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GENERIC DRUG: WHERE IT STANDS IN PHARMA INDUSTRY?

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Abstract:

Generic drugs are alternative to costly branded drugs which are almost equivalent to them in terms of quality, safety and efficacy. Their prices are much less than the branded medicines. Hence, with the equal therapeutic effects and affordability it proves to be a boon for the healthcare sector in many countries. In this paper a review on similarities and dissimilarities of generic drugs with different kind of medicines in terms of activity, quality, and legislative activity as well as some drawbacks regarding the issues related to safety in generic drugs have been done.

Keywords: Generic, Patents, Branded, compounded, counterfeit, FDA.

Introduction

Generic drugs are defined as the medicines that are produced after the expiration of the original patent and are therefore manufactured by other than the patent holders [1] [2]. It has been reported that the development and the production of a new medicine takes about 10-12 years and costs approximately 359 million dollars [3]. This shows that a large amount of investment is required in R&D sectors [4]. Therefore, with the use of the generic drugs, the investment in the R&D sector cuts to zero as compared to the branded drugs which requires more time and investment [5].

According to World Health Organization (WHO), the generic drug is defined as [6] [7]:

- The drug that is considered to be compatible with the leader product.
- The drug can be manufactured without the authorization from the patent holder companies.
- The drug, which is marketed after the termination of the copyright.

The basic principle of the generic medicine is that, it should be bioequivalent [8] [9]. The main reason for the establishment of bioequivalence is to exhibit equivalence between the generic drug and instigator or originator drug

[8] [10]. Bioequivalence is said to be established when the rate and the degree of absorption of the generic drug is found to be equal to the originator drug or the difference so exists is insignificant [11]. Bioequivalence is defined as the two drugs or pharmaceutical products that are equivalent if they contain same or equal quantities of active and inactive ingredients and their bioavailability after administration in the same molar amount is similar or equal [11]. The generic drug in a way is economic and affordable by major segments of the population [12] [13] [14]. It has been found that the generic drugs provide relief to the patients from the high price branded drugs because of the fact that it excludes the various taxes, which are implemented on the branded drugs [12] [13] [14]. It plays an important role in sustaining the vast number of patients who are suffering from various dreaded diseases and give them the opportunity to receive the same treatment at affordable cost [15] [16]. In this way it has been found that the generic equivalent is used by the healthcare system to reduce the costs and make the system more sustainable by providing a suitable alternative to the patients [17] [18].

FDA Approval

To make the drugs available in the market, the drugs must go through FDA approval. For generic drugs to get the approval, it must satisfy the following criterion or norms [19]:

- The drug must contain the same active and inactive compound (however, inactive ingredients may differ from the patented drugs), with that of the instigator drug.
- The generic drug should include the same potency as that of the branded drug.
- It should be bioequivalent.
- Should contain same route of administration like that of the branded medicines.
- It should be safe and effective like that of the branded drug.

Generic Drugs in Different Unions and Countries

It has been found that the authorization process regarding the pharmaceutical products in the EU is more intricate than in the US [20]. Authorization in the EU is done through 3 different types of routes:

- Centralized Procedure [CP]
- Decentralized Procedure (DCP)
- Mutual Recognition Procedure (MRP)

It has been reported approximately more than 2 million prescriptions are filled with the U.S using the generic drugs [21]. But, U.K has the highest prescription of the generic drugs in the world [22] [23]. However, a different situation scenario has been observed in Australia [6]. Here it has been found that there are no generic versions of Digoxin or Phenytoin, therefore no bioequivalence assessment has been done and followed [23] [24]. The aim of the generic substitution as implemented in the Czech Republic was to decrease the cost of Public Health insurance in the form of charge for medicine. In India, it has been reported that the generic drug has reached its 100 billion mark, dollar in 2010 [23].

A number of developing countries have made use of compulsory licensing or government use orders to enable the supply of more affordable generic drugs in recent years. India today has the distinction of manufacturing high eminence generic medicines that are distributed or marketed around the world [25] [26]. India tops in the world in exporting generic medicines, approximately Rs 50,000 core and currently, the Indian pharmaceutical industry is considered and accepted as one of the world's largest and most developed industry [27].

India ranks 17th in the world in the pharmaceutical exporting market and it has estimated by the year 2020 India will reach the fifth country globally [27]. However, the availability of the generic drug in India is very low.

