MARKETING AUTHORIZATION OF GENERIC DRUG: GLOBAL ISSUE AND CHALLENGES

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REVIEW ARTICLE

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ABSTRACT:

Generic medicines are those whose patent protection has expired, and which may be produced by manufacturers other than the innovator company. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Generic medicines are typically 20 to 90% cheaper than originator equivalents. The objective is to provide a high-level description of what generic medicines are and how they differ, at a regulatory and legislative level, from originator medicines. It describes the current and historical regulation of medicines in the world's two main pharmaceutical markets, in addition to the similarities, as well as the differences, between generics and their originator equivalents including the reasons for the cost differences seen between originator and generic medicines. This article refers to the general generic drug approval process in India, USA, and Japan. They have different regulation and approval process.

Key words: WHO, ANDA, FDA, CDSCO, MHLW

Introduction:

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public. Therefore, the aim of the pharmaceutical industry is to identify and develop a generic drug product which can be tailor made to meet the diverse market requirements. As per global market trend, it is estimated that approximately $150 billion worth of drugs will be off-patented during the period 2010 to 2017, which will serve as a platform for pharmaceutical companies to develop generic drugs (1). The pharmaceutical industry in India has shown a remarkable growth which in turn has risen the economy of India (2). After the introduction of the product patent regime in India, there was a need for pharmaceutical companies both in India and abroad to explore newer markets. Indian pharma majors are entering new markets with global ambitions, mergers and acquisitions. For sustained growth over the next few decades, firms have to concentrate on generic drug products. Government has the responsibility to protect their citizens. It is the responsibility of national governments to establish regulatory authorities with strong guidelines for quality assurance and drug regulations in the respective territories. Efforts to harmonize various elements of drug regulatory activities have been initiated by various inter-governmental organizations at regional and inter-regional level in the past decade. The driving force behind these efforts has been the increase in global trade in pharmaceutical products, and growth in the complexity of technical regulations related to drug efficacy, safety, and quality.

The Pharmaceutical market based on the diversity in the regulation region and marketing interest can be divided into two groups: Regulated and emerging markets. The regulated market involves those countries where there are defined regulatory requirements set by the regulatory bodies of that country and the emerging market countries are those who still lag behind in putting forward the well defined regulations for drugs. United States (US) and the EU are the biggest and the most potential markets for Pharmaceuticals in the world and are categorized under the regulated markets, whereas ROW (Rest of the World) market

includes all the emerging markets like Brazil (LATAM), Tanzania (Africa), Russia (CIS), Hong Kong (ASIA), etc. The term "generic drug" or "generic medicine" can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organisation (WHO), to mean a pharmaceutical product which (3):

– is usually intended to be interchangeable with an innovator product,
– is manufactured without a license from the innovator company, and
– is marketed after the expiry date of the patent or other exclusive rights.

There are differing legal requirements in different jurisdictions that define the specifics of what a generic medicine is. However, one of the main principles underpinning the safe and effective use of generic medicines is the concept of bioequivalence.

Bioequivalence has been defined as follows: *two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability's (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards* (4).

The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug.

The objective of this article is to provide an accessible resource describing the foundation of generic medicines, from their legal advent in the mid 1980's to how current legislation and regulation of generics affects, *inter alia*, their composition, regulatory approval, pricing, and ultimately acceptance by healthcare professionals and patients.

Generic Drug Approval Process in USA:

Generic drugs play an important role in the US system of health care. To stimulate generic drug entry, the FDA currently offers a period of marketing exclusivity to the first firm that gains approval for a generic version of a branded drug. During this 180-day period, only two firm can sell version of the drug: the original, branded drug maker and the first approved generic firm. After the period of exclusivity expires, other generic firms are free to enter the market. There are two ways that a drug can gain FDA approval and brought to the market. First, if the drug is novel product, the developer must submit it to the FDA using new drug application (NDA). Second, if the drug is a generic version of an existing drug, the generic drug maker can submit an Abbreviated New Drug Application (ANDA).

