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REVIEW ARTICLE

Regulatory pathway for pharmaceutical drug product registration and export in Gulf countries

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ABSTRACT

The Indian pharmaceutical market is the third largest in terms of generic production. It has developed a reputation as a center of industry and research in the international market. India offers some of the cost-effective manufacturing facilities globally. The Gulf cooperation council (GCC) region is regarded as a "developing market for pharmaceutical export". This study assessed the regulatory frameworks of the GCC member countries of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE) to build a coordinated approach. GCC regions are exposed to a partially regulated market. Most regulatory changes and developments must be kept up to date by pharmaceutical businesses, and GCC adopted the international council for harmonization common technical document (ICH CTD) format for new product registration. To fulfill the public demand for safe and effective treatments, regulations are needed for pharmaceutical drug products urgently due to rising healthcare costs, R&D expenditures, and other factors. Harmonizing the data on quality, safety, and efficacy reported in the application dossier is a main concern for the ICH committee. This review article provides the regulatory framework of GCC countries for effective control of pharmaceutical products.

KEY WORDS: Drug registration, Export, Gulf cooperation council, Indian pharmaceutical market

INTRODUCTION

The Indian pharmaceutical market has experienced significant expansion in recent years and is one of the fastest-growing industries in the nation. The pharmaceutical business also engages in contract research and manufacturing, clinical trials, contract R&D, and direct exports to developed and developing country markets, in addition to meeting domestic demand. The Indian market is one of the biggest manufacturers of generic pharmaceutical products and occupies a significant position in the global pharmaceutical market. More than 200 countries import drugs from the Indian pharmaceutical industry, including strictly regulated markets such as the US, Europe, and Japan. India fulfills more than half of Africa's need for generic drugs, 40% of the generic drug demand in the US, and 25% of the generic drug demand in the UK. Medicines and other pharmaceutical items require strict regulatory oversight and quality control, which is of extreme significance. The evaluation of drugs for the control of drug quality and commerce has advanced significantly as a result of the pharmaceutical industry's rising regulatory requirements. While laws provide a legal foundation for drug control, regulatory norms, and common tools serve as a foundation for their execution.[1] The Indian pharmaceutical industry is also known as the hub of generic medicines. At present, Indian Pharmaceutical business is in the third position in the manufacturing of pharmaceuticals by volume. In the past 9 years, the pharmaceutical industry

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in India has increased steadily at a CAGR of 9.43%. Even in 2020–2021, there will be a total pharmaceutical export of USD 24.35 billion.[2]

The Gulf cooperation council (GCC) is an international organization made up of six countries all located in the Persian Gulf region. The GCC was first founded in 1981 by the GCC charter, also termed the cooperation council for the Arab States of the Gulf. GCC is an association of six middle-eastern nations on the political and economic front. It is a framework of regional cooperation among the Arab Gulf states established to address the difficulties introduced by the surroundings. Additional elements that contributed to the formation of the GCC included the countries' proximity economically, the similarity of their legal systems, and the similarity of their economic and social situations. The GCC member states also have taken the initiative to establish centralized processes to increase patients' access to secure and efficient medications within the GCC region. The GCC regulatory body reduces their deviation and harmonizes regulatory procedures throughout the GCC Region.

This review article provides an in-depth knowledge of regulatory requirements for pharmaceutical companies seeking business in GCC countries. This includes the product registration process through various channels such as centralized and decentralized. These articles are also highlighting the regulatory requirements for the export of pharmaceutical products with special reference to the GCC countries.

GULF CO-OPERATION COUNCIL

A treaty signed on May 25, 1981, in Abu Dhabi (UAE), between Kuwait, Qatar, Oman, Bahrain, Saudi Arabia, and UAE established the GCC [Table 1], taking into account their specialties, proximity geographically, similar political systems based on Islamic principles, shared destiny, and shared goals. The total population of the Gulf member states is 65,507,000 and the total area is 2,673,108 square kilometers and has Arabic as an official language.[3] The GCC pharmaceutical business has advanced significantly over the years as a result of positive economic, demographic, and healthcare-related variables. Despite the advancements, the Gulf's pharmaceutical industry is still in its emerging phase, with drug production at a very early stage. Most of the medications used in the region are of an international brand. Over 80% of the pharmaceuticals required in this region are imported. In the GCC, Saudi Arabia is responsible for the largest portion of manufacturing facilities.

