

# Regulatory Aspects of Pharmaceuticals in Gulf Co-operation Council Countries

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## ABSTRACT

Regulatory authorities in both developed and developing countries share the responsibility of ensuring the access of safe and effective medicines to patients; however, their structures, strategies, and practices vary significantly. The Gulf Cooperation Council region is considered as “emerging market for pharmaceutical export and bilateral trade some incidents of year 2008-2009 generics will comprise a significant part of the pharmaceutical sector in the GCC the aim of this study was to evaluate the Gulf Cooperation Council (GCC) regulatory systems (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE) in order to develop a harmonized strategy. Seven GCC authorities to provide details of their review process and the quality measures used to improve their assessment procedures for applicability and practicality in the GCC region like recession or economic slowdown in highly well off and regulated market of EU and US, raised the demand for alternate destinations for business. Smaller pharma markets such as Qatar and Bahrain are likely to experience higher growth than the comparatively developed market of Saudi Arabia. The GCC pharmaceutical sector has been growing steadily along with the general uptrend within the region.

**Keywords:** Gulf Cooperation Council, Pharmaceutical, Regulatory Requirements, CTD.

## 1. INTRODUCTION

### Global Pharmaceuticals Industry

The growth in pharmaceutical markets in developing countries with emerging economies (E7 countries) has outpaced the overall growth of the global pharmaceutical market. In 2010, pharmaceutical market in E7 countries (Brazil, Russia, China, India, Turkey, Mexico, and Indonesia) was estimated at around US\$ 136 Billion, and it is expected to achieve a high growth during 2011-2014, thereby increasing their share in global pharmaceutical market.

### GCC Pharmaceuticals Industry

GCC represents less than 1% of the global sector Pharmaceuticals market to double from USD 5.5 billion within the next 9 years Growth of the sector is driven by, population growth, ageing population increased lifestyle diseases due to smoking and poor diet and requirement to maintain health insurance Between 7-12% of GCC annual budgets are allocated for healthcare spending 80% of drugs used in the region are imported. Represents USD 1 billion 75% patented products. Domestic producers focus mainly on the manufacture of generic drugs but, given these products' high prices, end-users tend to lean towards branded drugs, the report notes, pointing out that the World Health Organization (WHO) has estimated that drug products in the GCC are priced 13 times higher than the international standard. [4]



Fig. 1: Map of GCC Countries

**DRUG REGULATING AUTHORITIES OF GCC**

- Kingdom of Bahrain** : Pharmacy and drug control department
- State of Kuwait** : Pharmaceutical and herbal medicines registration and control administration, Kuwait drug and food
- State of Oman** : General directorate of pharmacy and drug control
- State of Qatar** : Pharmacy and drug control department
- Kingdom of Saudi Arabia** : Saudi food and drug authority
- United Arab Emirates** : Registration and drug control department

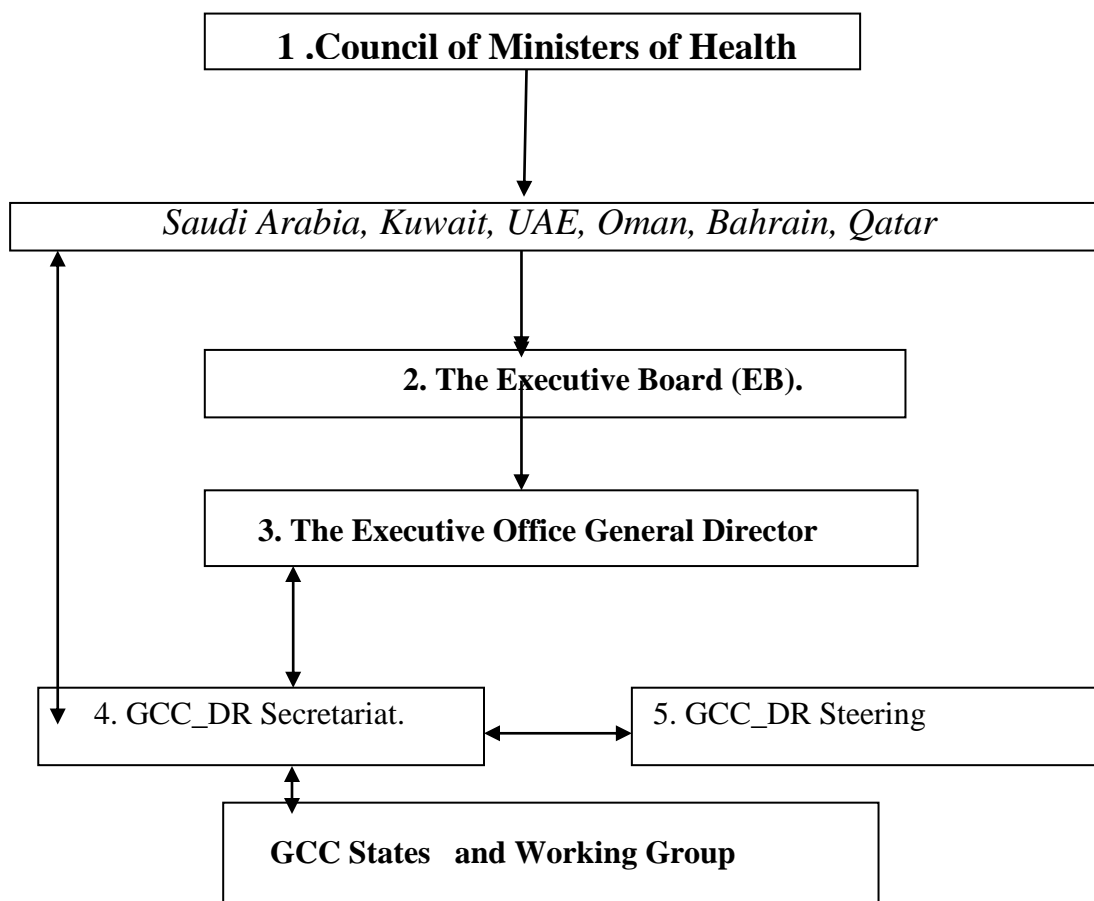


Fig. 2: Organizational structure

**Regional Harmonization:** The seven Gulf Cooperation Council (GCC) States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) also took the initiative after the EU centralized procedure to improve patients' access to safe and effective medicines in the GCC Region. The GCC Central Drug Registration (GCC-DR) Committee is composed of two members from each of the seven countries. The procedure is carried out by selecting two authorities alphabetically to review a registration dossier. However, all the GCC authorities are equally responsible for evaluating the quality, safety and efficacy of medicines and therefore all the seven states are provided with copies of the product registration dossier for their individual assessments. The seven member states meet four to five times a year to discuss the product review reports issued by the reviewers from each authority and the approval decision is made by agreement.