To gain FDA approval, a generic medicine must (5):

- Contain the same active ingredient as the originator medicine (inactive ingredients may vary)
- Be identical in strength, dosage form, and route of administration
- Should have the same use indications
- Should be bioequivalent
- Should meet the same batch requirements for identity, strength, purity, and quality
- Should be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for originator products.

The Hatch Waxman Act: Enacted in 1984, the US Drug Price Competition and Patent Term Act, informally known as the: "Hatch Waxman Act" standardized US procedure for the recognition of generic drug. The Waxman Hatch Act of 1984, among the other things, allowed the generic firm to submit ANDAs for drugs approved. The application is known as "abbreviated" because the generic manufacturer is no longer to repeat the tests showing the substance is safe and effective since the innovator had already done so (6). (Figure 7) A generic drug manufacturer can be file as per given regulations:

(I) That no patent information on that brand name drug has been submitted to the FDA.
(II) That the listed patent has expired.
(III) That the listed patent will be expire on a certain date, before which time the generic will not enter the market; or
(IV) That the patent is invalid or will not be infringed by manufacturer, use, or sale of the new drug for which the ANDA was submitted.

ANDA Approval Process in USA:

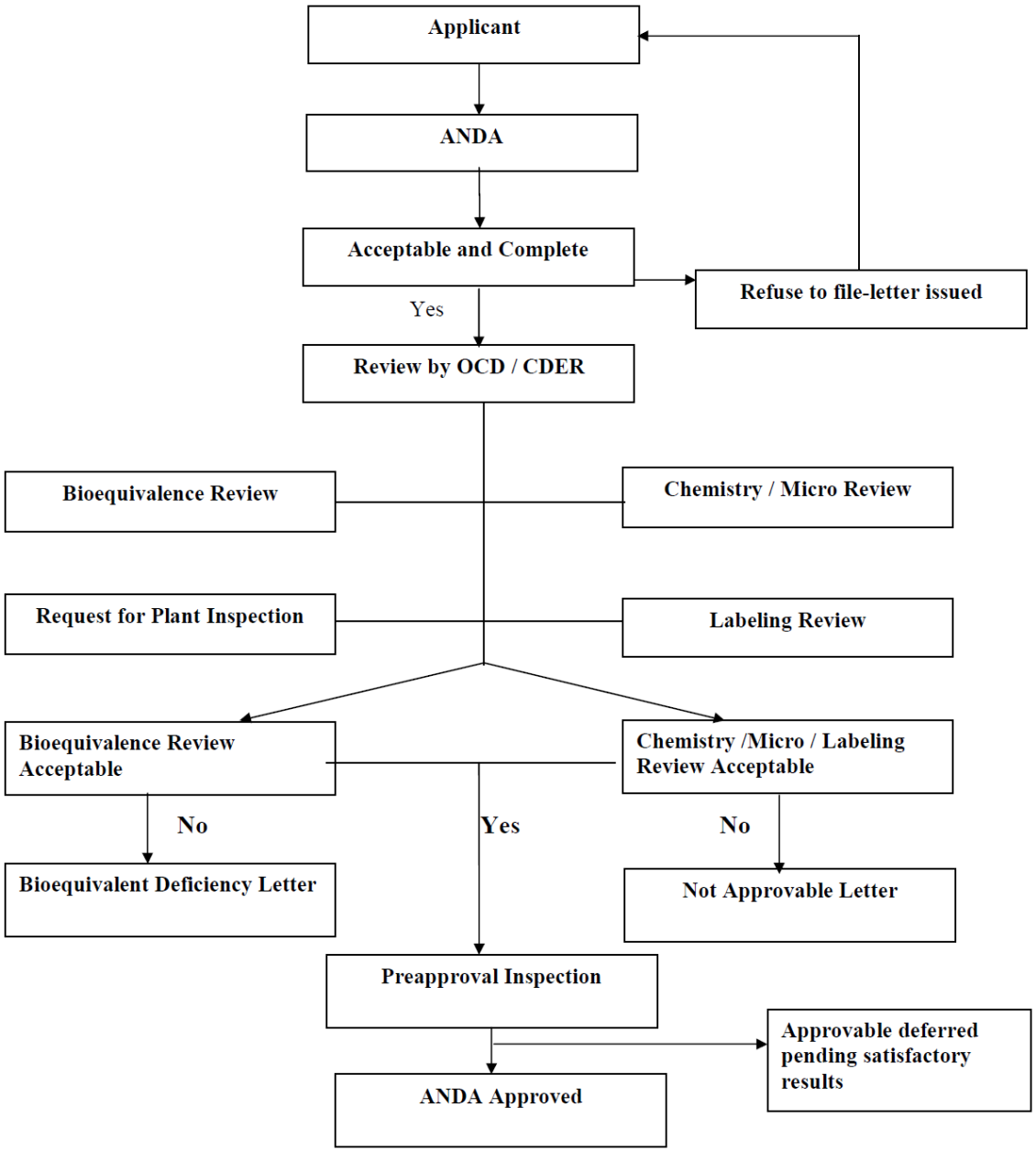

Figure: Generic drug approval process in USA (7)

Generic Drug Approval in India:

In India, the Drug and Cosmetics Act, 1940, dictates the requisites to import, manufacture, distribute and market a drug. The central regulatory authority, CDSCO also known as Drug Controller General of India (DCGI), is vested with the responsibility of providing authorizations to new drugs (8). In India,

second entrants with new dosage forms, new indication, vaccines, new fixed dose combination, etc. are considered as new drugs and have to be approved by DCGI. A generic drug is seeking authorization of an already approved within four years of the first authorization will also be considered as a new drug and hence, require to seek approval from DCGI. However, an applicant seeking authorization for the generic version of an already approved drug can seek permission for the manufacturing from the state FDA once the four year time from first authorization expires (9).

