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Review Article

THE IMPORTANCE OF GENERIC DRUGS IN INDIA

Ajoy Bera and Ashish Mukherjee

Central Drugs Laboratory, 3, Kyd Street, Kolkata, West Bengal, India.

ABSTRACT

After the expiry of patent or marketing rights of the patented drug, generic drugs are marketed. Generic drugs are available at affordable prices with maintaining quality. These 'Generic' formulations balance public interest as critical disease like cancer, AIDS etc. In situations where demand for medicines exceeds supply, criminally minded people tend to profit out of crime by manufacturing and distributing counterfeit medicines as a substitute for genuine medicines (branded and generic). India's Pharmaceutical market grew at 15.7% during December 2011. This paper presents various aspects of generic, branded and counterfeit drugs and their impact on the Indian Pharmaceutical Industry.

Keywords: Generic, Branded, Counterfeit.

1. INTRODUCTION

After the expiry of patent or marketing rights of the patented drug, generic drugs are marketed. Generic drugs are available at affordable prices with maintaining quality. These 'Generic' formulations balance public interest as critical disease like cancer, AIDS etc. It is widely accepted both developed and developing countries. An estimated half of all prescriptions in the USA are now filed with approved generic drugs. In order to market drugs, U.S. generic manufacturers must have a permit and approval from the Food and Drug Administration (FDA) indicating that the active ingredient is approximately the same as that of the brand name. The determination of drug approval is made according to whether it is pharmaceutically equivalent, bio-available, and bioequivalent.

World Health Organization (WHO) provided a definition for counterfeit drugs. In situations where demand for medicines exceeds supply, criminally minded people tend to profit out of crime by manufacturing and distributing counterfeit medicines as a substitute for genuine medicines (branded and generic). The consequence of this will be infiltration of counterfeit medicines into national distribution channels.

India's Pharmaceutical market grew at 15.7% during December 2011. Globally India ranks third in terms of manufacturing pharmaceuticals product by volume.[1a] The Indian pharmaceutical industry is expected to grow at a rate of 9.9% till 2010 and after that 9.5% till 2015. The Indian pharmaceutical market is expected to touch US $72 billion sale by 2020 from US $11 billion. The market has the further potential to reach US $70 billion by 2020. India ranks 17th in terms of exports its product to more than 200 countries around the globe including highly regulated markets of USA, Europe, Japan, and Australia. The paradox is that despite producing huge pharmaceutical products, India has been identified as one among

several developing countries that are regarded as the source of counterfeit medicines by the organisation for Economic Cooperation and Development (OECD).

On the other hand, WHO says 3.2% Indians will fall bellow the poverty line will because of high of high medical bills. 39 million Indians are pushed to poverty because of ill health every year. Around 30% in rural India didn't go for any treatment for financial constrains. The world health organization (WHO) is also worried about Indians high out-of-pocket (OOP) expenses to medicines.

This paper presents various aspects of generic, branded and counterfeit drugs and their impact on the Indian Pharmaceutical Industry.

2. Branded drugs and generic drugs

One of the most debated issues in health care today concerns the difference between brand name (also called branded, innovator, and pioneered) drugs and their generic versions. Evolution of every drug starts from a research laboratory and ends in a medical shop. Many new molecules are invented in research laboratories. Specific pharmacological formulations require tedious technology and procedures. Many of such molecules never achieve final approval. After formulation of a drug, it is tested on animals and then on human volunteers. These quality controls are stringent and FDA certification is necessary for avoiding side effects and toxicity of drugs. Only after testing the drug in large number of patients in drug trials, the drug comes in market. Drug companies spend lot of money in formulating each drug. Thus every drug cost depends on the expenditure of the research and procedures of approval. Every newly launched drug is thus very expensive to begin with. Companies have drug patent of their drug for a specific time period of 10 to 12 years and cost as much as 2.0 billion dollar. Each year, world wide, only about 25-30 new chemical entities drugs enter the market[1b]. These figures[2] indicate that pharmaceutical companies face huge difficulties during drug development. Hence their investments in research, resources, time, should be rewarded by taking patent protection. During this period, the drug cannot be copied by anybody. After the patent is over, the same drug can be copied by anybody and the costs reduce drastically. Many of the anti-diabetic, antihypertensive and antibiotic drugs are available now as 'Generic' formulations.

