

## COMPARATIVE STUDY FOR GENERIC DRUG APPROVAL PROCESS AND THEIR REGISTRATION AS PER CTD IN EUROPE, USA AND BRAZIL

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### REVIEW ARTICLE

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#### ABSTRACT

This aims to compare the generic drug approval and registration process in the regulatory market of Europe, USA and Brazil. Based on the information collected from various sources such as regulatory sites, Government websites, discussion with regulatory agent, 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. The different authorities' viz. European Medicines Evaluation Agency (EMA) of Europe, Food Drug Administration (FDA) of USA and National Health Surveillance Agency (ANVISA) of Brazil 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 drug approval, EMA, FDA, ANVISA.

#### 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

- i. The patent has expired
- ii. The generic company certifies the brand company's patents are either invalid, unenforceable or will not be infringed.
- iii. For drugs which have never held patents
- iv. 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 ongoing 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 remember a.e.g.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.

### Generic drug approval process in Europe

The European Medicines evaluation agency (EMA) is the decentralised body of the European Union with headquarters in London. The mission of the European medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health. The generic industry

is happened to be the major user of mutual recognition procedure for marketing authorisation in the EU market. It is expected that generic will be the major user of decentralised procedure and a new entrant will be seen too in Centralised procedure. (6)

### **Data exclusivity**

Data exclusivity prevents regulatory authorities from assessing the safety and efficacy profile of a generic application for a period of time beginning from the first marketing approval of the originator product. Generics applications do not use data from the originator registration file. They are approved on their own merits, using their own development data, under the same EU requirements as the originators. The originator's data is never released to third parties by the medicines authorities. It therefore is not and cannot be used by generics producers.

However, since generics contain well known, safe and effective quality substances, unnecessary animal testing and clinical trials on humans performed by the originators are not repeated. Instead, regulatory authorities evaluate the generic application against the originator documentation on file-but only after the period of data exclusivity has expired. The authorities carry out this assessment internally. In no instance is the originators research data released or disclosed to the generics producer or anyone. The generics manufacturer never sees the originator data.

Data exclusivity has nothing to do with protecting research data. Long after the data exclusivity period has expired, the originator documentation remains protected by copyright laws and other legal provisions. Data exclusivity merely extends the originator company's market monopoly over a product by not allowing the authorities to process an application for marketing authorization. Under Directive 2001/83/EC, EU data exclusivity laws guarantee market protection for originator medicines for either 6 or 10 years. (7)

The new EU pharmaceutical legislation adopted in 2004 has created a harmonised EU eight year data exclusivity provision with an additional two year market exclusivity provision. This effective 10 year market exclusivity can be

extended by an additional one year maximum if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. This so called 8+2+1 formula applies to new chemical entities (NCE) s in all procedures and to all member states (unless certain member states are awarded derogations, which they can request following publication of the new law.

Because of the adamant opposition to this overall increase in data exclusivity from the current six year countries, the new periods of data exclusivity will only take effect for reference products applying for marketing authorisation after the new law is fully in effect. Therefore the first generics applications under the 8+2+1 year data exclusivity period will not occur until late 2013.

### **Authorisation**

The Marketing Authorisation Process for Generic Medicines in the European union must currently be applied through one of two procedures: either the "Centralized procedure" or the "Mutual recognition Procedure"(MRP).A third a "Decentralised Procedure" will come into force with newly revised EU pharmaceutical Directive toward the end of 2005. (8)

### **The Centralized procedure**

The Centralized procedure is administered by EMEA in London. It consists of a single, application which, when approved, grants marketing authorisation for all markets within the European Union. This procedure is available to all new or so-called "innovative" pharmaceuticals and is obligatory for high tech and biotechnology derived products. It was not be open for generic applications until 2005when the 10 year data exclusivity periods granted to originator products authorised through this procedure begin to expire. (9)

### **Mutual recognition procedure (MRP)**

Currently, authorisations for generic medicines are normally applied through the MRP. Under

MRP, the assessment and marketing authorisation of one member state, "Reference Member State", should be "mutually recognised" by other "concerned member states". The MRP is set out in Directive 2001/83/EC, as amended by Directive 2004/27/EC, and further guidance is given in the notice to applicants, which forms chapter 2 of the rules governing medicinal products in the EU.

Generics applications typically include chemical-pharmaceutical data and results of bioequivalence studies, which demonstrate the quality and the "essential similarity" of the product for quality. For information concerning the safety and efficacy of the molecule, the regulatory agencies are referred to the data that was established in the originator products application for authorisation. This is only possible once the data exclusivity period has expired on that dossier. (10)

### **Decentralised procedure**

The decentralised procedure is to be used in order to obtain marketing authorisations in several member states where the medicinal product in question has not yet received a marketing authorisation in any member state at the time of application. The procedure to be followed will depend upon whether it is a member state or the marketing authorisation holder, which initiates the decentralised procedure.

