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Research Article

Pharmaceutical Drug Registration Procedure and Approval Process in Saudi Arabia

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Abstract

Human drugs or generic pharmaceuticals drug play a pivotal role in preserving public health, effectively preventing and treating illnesses, disabilities, and fatalities each year. Timely access to these medications is crucial for ensuring the well-being of populations. However, the diverse regulatory landscapes and procedural complexities in developing and emerging nations often hinder the registration and subsequent marketing authorization of high-quality, safe, and effective human drugs, leading to significant delays. This article aims to elucidate the registration prerequisites and approval procedures for human drugs in Saudi Arabia. It delineates the clear pathway for the submission and approval of dossiers intended for marketing authorization applications. Module 1 of the Common Technical Document (CTD) aligns with international standards such as the International Council for Harmonization (ICH) with exceptions noted for certain tests specific to human drugs. The dossier should comprehensively detail the human drug and present the findings of all relevant developmental studies. Understanding the registration requirements and the current regulatory review process administered by the Saudi Food and Drug Authority (SFDA) is essential. This involves identifying the agency's review models, key milestones, and associated timelines to navigate the approval process efficiently.

Keywords: Common Technical Document, Saudi Food and Drug Authority, International Council for Harmonization, Human Drugs.

INTRODUCTION

In the modern era, medicines need to be formulated with modified and up-to-date designs that prioritize human health by ensuring quality, safety, and efficacy.[1] The objective of this study is to evaluate, investigate, and describe the drug registration process in the SFDA (Saudi Market).[2] This research aims to facilitate the growth of Indian companies and expand their market presence, while also creating job opportunities for qualified individuals in the pharmaceutical industries. The main focus of this study is to register healthy, safe, and accurate medicines in compliance with the rules and regulations of the SFDA.[3]

Modern medicine regulations are crucial components of any country's drug policy, as they establish standards for drug approval processes and support a sustainable pharmaceutical industry. Throughout history,

governments worldwide have consistently regulated food and drug products to safeguard the public's health and well-being. This universal practice aims to ensure the quality, safety, and effectiveness of medicines. Such regulation is not limited to developed nations but has been increasingly emphasized in third-world countries as well.[4]

The fundamental premise behind this regulatory framework is to guarantee that new medications are thoroughly tested, evaluated, and responsibly marketed, thus minimizing any potential harm to consumers. Regulatory authorities, whether in developed or developing nations, share the vital responsibility of ensuring access to safe and effective medicines for patients.[5] However, their organizational structures, strategic approaches, and operational practices may vary significantly. In the Saudi Drug Market, which is emerging as a significant pharmaceutical market, there's a growing focus on regulatory harmonization to facilitate pharmaceutical exports and bilateral trade. Generic drugs are expected to play a substantial role in the SFDA pharmaceutical sector.[6] To address this, a study aims to evaluate the regulatory systems of Saudi Arabia and develop a unified strategy. Information will be gathered from the regulatory authorities of these nations to comprehend their review processes and the quality measures they employ to enhance assessment procedures, tailored to the SFDA region's needs. With economic downturns in highly regulated markets like the EU and the US, there's a heightened demand for alternative business destinations. Smaller pharmaceutical markets such as Qatar and Bahrain are anticipated to witness more significant growth compared to more established markets like Saudi Arabia. In the contemporary landscape, pharmaceutical products undergo stringent regulations in most countries, adhering to rigorous legislative criteria before receiving authorization for commercial distribution. SFDA country has its own pharmaceutical regulatory authority, responsible for ensuring the safety and efficacy of human and veterinary medications within its jurisdiction. These regulatory processes adhere to specific pharmaceutical laws and regulations unique to each country's legal framework.

MATERIALS AND METHODS

The process through which an organization, sponsor, or innovator obtains authorization to introduce a drug to the market is commonly referred to as the drug approval process. This process is integral to drug development and involves several stages, including conducting clinical trials, submitting a New Drug Application (NDA), and conducting post-marketing studies. Each country has its own regulatory authority responsible for enforcing rules, regulations, and issuing guidelines to oversee the marketing of drugs.