### **GCC Countries Import 90 % of Pharmaceutical Needs**

The pharmaceutical market in GCC countries exceeds 6 billion USD. This market is growing rapidly and is expected to reach around 10 billion USD by 2020. The aforesaid meeting, the first ever of its kind in that sector, is aimed at achieving several objectives including to create a forum for the exchange of ideas and dialogue among pharmaceutical companies in GCC, propose a multi-client study that will address the needs of the pharmaceutical industry in the region, and identify the need for establishing a pharmaceutical trade association for GCC producers.<sup>[5]</sup>

## **2. AIM AND OBJECTIVES**

### **AIM**

The aim of this study is to study the GCC regulatory authorities which would enhance their similarities, minimise their differences and standardise regulatory practices across the GCC Region.

### **OBJECTIVE**

- Assess the regulatory review process in Kuwait in order to develop an appropriate model for the evaluation of other GCC countries.
- Identify and assess the models and activities related to the submission, review and regulatory action for new drug application in the seven GCC States.
- Determine the similarities and differences between the regulatory processes that occur during the review of product dossiers within the GCC authorities.
- Identify best practices in order to improve the standard of the regulatory review process in the GCC states.
- Evaluate the quality measures that GCC member states are building into their regulatory review processes to ensure consistency, efficiency and transparency across the assessment procedures.
- Review the seven GCC authorities' vision and mission statements, goals, objectives and driving forces for change in order to determine their overall strategy for a successful GCC system.

## **3. METHODS AND DISCUSSION**

### **PHARMACEUTICAL MARKET PROFILE OF GCC COUNTRIES**

#### **QATAR**

Qatar, with a developing local pharmaceuticals manufacturing industry, had revenues of USD 227 million in 2010. Some recent developments such as establishment of a medical device company called Qatari German Company for Medical Devices (QGMD), and a biotech research company called Scientific Medical Applied Research and Development Company (SMARD) have come about in the pharmaceuticals sector.

- **Market Size:** USD 227 million.
- High per capita expenditure on drugs.
- Many government initiatives to strengthen R&D and local pharmaceutical industry.
- Drug expenditure is forecast to increase by a CAGR of 11% to reach USD 400 million by 2014.

#### **SAUDI ARABIA**

Currently, the Saudi Arabian Government is the chief financier of the GCC healthcare sector.

**Market Size:** USD 2.8 billion.

- Market expected to grow at CAGR of 6% until 2014.
- Leading position in GCC with 27 manufacturers.
- Government allows 100% foreign ownership, low cost loans and low cost power to encourage domestic production.
- Wholesale retailing of products is not allowed for foreign companies.

#### UAE

The UAE pharmaceuticals sector, which was estimated at USD 1.8 billion in 2010, is the second largest market in the GCC. The country, with eight domestic manufacturers in 2009, has relatively limited local production capacities.

- **Market Size: USD 1.8 Billion**
- Pharmaceutical market is projected to grow to USD 2.7 billion by 2014
- Per capita income on drug spending will be USD493 by 2014

#### BAHRAIN

Bahrain's pharmaceutical market is the GCC's smallest, with revenues of USD 118 million in 2010.

**Market Size:** USD 118 million.

- Drug expenditure will grow at an average CAGR of 4% until 2019.
- Domestic manufacturing is underdeveloped due to limited investments.
- Bahrain follows a policy of importing drugs directly from a manufacturer with licensed research capabilities in GCC countries.

#### KUWAIT

Kuwait represents the third largest pharmaceutical market in the GCC and its market value was pegged at USD 374 million in 2010. Only 20 per cent of pharmaceutical products, in terms of volume, were manufactured domestically in Kuwait in 2010.

- **Market Size:** USD 374 million.
- Only 20% of pharmaceutical products in terms of volume were manufactured locally Market dominated by imported and expensively priced patented drugs
- Kuwait has a strong pharmaceutical regulatory structure. Government taking measures to reduce costs of essential drugs, which are considered the highest in the Middle East.

#### OMAN

Oman is among the smallest drug markets in the GCC in terms of value. It was estimated at USD 52 million in 2010.

- **Market Size:** 152 million
- Small domestic market with only two producers
- Oman has lowest per capita expenditure in health care.

#### REGISTRATION PROCEDURE

Gulf co-operation council regulatory authorities Approved in May 1999 Located in the executive officer for health ministers, Riyadh, Saudi Arabia.

Drug registration: two processes of drug registration;

- A. Centralized Procedure
- B. Decentralized Procedure

#### A. CENTRALIZED REGISTRATION PROCEDURE

The executive office of GCC-DR assumes the receipt of registration files after ensuring the fulfillment of registration requirements and upon duly filling the following forms: The drug companies' registration form. A pharmaceutical chemical entity preparation registration form. Eight complete files for each chemical entity and 17 samples should be submitted to the executive office and two samples shall be dispatched to each country along with registration file. <sup>[16]</sup>

## B. DECENTRALIZED REGISTRATION PROCESS

Registration regulations in major countries of GCC although there is a centralized and quite harmonized process for drug registration in GCC countries, the regulatory requirements of few big countries like Saudi Arabia and UAE are separate these countries have their well-established regulatory system and its enforcement in this study we will discuss briefly the registration requirements of multi-source generic products of GCC countries Saudi Arabia, Bahrain, Kuwait, Oman, UAE [17].

