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Review Article

A REVIEW ON REGULATORY PROCESS AND APPROVAL PROCESS OF PHARMACEUTICALS IN GCC COUNTRIES

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ABSTRACT

Regulatory affairs is a profession which acts as the interface between the pharmaceutical industry and Drug Regulatory authorities across the world which ensures the access of safe and effective medicines to the patients. The gulf cooperation council region is considered as “Emerging market” for pharmaceuticals. The GCC healthcare market is projected to grow at 12.1% compound annual growth rate (CAGR) from an estimated US$ 40.3 billion to US$ 71.3 billion in 2020. The aim of the study was to develop a harmonized, regulatory review processes and timelines in the region with registration procedure of Kingdom of the Saudi Arabia and United Arab Emirates.

KEY WORDS: Gulf Cooperation Council, general review process, regulatory, Kingdom of Saudi Arabia (KSA), United Arab Emirates (UAE)

INTRODUCTION

The Gulf Central Committee for Drug Registration (GCC-DR) was formed in May 1999 with six Middle Eastern States – Saudi Arabia, Kuwait, Qatar, Bahrain, Oman and the United Arab Emirates; and in 2003 Yemen became the seventh member of the GCC-DR. The aim of the GCC-DR is to work together to

review/approve pharmaceutical companies and their drugs by means of a centralised registration procedure in order to provide the seven member states with safe and effective medicines with a reasonable price. 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. The GCC healthcare market is projected to grow at 12.1% compound annual growth rate (CAGR) from an estimated US$ 40.3 billion to US$ 71.3 billion in 2020. From US$ 24.0 billion in 2015, the outpatient market is expected to reach US$ 42.4 billion in 2020. In each of the GCC countries, the healthcare markets are expected to grow annually at an average rate of 11-13% from now until 2020. The UAE has traditionally imported the majority of medical care and pharmaceuticals. Recently however, **there has been a concerted effort to increase clinical trials, localise the manufacture of drugs, and attract talented medical professionals.** [1-2]

Fig 1: Map of GCC Countries

GCC REGIONAL HARMONIZATION

Cooperative action can be effective in strengthening regulatory capacity at the national level; the EU centralised Procedure is an established model, involving the largest number of countries, for such an approach. Following the EU example, the seven Gulf Cooperation Council (GCC) states (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) took the initiative to improve patient access to safe and effective medicines in the GCC region. This was accomplished by strengthening the technical and administrative capacities of the individual GCC regulatory authorities. This collaborative mechanism is designed to ensure a more transparent and streamlined process for marketing authorization of pharmaceutical products in the GCC region. The authorities have made their review processes equivalent to one another, leading to harmonization**.**

