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PHARMACEUTICAL PRODUCT REGISTRATION IN SAUDI ARABIA

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ABSTRACT

Saudi Arabia is one of the major markets for pharmaceutical companies in Gulf Cooperation Council (GCC) and Middle East and North Africa (MENA) region. Because of its population growth over a period, rise of lifestyle diseases like hypertension, diabetes and obesity there is a demand for the drug products. The affluence of the Saudi people had led to higher demand for imported patented drugs, now the government shifting the focus of the people allowing active private sector participation, making health insurance mandatory for expatriates and promoting the use of generic products. Saudi Arabian Food and Drug Authority (SFDA) is the pharmaceutical regulatory authority in Kingdom of Saudi Arabia that ensures the safety and efficacy of the medicinal product marketed in the country. SFDA provides different evaluations pathways for new chemical entities (NCE's), generics, herbal and for veterinary drugs, for pharmaceutical companies to market their products in KSA. This study encompasses organisation structure of SFDA, registration process of medicinal products, other regulatory requirements like stability, bioequivalence and labelling. The timeliness for the evaluation of different medicines is also discussed.

Keywords: SFDA, GCC, MENA, KSA, NCE and generics

INTRODUCTION

Introduction

The Kingdom of Saudi Arabia is a country situated in Southwest Asia, the largest country of Arabia, bordering the Persian Gulf and the Red Sea, north of Yemen. Its extensive coastlines on the Persian Gulf and Red Sea provide great leverage on shipping (especially crude oil) through the Persian Gulf and Suez Canal. The kingdom occupies 80% of the Arabian Peninsula. The Saudi government estimate is at 2,217,949 square kilometres, while other reputable estimates vary between 2,149,690 and 2,240,000 sq. kilometres. Less than 1% of the total area is suitable for cultivation, and in the early 1990s, population distribution varied greatly among the towns of the eastern and western coastal areas, the densely populated interior oases, and the vast, almost empty deserts[1]. The Government does not conduct census on religion, but estimates put the percentage of the majority Salafis at 85-90% while Shiites, who comprise the largest Muslim minority, at 10-15% of the population. Shiites (twelvers) are primarily concentrated in the eastern province, where they constitute over a third of the population. Other smaller communities (Ismailis and Zaidis) reside in the south, with Ismailis constituting around half of the population of the province of Nejran, and the holy islamic cities of Mecca and Medina[2].

Country profile:

- Full name: Kingdom of Saudi Arabia
- Population: 28 million (UN, 2011),
- Capital: Riyadh
- Area: 2.24 million sq km (864,869 sq miles)
- Major language: Arabic, also english is widely spoken
- Major religion: Islam
- Life expectancy: 73 years (men), 76 years (women) (UN)
- Currency: 1 Riyal = 100 halalah
- Main exports: Oil, gas, cereals
- GNI per capita: US $17,820 (world bank, 2011)[3]
- **International membership groups/organisations:** World trade organisation, Arab league, Gulf cooperation council, Organisation of the islamic conference, United nations, Organization of petroleum exporting countries, International monetary fund and World bank[4].

The Saudi Arabian pharmaceutical market is the largest in the Gulf cooperation council (GCC). The vast majority of the

market is currently provided by imports, mainly comprised of patented and over-the- counter (OTC) drugs. Local production is mainly involved in the secondary manufacturing of generic products, the Jeddah-based National commercial bank (NCB). Over the forecast period 2009-2012, the Saudi pharmaceutical market is set to experience steady growth at a CAGR of 5.92%. Market value is forecast to rise from 11.81 billion riyals in 2009 to roughly 14.04 billion riyals in 2012. Meanwhile, pharmaceutical demand per capita will increase from 465 riyals in 2009 to 15 riyals in 2012.

The leading Saudi drug makers are Saudi Pharmaceutical Industries and Medical Appliances Corporation (SPIMACO), Tabuk pharmaceuticals and Jamjoom Pharmacy with market shares of 7.2%, 3.9% and 3.2%, respectively, in 2009. Multinationals tend to enter the market through joint ventures with Saudi firms. Currently there are nine joint ventures in the kingdom. The largest UK investor in the market is GSK, which established production operation in 1992 and is currently the leading pharmaceutical company with 10.8% of market share. The company has a joint venture with local company Banaja Saudi Import, known as Glaxo Saudi Arabia, which has a 51% stake in the subsidiary[5].

