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# Regulatory requirement for the approval of Generic Drug in Cambodia as per ASEAN Common Technical Dossier (ACTD)

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## ABSTRACT

Drug approval process differs from one country to another country. In some countries only single body regulates the drug as well as responsible for all regulatory work which is a challenging task for the pharmaceutical companies to prepare single dossier that can be simultaneously submitted in many countries for approval. In all countries there is a similar characteristic in regulatory environment but there is a difference in their registration requirements. The purpose of this study is to give a comparative overview on generic drug market regulation in ASEAN Countries Cambodia and Malaysia. The aim of study is to facilitate proper knowledge regarding main critical issues, differences as well as similarities of related drug regulation. There is a different requirement for registration of generic product in each regulatory system but also comprises of some similar outline that includes some common rules. These are variances and regulatory hurdles such as Number of batches for submission in dossier, stability conditions, registration of product, analysis, bioequivalence and clinical study requirement. ASEAN countries for generic drug product approval ACTD submitted to country specific authority. For solid oral dosage forms as per ASEAN guideline there are 4 parts have to be submitted. Part I contains Administrative requirements which is not a part of common technical document. Part II is Quality contains 3 sections that are a) Table of Content b) Quality overall Summary c) Body of data. Part III contains Non clinical. Part IV contains Clinical data. For the generic drug product Part III and Part IV is not required.

**Keywords:** ASEAN Common Technical Document (ACTD), Regulatory Requirement, Cambodia, Malaysia

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## 1. Introduction

### *1.1. Introduction to ASEAN Countries*

ASEAN consultative committee on Safety and Quality (ACCSQ) developed the Association of South East Asian Nation (ASEAN) (1) on 8th August 1967 in Bangkok. The ASEAN Common Technical Document (ACTD) (2) is a guideline and the common format for the preparation of a well-structured Common Technical Dossier (CTD) application that are to be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals product for human use. There are 10 member states in ASEAN countries that include Singapore, Malaysia, Indonesia, Vietnam, Thailand, Cambodia, Myanmar, Philippines, Brunei, Laos (1). These countries follow ACTD Format for the registration of pharmaceutical products. ACTD is divided into four Part I, (Administrative data) Part II (Quality) Part III (Overview summary study report) Part III (Clinical Data). Figure 1 signifies ACTD guidelines.

### *1.2. Introduction to Cambodia*

The drug registration process started in 1994. Department of Drugs and Food (DDF) (3) is the regulatory agency under the Ministry of Health. It is responsible for the efficacy, safety, quality of drug, efficacy of food and cosmetics.

### *1.3. Introduction to Malaysia*

The regulatory body of Malaysia is National Pharmaceutical Regulatory Agency (NPRA) (4), formerly known as the National Pharmaceutical Control Bureau (BPFK), is located at Kuala Lumpur under the quality control activity of pharmacy and supply programme. This regulatory body was implemented with an aim to implement quality control on pharmaceutical products.

According to Malaysia country a generic medicine can be defined as a pharmaceutical product that is no longer protected by a patent & which can be copied by other company. It may be marketed either under its own brand or as an unbranded product.