It's important to remember that there are brand name and generic versions of medicines like high blood pressure, diabetes, etc. Today about 50% of all prescriptions are filled with generic drugs. The FDA has established standards for generic drugs that might seem complicated but are really simple. In accordance with Black's law dictionary,' the term "counterfeit drug" may be used to describe a drug made by someone other than the genuine manufacturer, by copying or imitating an original product without authority or right, with a view to deceive or defraud, and then marketing the copied or forged drug as the original. In reality, however, a counterfeit drug is defined differently in different countries.

The absence of a universally accepted definition not only makes information exchange between countries very difficult but it also limits the ability to understand the true extent of the problem at global level. In order to address this problem the following definition has been developed by the World Health Organization (WHO):

"A counterfeit medicine[3] is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."

According to the FDA, to substitute a generic for brand name drug must follow following criteria - It must contain the same active ingredients (the chemical substance that makes the drug work), the same dosage strength (the amount of active ingredients, for example 20 mg or 40 mg), the same dosage form (that it, it needs to be available

in the same form as the original – for example as liquid, pill, etc), have same route of administration (the way the medication is introduced into the body) and It must deliver similar amounts of the drug to the bloodstream (that is, it needs to deliver a comparable amount of drug into the blood-stream within time period as brand name drug).

According to the FDA, to substitute a generic for brand name drug differences in the following criteria- They look different (different sizes, shapes, color or markings and different names), might have different inactive ingredients. Drugs are made up of both active and inactive ingredients. Some people may be sensitive to inactive ingredients. For example, some people have reactions to certain dyes used in some drugs.

The most important advantage with generic drugs are less expensive than the branded versions. They are cheaper as no R & D investments are involved as in the case of branded or new drug. Generic manufacturers are able to sell their products for lower prices because they are not required to repeat the costly clinical trials of new drugs and generally do not pay for costly advertising, marketing, and promotion. In addition, multiple generic companies are often approved to market a single product; this creates competition in the market place, often resulting in lower prices. So Generics can cost between 20 and 80 percent less[4]. Generics vary by manufacturer (different pharmacies carry different generics). whether or not generics are always the same as brand is another question. "Different" doesn't always mean "not as good." In some cases a generic drug can be better than the branded version in more ways than just being significantly less expensive. Cheaper does not mean lower quality.

The authorized generic[5a] has identical size, shape, colour, taste, smell, mouth-feel and inactive ingredients as the brand-name drug whereas the generic version is different. The authorized generic provide consumers the highest brand quality at lower prices and can be marketed during the 180-day exclusively period and even the expiry of the product.

3. Growth of Generic Drug Industry

The generic market reached 100 billion dollar in 2010. The generic growth is three times higher than the overall growth of drugs. 20 drugs will lose patent protection between 2010 and 2014 with the total market value 107 billiion dollar[5b]. According to expectation of pharmaceutical industry, percentage of generic drugs in the US market will rise from 14 to 21. This growth will enhance the export of pharmaceutical products from India will double every year. In future contribution from the Indian pharmaceutical companies will increase due to low cost of worker, innovation, recent success in track record in design operation of high tech manufacturing, testing, quality control, research, clinical testing and biotechnology. Most of the Indian companies have United States Food and Drug Administration (USFDA) approved plants, about 20% of all Abbreviated New Drug Applications (ANDA) to the USFDA are field by Indian companies. Now India's share of the generic market is about to 35%. Hence the contribution of the Indian pharmaceutical industry for the growth of generic drugs in the world is very high.

Table 1: Top 20 Listed Indian Public Pharmaceutical companies (Rank wise 2010)[6]

Rank	Indian Public Pharmaceutical companiey	Rank	Indian Public Pharmaceutical companiey
1	Cilpa	11	Glaxo
2	Ranbaxy	12	IPCA Labs
3	Dr Reddy's Labs	13	Wockhardt
4	Lupin	14	Torrent Pharma
5	Aurobindo Pharma	15	Sterling Bio
6	Dabur	16	Biocon
7	Sun Pharma	17	Orchid Chemicals & Pharma

8	Calida Healthcare	18	Alembic
9	Jubilant Life Sciences	19	Aventis Pharma
10	Piramal Healthcare	20	Glenmark Pharma

Over the next few years, an abnormally large number of blockbuster drugs are scheduled to lose their patent protection, opening the doors to cheaper generic drugs. These drugs are Blockbuster-brand products and offer tremendous scope to generic manufactures.

