

Pharma Regulations for Generic Drug Products in India and US: Case Studies and Future Prospectives

Suryakanta Swain*, Ankita Dey, Chinam Niranjan Patra and Muddana Eswara Bhanaji Rao

Roland Institute of Pharmaceutical Sciences, Department of Pharmaceutics, Berhampur, Odisha, India

Abstract

Among the developing nations of the world, India has already carved out a special niche for itself in many business verticals of the pharmaceutical industry and is currently being recognized as the 'pharmacy of the world' for the generic drug products. The Indian generics market is growing day by day with Indian pharmaceutical companies seeking more Abbreviated New Drug Application approvals (ANDAs) in US. Generic medicines are formulated when patent and other exclusivity rights expire. To ensure the therapeutic efficacy of generic products, it must be pharmaceutically interchangeable and bioequivalent to the originator product. The contribution of the Indian pharmaceutical industry for the growth of generic drugs in the world is very high i.e. about to 35%. To sustain competition from developed world Indian generic manufacturer should plan the market strategy and regulatory requirement needed, very quickly because for generics production large number of application will be filed and competition from domestic market will also be there. This review enlists the validated regulations for manufacturing of generic drugs in India and US. Implementation and regulation, of the pharmaceutical sector at the state level, rather than on simply introducing new regulations is call of the hour. Henceforth, the use of drugs needs to be emphasized significantly for cost savings to the government and customers, in addition to its optimistic impact on health.

Keywords: Abbreviated new drug application approvals; Cases and incidents; Pharma regulations; Recent patents

Introduction

The Indian pharmaceutical industry has come a long way from being non-existent before independence to a prominent provider of medicines and health care products in the current decade. The Indian pharmaceutical industry at present is the global leader of growing pharmaceutical manufacturing companies, providing wide range capabilities in the complex field of technology and drug manufacturing. Indian pharma market growing at a rapid pace currently providing Indian pharmaceutical industry third rank all over the world in terms of volume and fourteen ranks, according to market value [1]. The major strength of currently growing Indian pharmaceutical sector is its capability to manufacture wide range of simple analgesic pills to complicated antibiotics, cardiac compounds with peer quality and efficacy and altogether exporting them to developed world. The industry bulk profit comes from exporting generics and API to the developed market mainly US followed by UK, Germany, Brazil etc. The total share of generics accounts in export is 58% providing the major boost, the Indian commerce ministry has set an ambitious export target of \$ 25 billion by 2013-14, which can be achieved only by major contribution from generics market [2]. The Indian generics market is growing day by day with Indian pharmaceutical companies seeking more Abbreviated New Drug Application approvals (ANDAs) in US in major segments such as cardiovascular, antibiotics and other groups. The major force for the development of generics market in US came in the form of enacting the Drug Price Competition and Patent Restoration Act of 1984, public law 98-417 better known as "The Hatch- Waxman Act" which created opportunities for developing and marketing generics or better called as abbreviated new drug applications for 180 days. Under ANDAs a pharmaceutical manufacturer can develop and market low price generic version of previously approved innovator drugs, thus providing the same product to patient in pregnable price with safety and efficacy. A generic or biosimilar drug product is one that is comparable to an innovators drug product in dosage form, strength and route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generics, are enlisted in FDA's orange book. Generic drug application are termed

as "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy instead, generics applicant must demonstrate that there product is bioequivalent (i.e., performs in similar manner to innovator products). India has its unique position all over the world generics market, providing drugs at low cost to the developed world, this is because of its rigid and flexible pharma regulations, patent act which is updated from time to time, thus Indian generics market is playing a major role in growth of Indian economy as it provides a major share in export, mainly exporting generics to US, therefore a proper set of rules and regulations is required in future for producing generics and exporting them, so that Indian pharmaceutical sector and economy maintains its growth and becomes leaders globally.

