Comparison of Regulatory Requirements for Registration of Pharmaceutical Drugs in ASEAN and GCC Regions

Mohit1,2, Aakash Deep1,*, Gaurav Khurana2, Jagdeep Kumar2 and Akshay Monga2

1Department of Pharmaceutical Sciences, Chaudhary Bansi Lal University, Bhiwani 127021, India; 2Rydburg Pharmaceuticals Ltd., New Delhi-110009, India

Abstract: Background: The product registration in rest of the world is a challenging task because they are not harmonized. ASEAN and GCC regions come under semi-regulated market. These regions have somewhat harmonized their regulatory organization. The significance of an emerging market is increasing globally. It is important for pharmaceutical companies to be up-to-date with the latest regulatory development. ASEAN used ACTD format and GCC used ICH CTD format for drug product Registration. ASEAN includes a group of countries like Singapore, Philippines etc. Whereas GCC includes Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and UAE.

Conclusion: This review article focuses on general regulatory requirements of registration of pharmaceuticals in ASEAN and GCC region.

Keywords: Regulation, ASEAN, GCC, pharmaceutical companies, drugs, guidelines.

1. INTRODUCTION

The perspective of ASEAN is to emphasize the development of region. In July 2009, an agreement was made for the ease of pharmaceutical regulations, (ACTD) is the common dossier for ASEAN countries [1]. ASEAN countries have various regulatory requirements for their drug to be registered. The acceptance of (ICH) and (EMA) guidelines are on the higher rate and beyond that, a country-specific requirements are also there for the victorious MA approval by Health Sciences Authority (HSA).

2. CURRENT MEMBERS OF ASEAN

Association of Southeast Asian Nations Pharmaceutical Product Working Group now currently has 10 members as listed below:

- Brunei Darussalam
- Cambodia
- Indonesia
- Laos
- Malaysia
- Myanmar
- Philippines
- Singapore
- Thailand
- Vietnam

ASEAN Pharmaceutical Products Working Group (PPWG) actions include conference and consultation of technical drug registration guidelines, regulatory system and requirements, and harmonized procedures applicable to the ASEAN pharmaceutical industries. The primary job is to develop management schemes of pharmaceutical regulations and the removal of technical barriers to trades [2, 3]. The quality, protection and value of drug are under the control of regulatory authorities [4]. Here, some information regarding regulatory agencies, their approval times and fees are being discussed.
Regulatory Authority: Drug regulatory authority is the regulatory agency that is responsible for drug approval. As the Health Sciences Authority (HSA) is the Ministry of Health (MOH) in Singapore which controls health and therapeutic products regulations and other e-services [5]. National Pharmaceutical Regulatory Agency (NPRA) is drug control authority of Malaysia and established under the control of drugs and cosmetic regulation 1984 [6]. In Thailand, Thailand FDA (TFDA) is the ministry of public health which oversees the drug product quality, safety and effectiveness for the purpose of protecting public health [7].

Philippines have its regulatory agency named as Food and Drug Administration (FDA) Philippines [8]. Health authority of Indonesia is the National Agency of Drug and Food Control (NADFC) [9]. These health authorities are responsible for the approval of new drugs in ASEAN region. To any modification in the drug, a company should have a change management system to be a good manufacturing practice [10] ACTD format is given below in Fig. (1).

![Diagram of ACTD](image)

**Country Specific data Not a part of ACTD**

**PART I**
Administrative Data & Product Information

**PART II**
(Quality) Overall Summaries And reports

**PART III**
(Non Clinical) Overview Summary And Study reports

**PART IV**
(Clinical) Overview Summary And Study reports

---

3. MARKETING AUTHORIZATION APPLICATION (MAA) APPROVAL TIMELINES

Marketing authorization application provides complete information about a pharmaceutical drug and also regulatory agencies to evaluate their quality, safety and efficacy benefits and risks. The drug regulatory authority of each respective country is responsible for the scientific evaluation of marketing authorization applications for each and every pharmaceutical drug. Once granted by the competent authority, the marketing authorization of a particular drug is valid all over the nation.

Firstly, if we talk about Singapore, there are two types of drug product licensing applications in Singapore: A New Drug Application (NDA) and a Generic Drug Application (GDA). The latter is required for a drug, which is identical to the currently registered drug in the same country. According to MAA approval timelines, the time required for NDA filing is 270 working days and for GDA is 240 working days and time required for verification is 120 working days. Secondly, in Malaysia for the filing of NDA, the time required is 245 working days and for GDA is 210 working days. Thirdly, for Thailand, time required for NDA filing is 210-280 working days and for the Philippines is 6-9 months as compared to Indonesia in which 300 working days are required.