Table 2: List of Blockbluster Drugs Gone Off-patents[6]

S. No.	Drugs	business	Use	Year
1.	Concerta (methylphenidate)	$1.33 billion.	Used for ADHD (attention deficit) in teens.	May 2011
2.	Levaquin (levofloxacin)	$1.63 billion.	An antibiotic used for treating bacterial infections.	June 2011
3.	Zyprexa (olanzapine)	$1.97 billion.	Used for treatment of schizophrenia and bipolar disorder.	Oct 2011
4.	Lipitor[a] (atorvastatin)	$6.05 billion.	Used for treating cholesterol.	Nov 2011
5.	Lexapro (escitalopram)	$2.56 billion.	Used for treating depression.	March 2012
6.	Seroquel (quetiapine)	$3.48 billion.	This is an antipsychotic medication.	March 2012
7.	Plavix (clopidogrel)	$4.56 billion.	Used to prevent unwanted blood clots to avoid heart attacks and strokes.	May 2012
8.	Tricor (fenofibrate)	$1.35 billion.	Helps reduce cholesterol and triglycerides (fatty acids) in the blood.	July 2012
9.	Singulair (montelukast)	$3.47 billion.	Used for asthma and allergies.	Aug 2012
10.	Actos (pioglitazone)	$2.78 billion.	This is an oral diabetic medication.	Aug 2012
11	Diovan HCT (valsartin/hydrochlorothiazide)	$1.38 billion.	These drugs are used for the treatment of hypertension.	Sep 2012

In December' 2011, Ranbaxy receives approval for the generic 'Atorvastatin' tablets of the original brand name drug 'Lipitor' owned by Pfizer, Inc.

In March 2012, Natco Pharma got compulsory License (CL) for 'Sorafenib tosylate' of the original brand name drug 'Nexavar' owned by Bayer Corp. under the provisions of the section 84 of the Indian Patent Act 1970. It is used for the treatment of Liver and Kidney cancer. Its price now Rs 8,800 for 120 tablets (one months therapy) as against Rs. 2,84,428 being the cost of 'Nexavar' sold by Bayer Corp.

Table 3: Top 10 International Generic companies[7]

S. No.	Company	Location	Revenues in 2010 (in $ billion)	Growth Over 2009 (%)
1.	Teva	Isreal	11.03	+17.90
2.	Sandoz	Germany	8.52	+13.70
3.	Mylan	US	4.99	+7.00
4.	Actavis	Switzerland	2.52 (estimated)	NA
5.	Hospira	US	2.35	+13.30
6.	Watson	US	2.27	+38.20
7.	Sanofi	France	2.04	+41.50
8.	Greenstone	US	1.72	(2009 revenues NA)
9.	Stada	Germany	1.50	0.70
10.	Dr Reddy's	India	1.16	16.70

NA=Not Applicable P **Johnson: $61.6 billion**

4. Availability of Generic drugs in the Indian Market

Availability of Generic drugs in the Indian Market is very low. It is only supplied to the

Government and other hospitals or to the physician's dispensary. For more profit, generally branded drugs are promoted to doctors while branded generics are sold at the Maximum Retail Price (MRP). But distributors buys branded generic from companies at the discount of 10-15% of the MRP. In present situation, consumer patients are not benefited and retail chemists earn huge profit.

5. Comparative studies

In a recent study published in the Journal of the American Medical Association, researchers compared generic and brand-name drugs for the treatment of heart and artery disease. The study included beta-blockers, diuretics, stains (for high LDL cholesterol) and warfarin (a blood thinner) – some of the most commonly prescribed medications worldwide. Thirty eight of the studies were randomized controlled trials – indicative of high reliability. In these studies, 36 of 38 found no real difference between generic and brand.

The decisions of FDA regarding bioequivalence studies aren't made public, so doctors have no way of knowing when the FDA has found a difference and how telling the difference is. Nor can they find out about differences in fillers and other additives, which might change the rates of release. So it comes as no surprise that only 12 of 43 medical journal commentaries on the subject of generic vs. brand encouraged the use of generics.

Generic Drugs are available all over the world at affordable prices with maintaining quality. These 'Generic' formulations balance public interest like critical disease like cancer, AIDS etc. FDA does not allow a 45 percent difference in the effectiveness of the generic drug product. The average difference in absorption into the body between the generic and the brand name was 3.5 percent[8]. Some generics were absorbed slightly more, some slightly less. This amount of difference would be expected and acceptable, whether for one batch of brand name drug tested against another batch of the same brand, or for a generic tested against a brand name drug. In fact, there have been studies in which brand name drugs were compared with themselves as well as with a generic. As a rule, the difference for the generic-to-brand (Any generic drug and brand name drug must perform approximately the same in the body as the brand name drug) comparison was about the same as the brand-to-brand comparison.