As set out in directive 2001/83/EC member states have to approve during the decentralised procedure the assessment report, have the summary of product characteristics, the package leaflet and the label. Specific national requirements have to be presented in a so called "blue-box". The decentralised procedure is divided in five steps:

- Validation step
- Assessment step I
- Assessment step II
- Discussion at the coordination group level, if needed
- National Marketing authorisation step.(11)

### **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.

### **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 FDA's 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)

### **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 struck 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)

### **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, excipients control

Manufacturing and controls

Batch formulation and records

Description of facilities

Specifications and tests

Packaging

Stability

### **Generic drug approval process in Brazil**

Agencia nacional de vigilancia Santeria (ANVISA) was established by the law 9.782 of Jan.26, 999. ANVISA is fashioned after FDA which has similar powers including cancellation of operation and permits for drugs, foods and medical product manufacturers and distributors. It is a public company under contract with the health ministry. The mission is to protect and promote health, ensuring the hygiene and safety of products and services and taking part in developing access to it.

### **Registration of medicines**

This section is intended to provide guidance for companies operating in the medical drugs area. It contains directions on how to submit applications for registering drugs, modifications, exemptions and renewals. It also provides information about the documentation required and instructions on how to complete the application forms.

### **List of documents required for registration**

- Application forms FP1 & FP2, completed, as appropriate, in original and one copy

- Receipt proving payment of fee based on government tariff, duly authenticated and /or stamped
- Copy of the published announcement confirming award of company operating license
- Receipt proving registration of the product, together with its original printed inserts, approved in the country of origin and in other countries if applicable
- Report of therapeutic testing, drafted and submitted in accordance with the sequence required according to resolution 01/88 of 5/1/89, of the national health council paying particular attention to the products bioavailability and toxicity.
- Technical report on the product which includes general data, pharmacodynamics, production and quality control and complementary data.
- Examples of the labels, printed inserts, typed in duplicate
- Copy of the operating license of the company and /or its health permit
- Written evidence that the manufacturing plant is overseen by the properly qualified responsible technical officer.

#### **Additional documents required**

- Copy, photocopy or transcript of the registered permit in the country of origin in the case of drugs, medicines or pharmaceutical inputs of foreign origin
- A report containing the recommendations, contra indications and warnings presented with the application for registration in the country of origin signed by the technical officer responsible for the product to be registered.
- The good practices manual used by the company observations
  - All the documentation must be signed by the legal representative of the company in question
  - Documentation referring to the technical aspects of the application must in addition be signed by the technical officer responsible.
  - The documents which have already been the subject of the health permit authorization do not need to be submitted.

### **Comparison of Generic Drug Approvals per CTD in three different countries -Europe, USA & Brazil**

#### **• Regulatory framework**

##### **➤ Europe**

The European Medicines Agency (EMA) is a decentralised body of the European Union. The EMA is responsible for the scientific evaluation of applications for European marketing authorization for medicinal products. Once granted by the European Commission, a centralized marketing authorisation is valid in all European union (EU) and EEA/EFTA states. (Iceland, Norway and Liechtenstein)

European Commission (EC) consists of 30 countries, 27 as a part of European Union and 3 as a part of European Economic Area European Free Trade Association (EEA/EFTA). Member countries have their own respective Drug Regulatory Authorities (DRAs). There are four types of marketing authorisation procedures in EU. There is no separate authority for generics.

The agency brings together the scientific resources of some 40 national competent authorities in 30 EU and EEA/EFTA countries in a network of over 4000 European experts. It contributes to the European Union's international activities through its work with the European Pharmacopoeia, the world health organization and the ICH and VICH trilateral (EU, Japan and US) conferences on harmonization, among other international organisations and initiatives. The EMA is headed by the executive director and has a secretariat of approximately 470 staff members in 2008. The management board is the supervisory body of the EMA, responsible, in particular, for budgetary matters. The agency is also involved in referral procedures relating to medicinal products that are approved or under consideration by Member states in non-centralised authorisation procedures.

The committee for medicinal products for human use (CHMP) is responsible for preparing the Agency's opinions on all questions concerning medicinal products for

human use, in accordance with regulation (EC no.726/2004)

#### ➤ USA

FDA is an agency within the department of Health and Human Services (HHS) and consists of nine centres/offices which is authorised by congress to enforce the federal food, drug and cosmetic act and several other public laws. The agency monitors the manufacture, import, transport, storage and sale of \$1trillion worth of goods annually, at a cost to taxpayers of about \$3 a person.