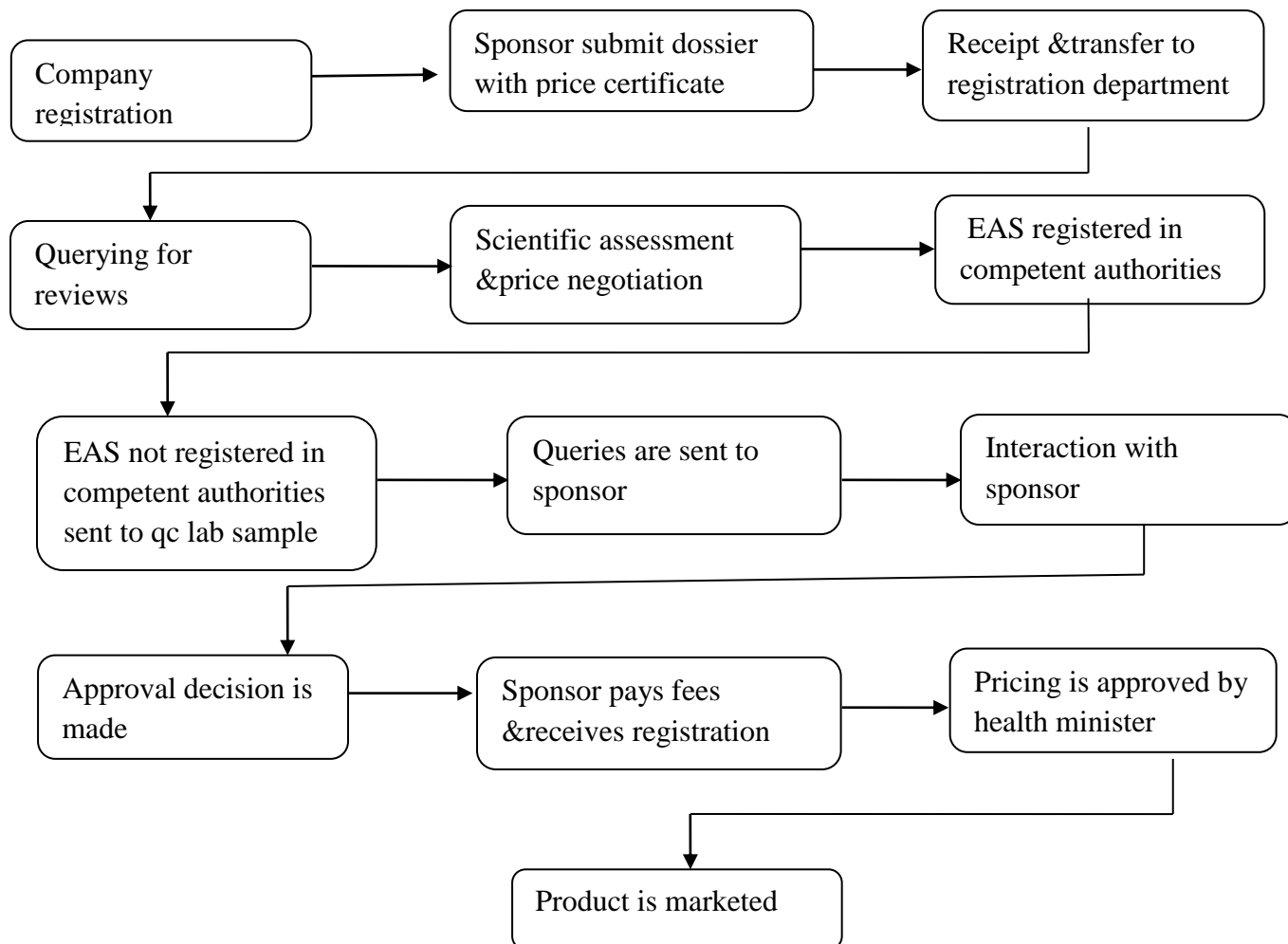


Fig. 3: Regulatory Process of Kuwait (17,18)

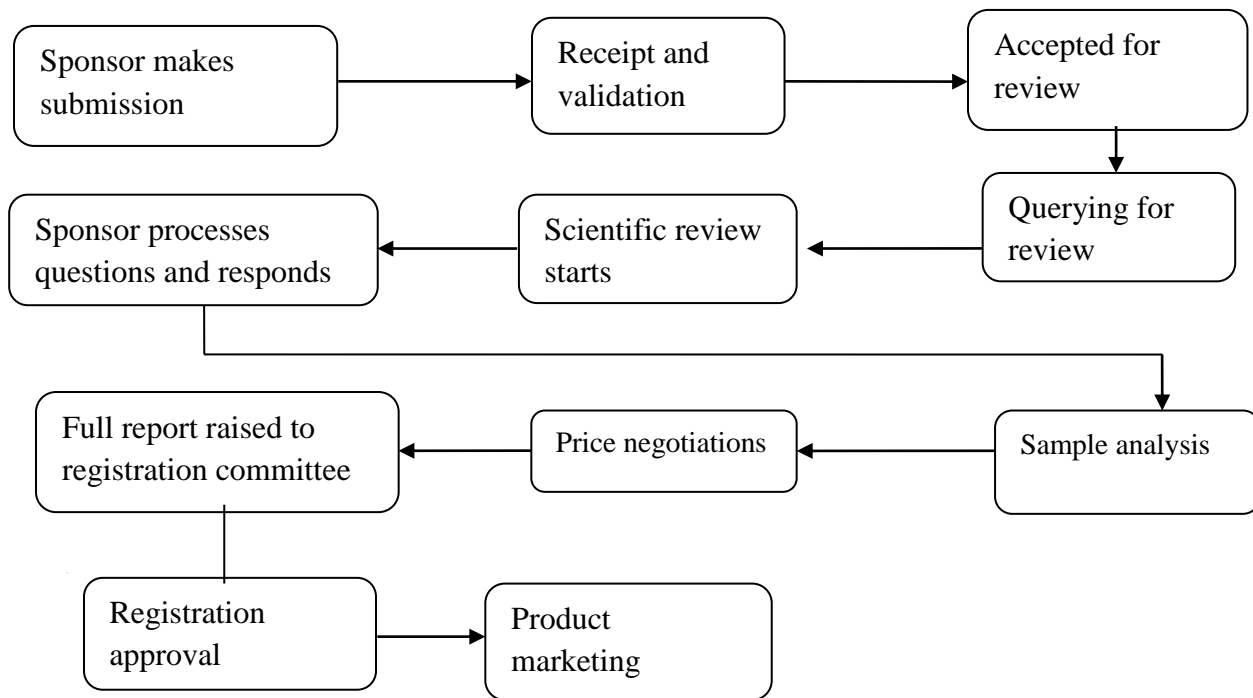


Fig. 4: Regulatory Process of Bahrain (19)