The marketing authorization for new drugs, in India, is obtained through submission of form 44 to the CDSCO. Once the marketing authorization is granted by the CDSCO, an application to the state FDA is to be made to receive a permission to manufacture the drug. The state FDA then provides a license to the manufacture the drug by way of form 29. The requirement and guidelines for authorization are provided in Schedule Y. The need for data exclusivity and orphan drug exclusivity as an incentive to innovation has been debated earlier (10). However, the impact that exclusivity provision would have on access of cheaper medicine to public has been discouraging the implementation of any exclusivity provision.

Scope of generic drugs in India

In today's era, the scope of generic drugs is increasing day by day specially in several ill health conditions such as diabetes, cardiovascular and in microbial diseases etc. When any patent expires, new generics are introduced into the market. The scope is also increased due to Para IV filings and Bolar provisions.

Recently, Para IV filing strategy has been adopted by leading Indian pharmaceutical companies to introduce generic drug of its own taking advantage of shortcoming in patent application of patent holders. According to this, a generic manufacturer challenges the original patented drug and claims that the generic version proposed to be launched by the manufacturer does not infringe the patent holder's version. In case a patent challenge is won, it entitles the first to file Para IV generic manufacturer a 180 days exclusivity, if company come up with an equivalent of the innovator's branded formulation (11) .

'Bolar provision' allows generic manufacturers to prepare and develop regulatory procedures before patent expires, so that, products are ready for market as soon as the patent ends. With these provisions, in India, the scope of generic drug manufacturing has also increased (12).

Compulsory Licensing Provision in India:

The compulsory licensing provision is permitted in the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement under Article 31. The agreement does not limit the grounds upon which compulsory license may be granted and only sets forth the conditions to be applied in the case of granting. This includes specification of grounds of compulsory licensing and reasonable rate of licensing fees to the patent holder.

