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A REVIEW ON GENERIC DRUGS REGISTRATION PROCEDURE IN USA & CANADA

M. V. S. Kavitha*, G. Indu, M. V. Nagabhushnam, Brahmaiah Bonthagara, D. Nagarjuna Reddy

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amravati road, Guntur, A.P, India- 522002.

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***Corresponding Author**
M. V. S. Kavitha
Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amravati road, Guntur, A.P, India- 522002.

ABSTRACT

This study aims to compare the generic drug approval and registration processes in the regulatory markets of USA and Canada. Based on the information collected from various sources such as regulatory agencies sites, Government websites, discussion with regulatory agents, interviewing pharma professionals and literature survey from various journals, a clear picture on the generic drug approval and registration process of each country was drawn. Different regulatory authorities *viz.,* Food and Drug Administration (FDA) of USA and Health Canada carried out the generic drug approval and registration process in the respective countries. After analysing the various requirements for the generic drug approval in the above stated countries, it was concluded that the regulatory guidelines of Europe and Brazil was not well defined. But FDA gives very much well defined requirements.

KEYWORDS: Generic drugs, USA, Canada.

1. INTRODUCTION

A generic drug product is a drug which is produced and distributed without patent protection. The generic drug may still have a patent on the formulation, but not on the active ingredient. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, and route of administration, quality, performance characteristics and intended use.[1]

Innovator drug products are those drug products which are having a new molecular entity, a new or modified structure, a new indication, a new dosage form, a new dosage administration route, a new combination or a new therapeutic role. Innovator drug products form the basis for the development of generic drug products.

Generic drug products are identified by its own brand name or approved INN (International Non-proprietary Name). It must be marketed in compliance with international patent law. It must be bioequivalent which means that when compared scientifically the generic medicine and the innovator product demonstrate essentially the same rate and extent of biological availability of the active substance in the body when administered in the same dose.

Generics are widely used in many countries as they are cost effective alternative to high priced innovator pharmaceutical products. A generic must contain the same active ingredients as the original formulation. According to the US Food and Drug Administration (FDA) generic drugs are identical or bioequivalent to the brand name counterpart with respect to pharmacokinetic and pharmacodynamics properties. By extension, therefore, generics are identical in dose, strength, route of administration, safety and efficacy and intended use. In most cases, generic products are available once the patent protections afforded to the original developer have expired.

Generic drug products are "Essentially Similar" to their counter parts, equally effective and are therefore interchangeable with, the innovator product.[2] A generic drug application does not require to include preclinical data (animals) and clinical data (human beings) to establish safety and effectiveness as in case of new drug application.

Conditions for generic drugs application includes

- The patent has expired
- The generic company certifies the brand company's patents are either invalid, unenforceable or will not be infringed.
- For drugs which have never held patents
- In countries where a patent(s) is /are not in force

When generic products become available, the market competition often leads to substantially lower prices for both the original brand name product and the generic forms. The time it takes a generic drug to appear on the market varies. In the US, drug patents give twenty years of

protection, but they are applied for before clinical trials begin, so the effective life of a drug patent tends to be between 7-12 years.

The principal reason for the relatively low price of generic medicines is that competition increases among producers when drugs no longer are protected by patents. Companies also incur fewer costs in creating the generic drug and are therefore able to maintain profitability while offering the drug at a lower cost to consumers. The costs of these generic drugs are so low that many developing countries can easily afford them. For example, Thailand is going to import millions of pills of the generic version of Plavix, a blood thinning treatment to prevent heart attacks, at a cost of 3 US cents per pill from India, the leading manufacturer of generic drugs.[3]

Generic drugs do not incur the cost of discovery, and instead are able to reverse engineer known drug compounds to allow them to manufacture bioequivalent versions. Generic manufacturers also do not bear the burden of proving the safety and efficacy of the drugs through clinical trials, since these trials have already been conducted by the brand name company.

