4. DRUG REGULATIONS IN VARIOUS COUNTRIES

4.1 IMPORTANCE OF REGULATIONS

People and government willingly spend money on drugs because of the role they play in saving lives, restoring health, preventing diseases and stopping epidemics. But in order to do so, drugs must be safe effective affordable, good quality and used appropriately. This means, in turn, that their development, production, importation, exportation and subsequent distribution must be regulated to ensure that they meet the prescribed standards of their quality. Ineffective regulations of production and trade in pharmaceutical products results in circulation of toxic, substandard and counterfeit medicines on the national and international market. The use of such toxic, substandard and counterfeit drugs is not only a waste of money but may also threaten the health and life of those who take them. For example, sulfanilamide incident led to the death of 107 children in the U.S.A. in mid 1930 (Geiling et al., 1938) and the thalidomide disaster of 1960s, which caused birth defects in children (Duke, 1985). More recently, diethylene glycol contamination in drug preparations like paracetamol have led to multiple tragedies in Haiti and India (O’Brien et al., 1988; Singh et al., 2001). In Niger, fake meningitis vaccines, administered during an epidemic in which more than 26700 people had contracted the disease, led to the death of 2500 people (http://www.nafdacnigeria.org/publichealth.html). Substandard and counterfeit medicines are not only a problem in the developing countries but in developed countries as well (Wertheimer et al., 2003; Csillag, 1998).

While counterfeit products are a major problem for the global pharmaceutical industry, 192,000 people died in China from consuming counterfeit in 2003 (Wertheimer et al., 2003), this is not such a problem for India. The Chinese authorities closed 1300 factories while investigating numerous cases of counterfeit medicines worth 57 million US$. The Chinese authorities arrested 22 manufacturers of grossly substandard infant milk powder after the death of over 22 infants (http://www.artandopinion.com).

Before the revision of Chinese Pharmaceutical Law in 2001, the provincial drug administration was assigned with the authority to streamline the process of registering a generic drug. Consequently, this regional authority was exploited resulting in excessive duplication of the same drugs. For example, a fluoroquinolone type medicine was registered and manufactured by more than 1000 enterprises (Chen et al., 2001). Even the
pharmaceutical manufacturers did not need to conduct systemic scientific experiments on new drugs & local companies easily received approval from the provincial department of health to make a drug anywhere in China. The Drug Administrative Law revised on February 28, 2001 stipulated pre market testing, approval for new products and prohibition of drug adulteration which marked beginning of a new era of drug regulations in China (Deng et al., 2004).

Guaranteeing the safety, efficacy, quality, availability and affordability of medicines to the public is the prime goal of drug regulation, and by establishing an effective drug regulatory system these problems can be tackled effectively. Drug regulation is a public policy that restricts private sector activities in order to attain social goals set by the State. Drug regulation is the totality of all measures- legal, administrative, and technical- which the government takes to ensure the safety, efficacy, quality, availability and affordability of drugs. Public health and safety concerns have obliged the governments to intervene in the activities of pharmaceutical sector.

Regulation of drugs encompasses a variety of functions. Key functions includes licensing, inspection of manufacturing and sale /distribution channels, product assessment and registration, adverse drug reaction monitoring, quality control of drugs, drug promotion and advertising, and control of clinical trials. Each of these functions targets a different aspect of pharmaceutical activity. All of these functions must act in concert for effective consumer protection.

In some countries all functions related to drug regulation come under the jurisdiction of a single agency, while in others, drug regulatory functions are assigned to two or more agencies. When drug laws assign different responsibilities to different regulatory bodies, the exercise of drug regulations is fragmented. Therefore, drug regulatory structure should be designed in such a way that there is a central coordinating body with overall responsibility and accountability for all the aspects of drug regulations for the entire country, with no other function.

4.2 DRUG REGULATIONS IN INDIA

In the beginning of the 20th century the drug industry was virtually non-existent in India and drugs were imported from abroad. Increase in demands of drugs during and after
Drug Regulations in Various Countries

the 1st World War resulted in the production of cheaper and inferior quality drugs by some Indian companies, as compare to imported. To control the situation, government passed the Poison Act and Dangerous Drugs Act in 1919 and 1930 respectively, but to have a comprehensive legislation the Indian government appointed a Drug Enquiry Committee under the chairmanship of Lt. Col. R.N.Chopra to make recommendation about the ways and means to control the production and sales of drugs and pharmaceuticals in the interest of public health. The Drugs Act was passed in 1940 to regulate the import, manufacture, distribution and sale of drugs in India, as per Chopra committee recommendations. Drug Rules were framed in the year 1945 to give effect to the provisions of the Act.

The Indian Drugs and Cosmetics Act, 1940 has been recently amended by the Act of Parliament to incorporate stringent penal provisions for various offences including for manufacture and sale of spurious/counterfeit medicines. Offences have been made cognizable, non-bailable and trial by special designated courts, to act as deterrent to the anti-social elements indulging in manufacture and sale of spurious, counterfeit and adulterated medicines.

In context with the drugs and cosmetics, the Indian Parliament has enacted various laws to regulate the manufacture, sale, import, export, distribution, affordability, availability, advertisements, pricing and clinical research thereof in India.

1. Drugs and Cosmetics Act 1940.
2. Drugs and Cosmetics Rules 1945.

There are some other laws which have bearing on the manufacture, distribution and sale of drugs and cosmetics in India. The important ones are:

1. The Industries (Development and Regulations) Act 1951.
The State as well as the Central Government has appointed various regulatory agencies under the provisions of the above said statutes as their custodian. The manufacture, sale, distribution and quality of drugs is regulated through Drugs and Cosmetics Act 1940 and Rules 1945, while the affordability and availability of medicines is governed by Drugs (Price Control) Order 1995.

**DRUGS AND COSMETICS ACT 1940 AND RULES 1945**

The Drugs and Cosmetics Act was passed in 1940 with the object to regulate the import, manufacture, distribution and sale of drugs in India. The Drugs and Cosmetics Rules were framed in the year 1945 as provided under the Act. It is applicable to Allopathic, Homoeopathic, Ayurvedic, Unani and Sidha drugs as well as mechanical contraceptives, disinfectants, cosmetics, blood, blood products, blood components, in vitro blood grouping sera, medical devices, orthopedic implants etc. The Central Government has constituted the Drug Technical Advisory Board (DTAB) to advise the Central and State Governments on technical matters relating to the drugs. India has a decentralized drug regulatory structure, with separation of powers at the federal and state levels. The Drugs Controller General India (DCGI) heads the Central Drugs Standard Control Organization (CDSCO) and discharge the functions attributed to the Central government. The DCGI is a statutory authority under the Act and has port offices, zonal offices, sub zonal offices with drugs inspectors and drug testing laboratories functioning under it.

**FUNCTIONS UNDERTAKEN BY THE CENTRAL/ UNION GOVERNMENT (Malik, 2010)**

Statutory functions:

1. Laying down standards of drugs, cosmetics, diagnostics and devices.
2. Laying down regulatory measures, amendments to the Act and Rules.
3. To regulate market authorization of new drugs.
4. To regulate clinical research in India.
5. To approve license to manufacture certain categories of drugs as Central License Approving Authority, *i.e.* for blood, blood components, blood products, large volume parenterals and vaccines/sera.
6. To regulate standards of imported drugs.
7. Work related to Drug Technical Advisory Board (DTAB) and Drug Consultative Committee (DCC).

8. Testing of drugs by Central Drugs Laboratory.

9. Publication of Indian Pharmacopoeia.

Other functions:

1. Coordinating the activities of state drug control organizations to achieve uniform implementation of the Act; and policy guidelines.

2. Guidance on technical matters.

3. Participation in WHO-GMP certification scheme.


5. Conducting training programs for regulatory officials and government analyst.

6. Distribution of quotas of narcotic drugs for use in medicinal formulations*.

7. Screening of drug formulations available in Indian market.


(*Recently this function has been taken out of the purview of drugs control.)

FUNCTIONS UNDERTAKEN BY THE STATE GOVERNMENTS (Malik, 2010)

Statutory Functions:

1. Licensing of drug manufacturing and sales establishments.

2. Licensing/approval of drug testing laboratories.

3. Approval of drug formulations for manufacture.

4. Monitoring the quality of drugs and cosmetics manufactured by the respective state units and those marketed in the state.