There is huge demand for the generics in the Saudi Arabian region because of higher prevalence of non-communicable diseases like obesity, hypertension and diabetes. According to the total population of the Kingdom is estimated to grow to 31.6 million by 2016 (22.8 million will comprise Saudi nationals), at a CAGR of 3.1 percent between 2011 and 201 6. In this regard, OTC consumption and penetration of generic drugs will increase. Saudi government's spending on healthcare remains the prime contributor (62.9 percent in 2010), while budgetary allocations reached an all-time high. So, the government is planning to shift the focus from health care provider to regulator allowing active private sector participation, making health insurance mandatory for expatriates and promoting the use of generic products[6].

Pharmaceutical market in the MENA region accounted for about 1.8 per cent of the world market, In MENA region GCC countries have highest per capita medicines consumption estimated at US$ 52 while in other countries, the figure is estimated at about US$ 20 in 2004. Among the GCC countries Saudi Arabia has the largest number of local pharmaceutical manufacturing plants totaling 27 with an investment of US$ 619 million[7].

DISCUSSION

Authority[8-10]:

Saudi Food and Drug Authority (SFDA) is the Saudi Arabian regulatory authority which ensures the safety of food, drug, biological, chemicals and electronic products for man and animal. It is an independent body, which directly reports to the president of council of ministers. SFDA membership includes HRH Minster of Municipality and Rural Affairs as vice-chairman, and all pertinent ministers (HRH Minister of Interior, Minister of Health, Minister of Commerce and Industry, Minster of Agriculture, Minister of Water and Electricity, Minister of Finance and Minister of Economic and Planning) and the Director General of Saudi Arabian Standards and Specification Organization, the chairperson of Council of Chambers of Commerce and Industry in the Kingdom, the Authority's Executive Chief, and a person specialize in food and drug.

The main objective of the authority is to regulate, oversee, and control food, drug, medical devices, as well as to set some standard specifications, whether they are imported or locally manufactured. The control and/or testing activities can be conducted in the SFDA or other agency's laboratories. Moreover, the SFDA is in charge of consumers awareness on all matters related to food, drug and medical devices and all other products and supplies.

The objectives of the authority are enlisted below:

- Observe the safety, security, and effectiveness of food, drug, biological, chemical substances, cosmetics, pesticides, medical devices and diagnostic devices for humans and animal.

- Launch clear policies and procedures for food and drug, and plan to achieve and implement these policies.

- Conduct research and applied studies to identify health problems, their causes, determine its impact on public, with the consideration of methods for research / studies evaluation. The authority shall establish scientific bases for awareness and consulting services and executive programs in the fields of food and drug.

- Control and supervise licenses procedures for food, drugs and medical devices factories.

- Disseminate and exchange information with local and international scientific and legal agencies, and setting up a database for food and drug.

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5.1 Organization structure of SFDA

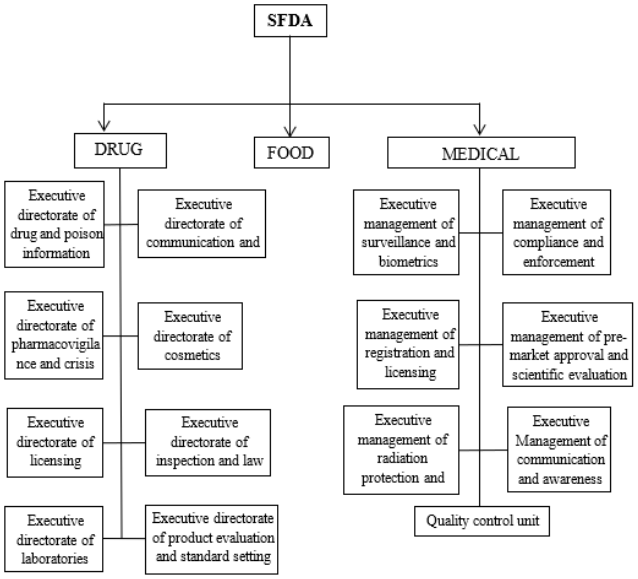

Figure 1 Organization structure of SFDA

According to the authority products under drug sector are classified as two types

1. Subject for registration

- Drug products
- Herbal products
- Health products (R)

2. Subject for listing

- Cosmetics
- Health products (L)

The definition drug product follows here, a "drug product" means a substance or a combination of substances which may be used in or administered to human or animal beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis.