In most countries, generic manufacturers must only prove that their preparation is bioequivalent to the existing drug in order to gain regulatory approval. It has been estimated that the average cost to brand name drug companies of discovering and testing a new innovative drug (with a new chemical entity) may be as much as $800 million.[4]

Generic drug companies may also receive the benefit of the previous marketing efforts of the brand name drug company including media advertising, presentations by drug representatives and distribution of free samples. Many of the drugs introduced by generic manufacturers have already been on the market for a decade or more and may already be well known to patients and providers. (Although often under their branded name)

Prior to the expiration of a drug patent, a brand name company enjoys a period of “market exclusivity” or monopoly, in which the company is able to set the price of the drug at the level which maximises profitability. This price often greatly exceeds the production costs of the drug, which can enable the drug company to make a significant profit on their investment in research and development. The advantage of generic drugs to consumers comes in the introduction of competition which prevents any single company from dictating the overall

market price of the drug. Competition is also seen between generic and name brand drugs with similar therapeutic uses when physicians or health planners adopt policies of preferentially prescribing generic drugs as an alternative therapy. With multiple firms producing the generic version of a drug the profit maximising price generally falls to the on-going cost of producing the drug, which is usually much lower than the monopoly price.[5] The FDA gives a list of 10 non-proprietary drug names (non IUPAC) for developing drug company to choose from and 10 brand names for the company to choose from. It is in the best interest of the company to choose a brand name that is easy to remembera.eg. 7-chloro-1- methyl-5-phenyl-1,3-dihydro-2H-1,4- benzodiazepin-2-one has a brand name of Valium and a non - proprietary name of diazepam.

2. Generic Drug approval process in USA

FDA is an agency within the department of health and human services (HHS).The regulations of the FDA are found in Title 21 of the United States Code of Federal regulations (CFR).There are other explanatory documents called "guidance documents". The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science based information in order to use medicines and foods to improve their health.

3. Abbreviated New Drug Application (ANDA) Process for Generics

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Centre for Drug Evaluation and Research, office of generic drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective and low cost alternative. All approved products, both innovator and generic, are listed in FDAs Approved drug products with Therapeutic equivalence evaluations (Orange Book).[12]

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent which gives them the rate of absorption, or bioavailability of the generic drug which they can compare to that of the innovator drug. The generic version must deliver the same amount of

active ingredients into a patient's blood stream in the same amount of time as the innovator drug.

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug price competition and patent term restoration Act of 1984", also known as the Hatch-Waxman Act.[13]

After all components of the application are found to be acceptable an approval or tentative approval letter is issued to the applicant. The letter details the conditions of the approval and allows with the concurrence of the local FDA district office, the applicant to market the generic drug product. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the circumstances associated with the tentative approval generic drug product and delays final approval until all patent/exclusivity issue expires. A tentative approval does not allow the applicant to market the generic drug product.[14]

4. Hatch-Waxman Act

The Hatch Waxman Act intended to make lower cost versions of generic drugs more widely available, while simultaneously ensuring that patent protection remained strong enough to adequately promote investments in new drug development. The legislation stuck a delicate compromise along this line by decreasing barriers to generic drug development while also extending the term of patent protection for new drugs. Since the passage of Hatch Waxman, the generics industry has made substantial headway capturing market in the US, where generic versions of drugs now capture 58 percent sales by volume. This reflects a substantial growth from when Hatch Waxman was first enacted in 1984, when generics accounted for only 19 percent of prescriptions filled. Moreover, due to the strong competition among generics created by the Act, Americans pay less for generic drugs relative to consumers in other countries. In fact, a recent study of drug prices found that prices for on patent prescription drugs are higher in the US than in most other countries they surveyed, prices of generics in the US are lower in the US than in any other countries.

Granting a patent monopoly necessarily prices some consumers out of the market for a particular drug, but patents also provide confidence that investments will be sufficiently rewarded to justify the risks and the investment capital needed to bring a drug to market.

Thus, on balance, all consumers benefit from the enhanced research and development of life Saving drugs stimulated by the patent monopoly.[15]

6. Chemistry Manufacture and control

This part is one of the important sections of any ANDA. This part is known as 21CFR314.50 (d).[1] This part gives the detailed information to the FDA (CDER) for the purpose of review of the application. CMC objective is to sufficiently characterize drug substance and drug product. The logic behind this is that important quality; safety and efficacy attributes are established and controlled.

CMC contains the following information

- Components and composition
- Active pharmaceutical ingredients, recipients control
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Specifications and tests Packaging
- Stability

5. Generic Drug approval process in Canada:

In Canada, the relevant law is set out in its Patent Act, certain regulations there-under, in particular the Patented Medicines (Notice of Compliance) Regulations (PM(NOC) Regulations), and in the Food and Drug Regulations' under the Food and Drug Act. A brief history of these enactments follows. Canada introduced provisions into its Patent Act allowing for the compulsory licensing of patented food and medicine products in 1923.In 1969, these provisions were expanded to allow the importation of active ingredients for licensed patented drug products. Under the compulsory licensing provisions, the Commissioner of Patents could grant a license to import a patented active ingredient to a generic manufacturer, usually requiring the manufacturer to pay a nominal royalty of four percent to the patentee.

