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Research Article

Generic Pharmaceuticals Drug Registration Requirements and Technical Data Comparison Between all GCC Countries

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Abstract

The Marketing Authorization Holder (MAH) is required to integrate technical specifications and various other documents about new pharmaceutical products to market them in different GCC countries. This research delves into the specific registration documentation necessary for the approval process of generic drugs in GCC (Gulf Cooperation Council) Countries. Each product must adhere to the distinct guidelines of the respective country it is seeking approval. The study focuses on the "Regulatory Guidelines for Generic Products Registration in GCC countries." Adhering to the guidance and regulations set forth by authoritative bodies such as the FDA (Food and Drug Administration), ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use), and WHO (World Health Organization) streamline the filing process for pharmaceuticals in GCC countries, ensuring efficiency and accuracy. In the dynamic landscape of pharmaceutical generics, this research endeavors to elucidate the disparities in registration document requirements among GCC countries, particularly through the Common Technical Document (CTD) format. By delineating these discrepancies, stakeholders can better navigate the details of regulatory compliance and streamline the process of bringing generic pharmaceuticals to market in GCC countries.

Keywords: Marketing Authorization Holder, Common Technical Document, International Council for Harmonization, Human Drugs, Gulf Cooperation Council.

INTRODUCTION

The GCC (Gulf Cooperation Council) States are located in the Arabian Peninsula, which is situated in southwest Asia. This region is bordered by Iraq and Jordan to the North, the Republic of Yemen and the Arabian Sea to the South, the Arabian Gulf to the East, and the Red Sea to the West. The GCC is comprised of six member states, with a combined population of 44,223,488 people, spanning a total area of 2,572,954 square kilometers. Yemen, although not yet a member, is in negotiations to join the GCC. It has expressed its aspiration to become a member by 2016. In anticipation of its potential membership, the GCC has already granted Yemen approval for

accession to certain areas. This includes participation in the GCC Council of Health Ministers and the GCC Council of Labour and Social Affairs Ministers.

Fig 1: Map of the GCC Countries

The GCC serves as a platform for cooperation and collaboration among its member states, fostering economic, social, cultural, and political ties. Membership in the GCC offers various benefits, including enhanced regional security, economic integration, and opportunities for collective decision-making on matters of mutual interest. For Yemen, joining the GCC could signify deeper engagement with neighboring countries and potential avenues for economic development and stability.

Objective of the study

The main aim of the study is to find out the data requirements and the data comparison of the pharmaceutical product in the Gulf region.

The following are the counties that belongs to GCC:

1. SFDA (Saudi Food and Drug Authority) – Kingdom of Saudi Arabia.
2. NHRA (National Health Regulatory Authority) – Bahrain.
3. Ministry of Health - Oman.
4. Ministry of Health - Kuwait.
5. Ministry of Health - UAE
6. Ministry of Health – Qatar.

METHODOLOGY

The Common Technical Document (CTD) was developed to establish a standardized structure for technical documentation submitted in applications for the registration of human pharmaceutical products in Europe, the USA, and Japan. The CTD dossier is structured into five main modules:

- Module 1 – Administrative Information: This module contains details about the manufacturer, brief product composition information, shelf life, and storage conditions. It is important to note that each country has its own specific application form and cover letter.
- Module 2 – Overviews and Summaries of Modules 3–5: This module provides an overview and summary of the information included in Modules 3 to 5.
- Module 3 – Quality: This section encompasses all information related to the drug substance and drug products' quality. It includes details on the active ingredients and finished products.
- Module 4 – Non-clinical Reports: This section includes pharmacology and toxicology reports. Generally, it is not applicable for generic formulas and is only required for innovative drug products.
- Module 5 – Clinical Study Reports: In this module, data from bioavailability (BA) and bioequivalence (BE) studies on humans are presented.

The following chart illustrates the complete structure of the CTD

Module 1 – Administrative Information
- Module 2 – Overviews and Summaries of Modules 3–5
- Module 3 – Quality
  - Drug Substance Information
  - Drug Product Information
- Module 4 – Non-clinical Reports (Pharmacology/Toxicology)
- Module 5 – Clinical Study Reports (Bioavailability & Bioequivalence Studies)