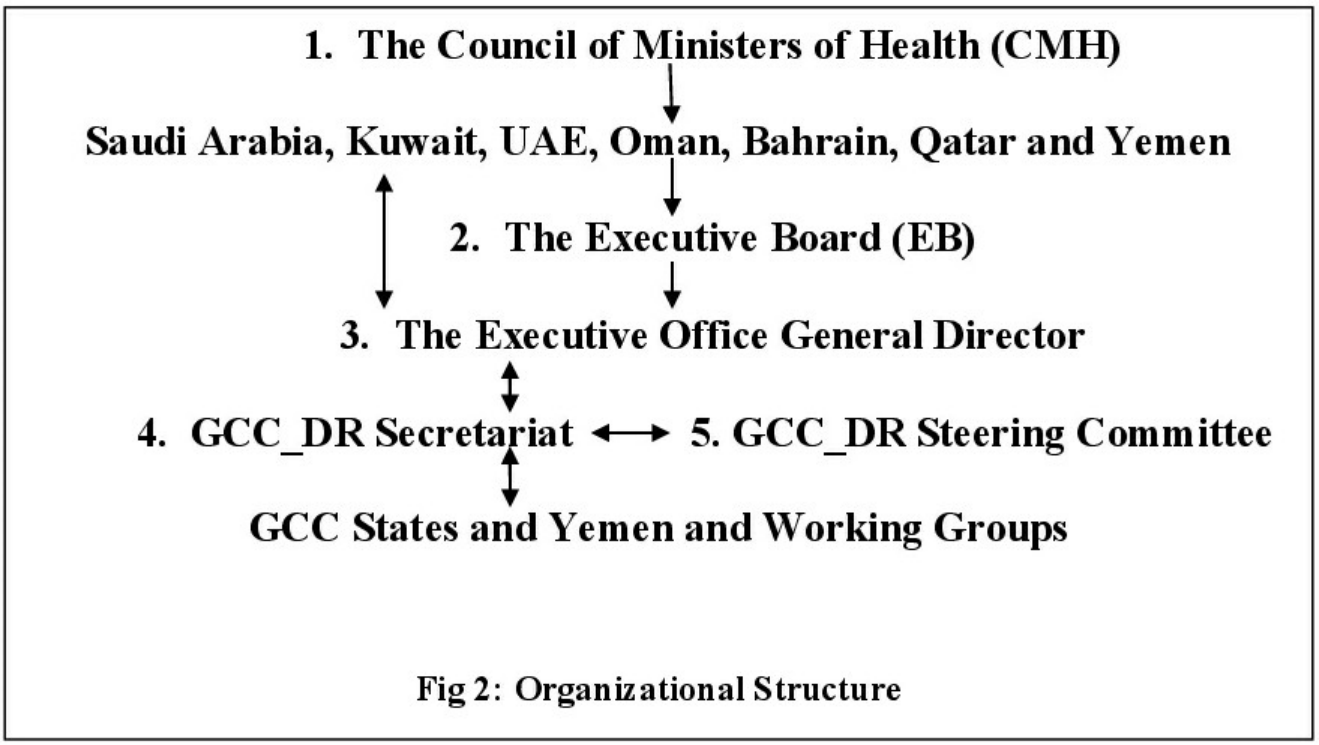

Fig 2: Organizational Structure

Table 1: Drug Regulating Authorities of GCC

Sr. no.	COUNTRY	AUTHORITY
1.	Saudi Arabia	Saudi food and drug authority
2.	Oman	The Directorate General of Pharmaceutical Affairs & Drug Control
3.	Bahrain	National health regulatory authority Bahrain
4.	Qatar	Pharmacy and drug control department
5.	United Arab Emirates	Registration and drug control department
6.	Kuwait	Pharmaceutical and herbal medicines registration and control administration, Kuwait drug and food
7.	Yemen	Supreme board of drugs and medical appliances

Scope of GCC drug regulatory activities

- Pre-marketing evaluation
- Post-marketing review
- GMP inspection
- Marketing authorization
- Technical guidelines [3-4]

GCC-DR Responsibilities

- Registration of pharmaceutical companies

- Registration of pharmaceutical products
- Approval of Quality Control Laboratories (QCL)
- Inspection of pharmaceutical companies for GMP compliance
- Reviewing of Technical and PMS reports [5]

REGULATORY REVIEW PROCESSES

The study examined 3 common phases in each of the 7 GCC regulatory review processes-namely, the submission phase, the evaluation phase, and the authorization phase.

A.Submission phase

The submission phase involves all the stages and processes which is carried out by the authorities administrative staff prior to the scientific assessment of the medicine. These include the receipt and validation stage and the queuing stage.

Receipt and validation stage: The 7 authorities record the date of receiving the registration dossier, and 5 authorities carry out a validation process to ensure that the documents submitted for registration are complete before they can be accepted for review. Kuwait and Yemen accept the dossier for review and carry out the validation process as part of the scientific assessment stage where all questions, queries, and missing data are requested from the sponsor after completing the scientific review process. Furthermore, all the GCC authorities, except Qatar, apply fees for the registration of medicines. The range of fees differs from country to country according to the funding structure and the services provided by each authority. It is agreed by all the authorities that to improve the regulatory review process, they need to improve their resources by increasing the number of expert reviewers, developing the information technology (IT) structure, and establishing training and continuing professional development (CPD) programs. However, without proper funding, the authorities will always face difficulties in improving their regulatory systems.