4. FEES

There are 3 types of NDA in Singapore as NDA 1, NDA 2 and NDA 3. The fees for NDA 1 and NDA 2 are approximately 8,800 USD and for NDA 3 is approx. 4,400 USD. 13,200 USD are
also needed for the NDA 1 and NDA 2 verification purpose. For Malaysia, this amount is low as for NDA filing is 1,220 USD as compared to GDA is 670 USD. The fees for Thailand are only 250 USD. In the Philippines and Indonesia, the fees are 465 USD and 2,000 USD [1].

Significant government agencies should admire suitable strategies or actions to build up drug product quality assurance and control system in a specific country [11].

5. MODULES

There is a difference in format for documents between ICH CTD and ACTD. As there are 5 modules in ICH CTD named as Module-I to Module-V and the documents in ACTD are named as part-I to part-IV because it does not involve common technical document overview and summaries like in CTD. The rest of the documents are administrative document and product information, quality document, nonclinical documents and clinical documents.

There are some additional documents required at the time of the approval of drug in various countries as samples of drug are not required in Singapore, Malaysia and Indonesia and required in Thailand and Philippines. Another document is the Certificate of Pharmaceutical Product (COPP) and manufacturing license which is required in all countries under the ASEAN region. GMP (Good Manufacturing Practices) is another document, which is PICs in Singapore, Malaysia and Indonesia but not in Thailand and Philippines [1].

In Myanmar, the care of basic healthcare and services like nutrition, environmental issues, motherly and child health care and many more is controlled by the Department of Public Health [12].

In Singapore, product license is required before the sale of a medical product. Each product license has a particular name, a formulation with a set of approved indications. For the approval of new drug in Singapore, there are two types of application, (NDA) and for Generic Drugs, is (GDA). The submission of an application includes 2 parts, PRISM (Pharmaceutical regulatory and information system) followed by ACTD format for dossier submission. ACTD is the common dossier format for ASEAN region. The regulation in this country is highly advanced and technical.

In Thailand, the registration of new drug is controlled by Thai FDA. Drug board does month wise meeting for the approval, withdraw or cancellation of license. The person who wants to sell, buy the drugs within the country has to obtain the license from FDA. The types of applications are same as Singapore as (NDA) and (GDA). There is unique activity in this country as there is 2 year period of safety monitoring program as per the amended registration procedure for new drugs adopted in August 1989.

In Indonesia, new drugs are typically divided into New Chemical Entity (NCE). Drug Registration requires pre-registration and submission of drug dossier, which is secured by the head of agency. Submission of the document includes registration forms as Form A, Form B1, Form B2, Form B3, Form B4, Form C1, Form C2, Form D, etc. All these forms have their significant roles as they contain information regarding personal details of the applicant; cover the area of efficacy, safety and quality of drug.

In Malaysia, the registration of new drug requires an application of new product followed by application of a generic product. The data, which support this, includes (Part-I to Part-IV) based on their unique works. In this country, many other activities are required for the registration as a letter of authorization, place of production, letter of acceptance and at last, the main document which is required for registration is Certificate of Pharmaceutical Product (COPP) from the authority signed by WHO.

In Philippines, as it is included in ASEAN country, it required registration dossier in accordance with ACTD format. Some of the information is required which include:- proposed text of labeling of pharmaceutical product, pharmacological class of drug, marketing information that in which country, the drug will sell, information regarding chemistry and manufacturing status, status of human body, benefits and risk of drug and various verification [13].
Gulf Co-operation Council Countries are also called Middle East Countries i.e. Bahrain, Qatar, Saudi Arabia, UAE and Kuwait [14]. The import of superior drug products is under the control of Gulf Countries [15]. The occurrence of a good regulatory system admires the excellent variety of medicines. The conservation of quality of medicines is regulated by the daily basis monitoring of all private markets factors [16].

The development of (GCC-DR) Gulf Central Committee for Drug Registration occurred in May 1999 including middle eastern states which comprises of Saudi Arabia, Oman, UAE, Bahrain, Kuwait and Qatar [17]. The registration of pharmaceuticals in GCC region requires CTD format [18].

Saudi Arabia empire is the highest financial strong in whole Middle East region which is continuously growing [19].

The aim of the (SFDA) is to make sure the protection, value and efficacy of the drug with medical devices according to their planned purposes [20]. The department of the National Health Regulatory Authority (NHRA) which regulates the pharmaceuticals products looks before the safety and effectiveness of drug products and health services in Bahrain [21].

The services of medical and health care in Kuwait are the responsibility of health district in the country [22].

CTD structure for human drug Submission includes I-V Modules:

5.1. Module-I

Module-I includes Regional administration information which consists of cover letter, table of content, application form, product information along with clinical and non-clinical information, pharmacovigilance work, certificate and documents of the drug which includes GMP certificate along with certificate of analysis of drug substance with suitability, it also consists of the patent information, after that, information of pricing of drug with lists of the price and in last, it has other related documents. All these information are combined to form the MODULE-I (Regional and Administration Information).