This definition will include the following products:

1. Products contain one or more vitamins and/or minerals with concentrations above the upper concentration limit of vitamins and minerals. The upper and lower concentrations limits will be calculated according to the product daily dose.

2. Products contain any of the following substances:

- Salicylic acid in concentration More than 2% (other than rinse off hair products)
- Glucosamine
- Hydroquinone
- Ichtammol
- Tretinoin (retinoic acid) and its salts

3. Products contain medicinal claims including but not limited to (treat, prevent, relieve symptoms, or to cure, remedy or heal a specific disease or adverse condition of body or mind (stress, anxiety and nervous tension), protect" or "avoid" excluding claims that fall within the cosmetic definition.

4. Saline and sterile water that are intended for intravenous, irrigation or ophthalmic use.

5. Body fluid replacements and nutrients including electrolyte products in powder form (not in food dosage form e.g. juice), plasma expanders, total parenteral nutrition solutions, blood substitutes, peritoneal dialysis solutions & substances prepacked for their preparation.

6. *In vivo* diagnostic agents including imaging agents.

7. Enema solutions products (rectal solution products)

8. Some pre-filled or pre-loaded devices intended to deliver a medicine.

9. An allergen tests are used internally and indicated in the diagnosis of specific allergies.

10. Any product injected into the body.

11. Haylorunic acid injections either for treatment or cosmetic purposes

12. Radiopharmaceuticals: Radioactive substances administered internally will be considered as a drug regardless its purpose of use wither it is for treatment or diagnosis.

5.2 Submission process[11]

There are 3 main steps involved in the drug registration process

1. Online filing of application

2. Acceptance of drug application

3. Phase II validation

1. Online filing of application

The applicant shall fill up the appropriate application form in the SDR system. Once completed, application form cannot be submitted unless the payment is received by SADAD. A reference number will be assigned to the application once submitted to facilitate the communication with the SFDA.

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Then, the applicant will be given an opportunity to book an appointment to hand over the drug application. The earliest appointment is 1 week, up to 12 weeks in advance. An automatic reminder will be sent 3 days before the appointment. The applicant can reschedule a week before the chosen appointment. If it is missed, the applicant has to book a new appointment again.

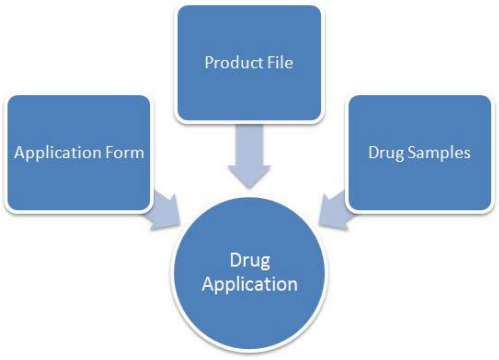

Figure 2: A "drug application" includes the application form, the product file and the drug samples

2. Acceptance of drug application

Upon receipt of the drug application in the appointment day, a checklist for 'Phase I Validation' will be used to verify that the information and materials provided are complete.

a. Drug application without deficiencies:

The applicant will be notified of the acceptability by printing an acknowledgement letter. Then, the drug application will be forwarded to the product manager (licensing department) for further processing and assessment. Once these applications are accepted, they will be assessed in the order in which they are received.

b. Drug application with deficiencies:

If deficiencies are identified, an acknowledgment letter stating the deficiencies will be issued. The applicant will be required to submit the requested information within 90 days from the date of the letter. The applicant shall send an e-mail to the drug sector (sdr.drug@sfda.gov.sa) requesting an appointment to complete the deficiencies.