5. Investigations and prosecution in respect of contraventions of the legal provisions.

6. Administrative actions.

7. Pre and post licensing inspection.

8. Recall of substandard drugs.

DRUGS CONTROL SET-UP AT THE CENTRE:

Regulation of manufacture, sale and distribution is primarily the concern of the state drug regulatory agency while the central authorities are responsible for approval of
new drugs, clinical trials in the country, laying down standards for drugs, control over imported drugs, coordination of activities of state drugs control organizations and providing expert advice with a view to achieve uniformity in the enforcement of the Drugs and Cosmetics Act 1940.

Drugs Controller General of India is responsible for approval of licenses for specific categories of drugs like blood, blood components, blood products, large volume parenterals, vaccines and sera; import licenses, new drug approvals etc.

Central Drugs Standard Control Organization (CDSCO) is located at FDA Bhawan, Kotla Road New Delhi and functions under the Director-General Health Services, with their zonal offices at Mumbai (west zone), Kolkata (east zone), Chennai (south zone), Ghaziabad (north zone) and two new zonal offices at Ahemdabad and Hyderabad; sub-zonal offices at Lucknow, Guwahati and various port offices(7) at Delhi, Kolkata, Mumbai, Chennai, Hyderabad, Kochi, Ahmedabad etc. These zonal and sub zonal offices work in close coordination with the state drugs control administration and assist them to achieve purposes of the Act and also ensures uniform enforcement of the Drugs and Cosmetics Act 1940 and other connected legislations on all India basis.

Central Drugs Laboratory (CDL) located at Kolkata is the national statutory laboratory of Government of India for quality control of drugs and cosmetics in the country. This laboratory has been established as per the provisions of Indian Drugs and Cosmetics Act 1940 and works under the administrative control of Director-General Health Services in the Ministry of Health and Family Welfare, Government of India, New Delhi. CIPL Ghaziabad, RDTL Mumbai, CDTL Chennai, RDTL Guwahati, CDL Kasauli, IVRI Izatnagar, NIB Noida, RDTL Chandigarh are other testing laboratories performing various statutory functions under the Act.

**DRUGS (PRICE CONTROL) ORDER 1995**

The “Essential Commodities Act” 1955, enacted by Government of India categorizes ‘drug’ in to the definition of ‘essential commodity’ under Section 2 of this Act. Similarly foodstuffs/food grains have also been included in the definition of ‘essential commodity’. Food is essential for sustaining the life of human being while the drug is essential for sustaining life as well as providing a quality life to a human being. Although
both drug and food are prerequisite for life preservation, drug has an upper edge over food
to achieve quality life. One can forgo food but cannot afford to forgo drug.

India was among the first countries in developing world to formulate a National
Drug Policy and introduce price control on pharmaceuticals. Control on the price of the
medicines were first introduced as early as in 1960s, as part of the Essential Commodity
Act, promulgated in the aftermath with India’s war with China in 1962. However, it was
only in 1978 that the first comprehensive price control mechanism was introduced in the
The Drug Policy of 1978 and DPCO 1979 were broadly based on the recommendations of
the Hathi Committee (www.scribd.com/doc/...hathi-committee-report-1975) set up in 1974
by the Indian Government under the leadership of Jaisukhlal Hathi. The Drugs Policy
1978 did not merely aim at controlling drug prices but was also a pro active attempt by the
government to promote the domestic drug industry- both the public as well as private
sector.

The DPCO 1979 brought 347 bulk drugs and over 4000 formulations marketed in
20,000 packs under price control. It covered about 90% of the drug market, at the time
when it was announced. Because of the serious flaw in 1978 policy, proposing differential
mark-ups, it led to companies shifting production of drugs away from price controlled
categories. The production of inessential medicines increased while there was a drop in
production of essential drugs. The Patents Act, 1970 promoted the growth of domestic
industry by allowing introduction of new drugs, which were under patent, within 3-5 years
of their introduction in the global market. This curbed the monopoly of multinational
companies over newer patented medicines and also introduced competition in this
segment.

The Drug Policy 1986 proposed a reduction in the span of price control and
allowed increase in the mark ups of price-controlled drugs. It both relaxed and abolished a
number of measures implemented under 1978 policy. The Policy introduced the criteria of
‘market competition’ and ‘minimum annual turn-over’ to include the drugs under price
control. The DPCO 1987 (based on the 1986 policy), reduced the number of price
controlled bulk drugs from 347 to 142, an estimated decrease from 90% of the market to
70% of the market.
The government announced its new Policy on Drugs and Pharmaceuticals in 1994 by giving major concessions to the industry in the form of reduced price and production controls. All the drugs under price control were brought under a single category with a uniform Maximum Allowable Post-manufacturing Expenses (MAPE) of 100%. The DPCO 1995 further reduced the number of price controlled bulk drugs from 142 to 74. Further, the Drug Policy 2002 was formulated against the backdrop of economic liberalization and the government’s commitment to strength patent laws, i.e. becoming TRIPS compliant by 2005. However, 2002 policy was never put in operation, as was challenged in the Supreme Court of India. Thus, the Drug Policy of 1994 and the DPCO 1995 remain in operation till date. If a new Drugs (Price Control) Order would have been formulated based on 2002 policy, it is estimated that 20-25 drugs would have remained under price control.

The basic plea from the industry to which the 1986, 1994 and 2002 policies responded positively, was that the drug industry should be de-controlled- both with regards to production and pricing. However the industry’s claim that their profitability had been going down due to excessive price control was not borne out by facts. Profits and turnover of drug companies have consistently shown a large increase over this period. The successive price control on medicines in the country has been depicted in Table 4.2.1.

NATIONAL PHARMACEUTICAL PRICING AUTHORITY (NPPA)

The Drug Policy 1994 envisaged setting up of an independent body of experts to be called the National Pharmaceutical Pricing Authority (NPPA) to perform the functions of price fixation/revision and monitoring of prices of scheduled / controlled bulk drugs and the formulations containing any of the scheduled bulk drugs, and to oversee the implementation of various provisions of DPCO, under the Ministry of Chemicals and Fertilizers. The NPPA was constituted by the Government of India on 29.08.1997 and various powers relating to price fixation of scheduled drugs and formulations based thereon, implementation, monitoring and enforcement of the prices, so fixed, were delegated to NPPA by Union of India on 04.09.1997.

This statutory body is empowered to regulate the prices of not only the scheduled drugs and formulations thereof but also non-scheduled drugs and formulations, if required in public interest. This statutory body, i.e., NPPA fixes/revises ‘ceiling prices’ of these 74
bulk drugs and their formulations from time to time, as per provisions under the Drugs (Price Control) Order 1995, which are binding for the pharmaceutical manufacturers. Any violation to the ceiling price so fixed or revised by the NPPA, empower the regulators to proceed against the offender firm/company as per the provisions existing under DPCO 1995. The provisions for criminal prosecutions as well as recovery of overcharged amount from the erring pharmaceutical company exist under the said statute.

In respect of non-scheduled drugs as well as the formulations, their prices are fixed/ revised by the manufacturers themselves without seeking any pre-approval from the Government/ NPPA. Such prices are normally fixed considering various factors like the cost of the bulk drug used in the formulation, cost of excipients, cost of R & D, cost of utilities /packing materials, sales promotion cost, trade margins, quality assurance cost, landed cost of imports etc. As a part of monitoring activities, NPPA regularly examines the movement in prices of non-scheduled formulations. The monthly reports of ORG- IMS and the information furnished by the individual manufacturer are utilized for the purposes of monitoring prices of non-scheduled formulations. Whenever a price increase beyond 10% is noticed, the concerned manufacturer is asked to bring down the price voluntarily failing which, subject to prescribed conditions, action is initiated under Paragraph 10 (b) of the DPCO 1995 for fixing the price of the formulation in public interest. This is an ongoing process. The NPPA so far, has until now brought 28 non-scheduled medicines under price control by invoking Paragraph 10(b) of the DPCO (Vivek, 2010) and many pharmaceutical companies have reduced prices voluntarily in case of 64 formulation packs of non-scheduled drugs.