A general difference was observed in the perception and time taken to validate the registration dossier from one country to another, with UAE performing the validation process within 24 hours, whereas Bahrain takes up to 14 days. Kuwait, however, indicated that it is a time-consuming process, particularly when carrying out a simple verification assessment.

Queuing stage: A queuing process was identified in all the Gulf authorities except Yemen. However, when the GCC authorities recognize the therapeutic urgency of a medicine, they carry out a priority review. Saudi Arabia expressed concerns in conducting priority reviews without having a set of guidelines and standard operating procedures (SOPs) that direct them toward appropriate decisions. The queuing time varies considerably across the Gulf region, ranging from 14 days in Bahrain and Oman to more than 180 days in

UAE. However, for a medicine to remain in this stage for several months unjustifiably delays patients access to medicines.

B.Evaluation Phase

The evaluation phase includes all the stages that involve the scientific assessment and quality control analysis carried out to ensure that the medicine is safe and effective. This phase consists of 3 stages that are common to the 7 GCC authorities: scientific assessment, sponsor's interaction, and sample analysis stage.

Scientific assessment stage: The scientific assessment stage play crucial role in the regulatory review process where the product's quality, safety, and efficacy dossier are evaluated. The starting date of the scientific assessment is generally recorded in most of the GCC states, except in UAE and Qatar, probably because the review process starts from the date of submission and ends at the date of granting the approval. Internal reviewers assess the quality, safety, and efficacy dossiers in 6 GCC states, whereas Yemen depends on external reviewers to provide a clinical opinion about the medicine.

External reviewers are used in Kuwait for assessing clinical studies for selected new active substances (NASs). Oman hires external experts to provide advice on certain technical issues under no contractual agreement with the authority. Saudi Arabia has an expert panel that consists of 10 to 15 consultants who provide a detailed assessment report and recommendation to the authority's staff. [6]

Five regulatory authorities in the Gulf region have scientific committees as part of their assessment process. Kuwait and Qatar do not have scientific committees, and the quality of the review report depends on the assessors experience and skills in evaluating the registration dossier. It is considered valuable by advanced regulatory authorities to have committees review the scientific assessment reports and make an appropriate recommendation about the final product approval decision as this provides in essence a peer-reviewed system that in turn adds to the quality and robustness of the review.

Stage Sponsor's interaction: The sponsor's interaction process is where communication occurs between the sponsor and the authority with regard to the registration of new medicines in each GCC State. Questions and queries arising during the scientific assessment are collected into a single batch to be sent to the sponsor by 6 of the GCC authorities. Yemen, however, communicates these questions to the sponsor as they arise during the assessment process. In Bahrain, Kuwait, Oman, and UAE, interaction with the sponsor is permitted with the internal staff under the supervision of the section manager, whereas Saudi Arabia has expressed concerns with communication process, specifying the need for proper guidelines and SOPs on how to monitor sponsor-staff interactions. Qatar applies restrictions to the handling of the authority's communication process with the sponsor and limits these interactions to official letters, e-mails, faxes, or scheduled meetings with senior managers only. Interaction and the ability to communicate effectively are necessary to maximize the value of this stage and its contribution to the review process.

Sample analysis stage: In general, the sample analysis stage is an essential part of the review process that affects the overall approval time for medicines in the 7 GCC authorities. It is carried out in parallel with the scientific assessment stage in some countries (Oman, Qatar, Saudi Arabia, UAE, and Yemen) and after the scientific assessment in others (Bahrain and Kuwait). The outcome of the sample analysis affects the final approval decision. Nonetheless, the GCC authorities waive the analytical stage for products registered in Kuwait, Saudi Arabia, Oman, UAE, the GCC central drug registration (GCC-DR), and/or countries with advanced regulatory systems such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

C.Authorization Phase

The authorization phase is carried out when a satisfactory outcome of the evaluation phase has been reached and covers the product pricing process and the final approval decision.

Pricing stage: Pricing agreement has a significant impact on the overall approval time. The pricing of a medicinal product is finalized prior to market into the GCC states. However, in 3 states (Bahrain, Oman, and Saudi Arabia), the pricing procedure starts at the end of the scientific assessment process, but it is carried out after granting the registration approval in Qatar, UAE, and Yemen.