The Common Technical Document (CTD) consists of five modules:

1) Administrative and Prescribing Information
2) Overview and Summary of Modules 3 to 5
3) Quality (Pharmaceutical Documentation)
4) Safety (Toxicology Studies)
5) Efficacy (Clinical Studies)

Module 1 focuses on region-specific administrative and prescribing information, while modules 2 through 5 are designed to be common across all regions:

Module 1: Administrative Information & Prescribing Information
Module 2: Common Technical Document Summaries
Module 3: Quality
Module 4: Nonclinical Study Reports
Module 5: Clinical Study Reports

The process of submitting a new Marketing Authorization Application (MAA) for a pharmaceutical product involves the following steps

Submission

The submission process for a new MAA comprises two steps:

Online Submission

1. The applicant must apply through the SDR (Submission and Drug Registration) system to fill out the application form and complete the payment of fees.
2. The product file should be uploaded following the requirements and guidelines published on the Saudi Food and Drug Authority (SFDA) website.

Validation

The product file submitted by the applicant will undergo validation on technical and business bases to ensure all requirements are met. The validation process includes two steps:

Technical Validation
The SDR system will automatically validate the submission once the company uploads the file to the SDR portal. The result of the technical validation will be communicated to the applicant via email through the SDR system.

Business Validation
1. The product file will be validated to ensure that all the provided information aligns with the required guidelines and criteria.
2. If any information is found to be missing or incorrect, the applicant will receive an electronic inquiry through the SDR system. The applicant will have 30 working days to provide the necessary updates or corrections to complete the file.
3. Once the completed file meets the validation requirements, it will proceed to the next steps for assessment.

The registration request will be rejected in the following cases
- If there is no response from the applicant within 30 working days.
- If the applicant fails to provide acceptable clarifications after the third wave of inquiries.

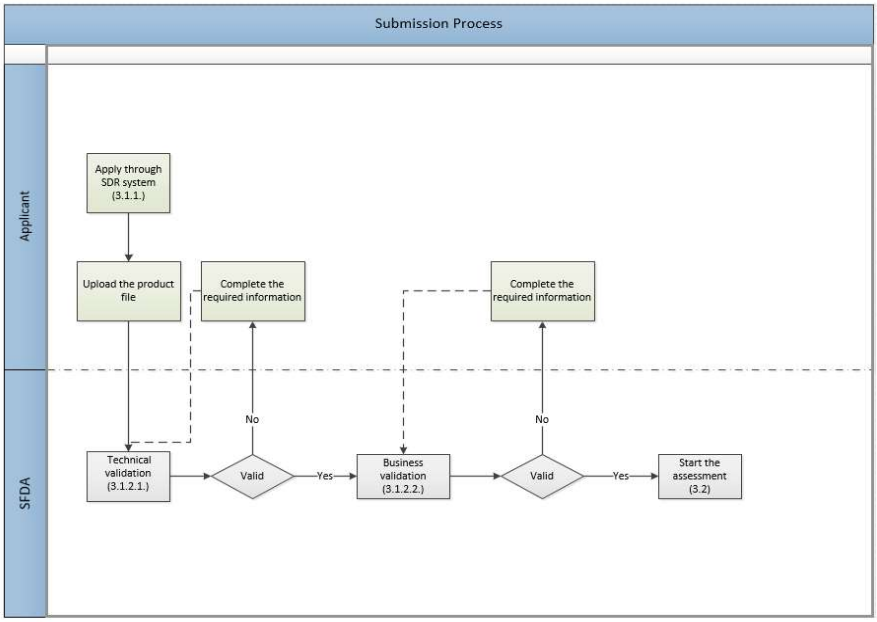

Fig 1: Schematic chart of the submission process.

