including the name and address of the supplier or manufacturer of the raw material, package material etc. provided in the 3.2.R.
17. Letter of Access is not mentioned in 3.2.R.
18. Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) certificates are not attached in this section whereas submit in DMF.
19. Certificate of suitability (CEP certificate) is not applicable.
20. Comparability protocols are not attached for both the drug substance and drug products.
21. The stability data for accelerated studies are submitted for three months at the time of original submission.
22. Node extension is not allowed in the eCTD XML in software.
23. Structured product labeling (SPL) and study tagging file (STF) is mandatory by the USFDA in eCTD of a drug registration application. Paper CTD format is not accepted by FDA at all.

For the registration of generic drugs in USA we should follow the ANDA regulatory review process.

### ANDA Regulatory Review Process<sup>4</sup>

The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff process the ANDA assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist. Within the first 60 days following the submission of an ANDA, a filing review is completed (Figure 1).

### Regulatory requirements for registration of generic drugs in Singapore<sup>5</sup>

Health Sciences Authority (HSA) is the regulatory authority for regulating pharmaceutical products in Singapore. For new product licenses, Singapore has a new drug application (NDA) and a generic drug application (GDA) for products already approved by certain regulatory agencies (such as

Australia's TGA, the US FDA, etc.), submitting an abridged dossier is possible. Applicants submit an online application through PRISM (Pharmaceutical Regulatory and Information System) and also submit a CTD dossier.

#### Application types

In applying for a new Product License for a medicinal product in Singapore, there are two categories of applications: a new drug application (NDA) and a generic drug application (GDA):

**GDA-1:** For the first strength of a generic chemical product.

**GDA-2:** For subsequent strength(s) of the generic chemical product that has been registered or has been submitted as a GDA-1. The product name and pharmaceutical dosage form shall be the same as that for the GDA-1.

### TECHNICAL DOCUMENTS REQUIRED

#### Administrative documents

- Comprehensive Table of Contents
- Introduction
- Application
- Labeling, Package Insert and Patient Information Leaflet
- Approved Summary Product Characteristics (SPC) / Patient Information Leaflet (PIL)
- Assessment Report from Reference Agencies
- Description of Batch Numbering System
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration
- Declaration on rejection, withdrawal and deferral
- Declaration for GDA verification
- Registration status in other countries

#### ACTD & ICH CTD overview and summaries

The overview and summary documents are to be inserted into Module 2 of the ICH CTD or into the relevant sections in Part II, III and IV of the ACTD.

A completed Singapore Quality Overall Summary (SQOS) must also be inserted into Module 2, section 2.3 of the ICH CTD or Part II, section B of the ACTD, irrespective of whether an ICH or ACTD QOS has been included in the application dossier. SQOS must be named and dated by the applicant prior to submission. The electronic copy of the Singapore QOS should be in Microsoft Word format (Table 1).

#### Quality documents

##### Body of Data

##### Drug Substance

- Drug Master File (DMF)
- Certificates of Suitability (CEP)
- Control of Drug Substance (3.2.S.4)
- Stability Data of Drug Substance (3.2.S.7)

##### Body of Data

- Drug Product
- Pharmaceutical Development (3.2.P.2)
- Process Validation (3.2.P.3.5)
- Control of Excipients (3.2.P.4)
- Control of Drug Product (3.2.P.5)
- Container Closure System (3.2.P.7)

- Stability Data of Drug Product (3.2.P.8)
- Product Interchangeability (3.2.P.9)
- Blank Production Batch Records

#### Registration dossier

The complete dossier should be submitted within 2 working days after the PRISM application submission to prevent delays in processing of the application. The date of submission will be defined as the date when HSA receives the complete data set for the application.

