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 consider as “emerging market for pharmaceutical export and bilateral trade some incidents of year 2008-09 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 sector, Regulatory Requirements.

INTRODUCTION

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. The emerging GCC drug pharmacy market is undergoing a sea change, with governments implementing reforms, simplifying regulations and upgrading and expanding healthcare infrastructure to compete with the global pharmaceuticals market. 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. There is no standardization in their prices, due to the small size of the market and increasing privatization within the sector. These strategies could include offering incentives to new local manufacturers to compete in the growing market, while existing participants could be encouraged to introduce improved technologies to survive in the multinational-dominated market.\cite{1}

![Map of GCC Countries](image)

**Fig: 1 Map of GCC Countries**

**Historical background**
Ministerial Resolutions about GCC central drug registration
1976 The first conference “studies the possibility to establish system for registration and monitoring pharmaceutical products”.
1977 The second conference they assigned committee to prepare the proposal.
1978 The resolution approved the proposal but as a guideline for each country.
1981 The 10th conference they assigned a committee to study the registration system in Kuwait, KSA, UAE.

1982 The 12th conference. Approved the proposal after a minor change.

1997 The unifying drug registration in GCC and requesting the executive office to study the subject again.

1997 The Kingdom of Bahrain introduced the complete proposal.

1997 The resolution conspiring the importance and necessary of central drug registration.

1998 The Ministers’ Council for GCC called upon reviewing the proposal which was introduced 1997.

1999 The Ministers’ Council approved the central drug registration system and its executive.

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**Fig: 2 Organizational Structure**

Table 1: Drug Regulating Authorities of GCC

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>AUTHORITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kingdom of Bahrain</td>
<td>Pharmacy and drug control department</td>
</tr>
<tr>
<td>State of Kuwait</td>
<td>Pharmaceutical and herbal medicines registration and control administration, Kuwait drug and food</td>
</tr>
<tr>
<td>State of Oman</td>
<td>General directorate of pharmacy and drug control</td>
</tr>
<tr>
<td>State of Qatar</td>
<td>Pharmacy and drug control department</td>
</tr>
<tr>
<td>Kingdom of Saudi Arabia</td>
<td>Saudi food and drug authority</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>Registration and drug control department</td>
</tr>
</tbody>
</table>
Scope of GCC Drug Regulatory Activities

- Pre-Marketing Evaluation.
- Marketing Authorization.
- Post-Marketing Review.
- GMP Inspection
- Technical Guidelines

Documents Prepared and/or maintained by DRA department

Licenses and certificates obtained by Drug regulatory Authorities, Egg; Mfg. License, GMP, COPP, ISO etc. Common Technical Document (CTD/eCTD) ASEAN Common Technical Document (ACTD) Drug Master File, Clinical Trial Reports, Bioavailability & Bioequivalence reports Quality Audit files and reports. [2]

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. Despite the growth of this market, local manufacturing is not able to meet the growing demand, and GCC countries continue to import most (90%) of their needs in medicines from abroad Therefore, significant opportunities exist for growth and expansion of this sector in GCC Expanding growth in this industry would also help to achieve the strategic objectives of the region in terms of industrial diversification into knowledge based industries. As a part of its mandate to promote technical and policy coordination. The proposed coordination meeting is the first of its kind in the sector and it could serve as a catalyst to promote further coordination at the horizontal and vertical levels 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. [3]

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 & 17 samples have to be submitted to the executive office and two samples shall be dispatched to each country along with registration file.\[^{[4]}\]

B. Decentralized Registration Procedure

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\[^{[5]}\]

REGULATORY PROCESS OF KUWAIT

The most important goal of the Kuwaiti review process is to ensure that (a) the product is registered and marketed in countries with recognized and competent regulatory authorities for at least twelve months, (b) that the product meets the desired, internationally recognized, quality standards to ensure that the product was manufactured for its intended use, (c) that the product is stable for the entire proposed shelf life and for six months under the stressed conditions of 40°C/75% relative humidity, and (d) the product price must be reasonable and affordable for local patients.

The Submission Phase

The review process starts with the local agent (or the sponsor) submitting the registration dossier along with a covering letter to the Director of Kuwait Drug and Food Control (KDFC) officially requesting the registration of the pharmaceutical product.

The Evaluation Phase

After entering the scientific review stage, the reviewer evaluates the Chemical and Manufacturing Control (CMC) data focusing on the following data,
1. Product specifications and detailed methods of analysis of the finished products with the reference pharmacopoeias.
2. Full stability studies in tabulated form addressing the proposed product shelf life.
3. Raw material specifications and their methods of analysis as well as the reference pharmacopoeia.