To further tighten the noose around the pharmaceutical companies, the Government of India is in the process of creating DPCO cell in all the States for better implementation of prices fixed/revised by the NPPA from time to time, detect cases of overcharging and follow up such cases for recovery of overcharged amount and criminal prosecution if warranted. This issue of creation of DPCO cell in all the States have also been supported by the task force under the chairmanship of Dr. Proneb Sen and have been included as part of the draft National Pharmaceutical Policy 2006. Further, the government has created a new department for pharmaceuticals as Department of Pharmaceuticals (DoP) under the Ministry of Chemicals and Fertilizers to achieve the goal of ensuring quality medicines at affordable prices.
Drug Regulations in Various Countries

The successive reduction in the price control on drugs with the basic pleading that free market competition will stabilize/lower the drug prices did not help to contain the drug prices because the drugs are not purchased by the consumer on the basis of his choice or preference; rather they are purchased on the directions of medical professionals. The contribution of price control policies in containing the medicine prices in India is highly doubtful (Singal et al., 2008). For example, Ciprofloxacin, a price controlled drug under DPCO 1995, showed a lot of variations in the prices of its generic and branded version during a survey carried out in different States of India in 2004 (Kotwani et al., 2007).

There is no control of prices of medicines in the alternative system of medicines such as Ayurveda, Unani, Sidha and Homeopathic as per Paragraph 2 of DPCO 1995.

DRUGS (PRICE CONTROL) ORDER & PREVALENT MARKET PRACTICES

India, although being well known as a producer of cost effective quality generic medicines world over, lacks appropriate policies to make them available at affordable prices to its own people. Unethical marketing strategies adopted by various indigenous pharmaceutical manufacturers in India by classifying/categorizing them as “branded” and “branded-generic” medicines to push their sales, creates confusion and misconception in the mind of physicians as well as the consumers. Medicine companies were found manufacturing and marketing their products under two or three different versions with same composition (as generics, branded and branded-generics) but with different price structure. The difference in the price structure of these different variants of same product were found alarming and matter of serious concern from the consumer as well as healthcare provider’s point of view. Comparative price structure of branded and their equivalent branded-generic versions of some of the commonly used medicines has been outlined in Table 4.2.2.

In-spite of the fact that both branded as well as branded generic medicines are regulated under the same regulations in India, yet there exist lot of variations in their price structure. Even the price controlled drugs and formulations are not exception to this fact. Price controlled drug formulations of Ciprofloxacin was found to exhibit enormous price variations in different versions available in the market. Branded Ciprofloxacin 500mg tablets (1x10 pack) was found costing about Rs.100 while its equivalent generic counterpart was available in less than Rs.20 (1x10 pack). Similarly, Cetirizine10mg
Drug Regulations in Various Countries

tables, a price de-controlled drug also exhibited multifold variations in price of its
generic/branded versions indicating gaps in price regulations under the present DPCO.

The variations in pricing of medicines were found at various levels. The price were
found varying depending upon as to whether these are branded, generics or supplied to the
government institutions. A close examination of the public procurement prices of various
medicines revealed that they are procured by the governmental agencies at very low prices
in the State of Haryana. The medicines were found supplied at one tenth to one seventieth
of the MRP printed on the label of medicines in case of sale to government institutions.
For example, Cetirizine tablets 10 mg with printed MRP of Rs.35.51 (sold under popular
brand name ‘Alerid’ by M/s Cipla) was found being supplied to government agencies at a
meager rate of Rs.0.56 per 1x10 pack. Comparative price structure of some commonly
used medicines (branded v/s government tender prices) is depicted in Table 4.2.3.

The price control regulations in India were found ineffective in achieving its goal
to provide medicines at affordable prices to the public at large. Even some of the
pharmaceutical companies were found engaged in adopting unethical marketing strategies
and illegal practices for financial gains. Interestingly, few single active ingredient
containing formulations were found being sold in the country with higher printed MRP
than their fixed dose combinations with other active ingredients, which in normal course
looks unusual as well as interesting. Atorvastatin 10 mg capsules (1x10) a price
decontrolled formulation was found being sold in the market with MRP Rs.81.00 while its
fixed dose combination with Aspirin 75 mg was found at a MRP Rs. 19.18, which is even
less than one fourth of the MRP of Atorvastatin 10 mg capsules. Such of the
pharmaceutical companies appear to be circumventing the price control regulations
without caring for the poor patients. Some of such interesting formulation pairs available
in the market with their price tags are given in Table 4.2.4. These trends in pharmaceutical
sector do not sound justifiable to a prudent man. No scientific explanation can be made for
such a glaring difference in the prices of paired formulations specially when viewed from
the angle of their composition but speaks a lot about the motives of pharmaceutical
companies.

On investigations, it was revealed that the price controlled bulk drugs as well as
their formulations are regulated by the NPPA under the provisions of DPCO 1995 while
there is no such check/control on non-scheduled bulk drugs/formulations. The drug/
pharmaceutical companies are required to fix the MRP of dosage forms containing Aspirin, Pseudoephedrine hydrochloride and Dexamethasone (which are listed under Schedule 1 of the DPCO 1995) as well as formulations containing any of these drugs, as covered in the definition of scheduled drugs and formulations respectively under the DPCO 1995 (Malik, 2010), as per their notified ceiling prices. However, no such provision exists for other drugs like Tobramycin, Loratidine etc. Such unethical/unusual marketing strategies being adopted by some of the pharmaceutical companies are not justified at all and need immediate intervention by the stake holders including the NPPA, as a matter of great concern.

MARKETING APPROVAL IN INDIA

The Indian laws prohibit manufacture for sale or for distribution, or sell, or stock or exhibit or offer for sale, or distribute any drug or cosmetic by any person himself or by any other person in this behalf except under, and in accordance with the conditions of, a license issued by the competent authority. Similarly, no person can import any drug or cosmetics for sale and distribution otherwise than under, and in accordance with, such license (Malik, 2010). Licensing authorities have been appointed and notified under the Drugs & Cosmetics Act 1940 and Rules 1945 by each State Government, to perform such statutory functions. Grant of permission / approval to manufacture, ‘new drug’, conduct of clinical trials and approval to manufacture certain special categories of drugs is regulated by Drugs Controller General (India).

APPROVAL PROCESS TO MANUFACTURE NEW DRUG IN INDIA

The application for approval to manufacture a new drug substance and its formulations is required to be made in Form 44 prescribed under the Rules to the Licensing Authority as defined in Rule 21 with a fee of fifty thousand rupees. The applicant is required to the application with the data as provided in Appendix I to Schedule Y of the Rules 1945 including the results of clinical trials carried out in the country in accordance with the guidelines specified in Schedule Y and their reports in the format as per Appendix II to the Schedule Y. In case of drugs already approved as new drug in the country the data as per Appendix-IA is required from the applicant. Clinical trial reports are not required for the drugs which had already been approved as new drug in the country (Malik, 2010).
The Licensing Authority after being satisfied that the drug if approved as raw material or as finished formulation shall be effective and safe for use in the country, shall approve to the applicant on Form 46 or 46-A. However, if the data provided or generated on the drug is inadequate, the applicant is intimated according for compliance thereof before approval is considered.

The applicant is further required to approach the concerned State Licensing Authority of the respective State in the country where it intends to manufacture the drug product to get the final manufacturing approval of the product. The approval on Form 46 or 46-A in the name of applicant is pre-requisite for submission of application to the State Licensing Authority.

PERMISSION TO CONDUCT CLINICAL TRIALS FOR NEW DRUG / INVESTIGATIONAL NEW DRUG

The application for grant of permission to conduct human clinical trials (Phase-I), exploratory clinical trials (Phase-II) or confirmatory clinical trials (Phase-III) for a new drug, investigational new drug as well as fixed dose combination is required to be made on Form 44 accompanied with the mandatory fees before the Licensing Authority. The applicant is not required to pay separate fee along with the application for manufacture of a new drug based on successful completion of phased clinical trials. The applicant is also required to submit the information/data as provided under Appendix I and Appendix VI to the Schedule Y (for fixed dose combinations) to the Licensing Authority.

The Drugs Controller General of India has issued recent guidelines for marketing approval of fixed dose combination (FDC) drugs which are considered new drug as per Rule 122(E) of the Rules 1945 in India. If the FDC is marketed abroad, only phase III clinical trials are required to be conducted in India. If such a combination is not marketed anywhere in the world, clinical trials right from phase I as appropriate are required to be conducted in the country (http://www.cdso.com).

The permission is granted by the Licensing Authority in Form 45 or Form 45-A or Form 46 or Form 46-A, as the case may be, subject to conditions therein.