Table 2: The Pricing Process in the Gulf Cooperation Council Regulatory Authorities

Pricing Procedure	Bahrain	Kuwait	Oman	Saudi Arabia	Qatar	UAE	Yemen
Parallel to the scientific review	X	√	X	x	X	x	x
After the scientific review	√	X	√	√	X	x	x
After issuing the registration approval	X	X	X	x	√	√	√
Pricing decision	RC	Minister	TCR&P	Head of authority	Minister	Minister	TCR
Affects the overall approval time	√	√	√	√	√	√	√

RC: Registration Committee; TCR&P: Technical Committee for Registration of Pharmaceutical Manufacturers and their Products and Pricing of Products.

The pricing step in other Gulf states is part of the regulatory review process, and registration committees are responsible for both the product registration and pricing decisions. Because of its political sensitivity, the medicines prices are approved by the minister of health in Kuwait, Qatar, and UAE and by the head of SFDA in Saudi Arabia. It is important to evaluate the quality, safety, and efficacy of the medicinal product to protect the public health, but ensuring that the product price is affordable by local patients is another important aspect to be considered.

Approval stage: In general, most authorities do not perform separate negotiations about the product information or package insert after the scientific opinion is reached or prior to issuing the final approval. However, if issues require further clarification, they can be share with official face-to-face meetings or by other appropriate means of communication with the company representative.

Bahrain, Qatar, and UAE were not able to specify their target approval times as several factors are involved in their judgments such as the types of products being registered (ie, whether they are NASs, EASs [existing active substances], or therapeutically important or lifesaving products), the quality of the submitted dossiers, and the level of follow-up and interaction between the pharmaceutical company and the authority. The other 4 authorities showed slight differences in their overall target approval times, with the shortest being in Oman (120 days). The time taken from reaching a positive opinion by the scientific committee to the final approval decision varies considerably across the region, taking less than 30 days in Kuwait, Oman, and Saudi Arabia; 90 days in Bahrain, Qatar, and UAE; and more than 180 days in Yemen. This is the time period to complete the final administrative procedures before granting the registration approval in each country. [7-8]

DRUG REGISTRATION PROCEDURE

Gulf Central Committee for Drug Registrations (GCC-DR)

- Approved in May 1999.
- Located in the executive office for Health Ministers, Riyadh, Saudi Arabia.

Drug registration: Two processes is there

A. Centralized registration procedure

B. Decentralized registration 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:
  - Drug companies registration form.
  - A pharmaceutical chemical entity/ preparation registration form.
- Eight complete files for each chemical entity and 17 samples have to be submitted to the executive office and two samples shall be dispatched to each country along with registration file.
- Every country shall study the registration files forwarded to it and then return those files with its recommendation to the committee.
- The sample given is dispatched by the executive office for analysis
- After approving the registration of company and or chemical entity centrally, the remaining authentication and documentation, fees are finalized as per their prescribed and established policies of country.
- The executive office issues the registration certificate.
- The companies have right to grief to the executive office within a period of two months effective from the date of notification about the registration of by GCC-DR. [9]

B. **Decentralized registration procedure**

Registration regulations in major countries of GCC are there as well established regulatory system and its enforcement. In this study, we will discuss briefly the registration requirements of multi-source generic products of the two main countries.

1. Kingdom of Saudi Arabia
2. United Arab Emirates [10]

REGULATORY PROCESS IN THE KINGDOM OF SAUDI ARABIA (KSA)

The Saudi Food and Drug Authority [SFDA] is the main drug regulatory body of Saudi Arabia. SFDA prefers the drug dossier submission in electronic format (eCTD). 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. [11-12]