5.2. Module-II

Module-II is for the Common Technical Document summaries, which include the summaries of the documents required during the approval of the drug. This Module has the general information related to drug substance, its manufacturing, control and the information regarding the reference standards of the drug. The technical document also includes stability of the drug, the product form which the drug has prepared with its description and complete composition along with reference standards of drug. Module 2 also includes information including novel percipients, regional information with clinical and nonclinical overview. This Module is very important for CTD structure as it contains data of biopharmaceutics of drug, clinical pharmacology, efficacy and safety. Summary of pharmacodynamics and pharmacokinetics of drug in body is also necessary. Methods of analysis of drug include the absorption, distribution, and metabolism of the drug in the body along with the excretion. This module also confers the toxicity of the drug as single-dose toxicity and repeated-dose toxicity. Tolerance of the drug is also an important factor. At last, this module refers to the summary of biopharmaceutics and associated analytical methods, summary of results along with clinical efficacy. It also includes a summary of clinical safety, factors affecting the drug which may be intrinsic or extrinsic or drug can be used in pregnancy and lactation, an overdose of drug and in last, post-marketing data.

5.3. Module-III

Module-III includes the quality of the drug. This Module deals with the quality of the drug along with its whole data. It consists of the information of the substance from which the drug has been prepared, the name of the same substance, its structure and its properties, its manufacturing details along with the description of the processes and control. This module also deals with the characterization of the drug. Specifications of the drug are also included in this. As this module deals with the quality of the drug so it also maintains the record of data of stability and reference standards of material. Quality also measures the drug product along with the description and composition of the same product. Pharmaceutical development along with formulation development is also added. Qual-
ity also checks the compatibility of the drug in the body. After that, it also has the data of manufacturing and batch formula along with a description of manufacturing and validation with evaluation. At last, this module includes analytical procedures by which the drug has been prepared with justification and specifications. By checking the quality, the impurities with their characteristics are also been studied by checking the ideal stability in last.

5.4. Module-IV

Module-IV deals with the non-clinical study reports. It includes pharmacological data along with primary and secondary pharmacodynamics and pharmacokinetics drug interaction. It provides the details of the drug as its absorption, distribution in the body, metabolism and excretion from the body. Non-clinical data also includes the toxicology of the drug as when it is taken singly or repeatedly. Genotoxicity is also a major factor to study. It conquers the in vitro and in vivo data along with carcinogenetic effects. This module consists of reports with long and short-term studies. As drugs can be toxic during the reproductive phase of life so checking of toxicity during this period is also a task along with fertility and early embryonic development. Effects of drug can be seen in pre and post-natal development followed by the juvenile and third generation studies and local tolerance of the drug. At last includes the studies of antigenicity and immunogenicity and very important mechanistic studies along with dependence.

5.5. Module-V

Module-V indicates or expresses the details of all clinical studies in accordance with its reports which include the reports of biopharmaceutics studies along with bioavailability of study reports. It also includes the in-vivo and in-vitro correlation of the clinical trials with the reports of bioanalytical methods. This module also involves the reports of hepatic metabolism and other biomaterial reports of human pharmacokinetics are also important to report in this Module which consists of patient PK and tolerability with intrinsic and extrinsic factors PK along with population PK and human pharmacodynamics. Patient PD and PK are reports and finally, report of post-marketing experience is involved [23].

6. MAJOR DIFFERENCES IN DATA REQUIREMENTS FOR REGISTRATIONS OF DRUG PRODUCT IN ASEAN AND GCC REGION

6.1. Site Registration

It is necessary for both ASEAN and GCC region.

6.2. Plant GMP Approval

ASEAN region accepts FDA/EU/PICs approval for Finished Product site but in GCC region, the approval of finished product site requires audit only by GCC member.

6.3. Stability Zone

ASEAN countries come under stability zone IVa and IVb while GCC countries come only under zone IVa.

6.4. Stability Requirement

In ASEAN region, the stability temperature and relative humidity requirement are 30±2°C/65±5% RH and 30±2°C/75±5% RH. While in GCC, the stability conditions are 30±2°C / 65±5% RH.

6.5. No. of Submission of Batches

In both the regions, data of 3 pilot scale batches are required for submission and registration of drug product.

6.6. Stability Data

Minimum 12 months stability data required for drug product in both regions along with ASEAN stability guidelines are mandatory for ASEAN countries and GCC stability guidelines for GCC countries.

6.7. Dossier Format

ACTD dossier format (Part-I to Part-IV) is followed in ASEAN region while CTD (Module-I to Module-V) format is followed in Gulf countries.