Table 1: Drug regulatory authority in different Gulf countries

Gulf States	Regulatory Authority
Kuwait	Kuwait food and drug authority (KuFDA)
Qatar	Supreme council of health
Oman	Directorate general of pharmaceutical affairs and drug control - Ministry of health
Bahrain	Ministry of Health
Saudi Arabia	Saudi food and drug authority
United Arab Emirates	UAE Ministry of Health

The Saudi pharmaceutical industries and medical appliances corporation (SPIMACO) is based in Saudi Arabia and the Gulf pharmaceutical industry (Julphar) is based in the United Arab Emirates. Abbott Laboratories and GlaxoSmithKline are both well-known global corporations that operate manufacturing facilities in the area. However, governments have been promoting joint ventures and license agreements with multinational pharmaceutical corporations to boost domestic medicine production and required less amount of drug imports. In comparison to many middle-eastern and North African nations, the GCC has lower pharmaceutical sales as a percentage of GDP. By 2020, the Gulf governments are widely anticipated to invest USD 12 billion in the pharmaceutical sector.[4]

Foreign drug exporters must only use regional importing and distribution businesses that have registered with the health ministry to sell their pharmaceutical products in GCC nations. The health ministry of each GCC nation has regulatory authority and responsibility over the pharmaceutical industry.[5] The regulating bodies for the GCC pharmaceuticals industry are the ministries of health of the GCC states (Kuwait, Qatar, Oman, Bahrain, Saudi Arabia, and UAE). They also control medicinal product prices. The GCC created a centralized structure, to modernize the regulatory process and harmonize prices across industries.[6] The Gulf central committee for drug registrations (GCC-DR), a regulatory organization covering the region, reached a turning point in May 1999, located in the executive office of the Saudi Arabia health ministers, Riyadh.[7] A Gulf member country involving drug policy, bioequivalence (BE) programming, GCC drug regulations, and central drug registration (DR) effective production techniques, quality central laboratories are certified by accreditation support for the regional pharmaceutical sector.[8]

DR PROCESS IN GCC

Before a drug product releasing into the market, all new drug items must be registered with the regulatory body in control of the target market. The safety, quality, and efficacy of drug products are ensured through the registration procedure. To improve public health and secure its position in the market, the pharmaceutical industry must satisfy crucial requirements of the regulatory framework. Drug product registration in the Gulf country is involved two types of procedures to provide a simple and reliable method for DR in the Gulf country. These procedures are

Centralized registration procedures

The executive office of GCC-DR accepts registration files on confirming that all registration requirements have been met and on properly completing the forms. Eight complete files and 17 samples must be presented to the executive office for each chemical entity. Two samples must also be sent with each registration file to each country. Each nation must carefully review the registration files required to carefully review registration files that are sent to it before returning them along with its suggestions to the committee. For the analysis of standard materials, and procedures, the manufacturer must provide a sample to the testing laboratory. The executive office transfers samples of the entity's chemicals for analysis to a reference-accredited lab. After central approval of the company registration or chemical entity, the remaining verification, documentation, and fees are finalized at the country level by that nation as per prescribed norms. Then finally the certificate of registration is granted by the executive office.[6] Figure 1 demonstrates the centralized registration procedure in GCC.

