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Research Article

A STUDY ON THE REGULATORY REQUIREMENTS FOR GENERIC DRUG PRODUCTS IN USA, SOUTH AFRICA AND RUSSIA.

Satbir Singh*, Dr Surya Prakash Gautam

Department of pharmaceutical management & regulatory affairs, CT institute of pharmaceutical sciences, Shahpur, Jalandhar, India

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E-mail: satbirsingh14291@gmail.com

Abstract

United States (US) and the EU are the largest and the most potential markets for in the world and are categorized under the regulated markets, while ROW (Rest of the World) market comprise of all the emerging markets like Brazil (LATAM), Africa, Russia (CIS), Hong Kong (ASIA), etc. The regulated market involves those countries where there are defined regulatory requirements fixed by the regulatory bodies of that country and the emerging market countries are those who still are behind in putting forward the well defined regulations for drugs. The regulatory agencies have the authority to control the registration, manufacturing, marketing authorization of the drugs. The regulatory bodies responsible for regulation in US, South Africa and Russia is USFDA, MCC and Roszdravnadzo, respectively. It includes the process of drug regulation and monitoring, and it also includes the process of manufacturing, distribution and promotion. Although the requirements are harmonized in regulated countries by CTD (Common technical document) filing, yet others have massive variety in requirements. It is vital for pharmaceutical industry to grip with the regulatory requirements for betterment of public and to ensure their place in the market. It has been noticed that with the coming years most of the blockbuster drugs will become off patent and this will open the opportunity for other companies to introduce their products inform of generics. This is expected to create market saturation. So a great deal of planning is needed by the companies in the future before introducing their products and also for their survival. This paper approaches the regulatory requirements for registration of pharmaceutical generic products in US, South Africa and Russia. This paper represents a thorough literature review of multiple sources including journal articles and government regulatory websites.

Keywords: USFDA, Roszdravnadzor, MCC, CTD/e-CTD, generic drugs

INTRODUCTION

The pharmaceutical area is enormously regulated industry, has to comply with many rules and regulations set and enforced by the government in order to protect the health and well being of the patients and the public. Therefore, the aim of the pharmaceutical industry is to find, identify, develop and formulate a generic drug product which can be tailor made to meet the various market requirements. As per global market tendency, it is estimated that around $150 billion worth of drugs and medicines will be off-patented during the period 2010 to 2017, which will serve as a stage for pharmaceutical corporations to progress generic drugs [1]. The pharmaceutical industry in India has revealed a notable growth which in turn has increased the economy of India [2].

After the induction of the product patent regime in India, there was a necessity for pharmaceutical companies both in India and abroad to explore and look for newer markets. Indian pharma majors are entering new markets with strategies and global goals, mergers and acquisitions are in focus with a motive to enter new market. Somewhat corresponding with the current harmonization and movement toward creating a mutual market for medicines inside the EU, the need for broader harmonization was felt by officials from Japan, EU, and US through International Conference of Drug Regulatory Authorities (ICDRA) prepared by world health organi-

zation (WHO). Pharmaceutical companies prepare dossier as per CTD / ASEAN CTD / non-CTD (country exact standard).CIS countries follow their own country specific dossier format. Pharmaceutical product registration is a challenging task in regulated, semi regulated and rest of world countries.

The regulatory bodies responsible for regulation in US, South Africa and Russia are USFDA, MCC and Roszdravnadzor respectively. The US and Russia are highly regulated market whereas South Africa is not upto that extent. It includes the process of drug regulation and monitoring, and it also includes the process of manufacturing, distribution and promotion. Although the necessities are coordinated in regulated countries by CTD (Common technical document) filing, yet others have vast diversity in requirements.

The aim of the pharmaceutical industry is to identify and develop a generic medicinal product which meets the regulatory necessities in different countries. In United states the documentation can be filed in CTD and eCTD format and Russia follows its different format. A generic drug is a drug stated as "a drug product that is analogous to brand or reference listed drug produce in dosage form, power, route of administration, quality and performance features, and intended use".