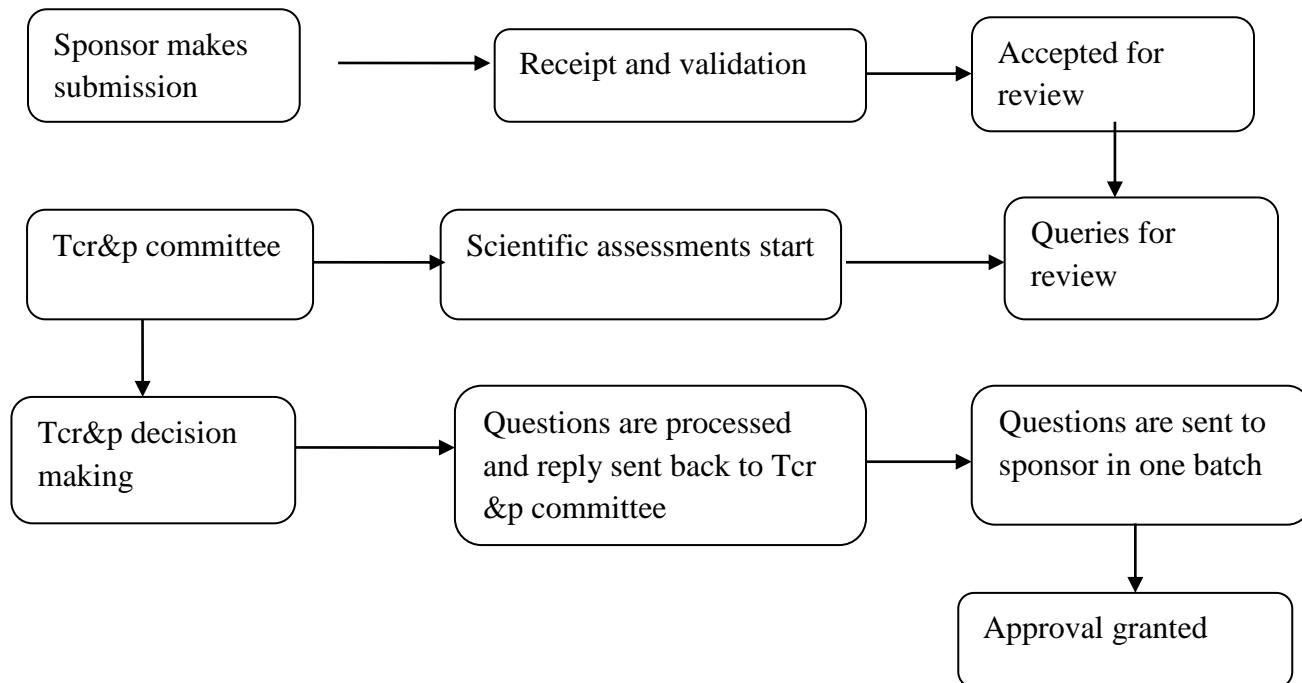
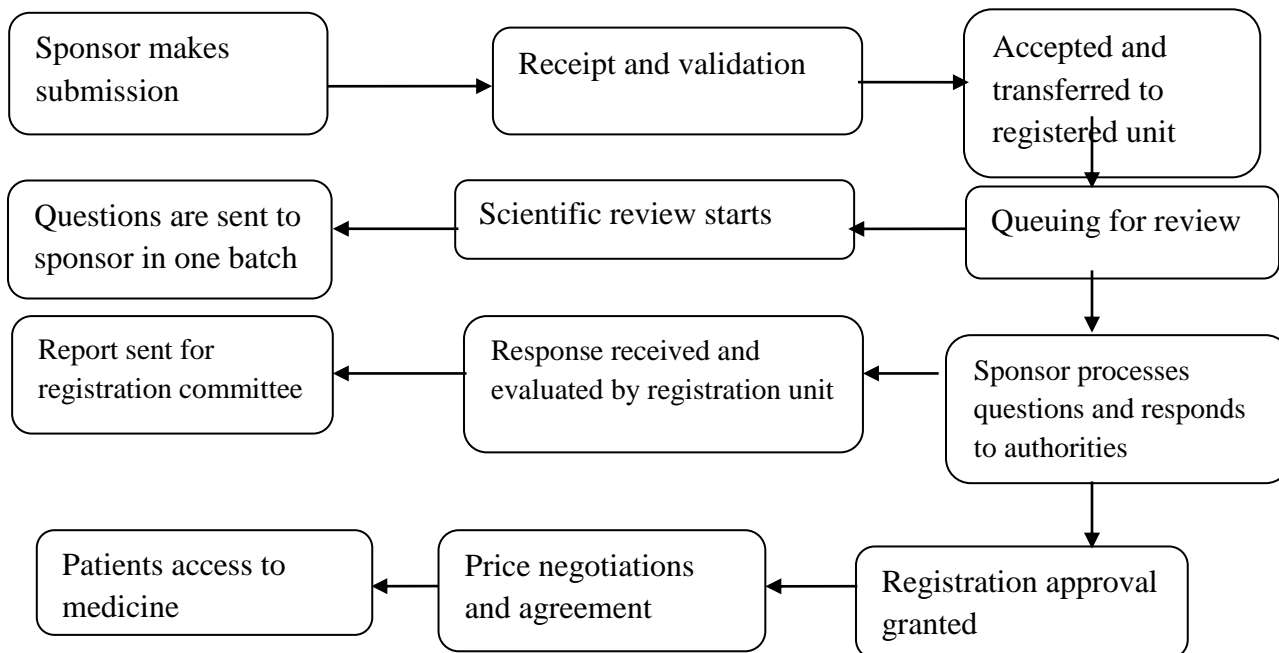
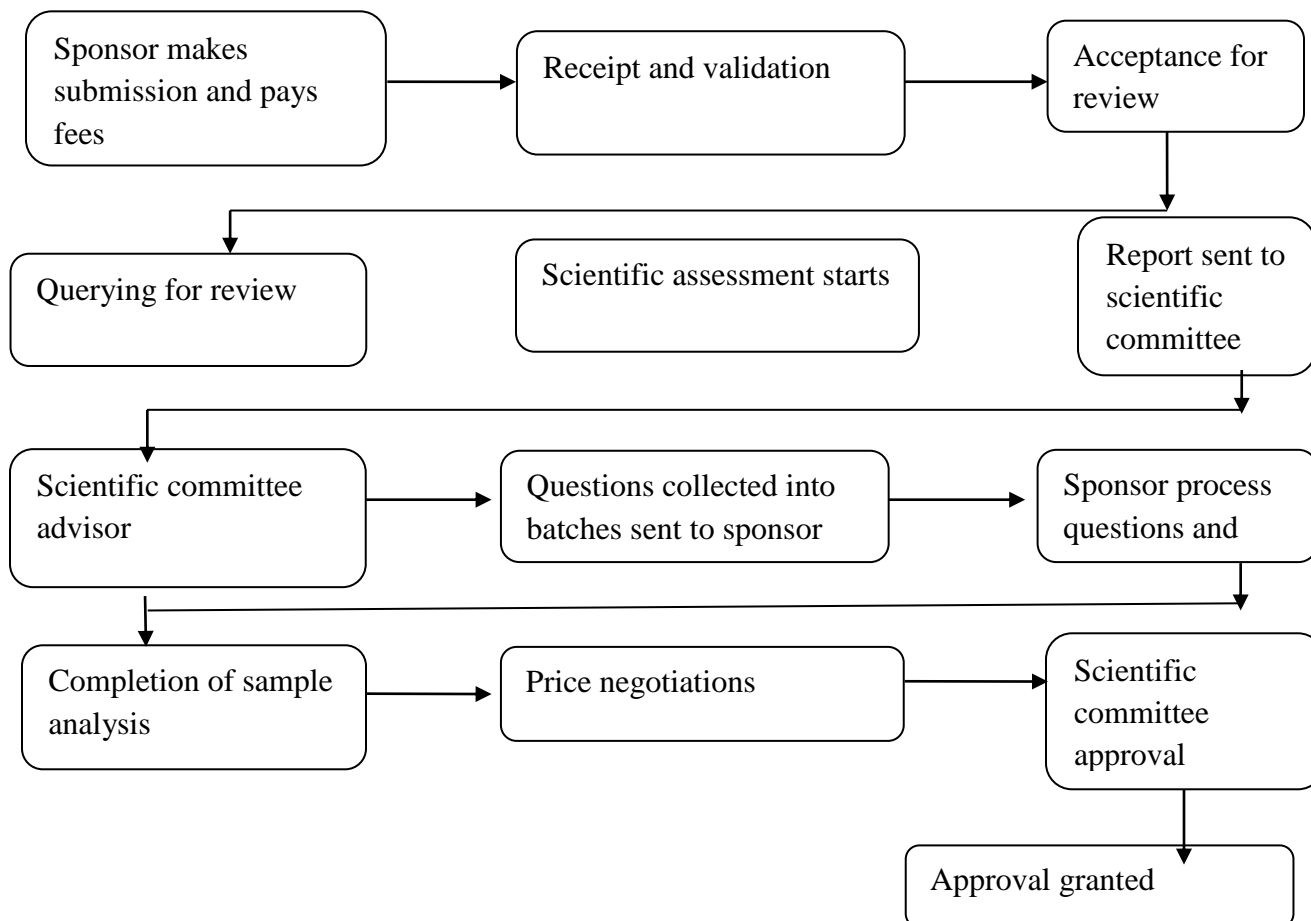