Assessment
The Marketing Authorization Application (MAA) for different drug submission types is subject to the following processes:

Evaluation/Inspection
1. The Regulatory Authority (RA) will distribute the registration request to the relevant departments for assessing quality, safety, and efficacy.
   - For Inspection: The department will check the approval status of the manufacturing line. If not approved:
   - A visit will be scheduled for inspection based on the mutual availability of inspectors and the company.
   - After the visit, the inspection report will be sent to the company. Please refer to the Good Manufacturing Practice for Medicinal Products.
2. If additional information or clarification is required, an electronic inquiry will be posted through the SDR system as one wave for evaluation and inspection. A response should be received within 60 working days.
3. Once the evaluation and inspection are completed, the registration request will be forwarded to the Pricing Department.

Testing
1. The registration request will be forwarded to the SFDA Central Laboratories for testing.
2. If more information or clarification is needed, an electronic inquiry will be posted through the SDR system.

Note: Testing will not delay the registration of a product.

Pricing

1. The Pricing Department will review the product's price according to the SFDs pricing rules.
2. If additional information or clarification is required, an electronic inquiry will be posted through the SDR system. A response should be received within 60 working days.
3. The product's price will be forwarded to the Registration Committee.

The registration request will be rejected in the following cases:
- No response from the applicant within 60 working days.
- Failure to provide acceptable clarifications after the 4th wave.

Important Note

The applicant will have a total of four (4) waves for Evaluation/Inspection and Pricing.

Product Licensing

1. The Registration Committee will review the registration request for approval, rejection, or request further information (if needed).
2. The SFDA CEO will approve the meeting minutes.
3. For approved registration requests, the applicant will be notified through the SDR system to issue the Marketing Authorization (MA).

Appeal Process

The applicant has the right to appeal against any decision within 60 calendar days. For more information, please refer to the Guidance for Submission.

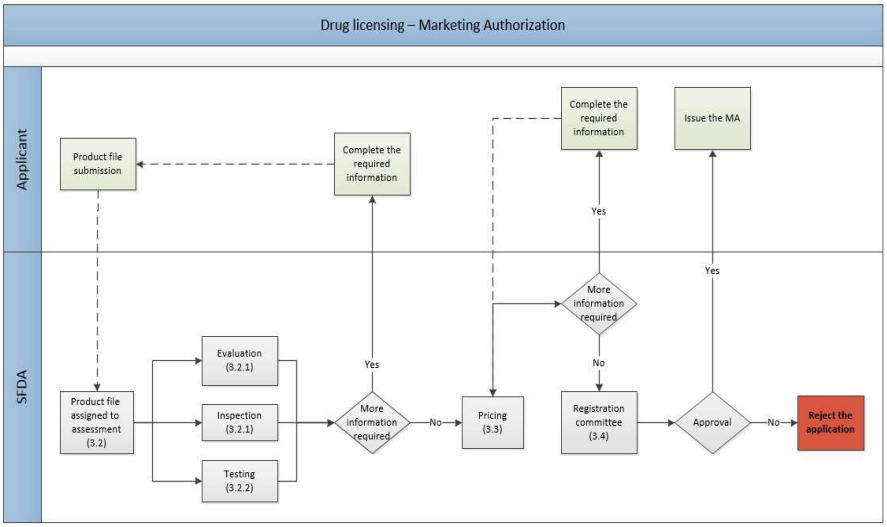

Fig 2: Schematic figure showing the different levels for getting marketing authorization.

Registration performance

- The performance target for each step will pause if clarification or additional information is required from the applicant and will resume after receiving the response.
- All days will be considered as working days.
- The total performance target is calculated without including the Business Validation for all pathways.

Regular review pathway

Table 1: Regular review pathway

Registration phases	Technical section 3.1.2.1	Business section 3.1.2.2	Evaluation section 3.2.1	Pricing section 3.3	Product section 3.4	Total

No. of Waves	-	3			-	
Human Generic	-	10	120	20	15	**155**
Human New Drugs	-	10	245	20	15	**280**
Human New Drugs not	-	10	370	20	15	**405**
Herbal & health products	-	10	120	20	15	**155**

Priority review pathway (40% reduction)

Table 2: Priority review pathway (40% reduction)