'Generic' meaning [3]:

The Dictionaries define a "generic" as a product — particularly a drug — that does not have a logo. For example, "paracetamol" is a chemical ingredient that is found in many brandname painkillers and is often vended as a (generic) medicine in its own right, lacking a brandname. This is "generic from a trademark point of view". When replicas of patent drugs are made by other manufactures, they are either sold under the name of the chemical component (making them clearly generic), or under another brandname (which means they are still generics from the point of opinion of patents).

Making and developing a generic drug product:

The developer and formulator must know the exact regulatory requirement of a country where the product is to be filed. In developing a generic drug product a different approach and strategy is needed as compared to a innovator product containing a new chemical entity or new molecule. Generic drug product developers must formulate a product which will have same quality, safety and efficacy of its original version. It means that the drug shows the pharmaceutical equivalence as well as bioequivalence. The Drug Price Competition and Patent Term Restoration Act" in 1984 altered the regulatory climate for generic drugs. This law allows for approval of many generic versions of many approved products after their patents have perished [4]. It has been noticed that all the regulatory agencies worldwide have almost same requirements yet they donot adopt a steady approach to drug approval requirements, and a result medicines are often approved quicker in some countries than others [5]. Therefore there is an urgent need for a harmonized drug regulation globally.

United States of America:

The United States is the world's chief market for pharmaceuticals and the world leader in biopharmaceutical research. The industry invests around 19% of sales profits to R&D. Pharmaceutical and biotechnology firms paid $65 billion on R&D in 2009 worldwide, out of which, the most, or 70% was consumed in the United States. The main goals of R&D investment were treatments for cancer, HIV/AIDS, autoimmune and infectious diseases and other diseases like Alzheimer's and multiple sclerosis, for which, presently, there are no effective cures[6,7,8,9].

The strengths of US pharmaceutical industry include a robust intellectual property system that identifies and prizes novelty and a science-based regulatory system that is considered the most rigorous in the world[10,11]. The globalization of the pharmaceutical industry and production has increased tasks for the FDA and manufacturers, in confirming that imported ingredients and finished dosage drugs meet safety and efficiency standards. For example, China and India have become the prime sources of active pharmaceutical ingredients (APIs) and generic drugs for the U.S. market, correspondingly[12].ANDA is filed for generic drug products which require market authorization and are identical or close alternatives of already approved products.

For many of their prescriptions, Americans purchase generic varieties of prescription drugs, certified by the Food and Drug Administration ("FDA") to be appropriate therapeutic substitutions for brandname variations of the same chemical compound[13]. Economists estimate that Americans save eight to ten billion dollars annually by procur-

ing generic alternatives to brand-name pharmaceuticals[14].In the United States, the FDA entails pharmaceutical manufacturers to essay "proof of safety and efficacy"[15].

The 1906 passage of the Federal Food and Drugs Act began the new era of pharmaceutical regulation in the United States. The Act created the Bureau of Chemistry, the ancestor to the modern FDA, which took its current name in 1930[16]. For the first three decades of its survival, the FDA primarily regulated the labeling of medications, gearing enforcement against product misrepresentation. However, in 1937, a deadly and largely untested new cough syrup, Elixir Sulfanilamide, directed to the deaths of over 107 Americans. Food, Drug and Cosmetic Act in 1938 Act and its later amendments generate a long-lasting regulatory approval process for new drugs to pass before being positioned on the market. For a new drug, this process necessitates FDA approval through a procedure now called the New Drug Application ("NDA") In the United States of America, private pharmaceutical companies and universities became the principal producers of new chemical entities ("NCEs"). Pharmaceuticals, like any other new product, are suitable for patent protection under American patent law, ensuring a legal remedy against infringement. Patent protection needs that the inventor apply within one year of the new conception entering the public territory; for pharmaceuticals, this means that the manufacturer needs to apply for patent protection within one year of beginning the FDA regulatory process[17]. Once a new pharmaceutical has been revealed and has gone through pre-clinical trials, the manufacturer must file an investigational NDA with the FDA[18].