It is observed in few cases where some people may experience an undesired effect when switching from brand name drug to a generic formulation or from one generic drug to another generic drug. FDA is actively engaged in making all regulated products – including generic drugs – safer.

FDA wants to understand what may cause problems with certain formulations if, in fact, they are linked to specific generic products. FDA is encouraging the generic industry to investigate whether, and under what circumstances, such problems occur. The Agency does not have the resources to perform independent clinical studies and lacks the regulatory authority to require industry to conduct such studies.

FDA monitors adverse events reports for generic drugs. The monitoring of adverse events for all drug products, including generic drugs, is one aspect of the overall FDA effort to evaluate the safety of drugs after approval. Many times, reports of adverse events describe a known reaction to the active drug ingredient. Reports are monitored and investigated, when appropriate. The investigations may lead to changes in how a product (brand name and generic counterparts) is used or manufactured.

6. Counterfeiting of drugs

There are so many factors encouraging counterfeiting of drugs. Medicines are high value items in relation to their bulk and the demand for medicines is very high. Furthermore, for the counterfeiter, ingredient costs can be very low if cheap substitutes are used or if these are omitted altogether, as is often the case. Producing counterfeit drugs may not require building huge infrastructure

or facilities. There are also no overhead costs due to quality assurance or meeting Good Manufacturing Practices (GMP) standards, since such standards are never implemented and gross margins are therefore very high. This would require strong government will and commitment to establish and operate a strong national drug regulatory authority and require proper drug regulation (legislation and regulations) If it does not exist then the criminal activity of counterfeiting of medicines is not treated as a crime. Currently, only a few of the WHO member states have enacted special national legislation addressing the issue of counterfeit drugs.

At present, out of the 191 WHO member states about 20% are known to have well developed drug regulation. Of the remaining member states, about 50% implement drug regulation at varying levels of development and operational capacity. The remaining 30% either have no drug regulation in place or a very limited capacity that hardly functions. Inadequate resources for drug regulation activities and absence of training of national drug regulatory authorities' personnel may also manifest itself as inefficiency and incompetence of national drug regulatory authorities. The efficiency of personnel is adversely affected by corruption and conflict of interest resulting in laws not being enforced and criminals not being arrested, prosecuted and convicted for their crimes. Intersectoral cooperation between regulatory authorities, police, and customs services and the judiciary is essential for effective control of the national drug market and enforcement of drug legislation.

Pharmaceuticals made for export are not regulated by many exporting countries to the same standard as those produced for domestic use. Trade in pharmaceuticals rarely takes place between the manufacturing country and the importing country. Currently, it takes place through one or more intermediate countries or trading houses. Activities in trading houses may sometimes involve repackaging and re-labeling which may be carried out without any controls under conditions that do not comply with good manufacturing practices' requirements.

In most cases, counterfeit drugs are not equivalent in safety, efficacy and quality to their genuine counterparts. Even if they are of the correct quality or contain the correct amount of active substance, their production and distribution are not within the control of the drug regulatory authority of the country concerned. This means that any associated defects and adverse reactions will not be easily recognized or monitored and, if needed, an effective product recall would not be possible.

Most nations require generic drug manufacturers to prove their formulation exhibits bioequivalence to the innovator product. 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 producing high quality generic medicines that are sold around the world. India tops in the world in exporting generic medicines worth of Rs 50,000 core and currently, the Indian pharmaceutical industry is one of the world's largest and most developed

The detrimental impact of this description of counterfeit drugs on Indian generic industry is very emphatic as situations here are also paradoxical. India on one hand has been identified as one among several developing countries that are regarded as the source of counterfeit medicines by the organisation for Economic Cooperation and Development (OECD). India is the fourth largest producer of pharmaceuticals in the world which accounts to 8% of world's production by volume and 1.5% by value. India pharmaceutical industry ranks 17th in terms of exports its product to more than 200 countries around the globe including highly regulated markets of USA, Europe, Japan, and Australia. According to Gold Saches study, it is estimated that India is estimated to be the fifth largest pharmaceutical market in the world by 2020.

In order to market drugs, U.S. generic manufacturers must have a permit and

approval from the Food and Drug Administration (FDA) indicating that the active ingredient is approximately the same as that of the brand name. The determination of drug approval is made according to whether it is pharmaceutically equivalent, bio-available, and bioequivalent.