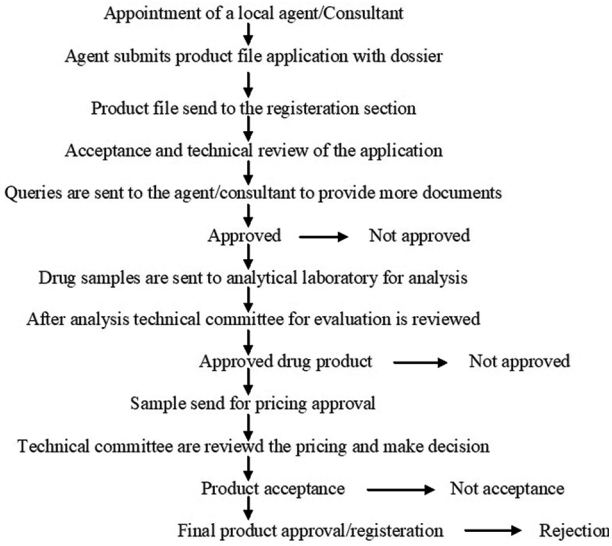

Figure 1: Centralized registration process in Gulf country

Decentralized registration procedures

Although the major GCC countries have a centralized process for the registration of drugs product, some big countries, like Saudi Arabia and the UAE, have their distinct regulatory criteria. These countries have a well-established regulatory framework. These nations have their in-built regulatory system and their enforcement.[9]

The consolidated purchasing must follow the decisions made for medicine registration by the central Gulf committee. The export price, which has been agreed upon by the committee following the conclusion of the registration processes in the country, must be sanctioned and approved by all nations.

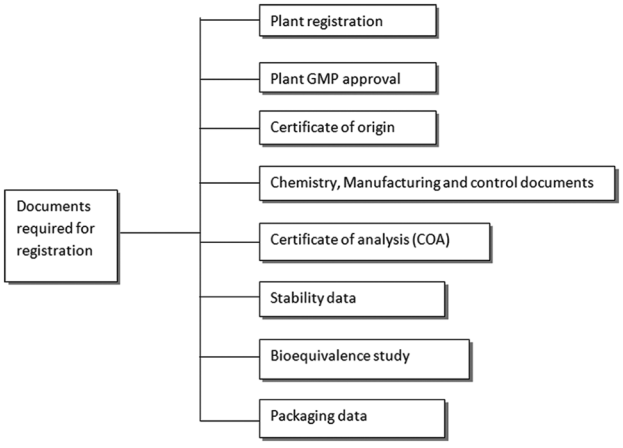

Figure 2: Regulatory documents for registration of drug

DR requirements for Gulf country

In Gulf nations, the Ministry of Health monitors drug products and follows the rules for DR. Since the ICH guidance was adopted 10 years ago, these requirements have undergone significant change. Even the submission information had undergone a significant change from the paper format to the present eCTD file, through CTD, Non-eCTD Electronic Submission, and finally the current format. Identifying the proper registration process is necessary for assisting you in strategic planning for your entry into or development into the Gulf market. Registration requirements follow many steps in Figure 2.

- Site registration is required for DR in the gulf states and complies with the gulf regulations, drug dossier, and submission procedure.
- The GCC area accepts only GCC members who are required to conduct an audit for the plant's GMP approval of the completed product site. It is intended to reduce any manufacturing risks that cannot be eliminated through testing the finished product in the pharmaceutical industry.[10]
- The administration record needs the exporter's intention to sell a specific number of items. According to the defined terms and circumstances established by the exporter and the importer, this document was issued.
- Administrative records include many documents like a certificate of origin and certificate of pharmaceutical product (COPP), license of the manufacturer, certificate of free sale, product information, labeling information, and information from the guidebook.
- WHO guidelines are followed by GMP certification. Compliance with the pharmaceutical manufacture's good manufacturing practice standards as verified by a GMP certificate.
- Documents related to chemistry, manufacturing, and controls. Drug master file (DMF) for active pharmaceutical ingredient (API) along with the

following information such as nomenclature, general, properties, the manufacturer's name and location of manufacture, the route of synthesis, a brief flowchart, structural elucidation, specifications, and approach of analysis, stability testing, and storage testing is provided.