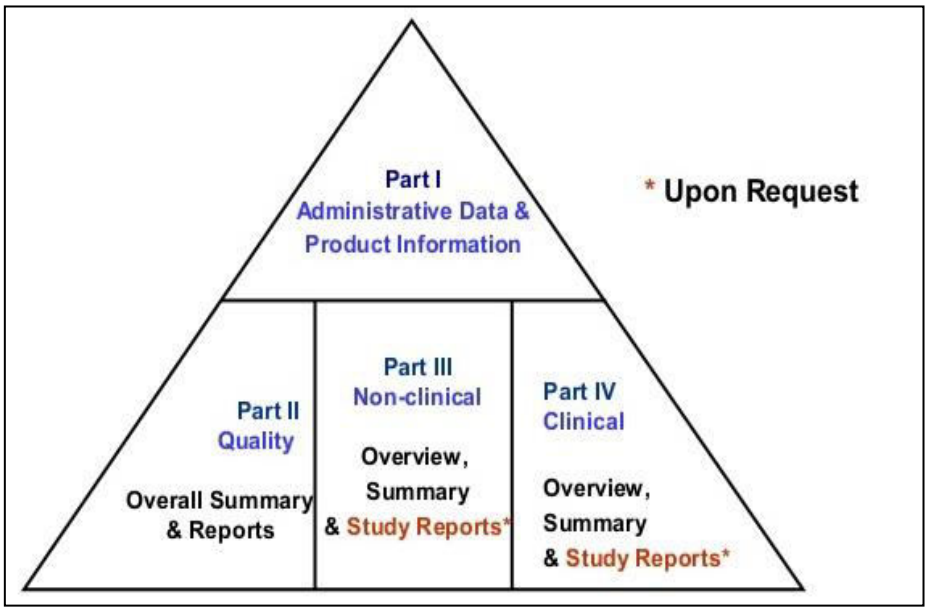


**Figure 1.** Diagrammatic explanation of ACTD

## 2. Discussion

In this section study of registration requirements for generic pharmaceutical product of selected countries was carried out and compared to understand the critical aspect of generic drug product data requirements.

Table 1 shows comparison of registration requirements for generic pharmaceutical product in Cambodia and Malaysia.

**Table 1** Comparison of registration requirements (3, 4)

| PARAMETERS | COMBODIA | MALAYSIA |
|---|---|---|
| | នាយកដ្ឋានឱសថ ចំណីអាហារ បរិក្ខារពេទ្យ និងគ្រឿងសំអាង Department of Drugs and Food | MINISTRY OF HEALTH MALAYSIA |
| **Regulatory Authority** | **Department of Drugs and Food under, Ministry of Health** | **National Pharmaceutical Control Bureau (NPCB)** |
| **Regulatory Guidelines** | Follows ACTD Format | Follows ACTD Format |
| **Administrative Information** | | |
| **Cover letter** | Not Required | Not Required |
| **Application Form** | Required | Required BPFK 438.1 for generic medicine |
| **Patient Information Leaflet** | Required compulsory for self-administered drug it should be in English & Combodian Language (Khmer) | Required compulsory for self-administered drug |
| **Summary of Product Characteristics (SmPC)** | Applicable | Applicable |
| **Label** | Required, must be in English and Combodian Language (Khmer) | Required, must be in English and Bahasa Malaysia |
| **Package insert** | Required, must be in English and Combodian Language (Khmer) | Required, must be in English and Bahasa Malaysia |
| **Fee** | No fees required | Single API- 2200.00 RM<br>Two/more API- 3000.00 RM |
| **Information about experts** | No specific requirement | No specific requirement |