Registration	Technical	Business	Evaluation	Pricing	Product	Total
	section	section	section	section	section	
	3.1.2.1	3.1.2.2	3.2.1	3.3	3.4	
No. of Waves	-	3			-	
Human Generic	-	10	72	12	9	**93**
Human New Drugs	-	10	147	12	9	**168**
Human New Drugs	-	10	222	12	9	**243**

Verification & abridged pathway

Table 3: Verification & abridged pathway

Registration	Technical	Business	Evaluation	Pricing	Product	Total
	section	section	section 3.2.1	section 3.3	section 3.4	
No. of Waves	-	3			-	
Verification	-	5	15	5	10	**30**
Abridged	-	5	40	10	10	**60**

RESULTS AND DISCUSSION

The registration process of generic pharmaceuticals products is very important for manufacturing pharmaceutical companies, without registered the products companies should not sell any products in the market. For selling and marketing medicine the registration process is required and it depends on the country's requirements and procedures. This study explained the registration procedure and approvals of the drugs in Saudi Arabia.

Registration for generic medicine in the SFDA has different types of requirements and it follows the CTD guidelines. Most of the GCC countries have similar requirements for registration of pharmaceuticals and few have different 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. There is a difference in format for documents between ICH CTD and ACTD.

There are 5 modules in ICH CTD named as Module-I to Module- V and the documents in ACTD are named as part-I to part-IV because it does not involve common technical document overview and summaries like in CTD. The rest of the documents are administrative documents and product information, quality documents, nonclinical documents and clinical documents. According to the ICH, the CTD includes 5 modules. Module 1 is not harmonized and contains regional/country information.

Module-I

Module I contains the administrative information and as per SFDA parameters all sections are evaluated in the study results are shown below in the table:

Section	ADMINISTRATIVE INFORMATION	SFDA REQUIREMENTS
1.0	Cover letter	To be addressed separately with MOH address
1.1	Comprehensive Table of Content	Complete table of contents should be provided M1 – M5
1.2	Application Form	Application form to be filled in eSDR system online
1.3	Product Information	Product information is in Arabic and English language.
1.3.1	Summary of Product Characteristics (SPC)	
1.3.2	Labeling Information	

1.3.3	Patient information leaflet (PIL)	
1.3.3.1	Arabic leaflet	
1.3.3.2	English leaflet	
1.3.4	Artwork (Mock-ups) (outer label, inner label and leaflet artworks)	
1.3.5	Samples	
1.4	Information on the experts	Information about quality, non -clinical and clinical
1.4.1	Quality Information	
1.4.2	Non- Clinical Information	
1.4.3	Clinical Information	
1.5	Environmental Risk Assessment	-
1.5.1	Non-Genetically Modified Organism (Non-GMO)	
1.5.2	GMO	
1.6	Pharmacovigilance	Registered pharmacovigilance person information required.
1.6.1	Pharmacovigilance System	
1.6.2	Risk Management Plan	
1.7	Certificates and documents	
1.7.1	Copy of valid GMP certificates for the manufacturing site(s)	Valid GMP certificates are required for the API and MAH.
1.7.2	Original legalized valid Certificate of Pharmaceutical Product (CPP)	CPP is Not Applicable for the country of origin but required for export countries
1.7.3	Certificate of Analysis - Drug Substance, Finished Product	2 batches of COA of Drug Substance and Finished Products are required.
1.7.4	Certificate of Analysis – Excipients	2 batches of Certificate of Analysis for all Excipients are required.
1.7.5	Alcohol-content declaration	Signed and stump Alcohol-free declarations are required in this section.
1.7.6	Pork-free declaration	The medicines should be pork-free with signed and stump declaration.
1.7.7	TSE/BSE free certificate	The medicines formula is free form TSE/ BSE and should be submitted signed and stump.
1.7.8	The diluents and coloring agents in the product formula	The formula contains diluents and coloring agents that's why the declaration should be provided with the proper name with signed and stump.
1.7.9	Patent Information	MAH should check the patency of the products before they register the medicines.
1.7.10	Letter of access DMF	In this section MAH should provide the DMF LOA if the DMF is US based. And if the DMF is Europe based then CEP is required.
1.8	Pricing	MAH are proposing the price of the drug before the registration.
1.8.1	Price certificate	
1.8.2	Other documents related	
1.9	Response to questions (Updates, questions, queries)	This is the part when MAH received the query from the MOH and MAH replied to the response.
	Additional Data	There is different requirements as per the country—this contents composition and other countries registration approval certificate.