- If the applicant has provided the requested information within 90 days, the application will be accepted and the drug application will be forwarded to the product manager for further processing and assessment.

- If the applicant has provided the requested information within 90 days, but it was found to be still incomplete, the applicant can complete the missing within the rest of the 90 days.

- If the applicant fails to provide the requested information within 90 days, the drug application will be rejected.

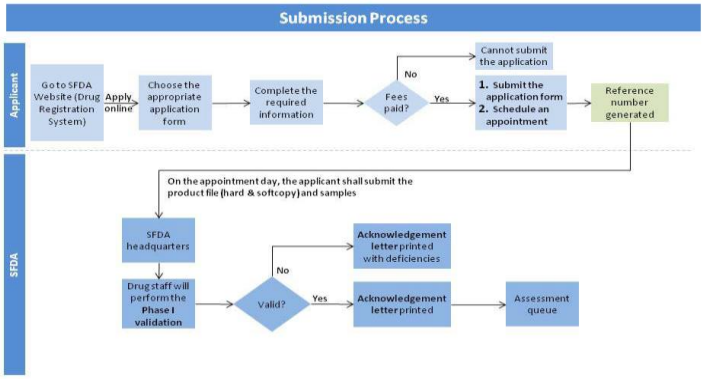

Figure 3: Submission process

3. Phase II validation

After accepting the drug application from the applicant, the submitted information and material will be validated to ensure that it has suitable quality to be assessed. However, if deficiencies are identified, the applicant will be asked to submit the required information, and it will follow one of the following cases:

- If the applicant has provided the requested information within 90 days, the product file will be forwarded for further processing and assessment. The applicant will be notified by email.

- If the applicant has provided the requested information within 90 days but it was found to be still incomplete, SFDA will study the case and may extend the period for another maximum 30 days. The applicant will be notified by e-mail.

- If the applicant fails to provide the requested information within 90 days, the drug application will be rejected.

Once the phase II validation is done, then the product will be distributed to different branches for further according to the authorities procedures

4. Assessment of Application

All applications will be assessed in terms of quality, safety and efficacy – as needed – depending on the type of the product. If issues are identified during the assessment, these issues will be resolved through electronic inquiry forms. Although there is no limitation of inquiries, it is expected that these issues be resolved by two to three inquiries. Responses to inquiries are required within 90 days.

5. Pricing

The pricing will be calculated according to the pricing rules outlined in the pricing guideline.

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6. Testing

All drug products will be subjected to appropriate testing according to the type of the application and dosage form. Moreover, the applicant is requested to deliver the samples to SFDA headquarters as part of the drug application. There will be no direct contact between the applicant and SFDA's laboratory.

7. Inspection

The head of the inspection unit will communicate with the applicant to decide the appropriate time for inspection – if needed, depending on the schedules of the inspectors. After the inspection is done, an inspection report will be written and a copy of this report will be sent to the applicant. In case of deficiencies, further details will follow.

8. Stop-clock

The stop-clock starts whenever SFDA issues an inquiry form. Inquiries may be raised at any time from the phase II validation to SFDA decision. The stop-clock ends whenever SFDA receives complete and acceptable responses from the applicant. If the applicant faces difficulties in responding to inquiries within the specified time, applicant should contact SFDA as soon as possible. A drug application will be considered rejected if the stop-clock time exceeds the SFDA deadline.

9. SFDA decision

The final decision is made based on the outcome of SFDA's assessment, pricing, testing and inspection. The decision can be one of the following:

- **Approval**: when the drug application has satisfied the registration requirements for quality, safety and efficacy.
- **More information is needed**: when the drug application has minor deficiencies.
- **Rejection**: when the drug application has not satisfied the registration requirements.

10. Appeal process

The applicant will have the right to appeal within 30 days against the SFDA decision. The relevant guidance will be published.