#### Documents required for generic drug registration in Thailand<sup>6</sup>

The procedure of generic drugs registration is divided into 2 main steps:

##### *Step1: Application for the permission to import or manufacture drugs ample intended to be registered.*

- a. Application form to be completely filled by authorized licensee
- b. Drug formula [active ingredient(s) only]
- c. Drug literature
- d. Drug labelling and packaging

##### *Step2: Application for the approval of granted credential certificate.*

- a. Application form to be completely filled by authorized licensee
- b. Permit to manufacture or import drug sample
- c. Drug sample
- d. Pharmacological and toxicological study (if any)
- e. Clinical trials, safety and efficacy study (if any)
- f. Complete drug formula
- g. Drug literature
- h. Labeling and packaging should consist of name of the drug, registration number, quantity of drug per packaging, formula which shows active ingredient (s) and quantity of strength, lot no. batch control number, name of manufacturer and address, manufacturing date, the words "dangerous drug"/"specially controlled"/ "for external use"/ "for topical use" written in Thai and in red color if the drug is considered to be one of them, the word "household remedy drug" written in Thai, if the drug is considered to be, the word "for veterinary use" written in Thai if the drug is considered to be, and the expiry date
- i. Certificate of Free sale (in case of imported drug)
- j. Manufacturing method
- k. In-process control with the relevant acceptable limits
- l. Raw material specifications of active(s) and inert ingredients with the corresponding control methods in details
- m. Finished product specification with the corresponding control methods in details
- n. Certificate of analysis of active ingredient (s) (raw material) [To be required in case of that active substance dose not conform to official pharmacopoeias (USP, NF, BP,.....etc)
- o. Drug analytical control method
- p. Packaging
- q. Storage condition
- r. Stability studies of finished product
- s. Certificate of GMP (in case of imported drug)

**a) FEES FOR APPROVAL**

b) Registration fees = 12, 0000 Thai bhat (approx 4000 US\$)

**Regulatory Bodies in Malaysia<sup>7</sup>**

1. Ministry of Health Malaysia
2. Drug Control Authority (DCA)
3. DCA is the licensing authority.
4. National Pharmaceutical Control Bureau (NPCB)

**National Pharmaceutical Control Bureau (NPCB)** of Malaysia is delegated the daily operations of drug registration and cosmetic notification, together with the attendant monitoring and surveillance activities. **DCA** is responsible for Registration of Pharmaceutical and Cosmetic products, Licensing of - premises for import, manufacturer, wholesale, monitoring the quality of product being market and adverse drug reaction in Malaysia (Figure

**Requirements for generic registration<sup>8</sup>**

**Part I – Administrative data**

**Part II – Data to support product quality**

**Online Registration Procedure for Products**

1. Log into NPCB website (www.bpfk.gov.my) register as Quest member (as First-time User)
2. After making payment to Digicert, within 7 working days (East Malaysia might take more time), Digicert will send the Digital certificate via POSLAJU. The login name and password will be emailed to the email address specified during the registration of Quest member.
3. With the login name and password, enter Quest, go under registration, and register the product on-line. All forms are available in the form tray.
4. Submit data requested
5. Correspondences with NPCB officer if additional data is needed
6. Products tabled to DCA meeting.