Module-II

Module II contains only summaries of module III, it is called Common Technical Document summaries, which include the summaries of the drug substance and finished products. All the documents are required during the approval of the drug and these are as follows.

2.1	**Table of Contents of Module 2**	**SFDA REQUIREMENTS**
2.2	Introduction	This is a very important information-based section that contains the summaries of the modules III. This includes summaries of the drug substance or
2.3	Quality overall Summary (QOS)	
2.3.S	Drug Substance	
2.3.P	Drug Product	

2.3.A	Appendices	short information of the DMF. Also contents the finished drug products information. A summary of Pharmacodynamic and pharmacokinetics information should be also highlighted.
2.3.R	Regional information	
2.4	Non-Clinical Overview	
2.5	Clinical Overview	
2.6	Non-Clinical Summaries	
2.6.1	Introduction	
2.6.2	Pharmacology written Summary	
2.6.3	Pharmacology Tabulated Summary	
2.6.4	Pharmacokinetics written Summary	
2.6.5	Pharmacokinetics Tabulated Summary	
2.6.6	Toxicology written Summary	
2.6.7	Toxicology Tabulated Summary	
2.7	Clinical Summaries	
2.7.1	Summary of Biopharmaceutical and associated analytical Methods	
2.7.2	Summary of Clinical Pharmacology Studies	
2.7.3	Summary of Clinical Efficacy	
2.7.4	Summary of Clinical Safety	
2.7.5	References	
2.7.6	Synopses of Individual Studies	

Module-III

Module III is a very important part of the registration approval section. It's also called the heart of the dossier. These sections are mandatory and it's divided into two parts.

Drug Substance Part

3.1	**Table of Contents of Module 3**	**SFDA REQUIREMENTS**
3.2	Body of Data	This section includes the quality of the drug. Related to the Drug master Files information. It consists information of about the substance from which the drug has been prepared, the name of the substance, its structure and its properties and also manufacturing details along with the description of the processes and control. This module also contains the characterization and impurities of the substance. Stability data is very important for this section and its depends on the country's atmosphere. Some of the sections are confidential, companies are providing direct to the agencies like Description of Process and Process Controls, Control of Materials, Control of Critical Steps and Intermediates. Specification and analytical procedures are prepared as per the pharmacopeial reference and all test are mandatory as per the pharmacopeia and within the limit.
3.2.S	Drug Substance	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	
3.2.S.1.2	Structure	
3.2.S.1.3	General Properties	
3.2.S.2	Manufacture	
3.2.S.2.1	Manufacture(s)	
3.2.S.2.2	Description of Process and Process Controls	
3.2.S.2.3	Control of Materials	
3.2.S.2.4	Control of Critical Steps and Intermediates	
3.2.S.2.5	Process Validation and/or Evaluation	
3.2.S.2.6	Manufacturing Process Development	
3.2.S.3	Characterization	
3.2.S.3.1	Elucidation of Structure and Other Characteristics	
3.2.S.3.2	Impurities	
3.2.S.4	Control of Drug Substance	
3.2.S.4.1	Specifications	
3.2.S.4.2	Analytical Procedures	
3.2.S.4.3	Validation of Analytical Procedures	
3.2.S.4.4	Batch Analyses	
3.2.S.4.5	Justification of Specification	
3.2.S.5	Reference Standards or Materials	
3.2.S.6	Container/Closure Systems	
3.2.S.7	Stability	
3.2.S.7.1	Stability Summary and Conclusions	
3.2.S.7.2	Post-approval Stability Protocol and Commitment	
3.2.S.7.3	Stability Data	