INDIAN PATENTS LAWS

India’s generic drug industry has made less expensive medications available in India and abroad for more than 30 years, making it possible for many people in developing
countries to treatment for various diseases including AIDS. The 1970 Indian Patents Act had granted “process patent” rather than the usual “product patent” that all western countries grant. This allowed drug companies in India to produce generic versions of medications patented in other countries as long as they used a different manufacturing process. As a result, several companies often produced the same drug using different processes, creating a competitive market that kept drug price low. Because of the tremendous growth in the pharmaceutical sector, India is being recognized as a major supplier of quality generic medicines at affordable prices throughout the world.

The increased growth in patenting in India is due to the introduction of the product patent regime and 20 year patent term in the year 2005, after India signed the Trade Related Aspects of Intellectual Property Rights (TRIPS), agreement of the World Trade Organization (WTO) in 1995. From the year 2005, till date about 13,000 patents have been issued in both chemicals and pharmaceuticals and about 70,000 patent applications are in pipeline for process and examination in the country (Golikeri, 2010). Medicines which constitute anywhere between 15-50% of total healthcare costs, are increasingly getting patented in India, implying a monopoly for the patent holder to charge any amount, he think appropriate. Several patents are being granted for products which are actually minor variations of existing medicines, and not breakthrough drugs as per the study by Indian Pharmaceutical Alliance (IPA). About 86 pharmaceutical patents granted by India after 2005 are for new forms of already known drugs and combination of various drugs indicating “ever-greening” -getting patent for minor variations to extend patent life of a product is becoming rampant in India, in spite of provisions for preventing ever-greening under Section 3(d) of the Indian Patents Act which is reproduced as below:

“the mere discovery of a new form of a known substance, which does not result in the enhancement of the known efficacy of that substance, shall not be treated as an invention” within the meaning of the Act.

It is expected that by 2015, when Indian pharmaceutical market rises to $ 20 billion, about 15% of the drugs would be patented molecules. Under such circumstances, when escalating healthcare costs are posing hurdles for the Governments across the globe, whether India can afford the patented medicines, is a big question and appropriate remedial steps are required to maintain affordability of medicines in India (Golikeri, 2010). The patent office in India has branch offices only in Chennai, New Delhi, and
Mumbai at present besides its head office in Kolkata, with a poor technical manpower of just 150 officers as patent examiners. It has planning to enter into agreement with the Centre of Science and Industrial Research (CSIR) to outsource part of its patent scrutiny work to this scientific body to ease the task. Provisions for online assessment of patent application including the notes and observations made by the examiners have been made by the Indian Patents Office to enhance transparency and easy accessibility.

In May 2003, Indian Patents Act was amended by insertion of a new Section 107-A providing for research exemption as an exception to the general rules of patent infringement, commonly known as ‘Bolar Provision’ enabling generic manufacturer to use a patented invention to obtain marketing approval without permission from patent owner. This section allows certain acts if performed solely for uses reasonably related to development and submission of information required to obtain regulatory approval for manufacture, construction, use, sale or import of any product (http://www/managingip.com).

IMPLICATIONS OF NEW PARENT REGIME IN INDIA

Most of the drugs presently manufactured and marketed in India are off-patent, i.e., not patentable in India for lack of novelty. 2ndly, several mail-box applications have been filed before January 1, 2005 for grant of patents. The problem of huge backlog of pending mail-box applications is likely to multiply with the expected increase in patent filing under the new regime. Thirdly, there are sufficient provisions in the amended patent law that will help generic drug companies continue to thrive, at least for some years. Therefore, the new patent era does not pose an immediate threat to its people.

In case of mail-box applications, patent right shall accrue to a patentee only from the date of grant of patent; there can thus be no liability by way of damages for any infringement before that date. The patent term of 20 years starts from the date of the application where as the patent rights come in to existence only after the grant of the patent, which may be some years after the application date. Section 3 of the Patent Act provides that ‘new use for a known substance’ was not a patentable subject matter. Section 111 of the Patent Act further provides that no damages for patent infringement can be claimed against an alleged infringer “who proves that at the date of infringement he was not aware and had no reasonable ground for believing that the patent existed.
DATA EXCLUSIVITY REGULATIONS IN INDIA

The Patents Act, 1970 was amended in the year 2005 to gain admittance to the World Trade Organization (WTO) and become TRIPS compliant. The Indian Government is debating over addition of data exclusivity provisions in the Drugs and Cosmetics Act 1940 which if enacted, would create tremendously large barriers to registering generic medicines in India. The data exclusivity is an independent intellectual property right and the data generated by the holder may not be referred to or used by another person or company for a specific period of time. With data exclusivity regulations in place, generic competitors would not be able to use the data generated by the patent holder for a minimum 5 years The US Trade Representative backed by PhRMA, though, would prefer to lengthen this time to the entire 20 year patent tenure, and thus generic production of new medicines would come to a virtual stand-still. Current TRIPS regulations do not include data exclusivity clauses and thus India is not obliged to add data exclusivity laws to their Drugs and Cosmetics Act 1940.

PATENT LINKAGE

The patent linkage is a system in which the drug control authority in a country refuses to grant or delay marketing approval to a generic company to manufacture and sell a drug, if it is under patent. Patent linkage is known to be against public health interests as it can delay entry of generics in the market and thus keep cheap medicines out of reach to those who need them. Such a practice is followed in some countries like US and is used by the patent holder to delay the entry of a generic product in the market. The USFDA, in contrast, restricts approval of drugs to 30 months if the innovator files an infringement suit within 45 days of the generic application.

In India, we do not have a patent linkage system. The patent system and the drug regulatory system are two separate and independent mechanisms and this is Parliament’s intent. Key function of the DCGI is to ensure safety and efficacy of medicines marketed in the country. Drugs Controller General (India) is not authorized to examine the patent status of a drug as he is not governed by the Patent Act. The Patents Act, on the other hand is regulated by a separate distinct authority designated as Controller General of Patents, Designs and Trademarks. Indian law provides the patent holder exclusive marketing rights for 20 years with no competition from generic low cost companies. However, there is no
provision for patent linkage either in the Patents Act or in the Drugs and Cosmetics Act 1940, two relevant laws in this regards.

The Delhi High Court has rejected the writ petition of a German based pharmaceutical multinational company (MNC) Bayer, which had indirectly sought ‘patent linkage’- linking regulatory approval of generic medicines with their patent status. Bayer sought an order that DCGI should consider the patent status of its drug, Sorafenib Tosylate (Nexavar) anti-cancer drug, before granting marketing approval to any generic drug company and also to refuse marketing approval. The High Court dismissed the petition with costs, and declared Bayer’s complaint to be an attempt to tweak public policies through court mandated regimes. The court further ruled that the drug regulator was not legally bound to link patent status to marketing approval as the powers and jurisdiction of the DCG(I) are circumscribed by the Drugs and Cosmetics Act 1940 and not by Patents Act.

The Supreme Court of India also dismissed the Bayer’s special leave petition filed by the company challenging the judgment of the Delhi High Court (www.thehindu businessline.in /2010/12/02/stories). It appears that these orders have put a lid on the patent linkage controversy, which would have delayed entry of generic version of medicines in the market, thereby adversely affecting access to cheaper medicines. The Supreme Court has now made the message quite loud and clear.

Similarly in another case the Delhi High Court directed Swiss MNC M/s Roche to pay Rs. 5 lakh towards the cost of litigation aimed at preventing Cipla, Indian generic company from marketing a low cost version of Erlotinib, a lung cancer drug over which Roche has an Indian patent. The third case is of B.Braun, the German medical device major, and Delhi based medical device maker, Poly Medicure for coming out with a ‘safety IV catheter’ that was similar to its patented product. There are over a dozen such cases pending with various courts across the country, on patent linkage (Mathew, 2009).

LABELLING PROVISIONS

As per the Indian laws labeling is mandatory for a drug to be manufactured for sale and distribution purposes in the market. The generic as well as branded medicines are required to be labeled as per provisions of Rule 96 to Rule 101 of the Rules. Labeling the drug products with its pharmacopoeial or international non-proprietary name (INN
labeling) is mandatory in addition to its trade or brand name. Further the generic/ INN name is required to be printed or written in more conspicuous manner than the trade name.