**Figure 1: ANDA Regulatory Review Process**

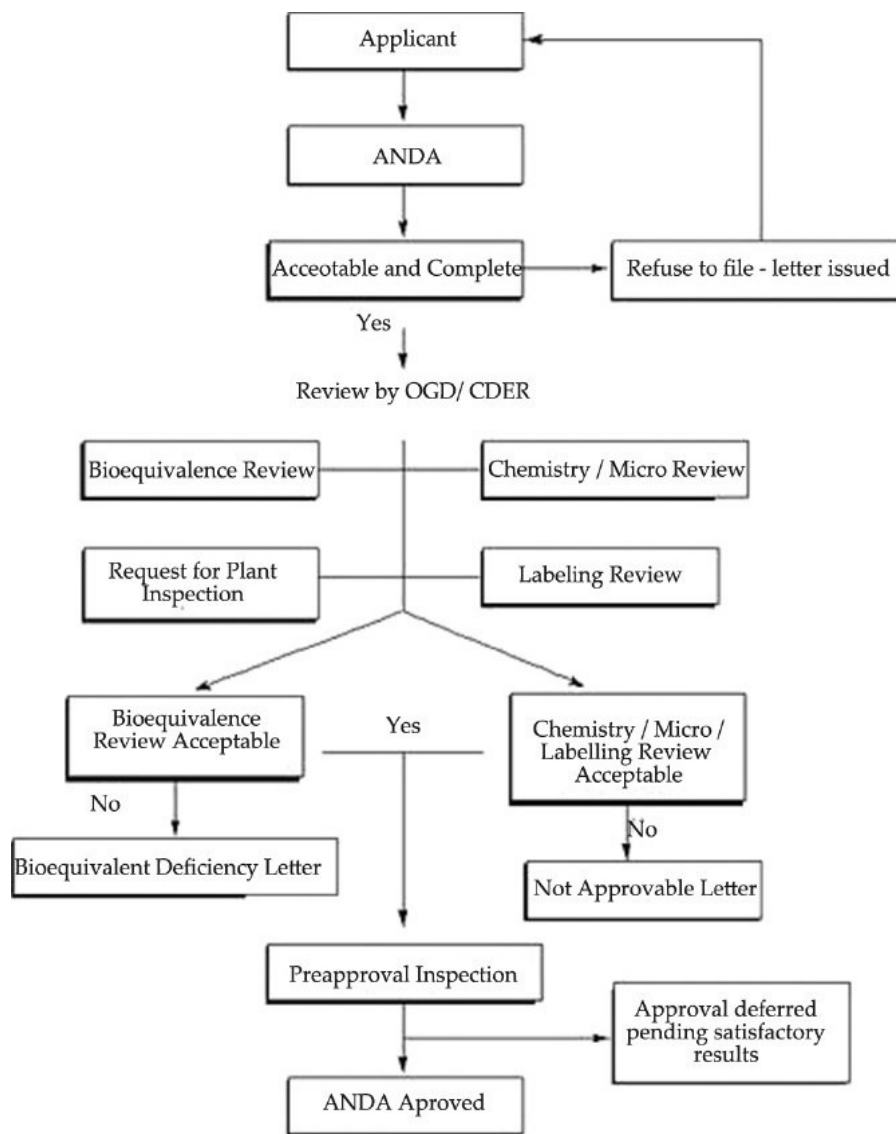