Fig. 5: Regulatory Process of Oman



**Fig. 6: Regulatory Process of Qatar**



**Fig. 7: Regulatory Process in The Kingdom of Saudi Arabia (KSA) (21,22)**

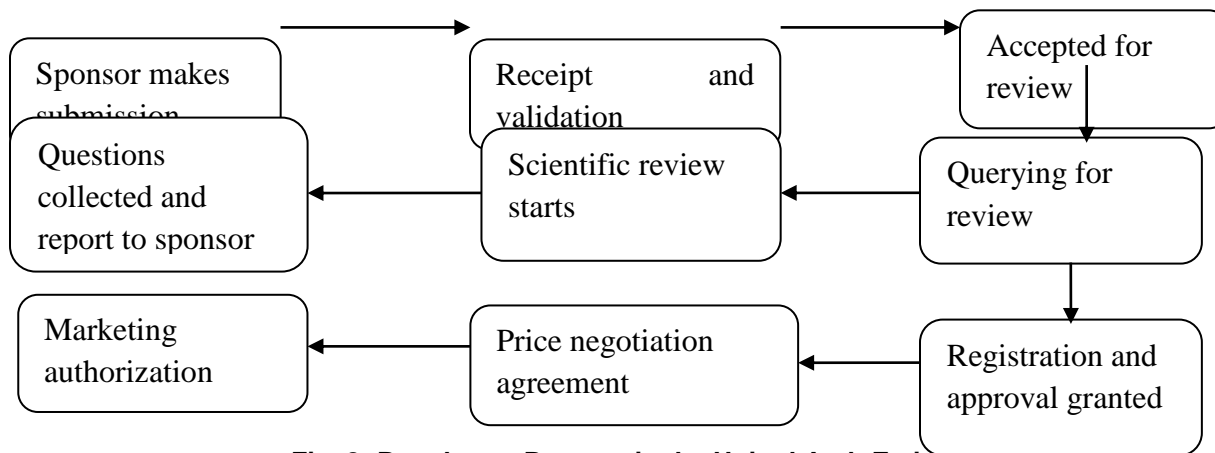


Fig. 8: Regulatory Process in the United Arab Emirates

Table 1: Data requirements of different regions and registration requirements in Saudi Arabia, Bahrain, Kuwait and UAE

	Saudi Arabia	Bahrain	Kuwait	UAE
Format	CTD format. eCTD recommended. Module 2 to 5: a/c to ICH CTD format. Module 1: regional requirements: <ul style="list-style-type: none"> <li>Cover letter</li> <li>Table of contents</li> <li>Application form</li> </ul> • Product information: Summary of product characteristics (SmPC), product information leaflet (PIL) and labelling all in WHO template format. • Information on experts involved in clinical, nonclinical studies. • Environment risk assessment. <ul style="list-style-type: none"> <li>Pharmacovigilance</li> </ul> • Certificate of pharmaceutical product (COPP).	Company profile <ul style="list-style-type: none"> <li>Number of manufacturing sites owned by company               <ul style="list-style-type: none"> <li>Address of each site</li> </ul> </li> <li>Legal &amp; commercial relations with all sites</li> <li>Manufacturing license with date in country of origin (COO).               <ul style="list-style-type: none"> <li>Address of applicant with contact details.</li> </ul> </li> <li>GMP certificate from country of origin.</li> <li>Number of employees in different section &amp; their qualification details.</li> <li>Graphic design &amp; flow of manufacturing line of site.               <ul style="list-style-type: none"> <li>List of all products manufactured at company's site or Relationship MAHs</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Reference standard with CoA.</li> <li>Finished product sample.               <ul style="list-style-type: none"> <li>Patient information leaflet (English and Arabic).</li> </ul> </li> <li>Source of supply of API and inactive ingredients.               <ul style="list-style-type: none"> <li>Raw material specifications.</li> </ul> </li> <li>Finished products specifications with quality control methods.               <ul style="list-style-type: none"> <li>Stability data:                   <ul style="list-style-type: none"> <li>Long term 3 batches</li> </ul> </li> </ul> </li> <li>Accelerated studies: six months, same three batches, used for long-term studies.               <ul style="list-style-type: none"> <li>Bioequivalence Study data</li> </ul> </li> </ul>	Distributor of product in UAE. <ul style="list-style-type: none"> <li>Manufacturing site.</li> <li>Marketing authorization holder &amp; power of attorney.</li> <li>Manufacturer of API.</li> <li>Regulatory status.               <ul style="list-style-type: none"> <li>Price list.</li> <li>Declaration</li> </ul> </li> </ul> (In accordance with the medicines' regulations of Drug Control Department- Ministry of Health -UAE)



<b>Certificates</b>	<p>Authenticated by the Ministry of health of the country of origin and additionally by Saudi Arabian embassy. Following Certificates required:</p> <ul style="list-style-type: none"> <li>• COPP/ free sale certificate.</li> <li>• CoA.</li> <li>• Pork-free declaration.</li> <li>• Price list</li> </ul>	<p>Contents of file</p> <ul style="list-style-type: none"> <li>• WHO-certificate of pharmaceutical product (COPP) issued by country of origin and legalized by any one GCC embassy.</li> <li>• Summary of product characteristics (SmPC).</li> <li>• Separate file for quality control laboratory including all quality data and information e.g. certificate of analysis, validation report etc.</li> <li>• Full description about API, and excipients.</li> <li>• Description about vehicles and carriers used.</li> <li>• Method of manufacturing.</li> <li>• Name and address of involved CROs (if any).</li> <li>• Description of outer pack and accessories used.</li> <li>• Concentration of product (per unit mass or volume).</li> <li>• Source of starting material.</li> <li>• Proposed label.</li> <li>• Product patient leaflet (Arabic/English).</li> <li>• Toxicological data (for NCE and newly introduced generic drugs only).</li> <li>• Bioequivalence study reports (for generic drug registration).</li> </ul>	<p>Distributor of product in UAE.</p> <ul style="list-style-type: none"> <li>• Manufacturing site.</li> <li>• Marketing authorization holder and power of attorney.</li> <li>• Manufacturer of API.</li> <li>• Regulatory status.</li> <li>• Price list.</li> <li>• Declaration (In accordance with the medicines' regulations of Drug Control Department- Ministry of Health -UAE)</li> </ul>
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**Table 2: Enclosures required for drug registration in five Gulf Cooperation Council countries**