Pharma Regulations for Generic Product in India and US

Generics have an important role to play in public health as they are well known to medical community and usually more affordable due to competition. They are formulated when patent and other exclusivity rights expire. The key for generic medicines is their therapeutic interchangeability with originator products. To ensure the therapeutic efficacy generic products must be pharmaceutically interchangeable (contain the same amount of active ingredient and have the same dosage form) and bioequivalent to the originator product. Bioequivalence is usually established using comparative in-vivo pharmacokinetic studies

***Corresponding author:** Suryakanta Swain, Assistant Professor, Roland Institute of Pharmaceutical Sciences, Department of Pharmaceutics, P.O.: Khodasingi, Berhampur-7600 10, Odisha, India, Tel: 91-943-803-8643; 909-037-4275; E-mail: swain_suryakant@yahoo.co.in

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with originator products. The detailed description how it is carried out is described in respective WHO document and national regulatory guidelines. Well resourced regulatory authorities require that a generic medicine must meet certain regulatory criteria [3,4]. The major regulatory requirement for generic drug is presented in Table 1. For applying the ANDA's in US, application is submitted under any of the below subsections of 505(j) of Federal act, it is important to comply with rule and regulations of US because it's the major export destination for Indian generics manufacturers [5], the various application which can be applied for ANDAs in US is depicted in Table 2. The ANDAs review process is most important for developing generics, the review by FDA and CDER is done for generic applicant to compare its therapeutic bioequivalent with brand drugs after its approval for equivalency generic version of drug can be marketed (Figure 1). The review for equivalency is done by taking into account the bioavailability of product with branded drug, its microbiology, chemistry and labeling of product, this are current regulation to follow for generic approvals given by respective FDA.

Future Generic Products in India and US

It is seen that there is an upward swing in the generic market. It has reached 100 billion dollars in the past and is estimated to be three times higher than the overall growth of drugs. The current trend exhibits that blockbuster drugs are scheduled to lose their patent protection, opening the doors to cheaper generic drugs between 2013 and 2015 with the total market value in billions. It is expected that the percentage of generic drugs in the US market will rise from 14 to 21. This growth will enhance the export prospect of India and it will be doubled every year. It will be due to increase in the number of low cost workers and degree of innovation. Recent success in track record in design operation

of high tech manufacturing, testing, quality control, research, clinical testing and biotechnology also contribute to this higher growth. Indian pharmaceutical industries those who have USFDA (United States Food and Drug Administration) affiliations and approval of ANDA (Abbreviated New Drug Applications) will stand benefited. Now India's global share in the field of generic market is stipulated at 35% which is very high [6,7]. Table 3 describes list of various drugs going to get off-patent in 2015. To make the situation more favorable the Indian government has also introduced scheme of providing generic drugs to patient in hospitals with various Jan-aushadhi Kendra (Facilitation Centre). Thus future prospects of generics in India and US are very high as they are the next big thing in health care scenario. Consistent with prior research, MEPs (Market Exclusivity Periods) for drugs experiencing initial generic entry in 2011-2012 was 12.6 years for New Molecular Entities (NMEs) with sales greater than \$100 million in the year prior to generic entry, and 12.9 years for all NMEs. Further research may reveal variation by type of NME, whether defined by molecule type or other classification. Generic competition has intensified over the past 10-15 years, and the MEP has become an even more important indicator of the economics of brand-name drugs. The MEP is critical to manufacturers' ability to earn profits on brand-name drugs to fund future research and development activities, and brand-name drug shares rapidly drop following initial generic entry. Over 80% of brand-name drugs experiencing initial generic entry in 2012 had faced at least one Paragraph IV patent challenge from a generic manufacturer, up from only 9% for drugs experiencing initial generic entry in 1995. These challenges are filed relatively early in the brand drug life cycle, on average within 7 years of brand launch. Developments for the generic pharmaceutical industry are encouraging as more brand-name drugs come off patent and payers push for cost cuts in health care. In

A Generic Drugs Must:	
■	Contain the same active ingredients as the innovator drug
■	Be identical in strength, dosage form, and route of administration
■	Have the same use indications
■	Be bioequivalent (as a marker for therapeutic interchangeability)
■	Meet the same batch requirements for identity, strength, purity and quality
■	Be manufactured under the same strict standards of GMP required for innovator products

Table 1: Regulatory requirements for generic drugs.