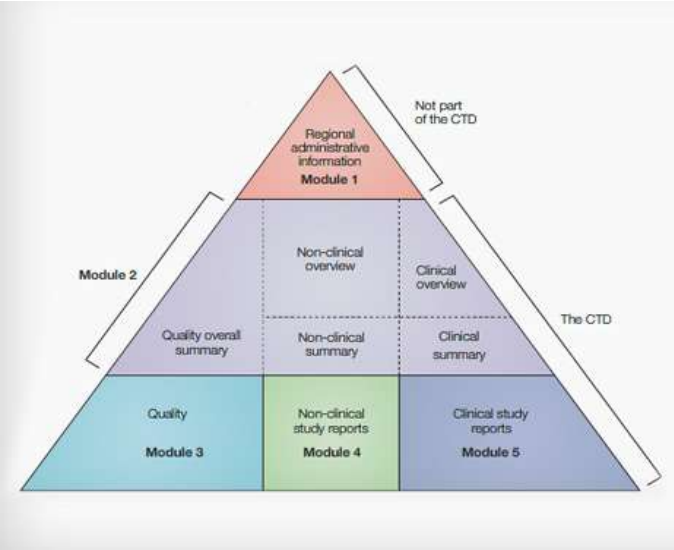

Fig 2: CTD structure

RESULTS AND DISCUSSION

The registration process for generic pharmaceutical products is a critical step for pharmaceutical companies, as products must be registered before they can be sold in the market. This process is essential for the sale and marketing of medicines and varies depending on the requirements and procedures of each country. This study specifically examines the registration document requirements and comparisons in GCC countries.

The registration of generic medicines with the GCC countries adheres to the Common Technical Document (CTD) guidelines. There are variations in guidelines among some countries. While the fundamental principles remain consistent across many countries, it's important to carefully consider these requirements on a country-by-country basis due to these differences. One notable difference lies in the document format between the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) CTD and the ASEAN Common Technical Document (ACTD). The ICH CTD consists of five modules, labeled Module I through Module V, whereas the ACTD organizes documents into parts, labeled Part I through Part IV. Unlike the CTD, the ACTD lacks a common technical document overview and summaries, with administrative documents, product information, quality documents, nonclinical documents, and clinical documents comprising the rest of the sections.

According to the ICH guidelines, Module 1 of the CTD is not standardized and typically contains regional or country-specific information, reflecting the unique regulatory landscape of each jurisdiction.

Module 1

Module 1 contains the administrative information and all countries have some documents in common and some documents different, all country's requirements and sections are evaluated in the study and the results are shown below in the table:

SECTION	ADMINISTRATIVE INFORMATION	SFDA / Oman/ Bahrain / Kuwait / Qatar / UAE
1.0	Cover letter	Each should be addressed separately with the respective GCC MOH address.
1.1	Comprehensive Table of Content	Common for all GCC
1.2	Application Form	Each country's application forms have unique requirements.
1.3	Product Information	Drug information are common for all GCC countries and it should be in the dual language Arabic and English languages.
1.3.1	Summary of Product Characteristics (SPC)	
1.3.2	Labeling Information	
1.3.3	Patient information leaflet (PIL)	
1.3.3.1	Arabic leaflet	
1.3.3.2	English leaflet	
1.3.4	Artwork (Mock-ups) (outer label, inner label and leaflet artworks)	
1.3.5	Samples	
1.4	Information on the experts	Information about drug quality, and non-clinical and clinical data requirements are common for all countries.
1.4.1	Quality Information	
1.4.2	Non- Clinical Information	
1.4.3	Clinical Information	
1.5	Environmental Risk Assessment	This is a common section for all GCC countries containing non-GMO declarations.
1.5.1	Non-Genetically Modified Organism (Non-GMO)	
1.5.2	GMO	
1.6	Pharmacovigilance	This is a common section for all GCC countries – containing Pharmacovigilance System information of the company.
1.6.1	Pharmacovigilance System	
1.6.2	Risk Management Plan	
1.7	Certificates and documents	
1.7.1	Copy of valid GMP certificates for the manufacturing site(s)	Valid GMP certificates are required for the API and MAH, this section are common for all countries.
1.7.2	Original legalized valid Certificate of Pharmaceutical Product (CPP)	CPP is Not Applicable to the country of origin but is required for the other countries
1.7.3	Certificate of Analysis - Drug Substance, Finished Product	2 batches COA of Drug Substance and Finished Products are required and this is also a common section for all countries.
1.7.4	Certificate of Analysis – Excipients	2 batches of Certificate of Analysis for all Excipients are required and this is also a common section for all countries.
1.7.5	Alcohol-content declaration	Signed and stump Alcohol-free declarations are mandatory in this section.
1.7.6	Pork-free declaration	The products should be pork-free and signed and stump declaration should be provided.
1.7.7	TSE/BSE free certificate	The medicines formula is free form TSE/ BSE and should be submitted signed and stump.
1.7.8	The diluents and coloring agents in the product formula	The formula contains diluents and coloring agents that's why the declaration should be provided with proper name with signed and stump.
1.7.9	Patent Information	MAH should check the patency of the products before they register the medicines in the specific countries.
1.7.10	Letter of access DMF	In this section MAH should provide the DMF letter of access if the DMF is US based. And if the DMF is Europe based then CEP is required.
1.8	Pricing	

1.8.1	Price certificate	MAH are proposing the price of the drug before the registration. The price are based on the country's currency.
1.8.2	Other documents related	
1.9	Response to questions (Updates, questions, queries)	This is the part when MAH receiving the query from the MOH and MAH replied the response.
	Additional Data	This is different requirements as per the country. This contents composition and other countries registration approval certificate.