**The Authorization Phase**

When the full assessment has been successfully completed, the final approval decision is made by the DRRS which is officially endorsed by the director of the authority.\([5, 6]\)

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**REGULATORY PROCESS OF BAHRAIN**

Bahrain has a unique medicines policy that clearly states the aims, the current situation and the objectives of the Bahraini medicines control system. It is called the “Bahrain Medicines Policy- BMP”. The goal of the policy is to serve as a guide for action and commitment to provide good quality, safe, and effective medicines which are rationally used and provided at reasonable costs for the people in Bahrain, and for coping with new developments in the field of pharmaceuticals.\([7]\)
The Submission Phase
Initially, the sponsor submits the product registration dossier with the complete documents for the official acceptance of the dossier to be made. The authority did not specify information about the logistics involved at the receiving stage.

Items are checked accordingly,
1. Legal status of applicant/local agent
2. GMP status of manufacturer
4. Acceptable format of the application
5. Organized format of the registration dossier including the three sections of scientific data.

The Evaluation Phase
When the product enters the scientific assessment stage, the dossier is split into three sections, which are assessed in parallel by the appointed reviewer who completes a product assessment template and collects all the resulting questions as they arise during the review into one batch for the sponsor including the laboratory requirements.

The Authorization Phase
The pricing process is the final step and price negotiations occur at the end of the scientific assessment. The sponsor is informed of a positive scientific opinion within 90 days of issuing the authorization.[8]

![Fig: 4 Regulatory Process of Bahrain](image-url)
REGULATORY PROCESS OF OMAN
The regulatory review process in Oman comprises ten stages which are considered critical and have an impact on the approval time of medicines

The Submission Phase
The sponsor submits the product registration file to the authority. All documents must be completed for official acceptance. The following items are checked at the validation stage,
1. Legal status of the applicant/local agent
2. GMP status of the manufacturer
3. Organization of the registration dossier
4. Certificate of a Pharmaceutical Product (CPP) authenticated by the respective embassy or consulate general.

The Evaluation Stage
There is a formal record for the starting time of the scientific assessment. In the primary scientific assessment procedure, an internal reviewer in the drug control department completes a scientific product report, detailing the trade, generic names, indication and country of origin.

The Authorization Phase
The registration committee is responsible for granting the marketing authorization and pricing of the product after completion of the review process.[9]

![Flowchart of Regulatory Process of Oman](image)

Fig: 5  Regulatory Process of Oman
REGULATORY PROCESS OF QATAR

The regulatory review process in Qatar is illustrated in consists of thirteen critical steps that have an impact on the overall time of patient access to the medicines.

The Submission Phase

The regulatory process in Qatar begins with the sponsor submitting the registration dossier to the department containing the complete documents for a successful and timely review process. Must be checked at the validation stage for the file to be accepted for review, these are.

1. Legal status of the applicant/local agent
2. GMP status of the manufacturer
3. Patent/IP status of the active ingredient
4. The CPP authenticated by the respective embassy or consulate general
5. The complete dossier in the acceptable format

Evaluation Phase

During the scientific assessment process, the registration dossier is split into quality, safety and efficacy and the appointed reviewer, who is a technical staff member, reviews all parts in parallel.

The Authorization Phase

The final report is sent to the registration committee for their review, which, on their agreement, makes the final decision to grant the product marketing authorization.[10]

![Image of the regulatory process flowchart]

Fig: 6 Regulatory Process of Qatar
REGULATORY PROCESS IN THE KINGDOM OF SAUDI ARABIA (KSA)

The regulatory review process for medicines in Saudi Arabia is carried out in the newly established autonomous “Saudi Food and Drug Authority.” The review process comprises thirteen steps which are critical to the whole process.

The Submission Phase

The authority’s approval process starts with the sponsor submitting the product registration dossier to the authority online. The applicant has to pay the application fees in order to submit the application form and schedule an appointment to deliver the hard and electronic copy of the product file. The sponsor must ensure that the dossier contains the complete documents for it to be officially accepted for assessment.

The Evaluation Phase

The authority’s technical staff carries out the scientific assessment process. Different procedures are carried out in different sections and departments particularly for New Chemical Entities (NCEs) and biological products. In the scientific assessment stage, the reviewing staff assesses the quality, safety and efficacy data in parallel.

The Authorization Phase

Towards the end of the scientific assessment, the authority requests the sponsor to submit the price list outlining the price of the product in countries where it is marketed.\textsuperscript{12, 13}

![Diagram of Regulatory Processes in the Kingdom of Saudi Arabia (KSA)]
REGULATORY PROCESS IN THE UNITED ARAB EMIRATES (UAE)

The regulatory review process in UAE consists of twelve critical stages that are considered essential and comprise a significant part of the review procedure.

The Submission Phase

The sponsor submits the registration dossier, which must contain all the required data to pass the validation stage and become accepted for review. An appointment is then arranged with the department’s administrative staff to submit the product for registration and an appointment sheet and evidence of the manufacturing site registration must be presented at this stage.

1. Legal status of applicant/local agent
2. Patent/IP status of the active ingredients
3. Evidence of payment of the relevant fees

The Evaluation Phase

The dossier is split into the three sections; quality, safety and efficacy; which are all reviewed together by the same appointed reviewer. The reviewer must complete a product evaluation template and print all the resulting requirements into one report for the sponsor.