7. Pharmaceutically Equivalent

Two drugs are considered pharmaceutical equivalents when they contain the same chemically active ingredient(s) and are identical in dosage form and strength. Pharmaceutical equivalence may be affected by many things.

1. Variations in inert ingredients
2. Plants in different parts of the world
3. In oral drugs, capsule content may be 7% over or 7% under the stated content, e.g. a 100 mg. capsule may be as low as 93 mg. or as high as 107 mg.
4. Manufacturers may shift their source of supply.
5. Once a drug has been approved by the FDA, manufacturers sometimes make changes to the formula which was originally submitted.
6. Many arthritic patients are elderly. The age of the patient may be a factor in pharmacokinetics. Digestive tract absorption of an oral drug may be altered by a variety of factors, including higher gastric pH, accelerated gastric emptying, and thinning and reduction of the absorptive surface.

In addition to general approval, the FDA rates drugs with codes. All drugs with an "A" code are rated as being therapeutically equivalent; "B" coded drugs are those not rated equivalent some pharmacies fill with B-rated drugs. At this time, it is recommended that no patient use a version of a drug with a B-rating. Clinical differences or serious bioequivalence problems with B-rated products have been reported for drugs such as prednisone, estrogen tablets, levodopa and phenytoin. In addition to The Orange Book[9], The Physician's Generics lists available generics as therapeutically equivalent or non-equivalent. Because the antibiotic protocol uses such low doses, leeway between versions which are effective and those which are not may be much more critical.

8. Bioavailability

In bioavailability, it can be assumed that the drug's effectiveness is related to the amount of product absorbed and the speed of absorption. However, in some cases, the pharmaceutically equivalent products can have different bioavailability. They may be absorbed either faster or slower than the brand name drug which may or may not be clinically significant.

The pH-dissolution profile of a product may have clinical relevance. Even if the coating is adequate to prevent release of the enzymes in the stomach where the ingredients are irreversibly inactivated, it may not dissolve at the pH of the duodenum after meals.

9. Bioequivalence

In bioequivalence studies, the goal of testing is to determine if the drugs are functionally equivalent. The FDA requires that any approved drug be effective within a 20% range of the original patented or brand name drug. This means that the effectiveness may be 20% greater or 20% less effective than the brand name so that two generic drugs could contain as much as a 40% difference from each other. Therefore, a drug may be legally ***chemically*** equivalent but not at the same time ***clinically*** equivalent. A study run on a generic of the anti-seizure, Tegretol, found the generic allowed breakthrough seizures.

An example of how the above factors may affect the bioavailability and clinical effectiveness is seen by applying these factors to tetracycline. At one extreme, a 500 mg. dose of tetracycline taken in 2-250 mg. capsules which is 20% lower in effectiveness, 7% low in the mg. amount in each capsule (14% dose total) and which is taken with food, decreasing the absorption rate (<50%), could provide as low as 136 mg of tetracycline that is available to the body. Correspondingly, the same 2-250 mg.

capsules making a total dose of 500 mg. which is 20% more effective, 7% over on mg. in capsule and taken without food (increasing the absorption rate to 77%), provides 555 mg that is functionally available to the system. It should be noted the food-drug interaction is less a factor with minocycline and doxycycline as they are absorbed differently. In addition to the ±20% difference allowed in bioavailability by the FDA and the ±7% of the stated capsule content allowed by the U.S. Pharmacopoeia, there are other considerations which should be considered when using a generic drug.

1. Some drugs lose potency while on the shelf, so drug companies increase the strength so as the drug ages, it will still provide a therapeutic level. This means patients who use the drug soon after production when the dose may be stronger may be getting an overdose.
2. There is a risk that a generic substitution could result in a change in serum concentration.
3. Such a change may lead to significant adverse effects or loss of benefit.
4. The risk that patients may receive different generics each time they fill their prescription, changing the response to the drug.
5. Cost of brand names is usually, but not always, higher than for a generic.
6. Blood tests can become necessary to determine adequate concentrations, excessive, possibly toxic concentrations or low, possibly ineffective concentrations.
7. The cost of the time and effort spent in adjusting the dose (if needed).

Bioequivalence may be affected by the type of study; e.g. two brand name pharmaceutical equivalents were each compared with a placebo in separate trials but were not compared with each other for bioequivalence. Thus while each was effective, it cannot be assumed that they produce the same clinical effect. Bioequivalence studies are performed on healthy volunteers and thus may not account for the full pharmacologic and therapeutic impact of generic substitution on patients with disease.