| | | |
|---|---|---|
| **Certificate of Suitability with European Pharmacopeia (CEP)** | No specific requirement | No specific requirement |
| **GMP certificate** | Required as per WHO &GMP guidelines | Required as per WHO &GMP guidelines |
| **Free sale certificate** | Not required | Required if CPP is not available |
| **Certificate of pharmaceutical product** | Not required | Required as per WHO format & applicant shall fill in form BPFK 412.2 |
| **Letter of Authorization** | Required | Required as per country specific |
| **Environmental Risk assessment** | No specific Requirement | Specific information as per GMP is required |
| **Third Party Agreement** | Required with detail information about the supplier | Required with detail information about the supplier |
| **Foreign regulatory status** | Not Required | Not Required |
| **Bio waiver request** | All bioequivalence study of product is required | All bioequivalence study of product is required |
| **Technical Information** | | |
| **Drug Master File** | Required as per ACTD format | Required as per ACTD format |
| **Batch Manufacturing Record** | Complete information of Commercial batches is required | Required copy of Master BMR or Complete BMR |
| **In process quality Control** | Details of *IPQC* and specifications for quality assurance of the *product* is required | Details of *IPQC* and specifications for quality assurance of the *product* is required |
| **Process Validation** | Required for 3 consecutive batches | Required, on 3 pilot or commercial batches |
| **Raw material Specification** | Specifications and test methods for *raw materials is required* | Specifications and test methods for *raw materials is required* |
| **Raw material analytical process** | Specifications for raw material analytical process is required | Specifications for raw material analytical process is required |
| **Analytical Method Validation** | Required | Not required for pharmacopeia materials |
| **Finished Product Specifications** | *Specifications* and control tests on the *finished product* is required | *Specifications* and control tests on the *finished product* is required |
| **Finished Product Analytical Process** | Detail information of finished product analytical process is required | Detail information of finished product analytical process is required |
| **Analytical Method Validation (FP)** | Required assay and related substance as per ICHQ2A and ICHQ2B | Required assay and related substance as per ICHQ2R1 |
| **Batch Analysis** | Required for 3 pilot batches | Required, for at least two pilot batches |
| **Justification of Specifications** | Complete information about product is required | Required as supporting document |
| **Reference Standard** | Required as per ACTD guidelines | Required as per ACTD guidelines |
| **Container Closure system** | Required for Primary and secondary packing | Specification including description of primary packaging components |
| **Stability Protocol** | Required as per climatic zone and ICH Guidelines for 3 batches | Required as per climatic zone & ICH Guidelines for 3 batches |
| **Climatic Zone** | Zone IVb | Zone II & IVb |
| **Stability Number of batches** | Atleast 03 batches for accelerated and 03 batches for real time stability study | Atleast 02 batches for accelerated and 03 batches for real time stability study |
| **Stability Data** | 40°C ± 2°C/ 75% ± 5% RH<br>30°C± 2°C/70% ± 5%RH | 40°C ± 2°C/ 75% ± 5% RH<br>30°C± 2°C/75% ± 5%RH |
| **Regional Information** | No specific requirement | No specific requirement |
| **Non clinical data** | General exempted for generics | General exempted for generics, applicable for schedule poison drug |
| **Clinical data** | General exempted for generics | General exempted for generics. |

## 3. Drug Registration Process and Approval System of Cambodia (3)

### *3.1 Regulatory Agency*

Department of Drugs and Food under, Ministry of Health, Cambodia (MOH)

Department of Drugs and Food under the MOH is responsible for the quality and control of pharmaceuticals.

The Department is composed of five bureaus each with their own speciality, three of which are:

- The Narcotic Control and Pharmaceutical Trade Bureau
- The Drug Regulation Bureau
- The Registration and Cosmetics Bureau

### *3.2 Licensing Regulation in Cambodia*

A person who wish to sell, or import drug into Cambodia have to license registered with the MOH Department of Drugs and Food Administration through the Registration and Cosmetics Bureau. Import licence can be issued within one week after submission of required document and application form. Import licence is valid for six months from the date of approval.

### *3.3 Drug Registration Process*

*Applicants:* Only Pharmacist or a Pharmaceutical company is qualified to apply for product registration.

*Manufacturing Plant:* GMP Compliance Flow chart of drug review process is shown in Figure 2.