Bill C-22 was presented primarily as legislation directed to correct the drug patent situation. Bill C-22 caused "a stormy public debate" within Canada and was often "front page news. "The amendments affecting compulsory licensing were strongly opposed by the Liberal Party of Canada, then in opposition but today the governing party in Canada's Parliament. The

Liberals feared that reducing the length of compulsory licenses would unduly increase drug prices in Canada. However, the Conservative government of the day ultimately succeeded in passing Bill C-22 into law.

The Food and Drug Regulations were substantially revised in 1995 to create an abbreviated new drug submission process, but this merely codified long-standing ad-ministrative practices at the Canadian health and safety regulatory body, TPP.

5.1. Patent Term

As stated above, Canada's patent term is twenty years from the filing date for patent applications filed on or after October 1, 1989 but seventeen years from the date of grant for patents arising from applications filed prior to that date, known as "old act" patents. There is no provision for patent term restoration. The United States recently challenged Canada's "old act" patent term success-fully under the WTO dispute settlement procedure. On May 5, 2000, the Panel ruled that Canada's seventeen-years-from-grant term for "old act" patents was not consistent with Article 33 of TRIPs. Article 33 requires that the term of a patent "shall not end before the expiration of a period of twenty years counted from the filing date. Canada has appealed. The outcome of the appeal is not known at the time of writing this article. It is not yet known precisely how Canada's law will change if the appeal does not succeed.

5.2. Bolar and Stockpiling Exceptions

Like the U.S. provision, Canada's Bolar exception, one of the Bill C-91 amendments in 1993, deems the use of a patented invention to seek regulatory approval not to be infringement of a patent.79 While the Bolar exception in the Hatch-Waxman Act was clearly a new benefit to generic manufacturers, this was less clear in Canada. Canada's Bolar exception is arguably a codification of a pre-existing exception under earlier case law holding that use of a patented invention to prepare a regulatory filing was within the common law "experimental use" exception to patent infringement. The stockpiling exception, not found in the equivalent U.S statute, allows other-wise infringing products to be manufactured for six months prior to the expiry of the patent, in preparation for entering the markets. The European Union recently challenged the Bolar and stockpiling exception before the WTO. On March 17, 2000, the Panel ruled that Canada's Bolar exception was consistent with TRIPs, but that the stockpiling exception was not. It is again not known at the time of writing this article precisely what changes to Canada's law will be made to comply with this ruling.

5.3. Abbreviated New Drug Submissions

In Canada, a generic manufacturer can obtain a Notice of Compliance (NOC) by filing an abbreviated new drug submission, equivalent to an ANDA, demonstrating that a generic drug is the pharmaceutical equivalent of a "Canadian reference product?".

5. 4. PM(NOC) Regulations

These regulations are variously known as the linkage regulations, 55.2 regulations, or NOC regulations. Described by the Supreme Court of Canada as "draconian" in their effect on generic manufacturers, they have been controversial. The courts have commented on the difficulties in interpreting the regulations.

Under the PM(NOC) Regulations, an innovator drug company having approval for a drug product in Canada, referred to as a "first person," may submit to the Minister of Health a patent list setting out any patent "that contains a claim for the medicine itself or a claim for the use of the medicine?" The Minister (in practice, the TPP) maintains a register of patents, roughly equivalent to the patents listed in the Orange Book in the United States.

If a generic manufacturer, referred to as a "second person," files a submission that it wishes to "compare" with a first person's drug, the second person must address patents listed for that drug. The generic manufacturer must either accept that it will not get regulatory approval until expiry of any patents listed for the reference drug, or make an "allegation" that the patent or patents are invalid or are not infringed by its submission. An allegation is thus roughly equivalent to a paragraph IV certification under the Hatch-Waxman Act.

The notice of allegation must be served on the first person and the Minister? The first person may, within forty-five days, commence a judicial review application for an order that the NOC not be issued to the generic drug.

If the first person commences the litigation, the NOC may not be issued for twenty-four months, or until the hearing, or patent expiry, whichever comes first. As the Federal Court of Appeal stated, merely commencing the proceeding, the applicant obtains what is tantamount to an interlocutory injunction for up to thirty months [as the time frame then was] without having satisfied any of the criteria a court would require before enjoining issuance of a NOC.