Table 1: List of top ten international generic companies [27]

RANK	COMPANIES
1	Teva
2	Sandoz
3	Mylan
4	Actavis
5	Hospira
6	Watson
7	Sanofi
8	Greenstone
9	Stada
10	Dr. Reddy's Lab

Table 2: Lists of top ten Indian pharmaceutical companies [3] [10] [27]

RANK	NAME OF THE INDIAN COMPANY
1	Cipla
2	Ranbaxy
3	Dr. Reddy's Lab
4	Lupin
5	Aurobindo Pharma
6	Dabur
7	Sun Pharma
8	Cadilla Healthcare
9	Jubilant Life Sciences
10	Piramal Healthcare

Branded Drug Vs Generic Drug

New drug production is highly complex and is one of the costly affairs. It takes about 10-12years to manufacture a new drug which costs about 800million dollars to 200 billion dollars. Then the drug is given an International Nonproprietary Name (INN) which later forms the brand name. The development of the new drug initially begins

with the production and refinement of the new chemical substance or ingredients followed by the preclinical studies which takes around 3 to 6years. This is followed by the clinical trials which takes another 6 to 7years for its completion. After successful completion of the clinical trials and studies, an application is submitted to the FDA, which leads to the registration of the newly formed drug. After the successful registration, the new medicine is marketed to reach the patients and post-marketing surveillance is done[27] [28]. In case of the generic drugs, these clinical trials are not required and are considered unethical if it was done so. Therefore, it reduces costs and time for the drug to be available and therefore further helps the mankind [28] [29].

Table 3: Processing of branded drugs & generic drugs.

Sl. No.	Branded Drugs	Generic Drugs
1.	Chemistry	Chemistry
2.	Manufacturing	Manufacturing
3.	Testing	Testing
4.	Labelling	Labelling
5.	Inspections	Inspections
6.	Animal studies	Bioequivalence
7.	Clinical studies	
8.	Bioavailability	

Compounded Drug Vs Generic Drug

Compound drug is different from the generic drug. Compound drug is based on the patient specific doses. This drug is subjected to the patient in unique or rare cases by changing the strength of the dosage, or state of the drug through changing the drug into pills or syrups or liquids based on the condition of the patient. The change is even brought through the addition of the flavoring by various formulations through trial or error method [28].

Unlike the generic drug, compounded drugs do not undergo any kind of tests and, therefore, fail to establish any bioequivalence. This leads to the safety and efficacy of the drug to suffer. Therefore, compound veterinary drug may cause adverse effects or reactions and is a major concern towards the health of the patient [28] [30].

Counterfeit Drugs Vs Generic Drugs [10]

A counterfeit drug is defined as the medicine or pharmaceutical product which is manufactured deliberately and sold out with the purpose to unrepresentatively signify its origin, authenticity or efficiency. Many counterfeit drugs or medicines look equally genuine products like the branded or generic drugs and therefore, misleading both professionals and patients [31] [32]. A counterfeit drug is one that contains in major cases, inapt quantity of active ingredients or chemicals or else none, improperly processed within the body, or may contain ingredients that are not

present or signified on the tag or maybe abounding with inaccurate or fake packaging and labeling [33]. It differs from genuine drugs in terms of quantity and efficacy. Generic drugs, however, consists of equal quality of chemical compositions and features as that of the branded drugs, but, in case of counterfeit drugs, they contain mainly inferior quality of active or inactive ingredients and also are produced in the name of generic drugs so as to earn and lure maximum profit from the people [31].

In order to manufacture counterfeit or fake drugs, it does not require any kind of high infrastructure or facilities like that of the generic or branded drugs and therefore do not require high level costs to meet the quality values [32] [33]. These counterfeit drugs look authentic, but are hazardous to people as their origin, ingredients and quality and efficiency remain unknown to the people and so is a serious threat to the health of the mankind.

To stop the spreading of fake counterfeit drugs, many countries have revised various laws for anti-counterfeit drugs. For example, in many developed as well as developing countries like Africa have recently revised their intellectual property laws that include anti-counterfeit measures. In Kenya, the laws to counter counterfeit drugs were made effective in 2008. Moreover, in Kenya, the generic drugs account for 90% of available medicines. In contrast, Australia, Canada, Japan, Mexico, Morocco, New Zealand is the countries which are negotiating with the Anti-Counterfeit Trade Agreement (ACTA) [34].

In India, the generic medicine industry is highly affected by the web of the counterfeit drugs, as because in India, there is no such law or legislation to stop or cease the counterfeit drug market. This makes the country to lag behind in pharmaceutical markets. In recent reports, it was found that some of the counterfeit drugs were captured in England, which had 'made in India' tag which the political members had denied it and implied that the drugs were produced by China [35].

The introduction of the generic drug discount program is another step ahead to introduce generic market among people so as to maximize the use of the generic drug among low income population. The discount program in generic drug was first introduced in the year 2006 by Wal-Mart and was later accepted in many retail outlets. To study the popularity of the drug discount program or GDDP, a study was held among the low income population. A remarkable result was appearing after the survey. It was found that, the participants who earned approximately $25 to 30,000 were more aware of GDDP than the lower income population. It was also found that if the doctors discussed about the GDDP among patients, the percentage of use of generic drug increases. This shows that, in order to increase the

use of GDDP, the physicians or the doctors must recommend the generic drug prescription whenever required in order to make familiar with the generic drug [36].

Threats To Generic Drugs

Various kinds of misleading conceptions are present among people that lead a major drawback in generic drug awareness [37]. Some of the myths familiar among people:

- Due to low costs, generic drugs are considered to be less effective than the branded or patented drug. Therefore, branded drugs are safe and more effective.
- Generic medicine contains an inferior quality of ingredients and therefore do not maintain its stability and efficacy.
- Generic drugs are considered as the second rate prescribed due to lack of public awareness and so influenced with branded drugs.
- According to people, the FDA does not monitor or screen generic drugs before releasing it on the market.
- People believe that generic drugs stand equally with the compounded and counterfeit drugs and are therefore harmful to the patients consuming other than the branded drugs.