The FDA's centre for drug evaluation and research (CDER) promotes and protects the health of Americans by assuring that all prescription and over the counter drugs are safe and effective. CDER also plays a critical role in providing health professionals and consumers information to use drugs appropriately and safely. There is a separate authority for generic drugs are Office of Generic Drugs (OGD).

#### ➤ Brazil

The National Health Surveillance Agency (ANVISA) was established by law 9.782of January 26, 2004. The agency is an independently administered, financially autonomous regulatory agency, with security of tenure for its directors during the period of their mandates. The agency is managed by a collegiate board of directors, comprised of 5members.

Within the structure of Federal Public Administration, the agency is linked to the Ministry of Health, under a management contract. The agency incorporated additional attributions; coordination of the national sanitary surveillance system (SNVS), the national program of blood and blood products and the national program of prevention and control of hospital infections; monitoring of drug prices and prices of medical devices; attributions pertaining to regulation, control and inspection of smoking products; technical support in granting of patents by the national institute of industrial property. There is also no separate authority for generics.

### • Registration procedural aspects

#### ➤ Europe

Europe has a quite distinct application procedure and is of 3 types. In **national procedure**, the product is marketed in one member country only. Another format is the **decentralised or mutual recognition procedure**, additional member states recognise the initial marketing authorisation granted by a single member country. Other member states have an option to protest and not have that drug in their country. The **EMA or centralized system** is compulsory only for biotechnology products but the EMA is moving to expand the single system to include non-biotechnology based prescription drugs. This procedure leads to one marketing authorisation in all countries of the European Union.

These procedures have different approval time periods and different fees amount. The task is difficult as one has to communicate to various countries, but fortunately among the respective drug regulatory authorities (DRAs) of individual countries. The format of application is CTD format.

The marketing authorisation holder (MAH) must be a resident of the European countries. The application and labelling language depends on the country. Europe has unique system called Communication and Tracking System (CTS) which is basically an IT tool for licensing authorities for implementing and running the MRP.

#### ➤ USA

Under the Hatch-Waxman Act, a company can seek approval from the FDA to market a generic drug and the generic drug manufacturer certifies in its Abbreviated New Drug Application (ANDA) that the branded product's patent are invalid or will not be infringed by the generic drug for which the ANDA applicant seeks approval. The Act then provides a 45 days window during which the patent holder may bring a patent infringement suit against the generic manufacturer. An infringement action notwithstanding, the first company to file an ANDA with the FDA is given the exclusive

right to market the generic drug for 180 days.

There is no fees payable for ANDA application. The MA holder needs not to be a resident of USA, but agent is must. The language is English for both application and labelling.

### ➤ **Brazil**

Organisation mainly files similar and generic drug products. Fee structure depends on the type of application and on the size of the company. Brazil is a Latin American country. The communication is easy for it. There are separate registration procedures for other countries of Mercosur (Argentina, Uruguay &Paraguay).The application and labelling language is Portuguese.

## **CONCLUSION**

India's leading pharmaceutical companies are truly global players-they have a presence in major markets worldwide. Except for Teva and Sandoz, most other generic companies are country specific. India's capacities and costs are spread over several markets. And unlike generic companies elsewhere, India has a large domestic market. The pharmaceutical industry will have its ups and downs, like any other industry. Pricing pressure hurts American and European generic firms more than Indian companies.

The only weak link for Indian companies has been market access to the US. To complete the value chain, Indian companies have been forming partnerships with US firms, acquiring US companies, or setting up marketing subsidiaries. Eight to ten companies are active in the US either on their own or through their partners. Most Indian acquisitions until now have been small.

At the end of the day, the generic industry is price driven. Cost pressures are fuelling consolidation in the global generic industry. It will mean fewer competitors. It will also mean more pricing discipline. India is still a small player in the \$25 billion US generic market with a share of only about \$1billion.India has a long way to go before emerging as a substantial player in the generics market but yes it has the qualities to become one. But above all to go

global in the market US and EU, regulatory approval is crucial. Pharmaceutical company should keep a close eye on the changing regulation and should consult with regulatory consultant for proper filing, so that they can enter without any hurdles.

The following conclusions were drawn after comparing the requirements for genetic approval in the above stated countries.

Unlike US, the regulatory guidelines of EU & Brazil are not that much well defined. One can't draw or get desired requirements for approval from the official sites of these countries (EU & Brazil). But FDA site gives very much well defined requirements.

Further since both US & EU are the active member of ICH & Brazil is totally different from ICH guideline, so many of the requirements are overlapping. But each country has their own particular requirements.

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## **CONFLICTS OF INTEREST**

The author declares that there are no conflicts of interest.

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