Subsection of 505(J)	Products Type
Paragraph I	For the products for which no patent information is available in the orange book.
Paragraph II	Used for the products for which all the applicable patents are expired
Paragraph III	Used for the products for which the some or all the applicable patents are valid and the applicant confirms that the product will not be placed in the market till such patents are expired.
Paragraph IV	Used for the products for which some or all the applicable patents are valid and applicant try to file the product which does not infringe those patents or applicant invalidates the granted patents. On successful outcome the generic applicant enjoys the six month exclusivity in the market.

Table 2: Different types of ANDA applications in US.

Sl. No.	Name of the Drug	Category	Patent Holder	Expiry Year
1	Eletriptan	Migraine	Merck	August, 2013
2	Teriparatide	Hormone	Eli Lilly	July, 2013
3	Imatinib Mesylate	Oncology	Novartis	May, 2013
4	Insulin Lispro	Diabetes	Eli Lilly	May, 2013
5	Linezolid	Antibiotic	Pharmacia	Nov, 2014
6	Transtuzumab	Biopharm	Gentech	Oct, 2014
7	Posaconazole	Antibiotic	Shering	Aug, 2014
8	Omalizumb	Respiratory	Roche	Feb, 2015
9	Telethromycin	Antibiotic	Aventis	April, 2015
10	Alemtuzumb	Oncology	Millennium	Dec, 2015

Table 3: List of some important drugs going to be off-patents.

addition, due to increasing FDA budget and staffing should begin to cut the backlog of branded and generic drug applications and increase the ability of the FDA to inspect facilities here and overseas as generic biologics get to market in the next few years [8].

Upcoming Challenges for Indian Generics Manufacturers in Global Market

The generic drug companies in India have broad technological and diversified market capabilities. As more and more patents expire, the generic portion of the pharmaceutical market is expected to continue to have increased sales. The scientific capability for manufacturing and supplying generic drugs of these companies will give them an edge over others and make them major players in the international generics market. Fortunately India has the best subject skills to galvanize foreign investors. The encouraging scenario of basic research and drug discovery will also support the changed dynamics. But their future sustainable growth depends on sustaining in competitive markets of developed world. The major challenges for generic manufactures are strengthening the existing regulatory system especially for enabling more detailed and universal classification of drugs and chemicals between branded generic and generics. High R&D cost and investment in research is also a major stumbling block in this direction [9].

Amendments in the Pharma Regulations for Generic Products

The Hatch-Waxman Act enacted 1984 is a landmark act. It allows generic drugs to enter the market without repeating expensive clinical trials required for their branded drugs. The legislation is meant for balancing the world of generic and branded drug industries. It provides accessibility to lower-cost generic drugs while still encouraging innovation and development of new drugs. Nevertheless, the legislation created unintended legal barriers that have slowed the entry of generic drugs into the market due to significant legal loopholes. The generic drug companies are allowed to market the drug after the patent and certain exclusivities expire. It has led to the prolific growth of generic drugs in the market. Thus some changes are required so that the loopholes can be filled and the regulation can be strengthened and selling of low cost drugs can be achieved. The change in rule related to alleged abuse of the 30-months stay provision is to be taken care were the ANDA applicant informs the original patent holder about the generic version filing, where they have 45 days to file a patent infringement suit against the generic applicant. If an infringement suit is filed within the 45-days period, FDA approval to market the generic version is automatically postponed for 30 months. These stays are extremely advantageous to innovating companies, because they provide over 2 years of additional market sales. Company takes profit by utilizing this route and delays the entry of generic drug in market; many steps have been taken by amending act of Greater Access to Affordable Pharmaceuticals Act passed in 2003 by American government. Extending the extensions by alleged abuse of the 30-month stay provision is done by many companies that holds patent, the companies are able to further delay the market entry of generic drugs is through multiple patent listings in the Orange Book, which is the FDA's official listing of all the approved products. There are instances in which brand-name companies listed related patents in the Orange Book after an ANDA had already been filed by a generic manufacturer. The effect of these "later-listings" is that the generic applicant is then required to re-certify that the later-listed patent is also invalid or not infringed and notify the patent holder of the re-certification. Thus more delay occurs in generic drug to reach market [10](Figure 2).

