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REVIEW ARTICLE

ARE GENERIC DRUGS THAT SAFE AND HAVE SAME EFFICACY WITH THAT OF BRAND DRUGS?

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Abstract

A drug is a biochemical substance which has biological effects in the body when ingested or otherwise introduced in the body. Its takes many years to discover a new drug as it is has to undergo several operations, several tests and clinical trials leading to huge cost based on expenditure of the research. The drug is to be marketed and manufactured in pharmaceutical industry only if it has passed the USFDA standards. Once the drug passes the USFDA standard the drug is manufactured, and the discoverer is awarded patent for that same drug for certain period of time. As the drug research is much costly the discoverer sets the prices for the drug which is too high, at least not affordable by common community. For this reason, Generic drugs are introduced in the market. In the recent era generic pharmaceutical are the largest contributor of drugs in the market and are in high demand due to cost effective. As all the generic drugs are approved by USFDA and are allowed to be marketed only when the brand drugs discoverer do not hold the patent for the same drug and the brand drugs is in the market for years and well-established safety profile. Although Generic Medication appear to be same as brand drugs, but variation in manufacturing facilities may lead to unseen adverse events. On other side, generic drugs are tested for bioequivalence properties within a certain range compared to brand discoverer drugs, safety and efficacy testing are not required; therefore, it can be said that generic drugs are not therapeutically equivalent to branded innovator drugs the question of requirements of Pharmacovigilance for generic arises when there is plethora of information available for brand drugs regarding safety and adverse effects. [1] [6]

Keywords: Generic Drugs, USFDA, Pharmacovigilance, Brand Drugs

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INTRODUCTION:

A generic drug is a pharmaceutical drug which is equivalent to a brand-name product in dosage, route of administration, strength, quality, Kinetics, and its intended use. It may also refer to any drug which is marketed under its chemical name without advertising. For getting the approval to market the generic drug an abbreviated new drug application termed as ANDA is to be submitted by the drug companies. The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, allowed ANDAs to be possible by making a compromise in the drug industries. Hence, the generic drug gained access to the market for the prescribed drugs and discoverer companies gained restoration of patent of their products. Any new drug is developed under patent protection. This patent protects the investments involved in the development of the drug by allowing the company to have the right to sell the drug while the patent is in the effect. The manufacturer can apply to the FDA for the selling of generic version after the expiration of the patent period. Further, the ANDA process doesn't require the sponsor to repeat test animals, ingredients or dosage forms which are already approved for the safety and its effectiveness. [6] [8]

The use of generic drugs is indicated from many countries in order to reduce medication price. However, some points, such as bioequivalence and the role of excipients, may be clarified regarding clinical efficacy and safety during the switch from brand to generic formulations [6].

A Generic Drug Must Contain following parameters:[4]

- It must contain the exact active ingredient as of the brand innovator drugs.
- It should be replica of dosage form, strength, and route of administration with respect to Brand drugs.
- It should have the same therapeutic uses.
- It should be bioequivalent
- It should meet the same batch requirement for identification, Purity, Strength, Bioavailability.
- It should be manufactured under exact GMP guidelines as of the Innovator drugs.

Although all the components in the generic drugs are same, there might be variation in excipients used in manufacturing or other activity enhancers. Excipients are the substance which are added to the formulations to render the drug in a compatible form for administrations or the stability related factor of drug over shelf life. These excipients are not in active form i.e they do not have any therapeutic activity as such hence they are inactive substance. Another arising factor which

add up to difference in generic from brand drugs is mismatched container system. Recently some parenteral formulations got recall from market due to issues with the final product which was due to mismatched container system. Recently several products were recalled from market by FDA due to problem in the final products.

Some Example of recalls by FDA for safety and efficacy factors are: [2]

Drug
Valsartan/Amlodipine/HCTZ Tablets
Levothyroxine and Liothyronine (Thyroid Tablet USP) 15mg, 30mg, 60mg, 90mg and 120mg
5% Dextrose Injection
Piperacillin and Tazobactum for injection USP 3.375g

Need of Pharmacovigilance for Generic Drugs

Due to high exposure and increasing use of Generic Drugs, its safety and efficacy are very important. At physiological factors, Generic medicines provides the same safety and activity as that of originator drug. The approval of process of Generic drugs do not involve clinical trials as in case of Brand Drugs. So the lack of Clinical Trials makes the need of Pharmacovigilance mandatory for Generic Drugs. Pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem".It has been found that adverse effects reporting for Brand Drugs remained same even after maximum use of generic drugs. In most of cases patients are switched from brand drugs to generic drugs to minimize the medical expense. Due to high reporting of adverse reaction for brand Drugs same applies with their respective Generic Drugs as they are biosimilar drugs with same activity and efficacy. Therefore, better Pharmacovigilance system is required for Generic Drugs. [3]