Generic Drug Product Registration Requirements in US[19]:

1. The eCTD is compulsory for the submission of the drug applications (NDA/ANDA).
2. The US FDA guidance (CFR) documents and FDA sections (e.g. 505 (b) for NDA and 505(j) for ANDA) must be followed for the making of the dossier for the drug approval applications.
3. The different applications filed are e.g. For novel drug- NDA, For generic drug – ANDA, For biological application – BLA
4. The application is directly submit to the USFDA by the applicant or through any permitted contact agent for whom a certification is provided to the agency according to the GDEA 1992.
5. Administrative info is different i.e. cover letter, forms (356h), application information, field replica certification, debarment certification, financial certification, Patent information and exclusivity.
6. The paper size for the proposal is Letter size (8.5x11 inches) with font size 12 in times new roman format. The tables and statistics have small font size i.e. 8 to 10.
7. Package inserts should be provided for drug product in labeling.
8. The proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided.
9. The information regarding the clinical investigators is provided in the Module 5 and in financial disclosure Statement section of this module.
10. Appeal for waiver of in-vivo BE studies is provided in the module 1.
11. Annotated draft labeling (side by side) for labels and cartons matched with the RLD with proper annotation is provided.
12. The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA of US is provided.
13. Risk management Plans segment is for the post advertising surveillance and controlling the adverse effects of the drugs by apt management.
14. The declaration is given for the residual solvents boundaries used or present in the drug substance and excipients according to the USP.
15. Information on components including the name and address of the provider or manufacturer of the raw material, package material etc. provided in the 3.2.R.
16. The letter of Access is not mentioned in 3.2.R.
17. Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) certificates are not involved in this section whereas submit in DMF.
18. Certificate of suitability (CEP certificate) is not valid.
19. Comparability protocols are not attached for both the drug substance and drug products.
20. The stability data for accelerated studies are submitted for three months at the time of original submission.

21. Node extension is not permitted in the eCTD XML in software.
22. Structured product labeling (SPL) and study tagging file (STF) is compulsory by the USFDA in eCTD of a drug registration application. Paper CTD format is not accepted by FDA at all.

For the registration of generic drugs in USA we must follow the ANDA regulatory review process.

ANDA Regulatory Review Process [20]:

The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff process the ANDA allots it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist. Within the first 60 days following the compliance of an ANDA, a filing review is finished.

The generic drug user fee amendments 2012 (GDUFA)[21]:

It is designed to speed access to safe and effective generic drugs to the public and reduce costs to industry. The law requires industry to pay user fees to supplement the cost of reviewing generic drug applications and inspecting facilities. Additional resources will enable the agency to reduce the current backlog of pending applications, cut the average time essential to review generic drug applications for safety, and increase risk based inspections. It will also enhance global supply chain safety by demanding that generic drug facilities and sites around the world self- identify. Present legislative authority for GDUFA will be over at the end of 2017.The ANDA fee is $76,030.

South Africa:

Medicines and other pharmaceutical products are essential to healthcare system and should be available to the residents of every country. Medicines regulation targets to ensure that medicines and other pharmaceutical products mingling in national and international markets are harmless, effective and of good quality, are accompanied by complete and accurate product data, and are manufactured, stored, distributed and used in accordance with good practices.[22]As a result, African national MRAs may have understanding in managing generics, but many have only restricted experience in evaluating, approving and registering innovator products[23].

It is found that the African MRAs are under resourced and lack skills and capacity to perform their functions adequately[22].After the assembling of the application for registration, the complete application is to be submitted to the MCC Secretariat.

The Registration and licensing requirements for the manufacture and sale of pharmaceuticals in South Africa[24]:

The medicines sold in South Africa should and must be registered by the Medicines Control Council, [MCC], the Medicines Controlling Specialist set up under the Medicines and Related Substances Control Act [Act 101 of 1965] as corrected, to regulate all aspects of the manufacture and sale of medicines.

Requirements:

1. The Company must be listed under the Company's Act and then secondly with the South African Pharmacy Council, and must have an functioning license from the Medicines Control Council.
2. A "liable pharmacist" must and should be appointed as the person legally accountable for obedience with all laws and regulations, codes of good practice and ethical obligations.
3. An application for the registration must be assembled in a specified format by a pharmaceutical company registered and operating in South Africa.