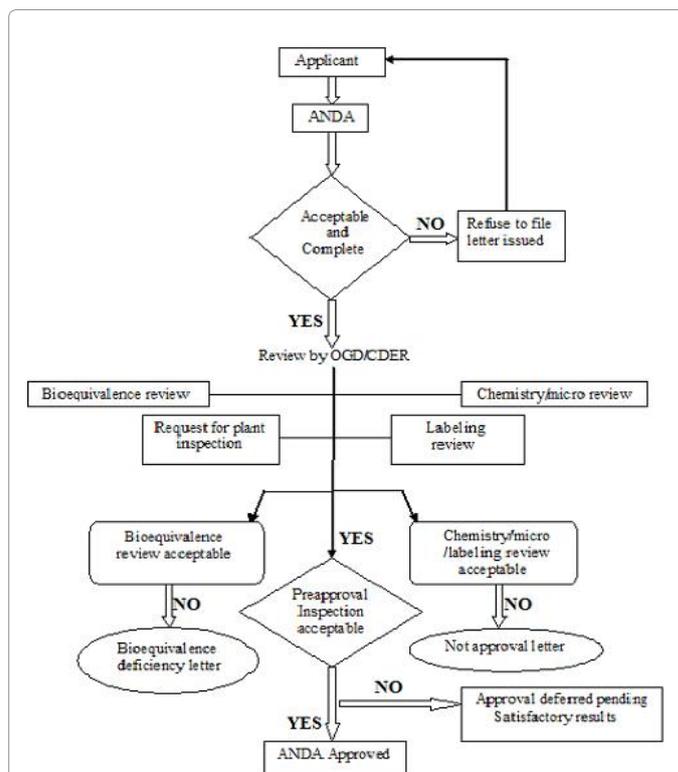


Figure 1: Explain the ANDA reviews process for development of generic drugs.

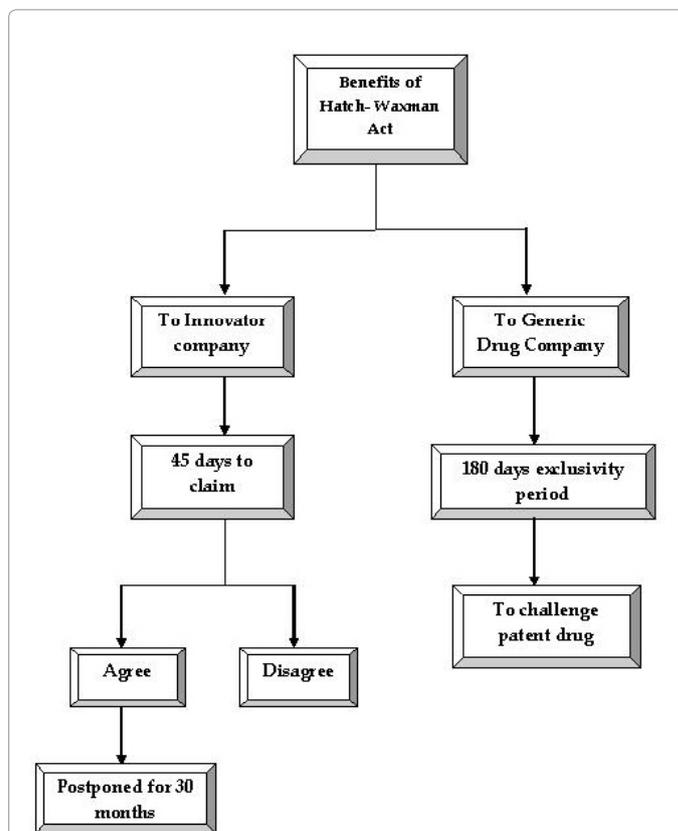


Figure 2: Schematic overview for the benefits of Hatch-Waxman Act.