There are no specific labeling provisions exclusively for the generic medicines, as exist in some overseas nations wherein the generic medicines carry identification mark on their packing for their identification by the consumers. Labeling the drug products with its composition, batch number, date of manufacture, date of expiry, name and address of the manufacturer, drug manufacturing license number and maximum retail price is mandatory. The Indian law does not require generic medicines to have lower price as compared to their branded counterpart. Both generic as well as branded medicines are governed by similar price regulations.

The prescription drugs are included under ‘Schedule H’ of the Drugs and Cosmetics Act 1940 and Rules 1945 and are popularly known as ‘Schedule H’ drugs. These are required to be labeled so with a warning- To be sold by retail on the prescription of a Registered Medical Practitioner only. The container of medicines for external use is required to be labeled with the words in capital ‘FOR EXTERNAL USE ONLY’. The medicines which are not labeled as per provisions under the Rules 1945 or making false claim for the drug or are misleading & hence, are termed as misbranded drugs under Section 17 of the Drugs and Cosmetics Act 1940.

SUBSTITUTION BY PHARMACIST

Unlike in US, Australia and other developed countries, dispensing pharmacist in India is legally prohibited from substituting the prescription of a doctor containing Schedule H drug. Substitution of medicine with other medicine, whether containing the same substance or not, is prohibited and constitute a criminal offence under the Act. The dispensing pharmacist thus cannot substitute the prescription even at the request of patient and thus does not have any active role in promotion of generic medicines. There exist no generic promotional schemes for the dispensing pharmacists.

CONCLUSION

Government of India has provided for a decentralized drug regulatory system with separation of powers at the federal and State levels. In spite of the fact, India being largest producer and supplier of generic medicines in the world there are no governmental
schemes to promote generics for improving its affordability to larger section of the society. Indian law even does not allow generic substitution. The Drugs and Cosmetics Act 1940 and the DPCO 1995 regulating the quality and pricing of medicines in India do not differentiate between generic and branded drug. Even the term generic drug has not been defined in any of its drug regulations.

There is immediate need to provide definition of generic medicine and pro-generic provisions like generic substitution, incentives for generic manufacturing and dispensing, lower printing of MRP on generics, identification mark on generics etc. under the Indian drug laws to improve its availability and affordability in the country. Any unfair and unethical sale promotional efforts by the pharmaceutical companies should be made a cognizable offence under the Drugs and Cosmetics Act 1940 and Rules 1945.

The Indian DPCO categorizes drugs as the scheduled and non-scheduled drugs. First Schedule attached to the DPCO 1995 provides a list of 74 bulk drugs which are scheduled or price controlled drugs. Obsolete as well as outdated drugs like Analgin, Chlороquin, Sulphadimidine etc. which are included as price controlled drugs must be taken out of this list and new molecules like anti cancer, anti HIV drugs should be brought under the ambit of price control. This list of scheduled drugs should be reviewed and made a comprehensive list so as to cover most of the essential medicines. The maximum sale/ceiling prices fixed by NPPA must be revised periodically on year to year basis, to make it a dynamic list.

4.3. REGULATIONS OF GENERICS IN USA

In nearly three decades since the passage of the Drug Price Competition and Patent Term Restoration Act (commonly referred to as the Hatch–Waxman Act), the US generic industry has grown into a powerful force for affordable medicines. In 2005, the generic industry represented more than 56 per cent of prescriptions dispensed, yet only US $0.13 of every dollar spent by Americans on prescription drugs. Today, the generic pharmaceutical industry records more than USS 22 billons in annual sales, and of the top five US pharmaceutical companies, based on the number of prescriptions dispensed, the top four companies are generic pharmaceutical developers and manufacturers.
HATCH WAXMAN ACT

INTRODUCTION

The generic drug industry has been awash in controversy since the establishment of the pharmacy and medical communities in the US. The first federal statute designed to protect US citizens from harmful drugs was the Import Drug Act 1848, which prohibited the importation of adulterated drugs. It was passed because anti-malarial medication for the US troops in Mexico was found to be grossly adulterated and lacking in potency. In 1888, the American Pharmaceutical Association (APhA) published the National Formulary to help prevent counterfeiting of branded products (Ascione et al., 2001; Higby, 1995). Congress came on board in 1906 with the passage of the Federal Food, and Drugs Act, the primary forerunner of today’s Food Drug and Cosmetic Act. This law, signed by President Theodore Roosevelt, was the first to require product labeling in an effort to prevent misbranding and adulteration, and it enabled the government to take action if a product caused substantial injury or death (Meyer, 1999). This was the beginning of pharmaceutical regulation by what was soon to become the FDA.

The 1906 Federal Food and Drug Act was a major advancement in prohibiting adulterating and misbranding of food and drugs in interstate commerce. The 1906 Act defined adulterated drugs and extended to prohibit drugs of substandard strength or purity. This Act with several minor amendments lasted until 1938 when Congress adopted new legislation. Concern arose in 1928 regarding the substitution of generic drugs for brand-name products. A well-accepted pharmacy magazine published articles commenting on the appropriateness of this practice and voiced its concern that generic substitution might be deceptive. This came at a time when many mainstream drugs were beginning to enter the market. Then, in 1938, in response to the 1937 Elixir Sulfanilamide incident, which killed 107 people, U.S. Congress passed the Federal Food, Drug, and Cosmetic Act (FDCA). The elixir was prepared using diethylene glycol as solvent, whose toxicity tests were not carried out.

The FDCA designated products introduced after 1938 as new drugs and required them to be proven safe through manufacturer testing and FDA clearance before they could be marketed. This was the beginning of the “approval process” for drugs in the United States- the process requiring the submission of a New Drug Application (NDA). Any compound that fell within the definition of ‘new drug’ under the Act required an NDA.
While the FDCA was an important step in improving the drug-regulation system, guidelines were not always followed when an identical or similar product was introduced after a patent on a pioneer drug expired. Because the drug was not always considered to be a new drug by the FDA, the same rigorous testing for safety and efficacy was not performed, resulting in a variety of original and derivative products of varying integrity (Meyer, 1999).

The Durham-Humphrey Amendment (FDCA #503[b][1]; 21U.S.C. # 353 [b][1]) was enacted in 1951 and took effect in 1952. This Act established two distinct categories of drugs: those that are unsafe to use without medical supervision and must be prescribed, and those that can be sold without a prescription (OTC drugs). Despite the differentiation, multiple products continued to appear in the market, which potentiated difficulties with inventory and drug counterfeiting. This led to efforts by the APhA to pass anti-substitution resolutions and state legislation requiring pharmacists to dispense either the branded drug prescribed or a generic drug from a specific manufacturer unless only a generic name was provided (Ascione et al., 2001). While these laws helped prevent substitution of low-quality products, it limited opportunities for the manufacture of generic products of sufficient quality.

In late 1961, the ‘thalidomide disaster’ began to unfold. It was marketed in West Germany under the trade name Contergan by Chemie Grunenthal in 1958 and was sold without prescription as a tranquilizer in the German Federal Republic until April 1961, when the drug was recognized as causing polyneuritis in adults. In November 1961, the drug first was believed to cause the severe birth defect phocomelia, or “seal limbs” and by that time thousands of infants had been born in West Germany without one or both arms or legs or with only partially formed extremities (Fink III et al., 2002)

Thalidomide had been widely tested around the world as a sedative and tranquilizer. It was found later to act as anti-nauseating in pregnancy, and its widespread use for that indication brought the horrible side effect to the surface. Thus, serious side effects caused by certain new drugs or caused by new uses for old drugs may not be discovered until the drug has had very wide clinical use-after some damage already is done. This thalidomide tragedy was the impetus for the Kefauver-Harris Amendment known as 1962 Drug Amendment Act.
The Kefauver-Harris Amendments, which became effective in 1963, were the first to require drug manufacturers to prove a product's safety and efficacy to the FDA prior to marketing it. Also at that time, all products on the market that had been released between 1938 and 1962 were declared once again to be new drugs, and pioneer products had to submit efficacy data for evaluation by active ingredient. If a product was found to be ineffective, all related products, in addition to the pioneer product, were removed from the market (Meyer, 1999).

The Kefauver-Harris Drug Amendments also required all manufacturers of related products to submit an Abbreviated New Drug Application (ANDA) for products manufactured between 1938 and 1962. ANDAs contained information similar to that found in a pioneer drug application, with the exception of safety and efficacy. After 1962, the FDA established a new mechanism of proving safety and efficacy by allowing the "literature-based" New Drug Application. This meant that submission of published data regarding a branded product's safety and efficacy by a manufacturer of generic product was permitted (Meyer, 1999). Over the next several years, the Kefauver-Harris Drug Amendments were challenged, most notably in Upjohn v. Finch in 1970, in which the courts upheld the amendments by ruling that evidence of drug safety and efficacy cannot be substantiated by commercial success alone.