CASE REPORT – 1 [9]

A 32-year-old man in Jamnagar was visiting his Physician for Acute Bacterial Bronchitis. History described the presence of Blood Hypertension in treatment with ACE Inhibitor (Captopril – 12.5mg daily).On examination blood pressure was found to be 132/89 mm Hg, Body Temperature was around 38 degree Celsius and no other symptoms and adverse effects were observed.Clinical manifestations documented the presence of Short breathing, Cough with Greenish Mucus, and slight sneezing. Therefore, Paracetamol 500mg and Levofloxacin 500mg were prescribed, but after 7 days patient returned to the physician for persistence of Symptoms. A detailed Pharmacological evaluation founded that patient was advised by pharmacist to take

Generic Levofloxacin 500 mg due to lower price available generic Drug.Generic Levofloxacin was changed to Brand Drug which showed complete improvement of symptoms in 4 days and with no major side effects.

CASE REPORT – 2 [10]

A 25-year-old man in industrial area of Rajkot visited his physician for high fever (38°C), with no history of clinical manifestation or other systemic dieses. Some Clinical symptoms showed with little coughing and greenish Mucus and shortness of breath. After diagnosis acute bronchitis was hypothesized and treated with Paracetamol 500mg and Levofloxacin 500 mg was prescribed for 10 days.But unfortunately, patient returned to physician with increased symptoms of Cough and sneezing in addition to Headache and frequent Urination. On detailed diagnosis and evaluation, it was found that patient was using Generic Levofloxacin 500 mg.

Physician advised to use Branded Levofloxacin 500 mg for next days and the symptoms were resolved with no side effects. Physician also reported the Adverse Drug reaction in ADR center.

In the above cases the following things can be noted:

- The use of Generic drugs over Brand drugs or switching to generic Drugs from Brand Drugs was prescribed by pharmacist. The Pharmacist can recommend and sell Generic Drugs against Brand drugs if the doctor does not specifically ask for Brand drugs.

- In both the cases the use of Generic Drugs was limited to 3-4 days which showed no activity or even showed adverse reaction

- In the both the cases use of Generic drugs was only for 3-4 days which didn't show any Therapeutic activity which can be argued that also continuing to next few days the drug might show therapeutic activity.

In these cases a lack of efficacy was observed and during treatment with Generic Drugs can be hypothesized.A number of reasons could be involved in lack of efficacy and development of side-effects such as,

- Difference in excipients:

  Previous studies have suggested that a possible clarification in clinical difference between brand formulation and a generic one, might be characterized by the difference in excipients. The EMA guideline for bioequivalence explains about the presence of excipients that could influence "gastrointestinal transit (e.g., sorbitol, mannitol, etc.), absorption (e.g., surfactants or excipients that may affect transport proteins), *in vivo* solubility (e.g., co-solvents) or *in vivo* stability of the active substance" [11]

- Difference of ±20% of bioequivalence between generic and brand: It is important to highlight that in current law the difference of 20% in bioequivalence is between brand drug and its generic formulation, but it is not possible to outline the bioequivalence during the shift between generic formulations. This difference could play a role in the effectiveness of drugs and it is very relevant during treatment with antibiotic drugs. [12]

- Impurity of pharmaceutical preparation: Quite a lot of studies have shown that generics formulations had a total impurity rate higher to the 3% in comparison to brand formulation. This factor has been previously reported to affect the bioavailability of the drug and therefore, its therapeutic efficacy.[13]

In this manner, the change from brand to generic formulation might not always be considered favorable according to cost-effectiveness.Therefore, the Pharmacovigilance for Generic drugs are to be made mandatory to ensure safety and efficacy of the Generic Drugs.

CONCLUSION:

In country like India, which is still under developing stage and high below poverty ratio, awareness for use of Generic Drugs are to be made. Pharmacovigilance for drugs will continue to provide better safety aspects for both Brand and Generic Drugs. Generic Drugs are to be made mandatory for Pharmacovigilance as they do not involve Clinical trials. The pharmaceutical manufacturer can use low grade Active ingredient or excipient to produce the Generic Drugs leading to lack of efficacy and other side or adverse reactions. Several case reports states that use of Generic Drugs over Brand Drugs leaded to low efficacy and other adverse reaction. Generic Drugs are prepared to minimize the cost of Medicine, but if the Generic Medicine cannot induce or influence the efficacy or therapeutic activity it will eventually increase the cost of medicine. Therefore, the Pharmacovigilance for Generic Drugs are to be made strict and guidelines are to be made for the same.

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