Recent Cases and Incidents of Generic Products Regulation in India and US

The future prospects of generic product regulation in India and US are of great importance as they will decide the direction of growth of Indian Pharmaceutical Industries. Based on the recent cases and incidents that have occurred in India and US related to the generic product utilization, the new crucial roles will be implemented. The list of a few recent cases and incidents that happened in connection with generics in India & US are discussed in detail below (Figure 3).

The Karen L. Bartlett case

In December-2004, Physician of Karen L. Bartlett was prescribed Clinoril, the brand-name version of the Non-Steroidal Anti-Inflammatory Drug (NSAID) sulindac, for shoulder pain of Karen L. Bartlett. Her pharmacist dispensed a generic form of sulindac manufactured by petitioner Mutual Pharmaceutical. Karen L. Bartlett soon developed an acute case of toxic epidermal necrolysis. She is severely disfigured, has physical disabilities, and is nearly blind. At the time of the prescription, sulindacs label did not specifically refer to toxic epidermal necrolysis. By 2005, however, the FDA had recommended changing all NSAID labeling to contain a more explicit toxic epidermal necrolysis warning. Respondent sued Mutual in New Hampshire state court. A jury found Mutual liable on respondent's design-defect claim and awarded her over \$21 million. The First Circuit gets ratified. As relevant, it found that neither the FDCA nor the FDA's regulations pre-empted respondent's design-defect claim. It distinguished *PLIVA, Inc. v. Mensing*, 564 U.S. in which the Court held that failure-to-warn claims against generic manufacturers are pre-empted by the FDCA's prohibition on changes to generic drug labels by arguing that generic manufacturers facing design-defect claims could comply with both federal and state law simply by choosing not to make the drug at all. This case is being closely watched by pharmaceutical companies, federal regulators and others, the Supreme Court will decide on whether Mutual can be held responsible for Ms. Bartlett's injuries. The outcome is likely to further clarify the legal recourse for patients who take generic drugs, which now account for 80 percent of all prescriptions in the US. The verdict on both the sides will be playing a crucial role in

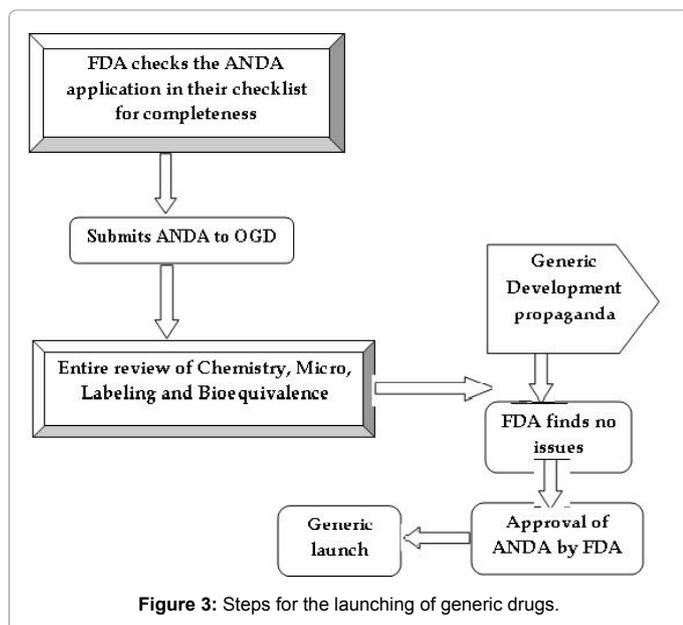
drafting future pharma regulations as if the court agrees with Mutual and rules that generic companies cannot be sued for defective products, trial lawyers warn that patients will be left with very few options if they are injured by a generic drug whereas manufacturers of generic drugs and other business groups have said that if the court sides with Ms. Bartlett, the decisions of individual juries could trump the authority of federal agencies like the Food and Drug Administration and potentially lead drug makers to remove valuable medicines from the market. Thus this case will be important for the future of generics drug market in US and India [11,12].