The Authorization Phase

The higher registration committee is the committee that is responsible for granting the final approval for a product, which is of political and administrative rather than of technical membership. The registration committee reviews the scientific committee report and makes a decision to grant marketing authorization for a product accordingly. [14, 15]

![Flowchart of Regulatory Processes in the United Arab Emirates](image-url)

Fig: 8 Regulatory Processes in the United Arab Emirates
Table: 2 Data requirements of different regions registration requirements in Saudi Arabia, Bahrain, Kuwait and UAE [16]

<table>
<thead>
<tr>
<th>Saudi Arabia</th>
<th>Bahrain</th>
<th>Kuwait</th>
<th>UAE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Format</strong></td>
<td>Company profile&lt;br&gt;• Number of manufacturing sites owned by company&lt;br&gt;• Address of each site&lt;br&gt;• Legal &amp; commercial relations with all sites&lt;br&gt;• Manufacturing license with date in country of origin (COO).&lt;br&gt;• Address of applicant with contact details.&lt;br&gt;• Number of employees in different section &amp; their qualification details.&lt;br&gt;• Graphic design &amp; flow of manufacturing line of site.&lt;br&gt;• List of all products manufactured at company’s site or Contract manufacturing Organization or other marketing authorization holder.&lt;br&gt;• Relationship MAHs.&lt;br&gt;• Any previous inspection by GCC health authorities or Arab health authorities</td>
<td><strong>Data requirements</strong>&lt;br&gt;• Reference standard with COA.&lt;br&gt;• Finished product sample.&lt;br&gt;• Patient information&lt;br&gt;• Source of supply of API and inactive ingredients.&lt;br&gt;• Raw material specifications.&lt;br&gt;• Finished products specifications with quality control Methods.&lt;br&gt;• Stability data: Long term batches&lt;br&gt;• Accelerated studies: six months, same three batches, used for long term studies.&lt;br&gt;• Bioequivalence Study data</td>
<td><strong>Distributor of product in UAE.</strong>&lt;br&gt;• Manufacturing Site.&lt;br&gt;• Marketing authorization Holder &amp; power of attorney.&lt;br&gt;• Manufacturer of API.&lt;br&gt;• Regulatory status.&lt;br&gt;• Price list.&lt;br&gt;• Declaration (In accordance with the medicines’ regulations of Drug Control Department- Ministry of Health -UAE)</td>
</tr>
</tbody>
</table>

- CTD format. eCTD recommended.<br>Module 2 to 5:a/c to ICH CTD format. Module 1: regional requirements:<br>• Cover letter<br>• Table of contents<br>• Application form<br>• Product information: Summary of product Characteristics (SMPC), product information leaflet (PIL) and labeling all in WHO template format.<br>• Information on experts involved in clinical, nonclinical studies.<br>• Environment risk assessment.<br>• Pharmacovigilance<br>• Certificate of pharmaceutical product (COPP)<br>• Pricing<br>• Response to questions asked by SFDA (in any)
## Encloruses required for drug registration in five Gulf Cooperation Council countries

<table>
<thead>
<tr>
<th>S.No</th>
<th>Enclosures</th>
<th>KSA</th>
<th>Kuwait</th>
<th>UAE</th>
<th>Oman</th>
<th>Bahrain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Control specification &amp; method of analysis</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>NR</td>
</tr>
<tr>
<td>2.</td>
<td>Certificate of analysis attested by health authority and country of origin</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>3.</td>
<td>Legalized free sale certificate issued by health authorities for COO, indicating that product register &amp; market with same name &amp; composition</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>4.</td>
<td>Legalized certificate indicating that diluents used are allowed to be in COO</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>5.</td>
<td>Legalized price certificate issued by component authority of COO &amp; attested by embassy including ex-factory price, wholesale price COO</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>6.</td>
<td>Retail/Public Price In COO</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>7.</td>
<td>Export price to country and neighboring countries</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>8.</td>
<td>Stability studies in various defined conditions</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>9.</td>
<td>Storage conditions</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>10.</td>
<td>Name of developed countries in which the product is registered</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>
SUMMARY

The main requirements for our study is usually a local representative, a Certificate of Free Sale from the country of origin, import license from the competent authority in the import country, registration of the company and the product. To accomplish this, it is necessary to fulfil the essential principles, classify the product, apply Good Manufacturing Practice and risk management, follow the labelling requirements and establish a documented post-market surveillance system. Technical documentation is also necessary and in most cases that can be submitted with the registration application. From the above comparative study it, can infer that “regulations for the safety of patient is same but rules and procedures followed to implement that are different", due to this reason a common framework & format like CTD cannot be implemented though the submission of the document is made electronically.
CONCLUSION

From the above study we have concluded the registration procedure may differ in minor variation and there are 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 analyzed 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 favor domestic and regional production, which may stint foreign investment in the sector.

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REFERENCES