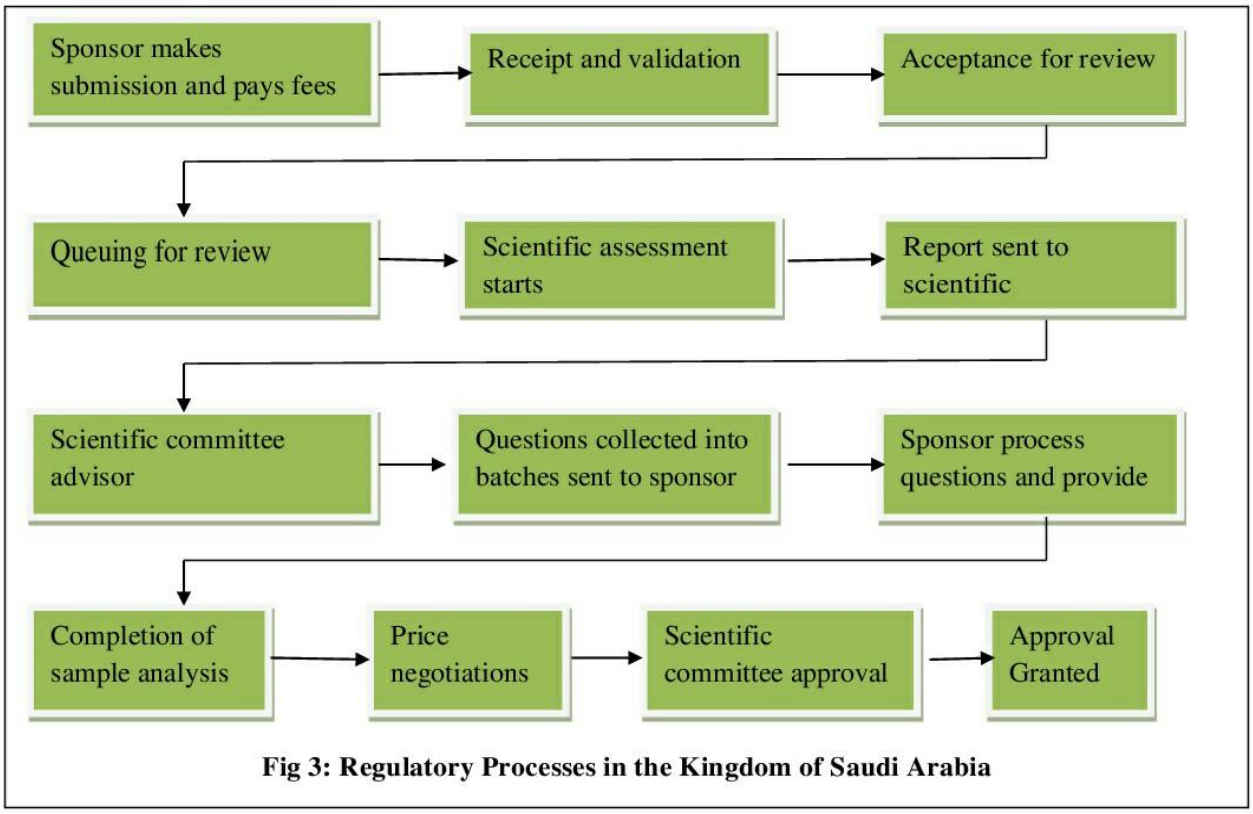

Fig 3: Regulatory Processes in the Kingdom of Saudi Arabia

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. [4]