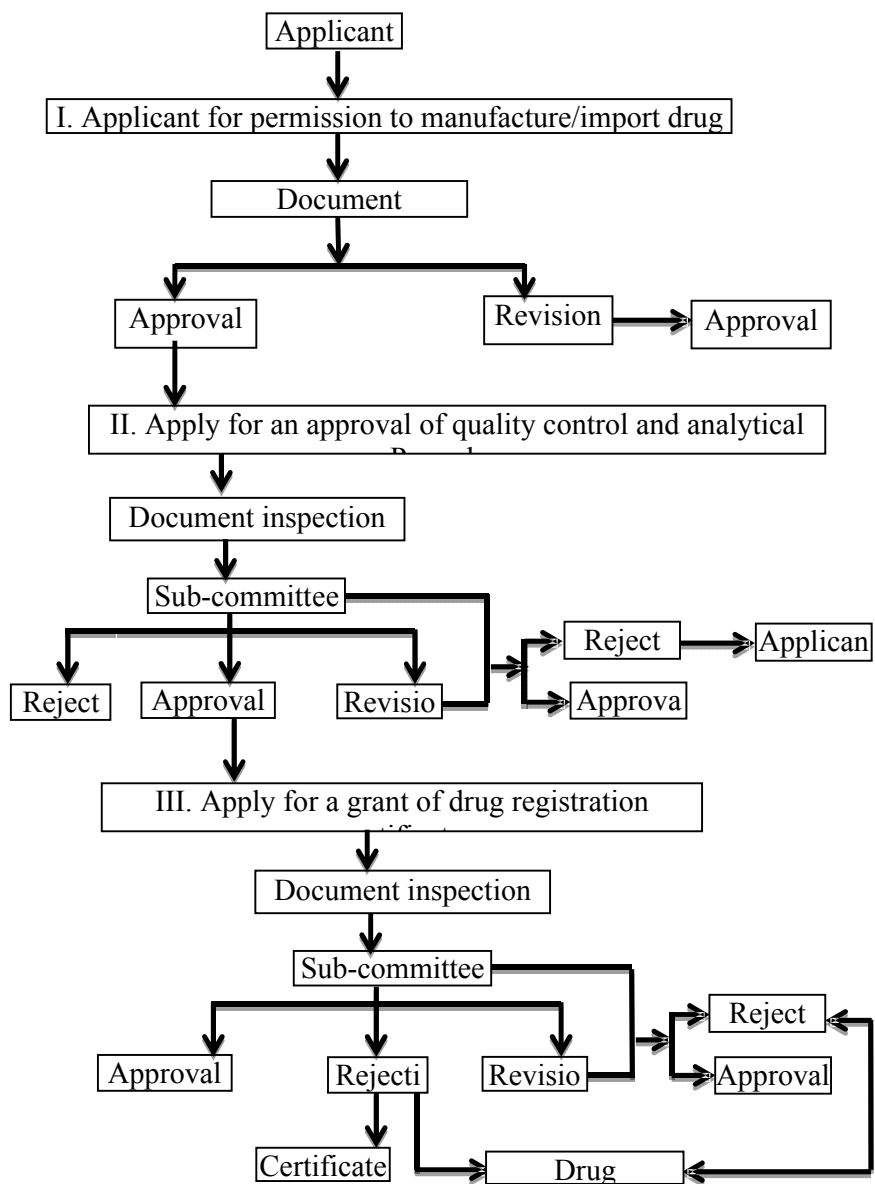
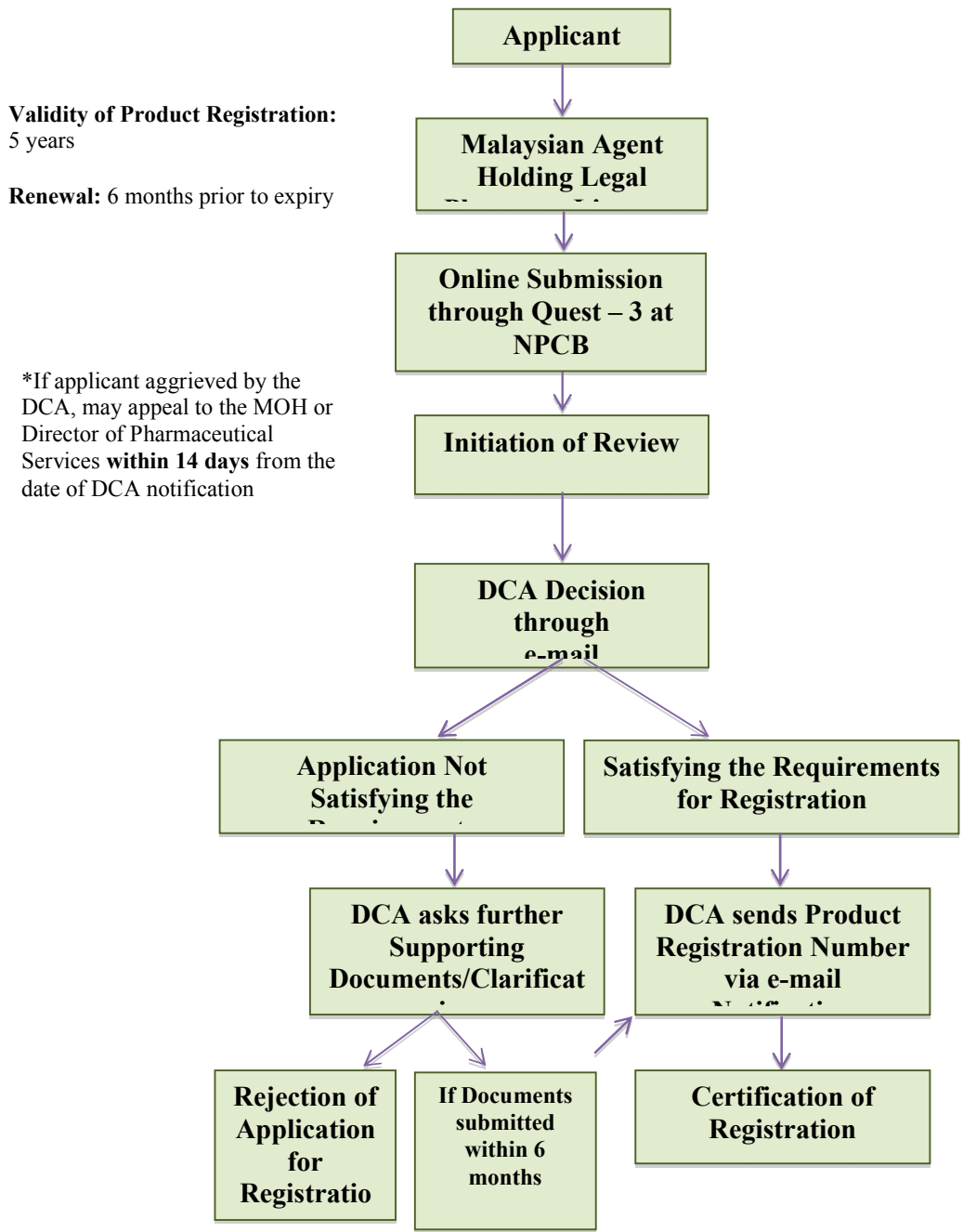