Grant of compulsory license (CL) is for the remaining term of the patent unless a shorter period looks reasonable and required in case to the controller. Further, it is to be noted that while granting the license the controller shall take into account the nature of invention, time elapsed, ability of applicant, his efforts for obtaining a license on reasonable terms. While granting CL reasonable royalty is also paid to the patentee, having regard to nature of invention, its utility, expenses incurred in maintaining patent grant in India and other factors.

Generic Drug Approval in Japan:

The Ministry for Health Labor and Welfare (MHLW) is the regulatory body in Japan responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in Japan and makes the decision on approval of drugs (13).

Since 1 April 2007, all companies marketing originator drugs in Japan must perform post-marketing surveys on new drugs so that efficacy and safety can be reconfirmed by re-examination by the MHLW for a specified

period of eight years. Applications for generic drugs cannot be filed until completion of the re-examination and expiration of patents—which last for 20 years in Japan. Brand-name products are protected from generics during this period.

Equivalency of generic drugs—that are supposed to be equivalent to new drugs—are examined by the MHLW through its Pharmaceutical and Medical Devices Agency based on the drug organization's research on equivalency to already approved items.

The Japanese government has set a target to raise the share of generic medicines by volume to 30% or more by 2012. The MHLW established the 'Action Programs for Promoting Safe Use of Generic Medicine' in October 2007 and efforts have been made in accordance with this programme to gain the trust of patients and medical professionals with regard to generic medicines.

Marketing Approval:

Formal approvals and licenses are required to marketing drugs in Japan, and formal approval and/or licenses must first be obtained from the Minister of the MHLW or prefectural governor (Japan Pharmaceutical Manufacturers Association, 2007) (14).The approval and licensing system has been revised in the amended Law and manufacturing (Import) approval became marketing approval from April 2005. Product licenses have been abolished and GMP compliance for each product has been specified as an approval condition (Japan Pharmaceutical Manufacturers Association, 2007). Marketing approval require a review to determine whether or not the product in the application is suitable as a drug to be marketed by a person who has obtained a marketing business license (marketing authorization holder) for the type of drug concerned and confirmation that the product has been manufactured in a plant compliant with GMP (Japan Pharmaceutical Manufacturers Association, 2007).

The PMDA covers the entire range of work from clinical trial consultations to reviews. Application forms for approval to market drugs are usually submitted to the PMDA. When application forms for new drugs are received by the PMDA (KIKO), a compliance review of the application data (certification from source data), GCP on-site inspection, and detailed review report (Japan Pharmaceutical Manufacturers Association,2007).

The approval review process consists of expert meeting of review team members and experts to discuss important problems. A general review conference attended by team members, experts and representatives of the applicant is held after the expert meeting. The evaluation process followed by the PMDA is as follows (15):

1. Interview (presentation, inquires and replies)
2. Team review
3. Inquiries and replies
4. Review report
5.Expert meeting (include at least three clinical specialists as experts)
6.General review conference (main agenda items and names of participating experts made available 2 weeks prior to meeting; presentation)
7. Follow up expert meeting
8. Review report
9. Report to the evaluation and licensing division, PFSB

Conclusion: Across most regional pharmaceutical markets, generics are emerging as strong challengers to branded medications. The demand of generic drugs is also set to increase following the imminent loss of patent protection for several blockbuster drugs. North America (USA & Canada) is the largest pharma market and has least restrictions. America has larger funding than the European and Asian countries, and the growth is expected to continue. Japan is also a large market but it is one of less penetrable market. Japan and India also has its own guidelines for approval of generic drugs. Indian generic players are seen as a major threat by European generic companies. The Indian pharmaceutical market is one of the most advanced among the developing countries. The ranking of Indian market is 4^{th} in volume and 13^{th} in value. Currently different countries have to follow different regulatory requirements for approval

of new drug. It is time consuming for the participating countries. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. But now harmonization exist in many Regulated & semi regulated countries.

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