S. No	Enclosures	Saudi Arabia	Kuwait	UAE	Oman	Bahrain
1.	Control specification and method of analysis	R	R	R	R	NR
2.	Certificate of analysis attested by health authority and country of origin	R	NR	R	NR	NR
3.	Legalized free sale certificate issued by health authorities for coo, indicating that product registered and marketed with same name & composition	R	R	R	R	R
4.	Legalized certificate indicating that diluents used are allowed to be in coo	R	NR	NR	NR	R
5.	Legalized price certificate issued by component authority of coo & attested by embassy including-factory price, wholesale price coo	R	R	R	NR	R
6.	Retail/Public Price in Coo	R	NR	R	NR	R
7.	EXPORT price to country and neighboring countries	R	NR	R	NR	R
8.	Stability studies in various defined conditions	R	R	R	R	R
9.	Storage conditions	R	R	R	R	R
10.	Name of developed countries in which the product is registered	R	R	R	R	R
11.	Abstract from scientific references about product	R	R	R	R	R
12.	Sealed sample of product and copies of label	R	R	R	R	R
13.	Quantity specified for each pack and outer pack of product	R	R	NR	NR	R

14.	Leaflet in Arabic and English, including					
A	Name of product	R	R	R	R	R
B.	Composition	R	R	R	R	R
C.	Mode of action	R	R	R	R	R
D	Effect	R	R	NR	R	R
E	Indications	R	R	NR	NR	R
F	Contraindications	R	R	NR	R	R
G	Precautions	R	R	NR	R	R
H	ADR	R	R	NR	R	R
I	Antidote	R	R	NR	NR	R

J	Dosage and administration	R	NR	NR	R	R
15	Product labeling	R	R	R	R	R
16	Bio availability studies	R	R	R	R	R
17	Scientific basis of justifying the formulation of combination product	R	R	R	NR	NR
18	Post market surveillance	R	NR	NR	NR	NR
19	Certificate of sterility and pyrogen free pharmaceutical product	NR	R	R	NR	NR
20	Copy of reference pharmacopoeia	R	R	R	NR	NR
21	CTD format for dossier submission	R	NR	NR	NR	NR
22	eCTD	R	NR	NR	NR	NR

R: Recommended by regulatory authority, NR: Generally, not recommended by regulatory authority

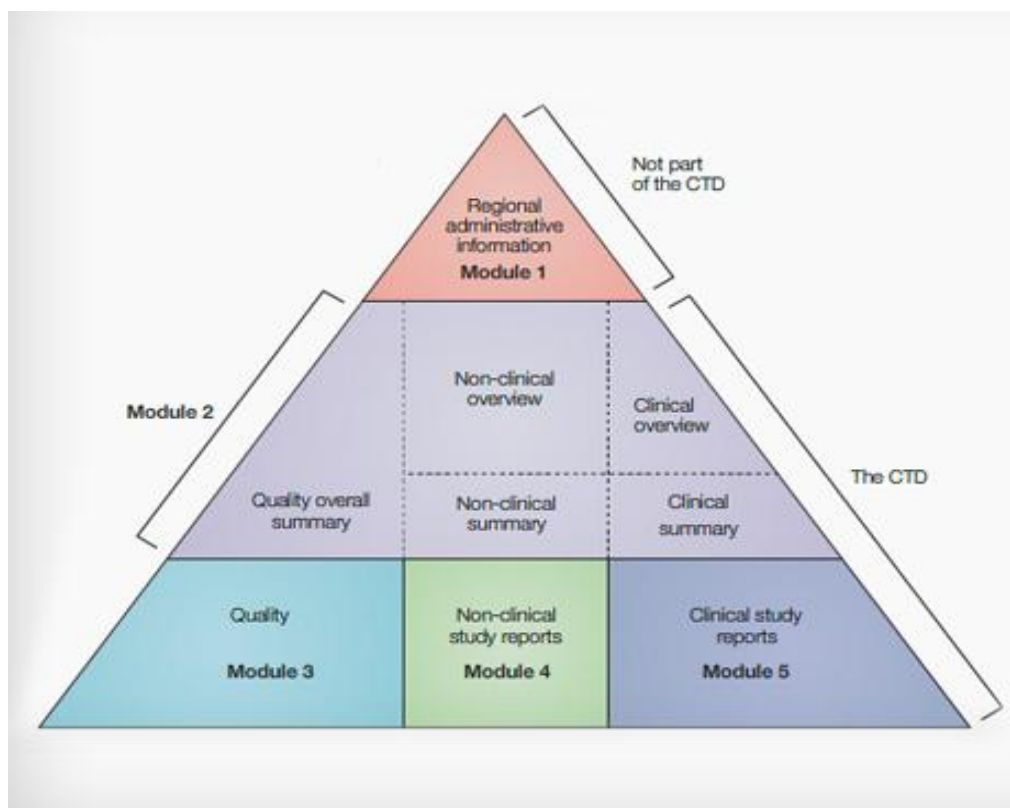


Fig. 9: CTD Triangle

Table 3: THE CTD STRUCTURE FOR HUMAN DRUGS SUBMISSION

DOCUMENTS	LOCATION IN		
	ICH CTD	ACTD	GCC CTD
Administrative Documents Product Information	Module 1	Part I	Module 1
Common Technical Document Overview & Summaries	Module 2	Incorporated in Parts II, III and IV	Module 2
Quality documents	Module 3	Part II	Module 3
Non-clinical documents	Module 4	Part III	Module 4
Clinical documents	Module 5	Part IV	Module 5

## Module 1 Regional Administrative Information

### 1. Cover letter

The applicant shall include a cover letter for each submission. A template is provided in the

#### 1.1. Comprehensive table of content

The table of content for the entire submission should list all documents included in all Modules.

#### 1.2. Application Form

The completed and signed application form printed out from the GCC (SDR) system <sup>(24)</sup>section.

#### 1.3. Product Information

This section contains the Summary of Product Characteristics (SPC), Labelling, Patient Information Leaflet (PIL) in Arabic and English, Artwork and the Samples.

##### 1.3.1. Summary of Product Characteristics (SPC)

The SPC should include the name of the product, strength, pharmaceutical form, quantity of active ingredients, posology, method of administration, indications, contraindications, excipients, shelf-life and any special warnings and precautions for use ... etc.

##### 1.3.2. Labelling

The labelling forms part of the authorization of the product and must therefore be approved by the GCC. The text of the labelling must be in compliance with the SPC.

##### 1.3.3. Patient Information Leaflet (PIL)

1.3.3.1. Arabic leaflet

1.3.3.2. English leaflet

The Patient Information Leaflet (PIL) forms part of the authorization of the product and must therefore be approved by the GCC.

##### 1.3.4. Samples

17 samples should be provided in order to perform complete testing. The required quantities of samples are further described in *the GCC Guidance for Submission*. The submitted samples must represent the final finished product to be marketed in GCC.