At a hearing, a judge of the Federal Court of Canada determines whether the generic manufacturer's allegation is "justified." If the court finds the allegation un-justified, it issues an order prohibiting the Minister from issuing the NOC until expiry of the patent or patents.
A peculiarity of the system, which makes it quite different in practice from the Hatch-Waxman Act, is that the issue of patent infringement or validity cannot be deter-mined in litigation under the PM (NOC) Regulations; "their object is solely to prohibit the issuance of a notice of compliance under the Food and Drug Regulations?"

Either party is therefore entitled to commence a parallel patent action. As the Federal Court of Appeal observed, patent invalidity, like patent infringement, cannot be litigated in this type of proceeding [that is, a judicial review application under the PM(NOC) Regulations]. The odd result is that there may be years of complex litigation with respect to a single drug under the PM (NOC) Regulations, sometimes involving several allegations and several judicial review proceedings, yet the actual patent issue remains unresolved.

A complex procedural jurisprudence has arisen unique to these types of proceedings, which deals with issues such as in what circumstances an allegation is "premature" and therefore improper, s whether repeated allegations may be made in respect of one drug, what patents may be properly listed on the register, in what circum-stances portions of the generic submission must be produced to the first person, and what rules, if any, limit the ability of first persons listing patents on alternative formulations, new uses, crystalline forms, and so on.

6. Five-Year Data Exclusivity

If a drug submission is made to TPP, and the Minister "examines" and "relies" on any information filed with the Minister in another new drug submission for a chemical or biological substance not previously approved for sale in Canada, the TPP may not issue a NOC to the second submission for five years after the originator's NOC. The TPP, however takes the position that it does not generally "examine" and "rely" (i.e., it does not physically review the file while reviewing the generic submission) on the information in the originator's submission file while reviewing an abbreviated new drug submission and, therefore, this section does not generally apply. This position was recently upheld by the courts.

SIMILARITIES AND DIFFERENCES

Generic Drug Specifications	Us	Canada
1.Patent term	Twenty years from the date of patent, but formerly seventeen years from the date of grant	Twenty years from the date of patent, but formerly seventeen years from the date of grant
2.Abbreviated submissions	Abbreviated New drug Application (ANDA)	Abbreviated New drug Submission (ANDS)
3."Bolar "Exception	Patent infringement as the Bolar exception	Patent infringement as the Bolar exception
4.Patent list	The regulatory is the food and drug administration(FDA)	The therapeutic products programme(TPPP)
5.Generic Must "Certify"toLlisted Patent	A generic manufacturer filling an abbreviated application submission "Paragraph 4 certification" in US	A generic manufacturer filling an abbreviated application submission "notice of allegation" in Canada
6.Originator may commence litigation in forty five days	Forty five days if the generic manufacturer serves notice on the innovator challenging the patent.	Forty five days if the generic manufacturer serves notice on the innovator challenging the patent.
7.Automatic Stay	The length of the automatic stay is thirty months	In Canada is the shorter of Twenty four months
8.pre expiry approval granted only in generic wins litigation	FDA approval in us	notice of compliances in Canada

7. CONCLUSION

Views will differ on whether the laws in Canada or the United States adequately achieve the necessary balancing of the interests of originator drug companies, the public, and generic manufacturers. There is no doubt pharmaceutical patent laws must ensure that innovator drug companies can achieve a sufficiently high return to attract investment into drug re-search. At the same time, access to affordable medications will remain a lively politi-cal issue. At present, capital invested in drug research appears to earn excellent returns, at least for larger players in the industry. The median return on equity of the twelve pharmaceutical members of the Fortune 500 was 35.8 % in 1999, more than double the median return for the Fortune 500 as a whole: 15.2%. These returns were net of the sector's large research expenses. Drug patent laws, particularly in the United States, which has the world's largest market for prescription drugs, presumably played a key role in achieving this remarkable financial performance. Is there a point at which pharmaceutical laws favour research too much, at the

expense of the affordability that comes from price competition? How should a proper balance be struck? Is a premium in earnings over what other sectors earn necessary to spur research in the pharmaceutical sector? If so, how big should that premium be? Does increasing the premium through thriller intellectual property protection always lead to more and better research? Law-makers in both Canada and the United States will have to address these complex questions in years to come, particularly as the populations age in both countries, and prescription drug consumption increases.

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