Most nations require generic drug manufacturers to prove their formulation exhibits bioequivalence to the innovator product.[10-15] In the U.S., the FDA must approve generic drugs just as innovator drugs must be approved[16]. The FDA requires the bioequivalence of the generic product to be between 80% and 125% of that of the innovator product.[17]

This value range is part of a statistical calculation, and does not mean the FDA allows generic drugs to differ from the brand name counterpart by up to 25 percent. FDA recently evaluated 2,070 human studies conducted between 1996 and 2007, which compared the absorption of brand name and generic drugs into a person's body; they were submitted to the FDA to support approval of generics. The average difference in absorption into the body between the generic and the brand name was 3.5 percent, comparable to differences between two different batches of a brand name drug.[18, 19]

Bioequivalence, however, does not mean generic drugs must be exactly the same ("pharmaceutical equivalent") as their innovator product counterparts, as chemical differences may exist (different salt or ester – a "pharmaceutical alternative").

A physician survey in the US found only 17% of prescribing physicians correctly identified the USFDA's standards for bioequivalence of generic drugs.[20]

A latest development to address this issue enables interested doctors and consumers to check generic drug interactions and outcomes detail to the specific drug and drug company.

10. The WHO Executive Board Meet

The most controversial part of definition of counterfeiting of drugs is that any 'false representation' in relation to 'identity, history or source'. False representation of identity and source applies not only to mere labeling of the products, but also to container or other packaging'. Thus, false representation with

regard to any of these would make the product 'counterfeit within the scope of the definition. The WHO Executive Board meeting in Geneva in January 2009, India's suggestion's were accepted and the word 'history' was deleted and modify the present defination.[21]

India has stressed that a generic or branded medicine not registered in a particular country, but available in that country is not counterfeit, but simply an unregistered product.[22]

Patient Perspective

• **Cost and compliance**. Theoretically, generic medications should improve management and patient compliance because the obstacle of cost has been removed.

• **Inferiority complex**. Another potential issue is that patients may be resistant to going on a generic medication because they perceive them as inferior to their branded counterpart.[22] Generics are often considered second-rate medications due to perceived poor compliance with standard manufacturing practices, lack of patient knowledge about generics, and influence of the brand-name company.[22, 23] We need to educate our patients so they can make an informed decision about their treatment and be willing to try a generic medication if the situation is appropriate. This is particularly true in the elderly who may be on multiple medications, as well as those with low socioeconomic status who could benefit from the savings.

• **Patient preferences**. We often need to consider our patient's personality and past experience when deciding between generic and brand drugs as well. One important question to ask our patients is whether they have taken generics before and what the outcome was. If the patient had a poor experience, they may be biased towards branded medications and willing to pay the higher price.

11. U.S. generics approval process

Enacted in 1984, the U.S. Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act, standardized U.S. procedures for recognition of generic drugs. An applicant files an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA), and seeks to demonstrate therapeutic equivalence to a specified, previously approved "reference listed drug". When an ANDA is approved, the FDA adds the drug to its Approved Drug Products list, also known as the Orange Book, and annotates the list to show equivalence between the references listed drug and the approved generic. The FDA also recognizes drugs using the same ingredients with different bioavailability, and divides them into therapeutic equivalence groups. For example, as of 2006, diltiazem hydrochloride had four equivalence groups, all using the same active ingredient, but considered equivalent only within a group.[23]

12. Patent System in the US

After getting the FDA approval for marketing, the drug innovator company may apply for manufacturing process and grant of exclusively rights for about 20 years. The Patient Protection and Affordable Care Act 2010 authorized FDA to approve generic versions of biological manufacturers 12 years of exclusive use before generics can be developed. On the other hand, after January 1, 2005, India enacted an amendment to its patent law that reinstated product patents for the first time since 1972. The legislation took effect on the deadline set by WTO's Trade Related aspects of Intellectual Property Right (TRIPs) agreement, which mandated patent protection on both product as-well-as processes for the period 20 years. Under this new law, India is forced to recognize not only new patents but also any patent filed after January 1, 1995.

13. Challenging patents

Brand-name drug companies have used a number of strategies to extend the period of market exclusivity on their drugs, and prevent generic competition. This may involve aggressive litigation to preserve or extend patent protection on their medicines,

which is called 'ever greening' of patents. Drug companies may seek new patents on the production of specific forms of these compounds, such as single enantiomers of drugs which can exist in both "left-handed" and "right-handed" forms,[24] different inactive components in a drug salt,[25] or a specific hydrate form of the drug salt. [26] If granted, these patents 'reset the clock' on patent expiration. These sorts of patents may later be targeted for invalidation ("paragraph IV certification")[27] by generic drug manufacturers.[28-30]

The USFDA offers 180 days exclusively period to the first successful generic manufacture, who argues that a patent is invalid or dose not violate the production of the original drug. After this exclusivity period, other manufacturers can enter the market. As a result that further lowers the price of the drug due to competition.