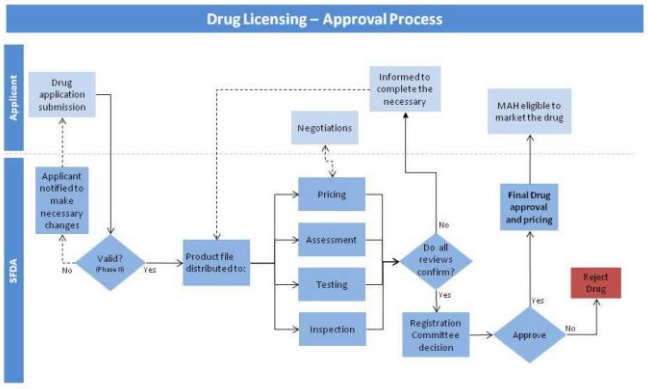

Figure 4: Drug licensing approval process[11]

CHECK LIST

5.2.1 Structure and content of submission:

The SFDA will require all applicants to submit their applications in accordance to the ICH Common Technical Document (CTD) format. The dossier requirements for each application will differ, depending on the type of application.

The Common Technical Document is an internationally agreed format for the preparation of a marketing authorization (MA) that is to be submitted to the regulatory authorities in the three ICH regions (USA, EU and Japan) and in some other countries and regions. The CTD is applicable for all types of products (new chemical entities, biologicals, herbals etc.)

The CTD is organized into five modules (Figure 5). Module 1 is region specific.

Modules 2, 3, 4, and 5 are intended to be common for all regions.

Module 1: Administrative Information and prescribing Information

Module 2: Common Technical Document Summaries

Module 3: Quality

Module 4: Non-Clinical Study Reports

Module 5: Clinical Study Reports

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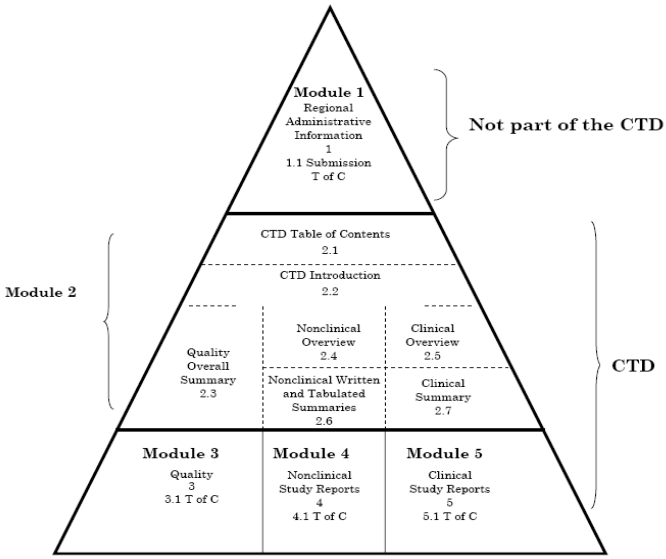

Figure 5: CTD triangle

Module 1: Regional Administrative Information

This module includes the required regional information specific to GCC, such as administrative information and certificates.

SUMMARY AND CONCLUSION

SFDA is the pharmaceutical regulatory authority in Kingdom of Saudi Arabia that ensures the safety and efficacy of the medicinal product marketed in the country. There are different applications for NCE's, generics, herbal and for veterinary drugs. This study has included various aspects related to Saudi Arabia's pharmaceutical regulatory subject.

As per SFDA a "drug product" means a substance or a combination of substances which may be used in or administered to human or animal beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis.

There are basically eight drug submission types classified by SFDA under drug section:

1. Generics
2. New drugs (NCE and Known active substances)
3. Biologics
4. Radiopharmaceuticals
5. Herbal & health products
6. Veterinary products
7. Renewal of MA
8. Variations type I & II

The information that to be submitted under these drug submission types are based on the ICH CTD and the eCTD specifications and the SFDA regulatory framework for drug approval.

Mentioned above drug submission types have common registration process and it involves following steps.

1. Online filing of application
2. Acceptance of drug application
3. Phase II validation
4. Assessment of application
5. Pricing
6. Testing
7. Inspection
8. Stop-clock
9. SFDA decision
10. Appeal process

These steps are explained in detail under discussion section in this dissertation. Beside this submission process, study involves stability criteria, information regarding stability requirements, bioequivalence requirements and labeling requirements. The stability and bioequivalence are adopted from other sources like WHO and EMA respectively.

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