In 1966, the FDA commissioned the National Academy of Sciences / National Research Council to evaluate drug products introduced between 1938 and 1962. Some 16,000 claims for more than 4000 drug products were reviewed and 14.7% were reported to be ineffective, 34.9% were reported to be possibly effective, 7.3% were reported to be probably effective, 19.1% were reported to be effective and 24% were reported to be “effective, but”. The FDA initiated an action to remove from the market those drug products that lack proof of efficacy. This process was known as the Drug Efficacy Study Implementation (DESI) project (Fink III et al., 2002).

The Medicaid and Medicare amendments to the Social Security Act (enacted in 1965) and additional legislation passed in 1967 helped move generic drug products into the forefront. After a cost-effectiveness analysis of drug products conducted by Congress, the use of generic products by federal health and welfare programs was strongly encouraged to safeguard against inflated pricing arising from lack of competition (Ascione et al., 2001).
The marketing approval process for a new drug has undergone significant changes at United States Food and Drug Administration (USFDA) in the year 1962. Prior to the year 1962, a new drug used to get marketing approval by USFDA on the basis of safety profile alone. However, in 1962, Kefauver-Harris Amendments made to the Federal Food, Drug, and Cosmetics Act added a new and compulsory requirement of “proof-of-efficacy” for obtaining marketing approval for a new drug. As a result, all drug products approved before 1962 by the USFDA were reviewed again for efficacy through the Drug Efficacy Study Implementation (DESI) program. DESI was a program initiated by the USFDA following Kefauver-Harris Amendments to establish safety and efficacy requirements for approval of new drugs as well as for reconsidering the safety and efficacy of prior approved drugs. To prove that new drugs were safe and effective enough so as to get the USFDA approval, new drugs manufacturers were required to conduct clinical trials on a limited number of human individuals so as to determine the efficacy and safety of the new drugs and submit the results of the same to the USFDA along with their New Drug Application (NDA). Also, innovator drug manufacturers usually secure patent rights over the drug molecules produced in their R&D laboratories at an early development stage itself. They do so to exclude others from making, using, or selling their molecules at a later stage and also to gain profits in case a drug molecule succeeds to become a blockbuster drug. Usually, the discovery and development of new drug incurs a lot of monetary expense, efforts and time and hence the effective patent term for which the manufacturer can recoup the investments and reap benefits get reduced as time is lost in developing the drug into a dosage form. To add to this lost time, USFDA approval required to market the drug to take another couple of years. Thereby the effective term of many drug patents get shortened further due to the time required for obtaining the safety and efficacy data. Sadly, however, there was no provision for patent term extension prior to enactment of the Hatch Waxman Act, to make up for the time lost out of the total patent term during the marketing approval process.

On the other hand, the companies seeking to market a generic version of an innovator (also called branded drug) were also required to carry out their own safety and efficacy studies, i.e., clinical trials, much like the innovator drugs companies. Due to the high costs involved in conducting clinical trials, only a few generic companies showed interest in launching products in the US. As a result, by 1984, there were approximately 150 innovator drugs whose patents had expired, and for them there were no generic
 equivalents available in the market (according to the USFDA estimation). This indirectly maintained the monopoly of the patent holders of the innovator drugs as no other players were there in the market.

Another factor that complicated the approvals of generic drugs was the timing when generic drug companies were allowed to perform their clinical trials. A generic drug company was not allowed to begin the required USFDA approval process for a generic drug until the patents on the corresponding innovator drug had expired. Generally speaking, even if a generic drugs manufacturer gets access to the clinical data of the innovator drugs, making copies of a pharmaceutical product was not simple. Procuring active ingredients, performing bio-equivalence studies, assuring quality, putting together a dossier, establishing patient information leaflets and going through the regulatory process could take two to three years. Manufacturing needed another three to six months. Consequently, patent protection for the innovator drugs used to unduly get extended by two to three years before the generics manufacturers could come up with the approved generic versions for those innovator drugs. This discouraged the entry of generic drugs in the market.

In order to address the above mentioned problems, a provision in the law was needed which would allow the generic manufacturers to use the clinical trial data of the innovator drug and also allow the experimental use of the patented innovator drug so as to come up with the generic version of the innovator drug well before the patent for the innovator drug expires. This was needed in order to get the marketing approval of generic version before the expiry of the patent for the innovator drug so that the generic version could enter the market as soon as the patent for the innovator drug expires. This was also necessary to avoid the undue extra patent protection enjoyed by the innovator drug company and thereby avoid monopoly. Further, there was a need for a provision of extending the life term of patents related to pharmaceutical drugs to compensate for the time lost in seeking USFDA approvals.

Legislation to expedite the availability of generic drug products was passed in 1984. The Drug Price Competition and Patent Term Restoration Act, more commonly known as the Hatch-Waxman Act, allowed the FDA to approve applications to market generic versions of brand-name drugs released after 1962 without repeating efficacy and safety research. This legislation also allowed brand-name manufacturers to extend their
Drug Regulations in Various Countries

patent protection for up to 5 years for new products. This meant that these manufacturers could make up for time lost while their products were going through the FDA approval process. Despite the increase in patent protection, the Hatch-Waxman Act is considered to be one of the most pivotal legislative moves on behalf of the generic drug industry. The 1984 Act provided patent extensions and guarantees of market exclusivity to innovator drug companies. Generic companies, in turn, won the right to market generic copies by submitting Abbreviated New Drug Applications (ANDAs) showing that the generic formulation is bioequivalent to the brand name drug. In 1994, through the passage of the Uruguay Rounds Agreements Act, the patent term of drugs manufactured in the U.S. was extended from 17 to 20 years after original filing.

The new law made it much easier and cheaper to bring a new generic drug to market. Instead of going through lengthy human trials, companies merely had to prove that their drug had the same active ingredients and that they performed in the body the same way as the brand-name drug. The act also increased the amount of time a company could hold an exclusive patent on a new drug. Within a year, the FDA received more than 1,000 applications for new generic drugs, and an industry was born. The Act dramatically changed the face of medicine over the world. Generic drugs now account for consumer saving of about $8 billion to $10 billion every year in United States alone. After a long way since the time when generic aspirin first hit the shelves, consumer’s worries about the high cost of medications is over, that’s a real relief. Fortunately, this legislation brought needed change and credibility to the generic drug industry and was a timely move toward restoring the integrity of the industry in a time of greatly rising health care costs.

Today, the rate of competition is closer to 100 percent. Generic versions crop up almost immediately after the patent on a brand name drug expires. The floodgates opened in 1984 with the passage of the Drug Price Competition and Patent Term Restoration Act. The FDA calls it "one of the most successful pieces of legislation ever passed." After the enactment of 1984 Act, one of its authors Henry Waxman declared that “the war between generics and brands is over” but in reality the exchange of gunfire between the brand name manufacturers and generic drug firms was just beginning.

OBJECTIVES OF HATCH-WAXMAN ACT

The Drug Price Competition and Patent Term Restoration Act was passed by the Congress in 1984 to address the inadequacies in the pharmaceutical regulatory system.
This Act is informally called the Hatch-Waxman Act (hereinafter, referred to as HWA) which permitted the manufacturers to file an (ANDA) for generic versions of all post-1962 approved pharmaceutical products. It also reversed a 1984 ruling and allowed the generic manufacturer to begin test required for FDA approval before the patent expiry reducing the time for generic entry from 3 years to less than 3 months after patent expiry. The branded companies tended to extend patent protection on their medicines to keep the generic version off the market by aggressive litigations; this process is termed as “evergreening”. This new law came as a blow to innovators and the generics companies were required to prove that their drug had the same active ingredients and they were absorbed in to the body at a rate within ±20% of the rate of the branded counterpart.

Generic drug applications are termed ‘abbreviated’ because they are generally not required to include pre-clinical and clinical data to establish safety and effectiveness. The generic product must be bio-equivalent to their branded counterpart which establishes that both will be therapeutically equivalent. The major components of an ANDA review process include bio-equivalence evaluation, chemistry/micro-biological evaluation; inspection of the manufacturing facilities and review of proposed label.