14. Prescription in the US

A pharmacist may legally fill a prescription in the United States with either the brand name or a generic without consulting either the patient or the physician. A prescription may not even be filled consistently with the same generic. To assure continuity for the patient, the physician should indicate on the prescription no substitutions or dispense as written.

It must keep in mind that it is not to assume that all drugs with the same generic title are equal and will have the same clinical effect, even though many drug reps say they are equal.

15. Litigation and U.S. Supreme Court ruling

Two women, who claimed to have suffered severe medical complications from a generic drug, lost their Supreme Court appeal on Thursday, June 23, 2011, essentially ending their separate lawsuits against pharmaceutical manufacturers.

The justices in a 5-4 ruling said generic drug companies do not share the same level of responsibility as makers of brand-name equivalents and do not have to update their warning labels when significant new risks emerge. The financial and safety implications from the court's ruling could prove decisive.

16. CONCLUSION

In situations where demand for medicines exceeds supply, criminally minded people tend to profit out of crime by manufacturing and distributing counterfeit medicines as a substitute for genuine medicines. Also, consumers who use medicines inappropriately generate demand for such medicines, the sources of which may be counterfeit. In many cases counterfeit drugs have been found to be without active ingredients, or with wrong ingredients or with incorrect quantities of active ingredients. Treatment with ineffective counterfeit drugs such as antibiotics can lead to the emergence of resistant organisms and may have a deleterious effect on a wide section of the population. In extreme cases, counterfeit drugs may even cause death.

As a consequence of such damaging effects, counterfeit drugs may erode public confidence in health care systems, health care professionals, the suppliers and sellers of genuine drugs (branded or generic), the pharmaceutical industry and national Drug Regulatory Authorities (DRAs). Incorrect labeling as to the source can also be detrimental to the reputation and financial standing of the original and/or current manufacturer whose name has been fraudulently used. The consequence of this will be infiltration of counterfeit medicines into national distribution channels.

There is no simple solution or remedy that can be applied to eliminate counterfeit medicines nor can the problem be solved by an individual company or government. The problem has reached a global dimension and needs a global approach. Governments need to develop strategies to reduce corruption and powerful act counterfeiting legislation.

The WHO has developed guidelines for the development of measures to combat counterfeit drugs." These guidelines provide advise on measures that should be taken by

the various stakeholders and interested parties to combat counterfeiting of drugs. The Indian pharmaceutical industry's contribution for the growth of the global generics market is very high. On the other hand WHO says 3.2% Indians will fall bellow the poverty line will because of high of high medical bills. 39 million Indians are pushed to poverty because of ill health every year. Around 30% in rural India didn't go for any treatment for financial constrains. About 47% rural and 31% urban hospitalizations financed by loans and sale of assets.[31]

The world health organization (WHO) is worried about Indians high out-of-pocket (OOP) expenses to medicines. About 70% Indians are spending their OOP income on medicines and healthcare services in compares to 30%-40% in other Asian Countries and are still suffering from infected disease due to lack of best quality drugs and healthcare facilities. WHO stressed the need for effective monitoring system in India like Drugs and Therapeutics committee (DTC) and Pharmacy and Therapeutic committee (PTC) in Indian hospital. These committees can play an effective role to provide patients more efficient and rational use of medicine. The planning commission accepts that OOP to pay for healthcare costs is a growing problem. Non-availability of free medicines in healthcare facilities is major factors discouraging people from accessing public sector health Unit.

The government has decided to create a database[32] of generic equivalents of branded medicine, paving the way for mandatory prescription of such low-cost drugs along with their costlier versions. The ministry plans to make it compulsorily for Doctors to write name of generic drugs along with brand names, a move that can reduce cost of medicines by more than half. There are an estimated 90,000 drugs brands sold in the country and it was practically impossible for physicians to remember the generic equivalents, many of which are combination of two or more chemicals Doctors can immediately write the generic equivalent in the prescription by referring to the database.

The department of pharmaceutical plans to include a provision of generic drugs in the final draft of the proposed drug pricing policy. But experts say doctors won't have the time to list out the generic equivalents. Also chemists will have the power to sell the generic drugs of the company of his choice. Many of brands are combinations drugs and their generic equivalents are may not be available.