- Limitation for impurity boundary: The following elements must be taken into account when determining the specific criteria: API impurities limit data, ICH standards, pharmacopeia limits, API stability reports, and finished product reports.
- A manufacturing formula and description of the manufacturing process are necessary for DR. Protocols or reports for process validation three batches of reports and protocols for process validation must be submitted. Three batches following the same manufacturing method and the same size.
- Drug product batch analysis results from at least one batch should be provided. In genral, it should be from the batch in which the registration-related samples will be taken. It might be from the most recent batch if the agency in the relevant nation demands. It is required to be given as an analysis certificate.
- Stability data are the ability of pharmaceutical goods to maintain their property within certain parameters during the duration of their shelf life. Guidance for the stability data necessary for the drug substance should be made as per the GCC standards for "Stability testing of API and finished pharmaceutical products". Three batches of data must generally be provided. Testing needs to include evaluations of the product's functionality, preservative content, and physical, chemical, biological, and microbiological characteristics.
- Excipients of natural origin microbial limits should be specified. Transmissible spongiform encephalopathy and bovine spongiform encephalopathy manufacturer certifications for products of human or animal origin should be used. The uses of permitted and approved colors and flavors, as well as information on adventitious agents, are recommended. Certificate of analysis for excipients requirements.
- Specifications for the finished product and the analysis method. Additional product-related specifications, such as the description, hardness, friability, average weight, dimensions, and identification of colorants, should be given as internal specifications are based on Pharmacopoeia. In some nations, a copy of the monograph is allowed. Methods for further testing should be provided. A copy of the compendia monograph as well as any methodologies it references must be submitted if the test is based on it. Specifications and testing procedures that go beyond those outlined in Pharmacopoeia must be described in detail.[11]
- The material used for packaging should be compatible, acceptable for storage, and easy to transport. Specifications and methods of examination that are in-depth and that include the identification of the building material needed for primary packaging material. Specifications and a method of analysis are necessary for secondary packaging material. printed packaging, samples, and/or colored artwork requires a certificate of analysis and batch packaging record.[12]
- Drug product BE correlates the systemic observation profile of a test product to that of a reference product. The test product must have the same percentage and degree of absorption as the reference product to order to be considered bioequivalent. In the absence of a BE study, multipoint comparative dissolution profile data comparing the product with the innovator product should be presented. BE analysis is necessary for tablets, capsules, and oral suspensions.
- The dossier includes pharmacological and toxicological published references, and data reports, and includes the references and published data on clinical trials.[13]
- A required certificate of analysis is a document that conveys the outcomes of a scientific test conducted on a product, such as food or medication. The certificate of analysis is made to make sure all significant rules are fulfilled and followed, and it also includes a list of the chemicals used in the production and testing of the product. The manufacturer provides the certificate of analysis, which is based on the manufacturer's capabilities, internal quality standards and if appropriate, the regulatory quality standard of the manufacturer's city or nation. The following are the components of a certificate of analysis: The name and contact information of the manufacturer, the product name, the batch number, the API, and the expiration date.
- The COPP, which is in the format recommended by the WHO, establishes the condition of the pharmaceutical product and the applicant for the certificate in the exporting country. It is just for a single product because different dosage forms and strengths may require separate manufacturing processes and approved information. The certificate refers reference to the standards for ethical drug manufacturing and quality control processes. The certificate or an attachment should include the dosage form's formula. This refers to the document created by several national regulatory agencies that explanation of the technical foundation to which the product has received a license.[14]
- Gulf countries are coming under stability investigation Zone IV a. Stability conditions are 30 ± 2°C temperature and relative humidity are 65 ± 5%.[15]
- In the GCC region, the typical registration deadline for new and generic human pharmaceutical drugs is 24–36 months.[16]

Procedure for export of pharmaceutical products

Export marketing is the process of selling products abroad. The central Government of India, acting under the authority granted by the Foreign Trade Act 1992, issues the foreign trade policy (FTP), which regulates exports and

imports in overseas markets. A set of rules regarding the import and export of products and services makes up the FTP. These are put in place by the Ministry of Commerce and Industry's directorate general of foreign trade, which oversees the promotion and facilitation of exports and imports. Although the trading strategy addresses both imports and exports, its main goal is to promote commerce by lowering transaction costs and times, making Indian exports more competitive on a global scale.