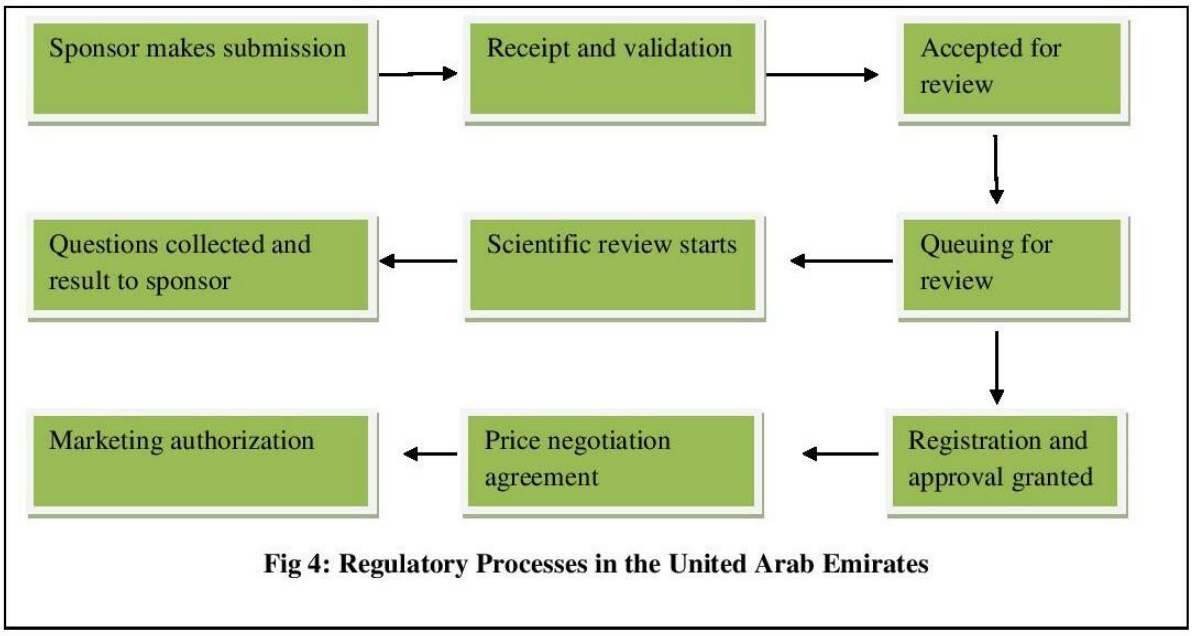

Fig 4: Regulatory Processes in the United Arab Emirates

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. 13-14

STRUCTURE, RESPONSIBILITIES AND SCOPE OF ACTIVITIES WITHIN EACH OF THE SEVEN GULFCOOPERATION COUNCIL (GCC) REGULATORY AUTHORITIES

To this end, the structure, responsibilities and scope of the individual GCC regulatory authorities were

explored through personal communication with key regulators in the region (see Table 3). Five authorities fall under the Ministry of Health and are fully funded by their respective governments. Saudi Arabia and Yemen, however, have independent, authorities relying on registration fees as the major source of their funding. All seven GCC authorities regulate pharmaceutical products for human use with their main scope of activities revolving around marketing authorization, post market surveillance and quality control analysis. They also have a variety of other responsibilities depending upon their size and resources. [15]

Table 3. Structure, Responsibilities and Scope of Activities within Each of the Seven Gulf Cooperation

Name of Authority		**The Pharmacy & Drug Control Department**	**Kuwait Drug and Food Control**	**The General Directorate of Pharmacy & Drug Control**	**The Pharmacy & Drug Control Department**	**Saudi Food & Drug Authority**	**The Registration & Drug Control Department**	**Supreme Board of Drugs & Medical Appliances**
Scope of registration responsibilities	Medicines for human use	√	√	√	√	√	√	√
	Veterinary medicines	x	√	x	x	√	√	√
	Medical devices and in-vitro diagnostics	√	√	√	√	√	√	X
	Cosmetic products	x	√	x	x	x	x	X
	Food supplements	x	√	x	x	x	x	X
	Herbal medicines	x	√	x	x	x	x	X
Scope of activities	Marketing authorization	√	√	√	√	√	√	√
	Postmarketing surveillance	√	√	√	√	√	√	√
	Sample analysis	√	√	√	√	√	√	√
	Advertising control	x	√	√	x	√	√	X
	Price regulation	√	√	x	√	√	√	√
	GMP inspection	-	√	x	x	√	x	X
	Clinical trial authorization	√	x	√	x	√	√	X

CONCLUSION

From the above review study we have concluded that seven GCC states have well-established authorities that

demonstrate well experience in the registration process for the implementation of critical quality management systems that can achieve standardized good review practices in the region. Information collected and analyzed from Saudi Arabia and UAE regulatory system for pharmaceuticals which brings to view the difficulties encountered in each of them. Generally most of countries have similar requirements for registration of pharmaceuticals and are striving to harmonize their requirement guidelines. The important 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. This study also compared the structure, responsibilities and scope of activities within the seven GCC regulatory authorities. Therefore, review process and drug registration procedure are milestones for drug approval process in the country.

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