Recently, some state namely Gujarat, Rajasthan, Mumbai etc. has already taken initiative to make available affordable generic drugs for the public by opening a number of medical stores for generic drugs and branded generics. Gujarat govt. has also selling medicines at subsidized rates in some stores. The Indian government was studying the feasibility of 'providing free medicines to all' especially to the urban and the rural poor. The scheme will be a great support to the sale of generic drugs in the domestic market and thus, would benefit consumers[5a].

At the same time affordable generic drug, which are present only hospitals only. It must be available in all medicine shop.

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REFERENCES

1. 1a. A brief Report Pharmaceutical Industry in India, March, 2012
   1b. Adams C, Brantner V, Estimating the cost of new drug development: Is it really 802 million dollars? Health Aff (Millwood), 25 (2) (2006) 420-428.
2. DiMasi J A, Hansen R W, Grabowski H G, The price of invotion: New Estimation of drugs of drug

development costs, Jounal of Health Economics, 22 (2) (2003) 151-185.
3. http:/www.who.int/medicines/services/counterfeit/overview/en/(28February 2009)
4. SAVINGS An Economic Analysis of Generic Drug Usage in the U.S., GPhA, September 2011, page 1.
5. 5a.O.R. Gattani; 'Branded to Generic Drugs', The Indian Pharmacist-June-2012.
   5b. IMS-June 2010
6. http://money.usnews.com/money/blogs/the-best-life/2011/04/29/blockbuster-drugs-that-will-Gone Off-patents
7. WorldPharmaceuticalFrontiers | www.worldpharmaceuticals.net
8. Davit et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother. 2009;43(10):1583-97.
9. http://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm
10. WHO Technical Report Series No. 937: Annex 7 (pdf) WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth Report (WHO Technical Report Series No. 937): Annex 7 - Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, May 2006. Accessed 2008-06-15
11. Food and Drug Administration, Department of Health and Human Services: Code of Federal Regulations 320 Title 21, Volume 5, Revised as of April 1, 2008 CFR 320 21/5, Revised as of April 1, 2008. Accessed 2008-06-15
12. Health Canada, Drugs and Health Products, Bioavailability and Bioequivalence Health Canada, Guidance Documents. Accessed 2008-06-15
13. EudraLex – The Rules Governing Medicinal Products in the European Union EudraLex. Accessed 2008-06-15
14. European Medicines Agency EMEA. Accessed 2008-06-15
15. Japan, National Institute for Health Sciences, Division of Drugs Guidances Japan, NIHS, Division of Drugs. Accessed 2008-06-15
16. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/default.htm
17. "Orange Book Annual Preface, Statistical Criteria for Bioequivalence". *Approved Drug Products with Therapeutic Equivalence Evaluations 29th Edition*. U.S. Food and Drug Administration Center for Drug Evaluation and Research. 2009-06-18.
    http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm. Retrieved 2009-08-10.
18. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm
19. Davit *et al.* (2009). "Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration". *Ann Pharmacother* 43 (10): 1583–97.
20. Banahan Bf, 3rd; Kolassa, EM (1997). "A physician survey on generic drugs and substitution of critical dose medications". *Archives of Internal Medicine* 157 (18): 2080–8. PMID 9382664.
21. The Times of India, New Delhi edition, 29th January 2009.
22. Nitin S, Tanushree S, Generic Drug Industry in India: The Counterfeit Spin: Journal of Intellectual Property Rights Vol 14 May 2009 pp 236-240.
23. Approved Drug Products with Therapeutic Equivalence Evaluations,

Preface. - an explanation of FDA terms and procedures.
24. U.S. Patent 4,721,723: Dextro-rotatory enantiomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thieno pyridyl) (2-chlorophenyl)-acetate
25. U.S. Patent 4,879,303: Amlodipine besylate
26. U.S. Patent 4,721,723: Paroxetine hydrochloride hemihydrate
27. "Paragraph IV Drug Product Applications: Generic Drug Patent Challenge Notifications". FDA, Office of Generic Drugs (OGD). 2008-06-11. http://www.fda.gov/cder/ogd/#paragraph. Retrieved 2008-06-16.
28. Brisol-Myers Squibb press release on successful defense of Plavix patent
29. Apotex press release on successful challenge of Norvasc patent
30. Apotex press release on successful challenge of Paxil patent
31. Repot of World Health Organisation (WHO) in november 2011
32. Ecconomics Times (ET) News