The main objectives of the HWA were as follows:

**COST REDUCTION FOR GENERIC DRUG APPROVAL**

For getting the marketing approval for generic drugs, the generic drugs companies were no longer required to conduct the costly and time consuming clinical trials on their own. The generic drug companies were allowed to rely on the clinical studies done by the branded drug manufacturer. All that was required from the generic drug manufacturer was to prove that his generic version is bioequivalent to the innovator drug.

**ALLOWING EARLY EXPERIMENTAL USE**

Before the HWA even the experimental use of a patented drug was considered to be infringement. The generic drug manufacturers had to wait until the expiry of the innovator drug patents before starting to prepare for marketing approval of the generic version of that innovator drug which resulted in undue prolongation of patent protection for the innovator drug as the approval of the generic version would take another 2-3 years to enter the market. Hence, it was an objective of the HWA to allow the early experimental use of the patented drug and not to consider this pre-patent-expiration use as infringement.
This provision was embodied in 35 USC § 271 (e) (1) of the US Patent Act, and passed as part of the HWA. This provision is also called safe harbor provision and it allowed generic manufacturers sufficient lead time to develop, perform necessary testing and to seek USFDA approval so they could be ready to launch their products upon expiration of a patent covering the innovator product. The branded drug manufacturers were allowed a patent term extension (maximum of 5 years) to compensate for the time lost in the time-consuming regulatory approvals.

**MOTIVATING GENERIC DRUG MANUFACTURERS**

The HWA also established the concept of Market Exclusivity in the Federal Food, Drugs and Cosmetic Act. Under this provision, exclusive marketing rights for 180 days were granted to the generic drug manufacturer who was the first one to file the application for marketing of the generic version of the innovator drug. This provision provided incentive for the generic drug manufacturers to file Abbreviated New Drug Application (ANDA) and promoted healthy competition so that drugs could be available to public at relatively lower prices once they go off-patent.

Thus, the HWA strives to strike a balance between the interests of branded drug manufacturers, generic drug manufacturers and the consumers. It strives to provide optimum term of protection for the innovator to get back the returns from his innovation. Further, the HWA also allows the generic manufacturers to carry out the pre-marketing approval studies on the patented drugs so that they can come up with the generic versions of the drug as soon as the term of protection of the patented drug gets over. Unlike the pre-HWA era, no undue patent extension is now enjoyed by the innovator as the generic versions may be made available as soon as the patent term of the patented product is over. This results in availability of low-cost quality drugs for the consumers immediately after patent expiry.

**GENERAL PROVISIONS OF HATCH WAXMAN ACT**

The generic drug process approval has evolved over the past 40 years. In 1970 FDA established the Abbreviated New Drug Application (ANDA) as a mechanism for the review and approval of generic versions of drug products that had been approved between 1938 and 1962. For drugs approved after 1962 manufacturers of generic drugs were
required to submit complete safety and efficacy through clinical trials. After 1978, however, manufacturers were required to cite published reports of such trials documenting safety and efficacy.

The HWA provides an expedited USFDA drug approval program for speedy generic drugs entry in the market. It provides patent term extension for innovator drugs and Market Exclusivity for the generic drugs manufacturer as an incentive for continued innovation.

The HWA modified the Patents Act of 1952 by statutory exemption of certain provisions related to patent infringement. Although the HWA provides a safe harbor from patent infringement, it requires generic drugs manufacturers to engage in a specialized certification procedure. Under the provisions of the HWA a generic drugs firm must certify its intentions with respect to each patent associated with the generic drug it seeks to market. For a generic drug manufacturer to submit ANDA, four possibilities exist under HWA:

- That patent information on the drug has not been filed, i.e., no patent information appears in the orange book.
- That the patent has already expired.
- That the patent will expire before the marketing of generic drug.
- That the patent is invalid or will not be infringed by the manufacture, use or sale of the drug for which the ANDA is submitted.

These certifications are termed as Paragraph I, II, III, and IV certifications respectively.

Further, each holder of an approved NDA must list pertinent patents it believes would be infringed if a generic drug were marketed before the expiration of these patents. The US FDA maintains this list of patents in its publication, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book.

**PROVISIONS WITH REGARD TO PARAGRAPH IV FILING**

An ANDA certified under Paragraphs I or II is approved immediately after meeting all applicable regulatory and scientific (efficacy, safety and bioequivalence)
requirements. This means that the generic drugs manufacturer may get immediate approval for manufacturing the generic versions of the branded drugs upon filing an ANDA if, the patent information on the branded drug has not been filed by the branded drug manufacturer or if the patent for the branded drug has expired. A Para III filing is made when the ANDA applicant does not have any plans to sell the generic drug until the original drug is off patent. In case of Para III the application is processed for approval, however its approval status depends upon the product’s patent expiry. ANDA approval under Para III certification is made effective from the date of patent expiration.

An ANDA applicant filing a Paragraph IV certification must notify the proprietor of the patent. The patent holder may bring a patent infringement suit within 45 days of receiving such notification. If the patent owner timely brings a patent infringement charge against the ANDA applicant, then the USFDA suspends the approval of the ANDA until: the date of the court’s decision that the listed drug patent is either invalid or not infringed; the date on which the listed drug patent expires, if the court finds the listed drug’s patent is infringed; or the date that is 30 months from the date the owner of the listed drug’s patent received notice of the filing of a Paragraph IV certification (subject to modification by the court). This means that for a maximum period of 30 months from the date of receipt of notice of Para IV filing, no ANDA can be approved.

In other words, once the branded drug company indicates its intent to begin a patent infringement suit against the generic company as a result of the Paragraph IV filing, the USFDA is prohibited from approving the drug in question for thirty months or until such time that the patent is found to be invalid or not infringed. If, prior to the expiration of thirty months, the court holds that the patent is invalid or would not be infringed, then the USFDA approves the ANDA when that decision occurs. Conversely, if the court holds that the patent is valid and would be infringed by the product proposed in the ANDA prior to the expiration of thirty months, then the USFDA does not approve the ANDA until the patent expires. The first generic applicant to file a Paragraph IV certification is awarded a 180-day market exclusivity period by the USFDA. The 180-day market exclusivity period ordinarily begins on the earlier of two dates: The day the approved generic drug is first commercially marketed; or the day a court decision holds that the patent which is the subject of the certification is invalid or not infringed [21 U.S.C. 355(j)(5)(B)(iv)(I) and (III)]. A successful defense of a patent infringement suit is not necessary to obtain this
exclusivity period. ANDA Patent Certification Options and Paragraph IV Certification are depicted in Figures 4.3.1 and 4.3.2 respectively.

PARAGRAPh IV LITIGATIONS

Paragraph IV filings are generally associated with litigations. The issues that arise in ANDA patent infringement litigation are generally the same as those which arise in other patent litigations. One exception is that a patent holder usually cannot recover monetary damages in an ANDA case because the infringement is prospective in nature. This means that within the period an ANDA has been filed by a generic drug manufacturer and an infringement suit is filed by the innovator, no commercial use of the drug takes place. This is the reason why the patent holder does not get any monetary damages.

An act of filing the ANDA with intent of marketing the drug in question before the corresponding patent expires is considered as infringement of that patent. If the owner of that patent files an infringement suit against the generic drug manufacturer, within 45 days of receipt of a notice along with explanation, the USFDA cannot approve the ANDA for thirty months or for such a period as decided by the court involved. The patent owner can sue the generic drug manufacturer even after expiration of the 45 days from the date of receipt of notice but, is not then entitled to de facto preliminary injunction of 30 months.

IMPORTANT INFORMATION ON THE HWACT

The 30-month stay is permitted only once, in case of those patents listed in the Orange Book, when an ANDA is filed under Paragraph IV certification. Modifications to the 30-month stay are allowed based on district court judgments. The generic drug manufacturers filing ANDA under Paragraph IV are required to submit full and complete information over and above what is necessary under current law and must notify the patent owner within 20 days. If the patent owner does not file infringement proceeding within 45 days of notification issued by ANDA applicant, the applicant may request for a declaratory judgment and thus avoid being sued. Even if the applicant is sued, applicant may file a counter claim requiring patent owner to make changes in the Orange Book listings. This favors the patent holder, because he does not have to pay any damages for not modifying the Orange Book listing in time and there is apparently no time limit for making such modifications.
New molecular entities (NME) approved by the FDA will enjoy data exclusivity for a period of 5 years from the date of approval of the NME by the FDA. A generic version cannot be approved during this period. Supplements requiring clinical trials will enjoy 3 years data exclusivity period. The original patent term can be extended by a maximum 5 years, if undue delay takes place during the regulatory process by FDA (Glover, 2007).