Module 2

Module 2 contains summaries of Module III, referred to as the Common Technical Document summaries, encompassing summaries of both the drug substance and finished products. Across GCC countries, guidelines for Module II are generally uniform, with the exception of the UAE where Module II is not mandatory. During the drug approval process, various documents are essential for submission. These documents typically include:

2.1	Table of Contents of Module 2	SFDA / Oman/ Bahrain / Kuwait / Qatar	UAE
2.2	Introduction	In contrast to the UAE, all other GCC countries share identical common documents for the registration process. This section holds critical information, particularly summaries of Module III. It encompasses brief details about the drug substance or abbreviated information from the Drug Master File (DMF), as well as information regarding finished drug products. A summary of Pharmacodynamic and pharmacokinetics information should be also highlighted.	For UAE market module 2 is not required.
2.3	Quality overall Summary (QOS)		
2.3.S	Drug Substance		
2.3.P	Drug Product		
2.3.A	Appendices		
2.3.R	Regional information		
2.4	Non-Clinical Overview		
2.5	Clinical Overview		
2.6	Non-Clinical Summaries		
2.6.1	Introduction		
2.6.2	Pharmacology written Summary		
2.6.3	Pharmacology Tabulated Summary		
2.6.4	Pharmacokinetics written Summary		
2.6.5	Pharmacokinetics Tabulated Summary		
2.6.6	Toxicology written Summary		
2.6.7	Toxicology Tabulated Summary		
2.7	Clinical Summaries		
2.7.1	Summary of Biopharmaceutical and Associated Analytical Methods		
2.7.2	Summary of Clinical Pharmacology Studies		
2.7.3	Summary of Clinical Efficacy		
2.7.4	Summary of Clinical Safety		
2.7.5	References		
2.7.6	Synopses of Individual Studies		

Module 3

Module 3 is a very important part of the registration approval section. It's also called the heart of the dossier. These sections are mandatory for all the countries and it's divided into two parts. The following section are as follows in table below.

Drug Substance Part

3.1	Table of Contents of Module 3	SFDA / Oman/ Bahrain / Kuwait / Qatar / UAE
3.2	Body of Data	This section pertains to the quality aspects of the drug, particularly focusing on the information contained in the Drug Master Files (DMFs). It encompasses details regarding the substance used in the drug formulation, including its name, structure, properties, and manufacturing processes.
3.2.S	Drug Substance	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	
3.2.S.1.2	Structure	
3.2.S.1.3	General Properties	
3.2.S.2	Manufacture	

3.2.S.2.1	Manufacture(s)	Additionally, it outlines the characterization of the substance and addresses any impurities present. Stability data holds significant importance within this module, as it is influenced by the environmental conditions of the respective countries. Certain sections within this module, such as Description of Process and Process Controls, Control of Materials, Control of Critical Steps, and Intermediates, may contain confidential information, which companies may submit directly to regulatory agencies. Specifications and analytical procedures are developed in accordance with pharmacopeial references, and all tests conducted must adhere to the standards outlined in the pharmacopeia and fall within specified limits.
3.2.S.2.2	Description of Process and Process Controls	
3.2.S.2.3	Control of Materials	
3.2.S.2.4	Control of Critical Steps and Intermediates	
3.2.S.2.5	Process Validation and/or Evaluation	
3.2.S.2.6	Manufacturing Process Development	
3.2.S.3	Characterization	
3.2.S.3.1	Elucidation of Structure and Other Characteristics	
3.2.S.3.2	Impurities	
3.2.S.4	Control of Drug Substance	
3.2.S.4.1	Specifications	
3.2.S.4.2	Analytical Procedures	
3.2.S.4.3	Validation of Analytical Procedures	
3.2.S.4.4	Batch Analyses	
3.2.S.4.5	Justification of Specification	
3.2.S.5	Reference Standards or Materials	
3.2.S.6	Container/Closure Systems	
3.2.S.7	Stability	
3.2.S.7.1	Stability Summary and Conclusions	
3.2.S.7.2	Post-approval Stability Protocol and Commitment	
3.2.S.7.3	Stability Data	