### 1.4. Information on the experts

#### 1.4.1. Quality

#### 1.4.2. Non-Clinical

#### 1.4.3. Clinical

It is important to emphasize that well prepared expert reports greatly facilitate the task of the GCC in evaluating the dossier and contribute towards the speedy processing of applications.

Each expert report should consist of:

- An abbreviated product profile;
- A critical evaluation of the dossier.

### 1.5. Environmental Risk Assessment

#### 1.5.1. Non-Genetically Modified Organism (Non-GMO)

#### 1.5.2. GMO

The applicant shall include an evaluation for any potential risks of the product to the environment. This should include risks to the environment arising from use, storage and disposal of products and not for risks arising from the synthesis or manufacture of products.

### 1.6. Pharmacovigilance

#### 1.6.1. Pharmacovigilance System

It shall contain a detailed description of the pharmacovigilance system including the proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction.

#### 1.6.2. Risk Management Plan

A detailed description of the risk management system which the applicant will introduce should be provided, where appropriate. The detailed description of a risk management system should be submitted in the form of GCC Risk Management Plan (GCC-RMP).

### 1.7. Certificates and Documents

#### 1.7.1. GMP Certificate

A valid GMP Certificate should be submitted.

#### 1.7.2. CPP

The CPP should be in accordance with WHO guidelines. However, if the CPP is not available, a marketing authorization from the country of origin (COO) should be submitted.

### 1.7.3. Certificate of analysis – Drug Substance/Finished Product

Certificates of analysis for more than one batch of the drug substance should be submitted from the API supplier & finished product manufacturer.

Certificates of analysis for more than one batch of the finished product should be submitted from the finished product manufacturer.

### 1.7.4. Certificate of analysis – Excipients

Certificates of analysis for more than one batch of the excipients may be submitted to support the application.

### 1.7.5. Alcohol-free declaration

This section should contain a declaration letter in an official company letterhead stating that the product is free from alcohol. In case if the medicinal product contains alcohol, justification should be submitted.

### 1.7.6. Pork-free declaration

This section should contain a declaration letter in an official company letterhead stating that the product is free from any materials of pork/porcine source. In case if the medicinal product contains any materials of porcine source, justification should be submitted.

### 1.7.7. Certificate of suitability for TSE

This section should contain a valid TSE Certificate of Suitability issued by the European Directorate for the Quality of Medicines (EDQM).

### 1.7.8. Patent Information

This section should contain a declaration letter in an official company letterhead stating the patent status of the product in GCC patent office.

### 1.7.9. Letter of access or acknowledgment to DMF

A letter written by the DMF Owner or authorized Agent permitting GCC to reference information in the DMF on behalf of the Applicant.

## 1.8. Pricing

The applicant shall include the price of the product in countries listed in the *GCC Guidance for Submission*.

## Module 2 Common Technical Document Summaries

### Quality Overall Summary

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (*e.g. qualification of impurities via toxicological studies discussed under*).

**Non-Clinical Overview:** Nonclinical Overview should provide an integrated overall analysis of the information in the CTD. In general, the Nonclinical Overview should not exceed 30 pages.

The Nonclinical Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy.
- Pharmacology.
- Pharmacokinetics.
- Toxicology.

### Clinical Overview:

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (*ICH E3*), and other relevant reports.

**Clinical Summary:** The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports.

## Module 3 Quality

### 3.1 Table of Contents of Module 3

The table of content should list all documents included in Module 3.

### 3.2 Body of data

#### 3.2.S Drug Substance

The drug substance information submitted should include the following for each of the options used.

### 1. Certificate of Suitability (CEP)

Certificate of suitability submitted should clearly state the validity period.

A complete copy of the CEP (including any annexes) should be provided in *Module 1*. Along with the CEP, the applicant should submit the following:

#### a) 3.2.S.1.3 General properties

Discussions on any additional applicable physicochemical and other relevant drug substance properties that are not controlled by the CEP and Ph. Eur. monograph, e.g. solubility's and polymorphs.

#### b) 3.2.S.3.1 Elucidation of structure and other characteristics

Studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable.

#### c) 3.2.S.4.1 Specification

The specifications of the finished product manufacturer including all tests and limits of the CEP and Ph. Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph. Eur. monograph, such as polymorphs and/or particle

#### d) 3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation

For any tests in addition to those in the CEP and Ph. Eur. monograph.

#### e) 3.2.S.4.4 Batch analysis

#### f) 3.2.S.5 Reference standards or materials

Information on the finished product manufacturer's reference standards.

#### g) 3.2.S.6 Container closure system

The specifications including descriptions and identification of primary packaging components should be included in this section, except where the CEP specifies a re-test period.

#### h) 3.2.S.7 Stability

The stability should be included in this section, except where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

### 2. Drug Master File (DMF)

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the drug substance may be submitted as DMF.

It is the responsibility of the applicant to ensure that the complete DMF (*i.e. both the applicant's Open part and the API manufacturer's restricted part*) is supplied to GCC directly by the API manufacturer and that the applicant has access to the relevant information in the DMF concerning the current manufacture of the drug substance. A copy of the letter of access should be provided in *Module 1*.

#### 3.2. S.1.1 Nomenclature

- Information on the nomenclature of the drug substance(s) should be provided. For example:
- Recommended International Nonproprietary Name (INN);
- Compendia name (if relevant);
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., *National Name*, *United States Adopted Name (USAN)*, *British Approved Name (BAN)*, and
- Chemical Abstracts Service (CAS) registry number.

#### 3.2.S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. For drug substance(s) existing as salts, the molecular mass of the free base or acid should be provided.

#### 3.2.S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance. This includes the physical description, solubility's in common solvents, polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for liquids), hygroscopic, partition coefficient, ... etc.

#### 3.2.S.2.2 Description of Process and Process Controls

- The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.

### 3.2.S.3 Characterization

#### 3.2.S.3.1 Elucidation of Structure and Other Characteristics

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. This should include copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the drug substance.

#### 3.2.S.3.2 Impurities

Information on impurities should be provided, including a discussion on the potential and actual impurities arising from the synthesis, manufacture, or degradation of the drug substance. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins.

#### 3.2.S.4 Control of Drug Substance

##### 3.2.S.4.1 Specifications

Copies of the drug substance specifications, dated and signed by the concerned individual(s) should be provided, including specifications from each drug substance manufacturer as well as those of the finished product manufacturer.

##### 3.2.S.4.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided. Copies of the non-compendia analytical procedures used to generate testing results provided in the dossier, as well as those proposed for routine testing of the drug substance by the finished product manufacturer, should be provided.

#### 3.2.S.7 stability

##### 3.2.S.7.1 Stability Summary and Conclusions

The GCC guidelines for “*Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)*” should be followed for recommendations on the stability data required for the drug substance(s).

#### 3.2P Drug product

##### 3.2.P.1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information provided should include, for example:

- Description of the dosage form;
- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., *compendia monographs or manufacturer’s specifications*);

##### 3.2.P.2.1 components of product

###### 3.2.P.2.1.1 Drug substance

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., *water content, solubility, particle size distribution, polymorphic or solid state form*) of the drug substance that can influence the performance of the drug product should be discussed.