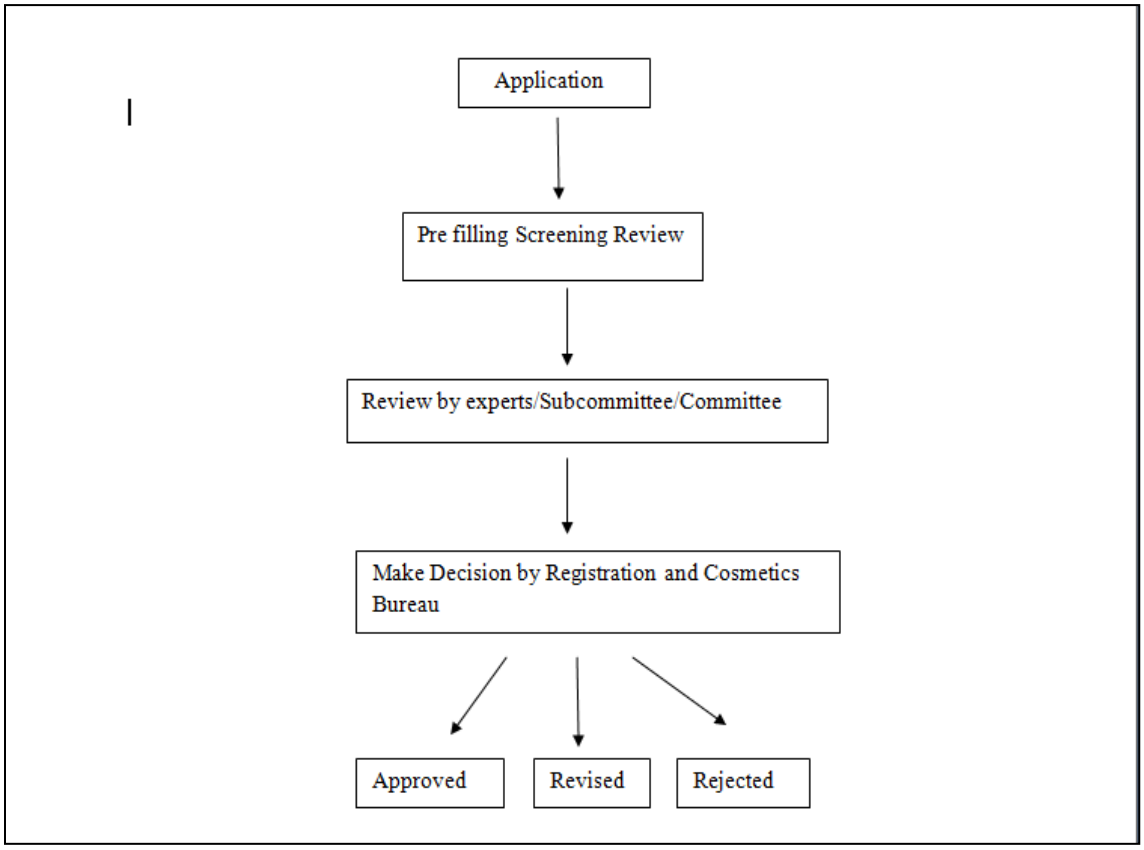


**Figure 2:** Flow chart of Drug Review Process for Cambodia (3)

### *3.4 Review Period of Generic Drug Registration*

There are no timelines regarding the review period and no information regarding notification of successful registration.

### *3.5 Review Fees of Generic Drug Registration*

No fees are charged for the Registration.

### *3.6 Labelling Requirement in Cambodia*

The law and regulation on labelling are stipulated as per the law on the Management of Quality and Safety of Products and Services.

Labelling requirements are as follows:

- Name of product
- Details of ingredients
- Composition
- User's guidelines (direction for use)
- Manufacturing Date
- Expiry Date
- Producer name and address
- Quantity
- Batch number

Package inserts also required and it's contain the product name, active ingredients, indications, instructions for use, including warnings, precautions, adverse drug reaction, and contraindication, dosage and storage information. All labelling requirements must be in Khmer or English.

## 4. Conclusion

From the study it was found that due to variation in regulatory requirement in various countries it is a major challenge for pharmaceutical companies to register their pharmaceutical products. For pharmaceutical companies in order to develop a drug formulation which can be simultaneously submitted in numerous countries for approval at the same time is difficult. Therefore, continuous process of harmonization is carried out all over the world to overcome this problem. It gives a brief information about the regulatory requirements for

registration of pharmaceutical Product from the comparison study of Cambodia & Malaysia. It can be concluded that the industry should target on submission or registration of pharmaceutical product at different countries depending on their stability, regional documents and other country specific documents.

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**Conflict of interest**

The authors declare no conflicts of interest.

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