Drug Product Section

3.2.P	Drug Product	SFDA / Oman/ Bahrain / Kuwait / Qatar / UAE
3.2.P.1	Description and Composition of the Drug Product	In this section, the Marketing Authorization Holder (MAH) provides comprehensive product information, including the composition formula, development process, details about the drug substance, and the excipients utilized in the formulation. Many drug products also incorporate overages to ensure the accuracy of the drug formula. Furthermore, it outlines and provides details regarding the container closure system or packaging materials used for the drug products.
3.2.P.2	Pharmaceutical Development	
3.2.P.2.1	Components of the Drug Product	
3.2.P.2.1.1	Drug substance	
3.2.P.2.1.2	Excipients	
3.2.P.2.2	Drug Product	
3.2.P.2.2.1	Formulation Development	
3.2.P.2.2.2	Overages	
3.2.P.2.2.3	Physiochemical and Biological Properties	
3.2.P.2.3	Manufacturing Process Development	
3.2.P.2.4	Container Closure System	
3.2.P.2.5	Microbiological Attributes	
3.2.P.2.6	Compatibility	
3.2.P.3	Manufacture	Section 3.2.P.3 encompasses details about the manufacturer and provides a comprehensive overview of the batch formula. An essential component of this section is process validation, which elucidates the manufacturing process and its critical steps in producing the drug products.
3.2.P.3.1	Manufacture(s)	
3.2.P.3.2	Batch Formula	
3.2.P.3.3	Description of Manufacturing Process and Process Controls	
3.2.P.3.4	Controls of Critical Steps and Intermediates	
3.2.P.3.5	Process Validation and/or Evaluation	
3.2.P.4	Control of Excipients	This section provides details concerning both compendial and non-compendial excipients, along with their respective specifications and analytical procedures for testing. If the excipients originate from animals, the Marketing Authorization Holder (MAH) must include a declaration of TSE/BSE certificate.
3.2.P.4.1	Specifications	
3.2.P.4.2	Analytical Procedures	
3.2.P.4.3	Validation of Analytical Procedures	
3.2.P.4.4	Justification of Specifications	
3.2.P.4.5	Excipients of Human or Animal Origin	
3.2.P.4.6	Novel Excipients	
3.2.P.5	Control of Drug Product	

3.2.P.5.1	Specifications	These sections are crucial for drug products, as they often prompt numerous inquiries from the Ministry of Health (MOH). This section contains information regarding the specifications and testing procedures of finished products. Batch analysis data for three batches are necessary.
3.2.P.5.2	Analytical Procedures	
3.2.P.5.3	Validation of Analytical Procedures	
3.2.P.5.4	Batch Analysis	
3.2.P.5.5	Characterization of Impurities	
3.2.P.5.6	Justification of Specifications	
3.2.P.6	Reference Standards or Materials	USP and BP reference standards are required during the registration procedure for the test parameter.
3.2.P.7	Container/Closure System	Container closures are crucial components of finished products. Various types of container closures are utilized, including bottle packs and blister packs.
3.2.P.8	Stability	The stability parameter is a crucial section, as all drugs must undergo stability testing according to the guidelines or regulations of the respective country. A minimum of 12 months of stability data for three batches is mandated.
3.2.P.8.1	Stability Summary and Conclusions	
3.2.P.8.2	Post-Approval Stability Protocol and Stability Commitments	
3.2.P.8.3	Stability data	
3.3	Literature References	Literature reference for the drugs products are required from US and UK based journals.

Module 4

Module 4 includes details regarding non-clinical studies, which are compulsory for innovative companies but not necessary for generic formulations during the registration process.

Module 5

Module 5 encompasses comprehensive details regarding clinical studies. The Marketing Authorization Holder (MAH) conducts clinical studies on their formulation and submits them to the regulatory agency for drug approval, alongside the complete Common Technical Document (CTD) files. These studies include the investigation of bioavailability/bioequivalence (BA/BE) as per the relevant guidelines, which is a mandatory requirement for the drug registration process.

Once the CTD dossier files are compiled and submitted to the regulatory agencies, they undergo thorough review. If any documents are found to be missing or incomplete, the agency will request the necessary supporting documents from the MAH. The MAH will then provide the requested documentation, and following a comprehensive evaluation by the agency, the MAH will obtain the registration certificate for the drug.

SUMMARY AND CONCLUSION

Based on our findings, we have determined that the registration procedures across GCC countries are largely similar, with consistent requirements for the Common Technical Document (CTD) dossier, although with a few exceptions as previously discussed. All GCC countries adhere to the International Council for Harmonisation (ICH) guidelines and parameters, and Marketing Authorization Holders (MAHs) must meet these standards to register drugs in GCC countries. The main divergent aspects are found in Module 1 sections, such as the application form, pricing information, patent details, Certificate of Pharmaceutical Product (CPP), and cover letter. However, aside from these variations, the remaining sections of the registration process follow a standardized framework across all GCC countries.

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