P Drug Product Section

3.2.P	Drug Product	SFDA REQUIREMENTS
3.2.P.1	Description and Composition of the Drug Product	In this section, MAH mentioned the complete product information like composition formula, development process, drug substance and excipients used in the formula, and many drug products including the overages that maintain the drug formula accurate. It describes and contains information about the container closure system or drug product packaging materials.
3.2.P.2	Pharmaceutical Development	
3.2.P.2.1	Components of the Drug Product	
3.2.P.2.1.1	Drug substance	
3.2.P.2.1.2	Excipients	
3.2.P.2.2	Drug Product	
3.2.P.2.2.1	Formulation Development	
3.2.P.2.2.2	Overages	
3.2.P.2.2.3	Physiochemical and Biological Properties	
3.2.P.2.3	Manufacturing Process Development	
3.2.P.2.4	Container Closure System	
3.2.P.2.5	Microbiological Attributes	
3.2.P.2.6	Compatibility	
3.2.P.3	Manufacture	3.2.P.3 sections are including information about the manufacturer, and complete details of the batch formula. Process validation is a very important section that describe the process and its critical steps during manufacturing of the drug products.
3.2.P.3.1	Manufacture(s)	
3.2.P.3.2	Batch Formula	
3.2.P.3.3	Description of Manufacturing Process and Process Controls	
3.2.P.3.4	Controls of Critical Steps and Intermediates	
3.2.P.3.5	Process Validation and/or Evaluation	
3.2.P.4	Control of Excipients	This section contains information about the compendial and non-compendial excipients and its specification and analytical procedure tests. If the excipients are made of animal origin MAH should mention the declaration of TSE/BSE certificate.
3.2.P.4.1	Specifications	
3.2.P.4.2	Analytical Procedures	
3.2.P.4.3	Validation of Analytical Procedures	
3.2.P.4.4	Justification of Specifications	
3.2.P.4.5	Excipients of Human or Animal Origin	
3.2.P.4.6	Novel Excipients	
3.2.P.5	Control of Drug Product	These sections are very important for the drug products, many inquiries are coming on this section through MOH—this section contains information about finished product specification tests and its procedure information. Batch analysis data are required for 3 batches.
3.2.P.5.1	Specifications	
3.2.P.5.2	Analytical Procedures	
3.2.P.5.3	Validation of Analytical Procedures	
3.2.P.5.4	Batch Analysis	
3.2.P.5.5	Characterization of Impurities	
3.2.P.5.6	Justification of Specifications	
3.2.P.6	Reference Standards or Materials	USP and BP reference standards are required during the registration procedure for the test parameter.
3.2.P.7	Container/Closure System	Container closers are very important parts of the finished products. Different types of container closure are used like bottle packs and blister packs.
3.2.P.8	Stability	The stability parameter is a very important section all the drugs are required to do the stability data as per the country's guidelines or regulations. A minimum of 12 months of stability data is required for 3 batches of data.
3.2.P.8.1	Stability Summary and Conclusions	
3.2.P.8.2	Post-Approval Stability Protocol and Stability Commitments	
3.2.P.8.3	Stability data	
3.3	Literature References	Literature reference for the drugs products are required from US and UK based journals.

Module-IV

Module IV contains information about the non-clinical study and it is mandatory for the innovative company. It's not required for the generic formula during registration.

Module-V

Module V contains the details of all clinical studies. MAH is doing a clinical study on their formulation and submit to the agency for drug approval along with the complete CTD files. It contains the complete study of BA/BE as per the bioequivalence guidelines. it is mandatory to submit during drug registration process.

As when completed the CTD dossier files will be submitted to the regulatory agencies and agencies review the dossier, if any documents are missing agency will ask for the supporting documents and the marketing authorization holder will provide the supporting documents and after all the evaluation MAH will get the registration certificate.

SUMMARY AND CONCLUSION

From the above study, we conclude that the registration process in the SFDA is easy and tricky if we have all the documents and requirements as per the agency then the marketing authorization holder can easily get the registration certificate and sell the pharmaceutical products in the SFDA market.

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