A lot of analysis must be done before establishing an export agency because export is a very broad concept. A manufacturer may obtain a NOC from the zonal office or sub-zonal offices of the central drugs standard control organization for export purposes only for approved or unapproved new drugs or for drugs that are prohibited in India if they are in access to validly licensed copy of Form. The following points must be considered for initiating export-related activities in Figure 3.[17]

- An impressive name and logo must be designed for a private concern, partnership business, or company before beginning an export business.
- The foreign markets must be chosen after conducting studies on the market's size, the competition, the necessary standards for quality, and conditions of payment. Exporters may also analyze the markets based on the export incentives provided by the FTP.
- It is essential to open a current bank account with a bank that is licensed to trade in foreign exchange.
- Every exporter needs to apply for a permanent account number from the income tax department.

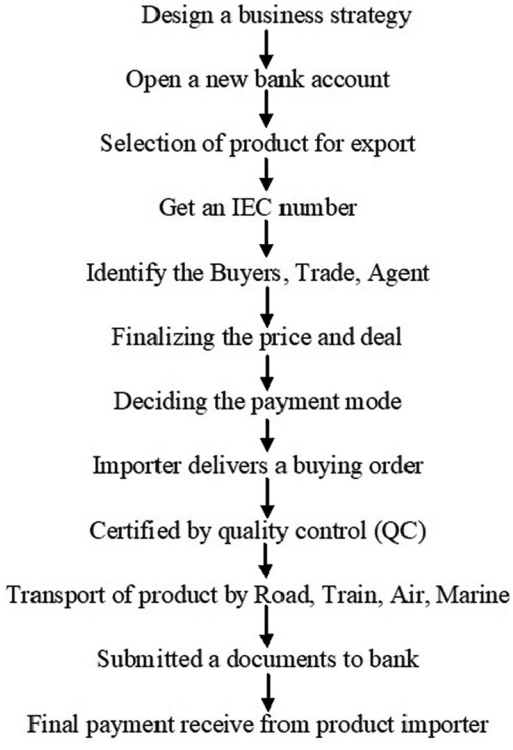

Figure 3: Procedure for export of pharmaceutical products

- Getting an importer-exporter code (IEC) number is compulsory for imports and exports from India, according to the FTP.
- The product choice will be beneficial for the export business. To determine which products can be involved in the export industry, specifically research the demand of products and their performance.
- Finding a buyer must create a user-friendly and expertly designed website for our company, Google Search, and create a social media strategy to connect with our product data platforms such as YouTube, Twitter, Facebook, Instagram, LinkedIn, Business-to-Business websites, and buyer-seller platforms, as well as governmental organizations like Export Promotion Councils. Trade fairs and exhibitions provide an opportunity for Indian exporters to interact directly with visiting foreign buyers and export-import companies.[18]

Factor affecting pharmaceutical product export

Designing the export and distribution of pharmaceuticals is seen to be affected by several factors. Physical, economic, and social environments are affecting the pharmaceutical export. The quality of exported products is affected pharmaceutical products.[17] The exporting nation's geographic location has an impact on exports as well. The right temperature conditions and air and rivers for transportation can facilitate international trade. Exporting country GDP rate increase or decrease involving of government involvement and trade restrictions is affecting the pharmaceutical export.[19]

Future of the pharmaceutical industry in the Gulf region

In contrast to international standards, the pharmaceutical business in the Gulf is still in its growing stage. However, it is improving by reforming and eliminating governmental rules, boosting its effectiveness, and improving the healthcare sector's infrastructure. The pharmaceutical industry in the GCC will undergo numerous changes, offer opportunities for foreign investment in this sector, and is anticipated to boost local production. The possibility of a pharmaceutical product becoming successful and the process is very time-consuming, expensive, and high-risk. The process of research and development has outlined the difficulties and challenges including geographical factors.[5]