6.8. Registration Time

The average registration timeline for drug product is 12-24 months in ASEAN countries and 24-36 months in GCC region [18].
7. GENERAL REQUIREMENTS FOR LABELING MATERIALS IN ASEAN COUNTRIES

The fundamental requirements for drug product labeling include; name of the product (only generic name or with brand name), dosage form and strength, pharmacologic category of drug, Rx symbol (in case of prescription drugs), name of manufacturer, complete address of manufacturer, name of importer/trader, presentation, formulation, indications and contraindications, precautions and warnings, batch number, manufacturing date, expiry date, registration number along with storage conditions etc. are given in Table 1.

8. DOCUMENTS REQUIRED FOR DRUG PRODUCTS REGISTRATION IN GULF COOPERATION COUNCIL COUNTRIES

The necessary documents required for the registration of drug product in UAE, Saudi Arabia, Bahrain, Kuwait and Oman are:

8.1. Free Sale Certificate

Legalized FSC issued by health authority is required in all the GCC member states.

8.2. Price Certificate

This document is required in legalized form in all the GCC member states except Oman.

8.3. Stability Studies

For various different applied conditions, this document is required in all the above-mentioned countries.

8.4. Drug Product Specification and Method of Analysis

The finished product specifications and analytical procedure adopted for analysis of drug product are mandatory in all the GCC countries.
Table 2. Difference between ICH CTD and ACTD format.

<table>
<thead>
<tr>
<th>Documents</th>
<th>ICH CTD</th>
<th>ACTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative Documents and Product Information</td>
<td>Module 1</td>
<td>Part I</td>
</tr>
<tr>
<td>Overview and Summaries</td>
<td>Module 2</td>
<td>Incorporated in Part II, III and IV</td>
</tr>
<tr>
<td>Quality Documents</td>
<td>Module 3</td>
<td>Part IIAB &amp; Part IIC</td>
</tr>
<tr>
<td>Non-clinical Documents</td>
<td>Module 4</td>
<td>Part III</td>
</tr>
<tr>
<td>Clinical Documents</td>
<td>Module 5</td>
<td>Part IV</td>
</tr>
</tbody>
</table>

8.5. Labeling

In every GCC members state, this document is required for all labeling materials with proper manner.

8.6. Copy of Reference Pharmacopoeia

Other countries should require the same document except for Bahrain and Oman at the time of registration.

8.7. Leaflet

Leaflet in both Arabic and English language is requisite in every GCC country along with other registration documents.

8.8. BA/BE Study

This is also an essential document for the registration of drug product [25].

9. DIFFERENCE BETWEEN REQUIREMENTS OF DOSSIER PREPARATION IN ICH CTD AND ASEAN ACTD

In ACTD format, documents such as administrative information of pharmaceutical drugs, overall summaries, quality testing of drug product as well as clinical and non-clinical documents comprises into different parts such as Part I-IV while in ICH CTD these same documents are defined by different Modules such as Module 1-5. The quality part of documents in ACTD is differentiated into two subparts as Part IIAB & Part IIC (Body of Data). Table 2 clearly shows the difference between ICH CTD and ACTD format.

CONCLUSION

The Association of South East Asian Countries (ASEAN) and Gulf cooperation council (GCC) regions come under the “Emerging market” for pharmaceutical export. The drug product regulations of ASEAN and Gulf countries are encouraging the import of quality generic products from other countries. ASEAN countries used standard ACTD format for the submissions of drug products for the purpose of registration of the product in reference country. The climatic zone stability requirements in both the regions are $30^\circ C \pm 2^\circ C$ and $65\% \pm 5\%$ RH [26].

LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASEAN</td>
<td>Association of Southeast Asian Nations</td>
</tr>
<tr>
<td>GCC</td>
<td>Gulf Cooperation Council</td>
</tr>
<tr>
<td>ACTD</td>
<td>ASEAN Common Technical Dossier</td>
</tr>
<tr>
<td>ICH CTD</td>
<td>International Conference on Harmonisation Common Technical Document</td>
</tr>
<tr>
<td>UAE</td>
<td>United Arab Emirates</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>HSA</td>
<td>Health Sciences Authority</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NPRA</td>
<td>National Pharmaceutical Regulatory Agency</td>
</tr>
<tr>
<td>TFDA</td>
<td>Thailand Food and Drug Administration</td>
</tr>
</tbody>
</table>
NADFC = National Agency of Drug and Food Control
MAA = Marketing Authorization Application
NDA = New Drug Application
GDA = Generic Drug Application
COPP = Certificate of Pharmaceutical Product
GCC-DR = Gulf Central Committee for Drug Registration
BA = Bioavailability
BE = Bioequivalence
PPWG = Pharmaceutical Products Working Group
PRISM = Pharmaceutical regulatory and information system
NCE = New Chemical Entity

CONSENT FOR PUBLICATION
Not applicable.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS
Declared none.

REFERENCES