###### 3.2.P.2.2 Drug Product

**3.2.P.2.2.1 Formulation Development** A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage.

###### 3.2.P.3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

###### 3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process (*including those that may not be added to every batch*)

###### 3.2.P.3.3 Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

### 3.2.P.4 Control of Excipients

#### 3.2.P.4.1 Specifications

The specifications should be provided for all excipients, including those that may not be added to every batch (*e.g. acid and alkali*), those that do not appear in the finished product (*e.g. solvents*) and any others used in the manufacturing process (*e.g. nitrogen, silicon for stoppers*).

#### 3.2.P.4.2 analytical procedures:

The analytical procedures used for testing the excipients should be provided. Copies of the non-compendia analytical procedures used to generate testing results should be provided. Unless modified, it is not necessary to provide copies of the compendia analytical procedures.

### 3.2.P.5 Control of Drug Product

#### 3.2.P.5.1 Specifications

The specification(s) for the drug product should be provided. A copy of the finished product specification(s) (release and shelf-life specifications) dated and signed by authorized personnel (*i.e. the person in charge of the quality control or quality assurance department*), should be provided.

#### 3.2.P.6 Reference standards or materials

Information on the reference standards or reference materials used for testing of the drug product should include the following, if not previously provided in "3.2. S.5 Reference Standards or Materials":

#### 3.2.P.7 Container/Closure System

A description of the container closure systems should be provided, including unit count or fill size, container size or volume, the identity of materials of construction of each primary packaging component, its specification and the supplier's name and address.

#### 3.2.P.8 Stability

##### 3.2.P.8.1 Stability Summary and Conclusions

The GCC guidelines for "*Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)*" should be followed for recommendations on the stability data required for the finished product(s).

## Module 4 Non-Clinical Study Reports

### 4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the CTD.

### 4.2 Study Reports

The study reports should be presented in the following order

#### 4.2.1 Pharmacology

This section should begin with a description of the content of the pharmacologic data package,

##### 4.2.1.1 Primary Pharmacodynamics

Studies on primary pharmacodynamics should be provided and evaluated.

##### 4.2.1.2 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics should be provided by organ system, where appropriate, and evaluated in this section

#### 4.2.2 Analytical Methods and Validation Reports

This section should contain the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure.

##### 4.2.2.2 Absorption

- The following data should be provided in this section:
- Absorption (*extent and rate of absorption, in vivo and in situ studies*).
- Kinetic parameters, bioequivalence and/or bioavailability

##### 4.2.2.3 Distribution

- The following data should be provided in this section:
- Tissue distribution studies.
- Protein binding and distribution in blood cells.
- Placental transfer studies.

##### 4.2.2.4 Metabolism

- The following data should be provided in this section:

- Chemical structures and quantities of metabolites in biological samples.
- Possible metabolic pathways.
- Pre-systemic metabolism (*GI/hepatic first-pass effects*).
- *In vitro* metabolism including P450 studies.
- Enzyme induction and inhibition.

#### **4.2.1.4 Pharmacodynamic Drug Interactions**

- If they have been performed, pharmacodynamic drug interaction studies should be provided in this section Routes and extent of excretion.
- Excretion in milk.

#### **4.2.2.6 Pharmacokinetic Drug Interactions**

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (*in vitro and/or in vivo*) should be provided in this section.

#### **4.2.3 Toxicology**

##### **4.2.3.1 Single-Dose Toxicity**

The single-dose data should be provided, in order by species, by route.

##### **4.2.3.2 Repeat-Dose Toxicity**

Studies should be provided in order by species, by route, and by duration, giving details of the methodology and highlighting important findings

##### **4.2.3.3 Genotoxicity**

- Studies should be provided in the following order:
- *In vitro* non-mammalian cell system.
- *In vitro* mammalian cell system.
- *In vivo* mammalian system (*including supportive toxicokinetic evaluation*).

##### **4.2.3.5 Reproductive and Development Toxicity**

Studies should be provided in the following order, giving details of the methodology and important findings:

###### **4.2.3.5.1 Fertility and Embryonic Development**

###### **4.2.3.5.2 Embryo-Foetal Development**

###### **4.2.3.5.3 Pre- and Post-Natal Development & Maternal Function**

###### **4.2.3.5.4 Offspring, Juvenile, Second & Third-Generation Studies**

If modified study designs are used, the sub-headings should be modified accordingly.

### **Module 5 Clinical Study Reports**

#### **5.1 Table of Contents of Module 5**

A Table of contents for the clinical study reports should be provided.

#### **5.2 Tabular Listing of All Clinical Studies**

##### **5.3.1 Reports of Biopharmaceutic Studies**

###### **5.3.1.1 Comparative BA & BE Study Reports**

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (*e.g., tablet to tablet*). Comparative Bioavailability (BA) or Bioequivalence (BE) studies may include comparisons between: The drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product

###### **5.3.1.2 In vitro/In vivo Correlation (IV/IVC) study reports**

*In vitro* dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in this section. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD.

##### **5.3.2. plasma protein binding reports**

*Ex vivo* protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies.

##### **5.3.3 Reports of Human Pharmacokinetic Studies**

Assessment of the PK of a drug in healthy subjects and/or patients is considered

1. Measure plasma drug and metabolite concentrations over time,
2. Measure drug and metabolite concentrations in urine or faeces when useful or necessary, and/or
3. Measure drug and metabolite binding to protein or red blood cells.



### 5.3.3.3 Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section.

### 5.3.3.4 Extrinsic factors PK study reports

Reports of PK studies to assess effects of extrinsic factors, should be placed in this section.

### 5.3.4 Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be provided in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data.

#### 5.3.5.1 Study reports of Controlled Clinical Studies pertinent to the claimed Indication

- The controlled clinical study reports should be sequenced by type of control:
- Placebo control (*could include other control groups, such as an active comparator or other doses*),

#### 5.3.5.2 Study reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (*e.g., reports of open label safety studies*) should be included in this section. This includes studies in conditions that are not the subject of the marketing application.

### 5.4 Literature References

Copies of referenced documents, *including important published articles, official meeting minutes*, or other regulatory guidance or advice should be provided here. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request<sup>[25]</sup>

## 5. CONCLUSION

From the above study, we have concluded the registration procedure may differ in minor variation and there is further needs for harmonization so the applicant does not modify the individual format & the information will become unambiguous and the transparent to facilitate the review and help a reviewer to become quickly oriented. Information collected and analysed from each country's regulatory system for GCC (Gulf co-operation council countries) pharmaceuticals brings to view the difficulties encountered in each of them. Most of the countries have similar requirements for registration of pharmaceuticals and are striving to harmonize their requirement guidelines. The essential principles are mainly the same in most of the countries studied, but there are some differences and therefore it is necessary to look at these requirements country by country. The price controls and IP regime favour domestic and regional production, which may stunt foreign investment in the sector.

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