Figure 2: Registration of Generic Drugs in Thailand<sup>6</sup>



**Figure 3:** Flow chart for Malaysia-MAA



**Table 1:** Documents Required according to HAS<sup>9</sup>

Primary Reference agency	Documentary requirements
Health Canada and MHRA	<ul style="list-style-type: none"> <li>• Complete Clinical and quality assessment reports, including assessment on the Question &amp; Answer documents between the Sponsor &amp; Agency and all annexes</li> <li>• Assessment reports and/or documents pertaining to post approval variations, if applicable.</li> </ul>
US FDA	<ul style="list-style-type: none"> <li>• Complete Clinical and quality assessment reports, including assessment on the Question &amp; Answer documents between the Sponsor &amp; Agency and all annexes</li> <li>• Assessment reports and/or documents pertaining to post approval variations, if applicable.</li> </ul>
EMA	<ul style="list-style-type: none"> <li>• Complete CHMP Assessment Report, including the following: <ul style="list-style-type: none"> <li>– Rapporteur’s and co-Rapporteur’s Day 80 Assessment Reports (non-clinical, clinical, quality, overview and list of question)</li> <li>– CHMP Day 120 list of Questions</li> <li>– Rapporteur’s Day 150 Assessment Report ( non-clinical, clinical, quality and overview)</li> <li>– Day 180 list of outstanding issues</li> <li>– All other annexes and appendices</li> </ul> </li> <li>• Summary of CHMP opinion</li> <li>• Assessment reports and/or documents pertaining to post approval variations if applicable</li> </ul>
TGA	<ul style="list-style-type: none"> <li>• Complete clinical Assessment Reports, including assessment on the question &amp; Agency and all annexes</li> <li>• Complete chemistry and Quality control Assessment Report including assessment on the Question &amp; answer documents between the sponsor &amp; Agency and all annexes.</li> <li>• Assessment reports and/or documents pertaining to post-approval variations, if applicable.</li> </ul>

**Table 2:** Timeline for drug registration in Singapore<sup>10</sup>

Dossier type	Target processing time (working days)		
	New Drug Application (NDA)	Generic Drug Application (GDA)	Major Variation Application (MAV-1)
Full	270	-	270
Abridged	180	240	180
Verification	60	-	60

**Table 3:** Product Registration Fees in Malaysia<sup>11</sup>

S. No.	Product Classification	Processing Fees (RM)	Analysis Fees (RM)	Total Fees (RM)
1	New Chemical Entity	1,000.00	Two or more active ingredients : 4,000.00	4,000.00
			Single active ingredient : 3,000.00	5,000.00
2	Pharmaceutical	1,000.00	Single active ingredient : 1,200.00	2,200.00
			Two or more active ingredients: 2,000.00	3,000.00
3	Traditional	500.00	700.00	1,200.00

## SUMMARY & CONCLUSION

During the last half century, the health systems in the USA have developed rapidly and along with this the medicinal product markets. A huge number of laws have been issued, amended or replaced by the national authorities while the pharmaceutical industry expanded into international markets, facing challenges due to different and increasing legal requirements in the different countries. Harmonization of legal requirements with regard to quality, safety and efficacy of medicinal products in US started slowly in the mid of the 60s and rapidly since the 90s. Mean while the requirements on the documentation for Marketing Authorization Applications

for medicinal products are basically harmonized and allow the submission of one dossier in US.