So, in order to counter the negative impact about the generic drug, public awareness and knowledge is required extensively.

Following policies should be used for the generic drugs in order to bring transparency towards the use of the drug [38] [39]:

- The management of the generic drugs should be improved as because the one of the major obstacles of the generic drug that is the high 'cost' has been removed so that all classes of people could buy the drug.
- Campaigning for generic drugs can help to reach out to the people and can easily be introduced among them.
- Generic substitution can be increased manifold by regulating the behavior of the pharmacist. In many states there has been a law which allows the pharmacist to fill a prescription containing the generic names, even if the doctor has prescribed for a branded name drug. For example, in about 40 states, the pharmacist has permission to prescribe the generic substitution of the branded drug or medicines.
- Increase in generic substitution helps to curb annual overall expenditures in drugs and medicines.

- Doctors and prescribers should be educated about the generic substitution and encourage them to write the generic names of the drug along with the branded names.
- Health plans help to promote generic medication utilization among people.
- The format of the prescription pads also plays an important role in promoting generic drugs. In some countries and states, there are two liner prescriptions where the physician can handwrite the generic substitute or the branded drug only.

Table 4: Brand name vs. generic name vs. compounded drug vs. counterfeit drug [6][34].

Criteria to achieve FDA approval	Branded drugs	Generic drug	Compounded drug	Counterfeit drug
Active ingredients	Present	Present	Absent	May be
Labeling	Present	Present	Absent	May be
Dosage strength	Present	Present	Absent	May be
Route of administration	Present	Present	May be	May be
Chemistry	Present	Present	Absent	May be
Manufacturing process	Present	Present	Absent	May be
Quality control measures	Present	Present	May be	May be
Stability studies	Present	Present	Absent	May be
Post marketing surveillance	Present	Present	Absent	May be

Case Study: To study the generic paradox, a survey was done following the method of empirical variation among 244 individuals by the investigators in Spain in 2002. It was found that, most of the individuals were found to be positive regarding the acceptance of generic drug among the patients and others [40].

To study the efficiency of the generic drug, a survey was done among the patients of epilepsy around the world from Canada, UK, Germany, France and Spain. It was reported that after switching the patients from branded drugs to generic drugs with anticonvulsant, they have shown serious side effects. Among the 974 patients, 14 patients were subjected to generic alternative of carbamazepine. It was reported that, 9 patients out of 14 shown side effects like nausea, dizziness, etc., however, serious side effects were reported among seven patients [41].

Generic Drug Safety Issues

There has been much debate among the investigators, physicians regarding the issues related to safety in generic drugs. The debate is much pronounced in the anti-epileptic generic drug which is a major concern in present days.

It has been found through a survey and investigations that, many companies have illegally micronized carbamazepine API without the approval of FDA, which lead to serious death toll among the epilepsy patients due to the altered blood levels. To decrease the risk rate of the generic drugs, various quality checking has been issued. One of the designs is known as Quality by Design (QbD). QbD encourages the pharmaceutical development of original ANDA product which includes control strategy and justification of the product, critical quality attributes of the drug product, product design and its processing and so on. This helps the consumers to receive quality products [42].

Hatch-Waxman Act and Generic Drug Scandal

The Hatch-Waxman Act or in definite term known as "The Drug Price Competition and Patent Term Restoration Act of 1984" (US Public Law 98-417) came into action on 24th September, 1984. The act was so passed in order to bring out the balance between the branded and generic drug. The Hatch-Waxman Act accepts the knack of the generic manufacturers to ascend a legitimacy test by neither incurring the cost of entry nor risking gigantic reimbursement coming from any possible violation [42].

With the discovery and popularity of the generic drug, there was also an increase in the hoax market to guzzle the generic market. The fraudulent market was active at its highest in the year between 1984 and 1989. This has lead to the addition of the negative impact of generic drugs among people, which simultaneously decreased the generic market [42]. With complete investigation and survey, it was found by the Department of Health and Human Service, that there has been a charge of bribery and fraud against the FDA and drug companies as there has been a submission of fraudulent data by many leading companies. The main culprit for such cases was the generic product presented by the Hatch-Waxman Act. In order to gain utmost profit, some companies engaged in criminal actions like manufacturing hoax or fraud medicines [42][43].

Conclusion

Post-patent entry of generic has been shown to reduce overall drug expenditure and increased access to medicines. Therefore, in order to benefit fully from the cost-lowering advantages of generic drugs, it is necessary to bridge the gap between generic policy intent and implementation in India. Additionally, there is a need to enhance the levels of

generic prescribing, education and public awareness on generic medicines, in order to create a right market environment for generic medicine production and market availability.

Conflict of Interest

No source of funding has been used in the preparation of this manuscript. The authors have no conflict of interests that are directly related to the content of the manuscript.

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