Guidelines for both the registration and the control of medicines by MCC[24]-

This includes:

1. The claims made for the medicine with regard to the indications for its use. These must be present on the package insert which must accompany each pack of a medicine.
2. Registration approval is based on these claims after MCC evaluation of the scientific and clinical data provided to support the claims.
3. The Specifications, provisions and quality control measures for all raw materials and packing materials, as well as the final dosage form in its final sales pack. These must be labelled in detail with exact specifications and control procedures described.

4. The Manufacturing processes and in-process quality controls.
5. A validation program to ensure that all components and processes produce products of a reliable quality every time.
6. A Site Master File with definite particulars of the real factory where the medicine is made.
7. For innovative medicines, details of the results of all pharmaceutical, animal and human testing must be supplied.
8. The studies may be done in South Africa or in other countries but the data must be evaluated and approved by the MCC for registration of the medicine to be approved.
9. For generic medicines the applicant must deliver proof that the product has a similar therapeutic result to that of the originator's product.
10. All advertising must be based on the permitted claims for the medicine i.e., those which look on the approved package insert.
11. Generally the industry controls breach of advertising and promotional practices by self-regulation e.g. PIASA has a Code of Practice for the Promotion of Medicines to healthcare professionals.
12. The production facility where a medicine is made, tested and packed is subject to inspections and approval by the MCC which may evaluate the product dossiers to guarantee that these have been kept updated.

Russia (CIS):

Russia is stated as very important pharmaceutical market in the world along with US, India, China, South Africa, etc. It is a member country of 'Commonwealth of independent states' ie CIS founded in 1991, and it is regional organization whose associate countries are former Soviet republics, formed after the dissolution of the Union of Soviet Socialist Republics (USSR). It is estimated to be among the top five pharmaceutical markets in terms of value in the next 5-10 years. Russia's pharmaceutical market remains to be one of the most eye-catching in the Emerging Europe region, primarily due to its sheer market size, growing economy and growing government investment in healthcare. Russia's recent World Trade Organization accession should drive expansions in the country's intellectual property (IP) environment, and enforcement in particular, which has been conspicuously lacking[25]. Registration in Russia is a national procedure and duration for registration is estimated upto 1.5 years. The documentation should be done in Russian language in a format compliant with the Russian requirements. The recommended submissions of a bioequivalence studies are carried out in certified research organizations within the Russian Federation's territory.

Registration file (or dossier) signifies the documents submitted to State Regulatory Authority for registration. Russian registration file consists from 6 parts[26]:

- Administrative documents
- Description of pharmaceutical properties
- Figures about production of pharmaceutical product
- Figures about quality control of the finished pharmaceutical product
- Figures about preclinical pharmacological and toxicological studies of pharmaceutical product
- Figures about clinical testing of pharmaceutical product

Registration of generics: The process is usually conducted in 3 stages[26]

Stage 1: (2 months)

The Compilation and assembling of dossier in Russian and its submission to the National Center of Pharmaceutical Products Expertise (FGU).

Stage 2: (12 months)

Expertise of the pharmaceutical product Quality, Efficacy and Safety in the National Center of Pharmaceutical Products Expertise (FGU).

Stage 3: (4 months)

Finishing of the expertise and submission of the dossier to Roszdravnadzorfor supplying of Registration Certificate.

CONCLUSION:

The world is divided in the drug approval procedures, so it is important for the manufacturers, especially the generic companies, to carefully evaluate the market interest, cost of development, target regions, regulatory requirements before the development of drugs. Looking at the different regulatory environment, it is impractical to get global marketing approval at same time and unveiling in all the regions at one go. By examining these markets individually, it would be easier to aim the areas where

they can precisely improve their regulatory barriers, thus leading the way for the rest of the countries. A number of blockbuster drugs will be going off patent in the next few years, opening the way to generic products and eliminating an important and major source of the pharmaceutical industry's profits. A lot of strategic planning is required before filing a generic product in a country. The planning includes the market research, competitors, swot analysis, cost, demand etc. Currently there is continuous process of harmonization going on globally but still there is huge tests to be overcome in case of generic pharmaceuticals's filing and development because of diversity in regulatory landscape of various countries. So the companies are facing huge challenges in developing and filing of generic applications. The Registration of pharmaceuticals should be seen as a serious step in ensuring entrance to safe and effective medicinal product in the market for the consumers.

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