The GCC's increasing population will be a major factor in the pharmaceutical industry's growth. Excessive levels of urbanization and a large population also contribute to the rise of pharmaceutical sales in the area. The senior population will also fuel growth since they make up a significant portion of the GCC's overall pharmaceutical consumption. The Saudi Arabian government's recently

unveiled vision 2030 is a great reason to advance the pharmaceutical industry because it will require health insurance, privatize or corporatize Saudi Arabia's health-care system, and invite foreign investors in the sector, including pharmaceuticals. Foreign investors received strong government support for this. Investors receive discounted land in industrial areas as well as several years of tax-free. This will support the expansion of the sector and the creation of more jobs for both domestic and foreign workers. The Gulf market is accessible to foreign investors, which is a source of considerable concern because the majority of pharmaceutical manufacturers in the GCC countries are producing generics. The original Saudi pharmaceutical businesses' ability to compete with foreign challengers and remain in business is uncertain.

Since non-communicable diseases are becoming more common and the health-care system has improved, Saudi Arabia is currently experiencing a strong development in the demand for pharmaceuticals. Worldwide corporations that hold a stake in the market, control the majority of the medicines business in Saudi Arabia. Growing healthcare spending and rising health awareness are some aspects anticipated to boost market expansion shortly the near future. Increasing health insurance company coverage and health-care policies including allowing 100% foreign direct investment in the pharmaceuticals sector are some additional major variables that are anticipated to promote market expansion.[4]

The biggest market in the GCC, Saudi Arabia, offers investors superior investment options, which are further enhanced by the country's required insurance standards and corporatization/privatization of its healthcare system. However, many significant challenges are anticipated to affect the overall growth of the Saudi Arabian pharmaceutical industry over the forecasted period. These include a lack of domestic research capacity, problems in patent registration, and a shortage of skilled people. The pharmaceutical industry is undergoing a digital transition, which is driving an increase in demand for qualified health-care developers. Because there are more pharmaceutical businesses in the market, there is also a higher necessity for pharmaceutical software.

Challenges to the pharmaceutical industry in the Gulf country

Pharmaceutical manufacturing in the GCC faces several difficulties, including a shortage of knowledge and experienced labor as well as ongoing changes to the laws and regulations governing the industry, which restricts its expansion and increases the region's reliance on foreign.[20] Labeling variations and a lack of quality manufacturing capabilities. The label must be printed, graphic, or written in English and Arab language. Label language should be easily understand the patient and provide all necessary information regarding the therapeutic effect of a drug product. In clinical trials and BE studies, they demand that local patients take part in phase I involvement is optional for the patient.[14] The GCC nations' higher-than-normal prescription prices and the spread of spurious medications are further issues. Moreover, imports of pharmaceutical manufacturing supplies, pharmaceutical components, and pharmaceutical drugs. GCC revenue from imported medications is significantly larger than from domestic manufacturers, which only accounts for 10% of total revenue. The Gulf manufacturers struggle to compete with global firms because they are mostly focused on manufacturing generic medications.[4]

CONCLUSION

The GCC market offers the Indian pharmaceutical business many opportunities that are very profitable. The main difficulties in registering and approving pharmaceutical items are very important aspects of commercialization in the Gulf nation. The six GCC states are working to integrate their regulatory framework because in general, they share similar standards for the registration of pharmaceuticals. It should prepare and assemble the documentation following the CTD module from a regulatory perspective. The regulatory agency must also receive supporting documents for assessment and approval, such as the import-export code, DMF, and related documents. The next phase in the evolution of the pharmaceutical sector in the Gulf region needs to be controlled in a way that ensures quality, integration, and R&D improvement within the new pharmaceutical businesses. Industrialists investing in the pharmaceutical sector should have a broad view of the future. They should support and encourage R&D because it results in the development of novel molecules or formulations.

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