Pay to delay pharmaceutical case

The question of whether the manufacturer of a branded drug can pay another drug manufacturer to keep a generic version of the drug off the market was heard by the United States Supreme Court on 25th March, 2013. The court will decide whether "pay-to-delay" or reverse settlements arrangements, in which the manufacturer of a branded medication pays another company to keep a generic version off the market, are legal or not, the outcome of the case is very important because it will decide for how many patients pay for medications. Federal Trade Commission challenges the payments. It sees these arrangements as collusion, design to stop competition in the market place and is meant for violation of antitrust laws of the nations. The drug makers, in contrast, see the settlements as a routine way of settling a legal dispute, with each side getting something it wants. The Hatch-Waxman Act 1984 has some loophole. Payments are made possible by using these loopholes. Certain amendments are made in the last decade to encourage generic manufacturers to challenge patents held by branded manufacturers before they are set to expire. Typically, the generic manufacturer files for FDA approval to market a generic version of a branded medication that is still under patent protection, and the branded manufacturer sues the generic manufacturer for patent infringement. An increasing number of such cases end in "pay-to-delay" agreements according to which the generic manufacturer agrees to hold off on introducing the generic version in exchange for payment from the branded manufacturer. The case in point is Androgen (testosterone gel), produced by Solvay Pharmaceuticals whose patent is set to expire in 2020. The bone of contention between Actavis (formerly Watson Pharmaceuticals) and Solvay Pharmaceuticals was Andro Gel. Actavis filed for FDA approval to market a generic version of Andro Gel in 2003, and Solvay sued. In 2006, the FDA approved the generic version for marketing of Actavis, but the suit remained status quo. Later in 2006, the companies came to a settlement according to which Solvay would pay Actavis \$20 to \$30 million per year in exchange for help with marketing and an agreement to keep its generic version of Andro Gel off the market until 2015. The FTC (Federal Trade Commission) contends that the drug companies colluded to maintain Solvay's monopoly on Andro Gel because, without the settlement, the generic version would have become available in 2006. A federal district court dismissed the FTC's argument in this case, but another district court in a similar case decided the opposite way, so it is now up to the Supreme Court to decide and decision is expected. Moreover the best verdict according to many experienced federal judges that supreme court should not generalize the law, where as it should be implemented on case to case basis, thus this case should be great importance for Pharma regulators to draw guidelines for future regulations of generics in India and US and it will be important for patients to decide whether they will opt for cheaper or expensive medicines [13,14].

The Ranbaxy saga case

The criminal fraud that Ranbaxy has done with US FDA has let



Generic Name	Generic Manufacturer	Brand Name	Approval Date	Year Of Exclusivity Rights Expire
Pioglitazone Hydrochloride and Glimepiride Tablets, 30 Mg/2 Mg and 30 Mg/4 Mg	Takeda Pharms USA	Duetact Tablets	Jul 28, 2006	2027
Fexofenadine Hydrochloride Orally Disintegrating Capsules or oral: 60 Mg	Sanofi Aventis USA	Children's Allegra Allergy & Allegra Hives	Jul 25, 1996	May 26, 2014
Mupirocin Calcium, Cream; topical	Glaxosmithkline	Bactroban Cream	Dec 11, 1997	Oct 29, 2013
Doxorubicin Hydrochloride Liposome Injectable, Liposomal; Injection 2 mg/ml	Janssen Res And Dev	Doxil Liposome Injection	Nov 17, 1995	May 17, 2014
Zoledronic Acid Injection, 4 Mg (Base)/5 Ml; Packaged In Single-Dose Vials	Novartis	Zometa Injection	Jun 17, 2011	2031
Esomeprazole sodium - injectable;intravenous (Eq 20mg base/vial)	Astrazeneca	Nexium I.V. For Injection	March 31, 2005	2025
Amlodipine besylate; hydrochlorothiazide; valsartan - tablet; oral (5Mg;12.5Mg;160Mg)	Novartis	Exforge Tablets	April 30, 2009	2029