In parallel to the activities within US, the International Conference of Harmonization (ICH) worked at harmonizing the requirements for the USA, Europe and Japan since 1990. A great lot has been reached so far, but there is still room for further harmonization and still some challenges for globally acting pharmaceutical industries. In parallel to the increasing amount of legal requirements and increasing costs for medicinal product developments, the generic industry emerged, offering low-price products. Along with the development of the generic industry, the originators increasingly protected their products with patents and data exclusivity to build hurdles for generics.

This paper deals with the development of generic dossiers suitable for the registration in the US and the ASEAN as well as with the transfer of available generic dossiers from one to the other region. The ASEAN pharmaceutical market is relatively small but the region remains attractive due to the predicted double digit growth potential in future. Moreover the worldwide pharmaceutical market is shifting from mature to pharmerging market. The pharmaceutical industries in each of the 10 ASEAN member countries-Brunei, Myanmar, Cambodia, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand and Vietnam –are at very different stages of development. The economic situation & health expenditure vary from one country to another country. Most of population in these low income countries like Vietnam, Philippines, Indonesia & Thailand depend on generic drugs. But countries like Singapore and Malaysia believe on innovation.

It is noticeable that harmonization of standards and regulations as well as MRA's are a major contribution to the integration of the ASEAN market. Even if tariffs are done away with and even with the most efficient transportation, true market integration will be out of ASEAN's reach if the flow of products is hampered and slowed down by inconsistent regulations and varying standards. ASEAN standards Bodies and Regulatory Authorities have been working closely with private sectors to address these technical barriers. None of the above achievements can happen without regional cooperation and strong collaboration of stakeholders. Moreover, regional cooperation on standards and conformance compels. Standards officers, regulators as well as industry to meet frequently and network effectively. Singapore and Malaysia are the only countries in ASEAN, who have well established pharmaceutical regulations and more strict to quality & safety of drugs. These countries believe on innovation and give full protection to them. Hence there may not be many opportunities for small and medium scale generic companies in these countries unless their manufacturing procedures are well to do with regulatory requirements.

## REFERENCES

1. The United States is the world's largest market for pharmaceuticals and the world leader in biopharmaceutical research. [Internet]. [Cited July 10 2013] Available from: <http://selectusa.commerce.gov/industry-snapshots/pharmaceutical-industry-united-states>

2. The ASEAN (Association of Southeast Asian Nations) group of nations, namely Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia. [Internet]. [Cited July 15 2013] Available from: <http://www.aseansec.org>
3. U.S. Food and Drug Administration. FDA Organization [Internet]. [Cited July 21 2013] Available from: <http://www.fda.gov/AboutFDA/CentersOffices/default.htm>
4. Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate- Release Solid Oral Dosage Forms Based on a Bio-pharmaceutics Classification System. [Internet]. [Cited Sept 05 2013]
5. All pharmaceuticals/drugs require a product license to import or sell in Singapore. [Internet] [Cited Sept 21 2013] Available from: <http://www.cde.org.tw/Data/CDEDoc/Documents/Regulatory%20Environment%20and%20Clinical%20Trials%20in%20South%20East%20Asia.pdf>
6. National Pharmaceutical Control Bureau, Malaysia. [Internet]. [Cited Oct 01 2013] Available from: [http://portal.bpfk.gov.my/view\\_file.cfm?fileid=126](http://portal.bpfk.gov.my/view_file.cfm?fileid=126)
7. Malaysia. ASEAN Labeling Requirements: Issues on Country Specific Requirements. [Internet]. [Cited Oct 03 2013] Available from: <http://portal.bpfk.gov.my/index.cfm?LineNbr=2&StartRow=11&menuid=124&parentid=82>
8. Malaysia. FAQ: Product Registration. [Internet]. [Cited Oct 14 2013] Available from: <http://portal.bpfk.gov.my/index.cfm?&menuid=96>
9. Guidance for the industry submitting department certifications [Internet]. [Cited Aug 27 2013] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080584.pdf>
10. Food and Drug Administration, Thailand. [Internet]. [Cited Sept 22 2013] Available from: <http://www.fda.moph.go.th/eng/drug/intro.stm>
11. Malaysia. Implementation of Bioequivalence Study for Generic Medicines in Malaysia [Internet]. [Cited Nov 19 2013] Available from: [http://portal.bpfk.gov.my/view\\_file.cfm?fileid=883](http://portal.bpfk.gov.my/view_file.cfm?fileid=883)

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