Table 4: Describes list of various new ANDAs approval in the year 2013.

down many but it's the fellow generics drug maker of India that will face the heat, this will be a very important incident which will decide fate of generics drug market of India in US and its regulation. Ranbaxy pharmaceutical of India is charged with producing low quality generic drugs in US and manipulating data's required for filing NDA and ANDA approvals in US, thus cheating their counter parts in many ways to be first in the race of producing generic version. Ranbaxy pleaded guilty to seven federal criminal counts of selling adulterated drugs with intent to defraud, failing to report that its drugs did not meet specifications, and making intentionally false statements to the government. Ranbaxy agreed to pay \$500 million in fines, forfeitures, and penalties-the most ever levied against a generic-drug company. The company, now majority owned by Japanese drug maker Daiichi Sankyo, sells its products in more than 150 countries and has 14,600 employees. It also came to light that even Ranbaxy scientist adulterated there generic testing drug with branded drugs for manipulating bioequivalence study.

Thus these serious allegations on one of the top India pharmaceutical company could be a major setback for generic manufactures and Indian Pharma regulator as they have failed to, therefore some strict regulations could be implemented by US FDA in future for Indian generics producers which could be a serious issue as it will lead to effect the generics drug market in India. Thus this will be the major factor which will decide the fate of future regulation of generics in India and US [15,16].

Miscellaneous cases and incidents

The study discusses the case of Swiss drug maker Novartis plea overruled recently by the Supreme Court was an attempt to win patent protection for its cancer drug Glivec. This was a serious blow to Western pharmaceutical firms who are increasingly focusing on India to drive sales and it also affects Indian and US generic market. Glivec (β -polymorphic form of imatinib mesylate) is indicated for treatment of certain blood and stomach cancers. The Supreme Court decision implies that a clutch of Indian companies, including Cipla, Ranbaxy and Natco, could continue marketing generic versions of the drug at a fraction of the cost of Novartis' product. While Novartis' Glivec costs over one lakh a month, local companies sell versions of the drug at roughly ten thousand a month. Supreme Court's ruling states that the drug has failed in "both the tests of invention and patentability" under Indian law. On the other hand, Glivec is widely recognized as one of the most important medical discoveries in decades, but it lost the battle on innovative quality grounds. The verdict can be interpreted as a battle between research and innovation on one side and public health and affordability on the other. It is true that the prospect of producing

cheaper generic versions of lifesaving drugs in the country, thus sale of generics will increase and generic market will be boosted up. Thus the case study suggests that the future of generics in India is bright and this case will be a benchmark for it. The well documented Novartis case in the 'Glivec' matter has brought the Indian patent system into sharp focus, whereas Indian regulatory authority should reform new rules for granting patent so that bigger MNCs should be attracted to India in future for better business [18-20].

Recent patents

With expiration of patent branded drugs are applied for generics version, some of the new ANDAs approval in year 2013 [17] are described briefly in Table 4.

Conclusion

In situations where demand for medicines exceeds supply, and cost effective drug in demand with minimum expenditure, generic drug are best choice fulfilling this demand. The current and future prospective of generics in India and US is very bright as Indian government looking towards generic drugs for providing better health care to public. Indian pharmaceutical industries grow rapidly all over the world and one of largest generic exporter in world where as, US being the major destination for export. Thus, the proper validated regulation is required for manufacturing generic drugs in India and US which requires proper symbiotic relation between India and US. Some amendments are warranted in Hatch Waxman Act 1984 for developing generic drug in better way, where as re-election of Barack Obama in US provides positive increase in generic market as his government extending health care insurance for additional 30 million Americans in the health care ambit, creating increased demand for generics.

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