PATENT LINKAGE

The most common means of twisting Hatch-Waxman Act in to a vehicle for big pharmaceutical companies to extend exclusivity is through patent litigation. An applicant that files a Paragraph IV certification must notify the patent owner and drug approval holder, and describe in detail the factual and legal basis for the certification that the patent is invalid or not infringed. If the patent owner sues the Paragraph IV ANDA filer within 45 days of being notified of the certification, the FDA will not consider any application related to drug in question for thirty months, essentially granting the patent holder an additional two and a half years of market exclusivity. The entry of generic in the market is delayed.

This encourages a NDA or patent holder to file suit every time any generic manufacturer files a Paragraph IV certification even if the suit would be frivolous, since regardless of the merits of the suit the FDA must automatically grant the stay, blocking all generic competition. This gives FDA extraordinary power to extend the exclusivity granted to a patent. Patents law is not the expertise of the FDA. Therefore, the agency grants the stay without any consideration of the merits of a patent challenge or the validity or the enforceability of the patent in question. The brand name companies enjoy the extension in exclusivity period by even frivolous lawsuits. Even multiple non-concurrent 30 month stays were possible to be applied to a given ANDA applicant.

MEDICARE PRESCRIPTION DRUG, IMPROVEMENT & MODERNIZATION ACT OF 2003 (MEDICARE ACT)

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 have closed some legal loopholes of HW Act that delayed generic drug approval. For example, it allows only one 30-month ‘stay’ of approval of generic when an innovator company sues a generic company over patent issue. According to a Federal Trade
Commission (FTC) study released in 2002, there were cases involving several brand name drugs between 1994 and 2000 in which repeated 30-month stays of approval delayed access to generic drugs. The study concluded that multiple stays can have substantial financial impact and are harmful to consumers. President George W. Bush has stated, “Our message to brand name manufacturers is clear: You deserve the fair rewards of your research and development; you do not have the right to keep generic drugs off the market for frivolous reasons.”

Hatch Waxman provisions in Medicare Act make changes to 30-month stay, 180-day exclusivity and bio-equivalence provisions of Hatch Waxman law, provide statutory authorities for generic companies to seek declaratory judgment on listed patents and impose a new FTC filing requirement in certain circumstance (Melissa, 2004; Sarah, 2003).

30 MONTH STAY PROVISIONS

The Hatch- Waxman Act provides 30 month stay to the patent holder if it brings an infringement suit against the ANDA filer within 45 days of receipt of the notice. Before the Medicare Act, it was possible for multiple non-concurrent 30-month stays to be applied to a given ANDA or 505(b)(2)application. Such non-concurrent 30- month stays significantly delayed the generic approval and entry in the market. The Medicare Act contains a provision that has the effect of granting no more than one 30-month stay of approval per ANDA or 505(b) (2) application. Submission of patent information to FDA before the ANDA application submission was made mandatory to have 30-month stay (Melissa, 2004).

ANTI-BUNDLING PROVISIONS

It aimed to prevent ANDA applicants from circumventing 30-month stay of approval for a drug by adding it to an existing application for a different drug. The amendments or supplements to seek approval of a drug that refers to a listed drug, different from the listed drug in the application except for the different strength of the same drug, is not allowed in the new Act.
TIMINGS OF NOTICE OF PARAGRAPH IV CERTIFICATION

The Medicare Act provides that the ANDA applicant must give notice no later than 20 days after the postmark on the notice from the FDA that the application has been accepted for filing.

DECLARATORY JUDGEMENT PROVISIONS

The Medicare Act provides an express right to file a declaratory judgment action for non-infringement or invalidity of a patent, which however, cannot be filed before expiry of 45 days. Secondly, the notice regarding non-infringement must offer to provide the patent holder with the confidential access to the ANDA or 505 (b)(2) application to enable patent holder to decide whether to bring an infringement action.

PROVISIONS FOR COUNTERCLAIM FOR DELISTING PATENTS

The ANDA applicant can assert a counterclaim seeking an order requiring drug approval holder to correct or delete patent information listed with the FDA for a given product. The Act does not authorize the assertion of such a claim in any other action, i.e., it does not provide for an independent cause of action to de-list or correct the listing of a patent 180-day Exclusivity Provisions.

The first applicant to file Paragraph IV certification is granted 180-days exclusivity to block approval of other ANDA for the same product during 180 days. Now, the FDA has interpreted to mean that any applicant(s) who files a Paragraph IV certification on the first day is “first applicant” allowing two or more applicants to share the exclusivity. Additionally, before the Medicare Act, the FDA determined exclusivity on a patent by patent basis. Exclusivity was granted to all applicants who filed on the first date a Paragraph IV certification for a particular listed patent, even if another applicant had already filed a Paragraph IV certification to another listed patent for the same product. Medicare Act on the contrary provides exclusivity on a product-by-product as opposed to patent by patent basis (Melissa, 2004).

FORFEITURE OF EXCLUSIVITY PROVISIONS

Exclusivity is forfeited if the first applicant fails to market the drug product 75 days after the effective approval of the first application or 30 month after submission of
the first application (whichever is earlier) or 75 days after a decision of a court from which no appeal has been or will be taken.

It may also be forfeited if the application is withdrawn; if the applicant amends or withdraws the certification of all patents that qualified the applicant for exclusivity, or if all such patents expire. It may also be forfeited if the applicant makes an arrangement with another generic applicant, the listed drug approval holder or patent owner.

**FTC REVIEW PROVISIONS**

Medicare Act provides that agreements made after January 7, 2004 between Paragraph IV filers regarding exclusivity or between a Paragraph IV filer and the approval holder regarding exclusivity or the manufacture, marketing or sale of the brand name or generic drug, be filed with the FTC within 10 business days of execution.

**CONSEQUENCES OF HATCH-WAXMAN ACT**

This Act has seems to have served the purposes for which it was enacted as is evident from the steep growth in the availability as well as affordability of generic medicines. There has been an increase in percentage of branded drugs that have a generic competitor in the market. Presently every off patent drug has generic version in the market, as compared to only 36% in 1983 (www.ftc.gov/speeches/leary/ learypharma.shtm).

The Act is being twisted by many pharmaceutical companies for extending the exclusivity through unnecessary patent litigations. As per the provisions FDA does not consider any generic approval application for 30 months; if its patent holder sues the Paragraph IV filer within 45 days eventually granting the patent holder an additional two and half years of marketing exclusivity. This encourages the NDA holders to file suit every time any generic files Paragraph IV certification; even if the suit is frivolous; to get the automatic 30 months stay; blocking generic entry.

Similarly the six month of exclusivity being granted to first Paragraph IV ANDA filer is misused commonly. The 6-month exclusivity begins on court decision or upon the commencement of marketing by the generic. The agreement between the patent holder and the generic company (the alleged infringer) wherein the generic company is paid heavily to defer or abandon marketing generics pursuant to the settlement delays the generic entry.
in the market. Therefore, the exclusivity provided under the Act provides incentives to the
generic and restrain competition in the market.

**DRUG APPROVAL PROCESS IN US**

Unlike the approval process for new chemical entities, that for generic drugs
allows use of the ANDA, which does not require the submission of clinical data regarding
safety and efficacy since this information was already provided for the pioneer product.
Since the original active ingredient was already proven safe and effective, the
manufacturer must now prove bioequivalence for the pharmaceutically equivalent generic
drug product.

In order to receive approval for marketing, a generic drug must meet the same
batch requirements for identity, strength, purity, and quality and be therapeutically
equivalent to the branded product. Additionally, the drug must be manufactured according
to the same Good Manufacturing Practice regulations required by the FDA. For the
generic drug to be therapeutically equivalent, two clinical characteristics must apply: It
must be pharmaceutically equivalent as well as bioequivalent. Pharmaceutical equivalence
means that the active ingredient(s), dosage form, route of administration, and strength are
the same for both the branded product and the generic product. Bioequivalence is when
both products have comparable bioavailability when studied under similar conditions

While pharmaceutical equivalence is relatively easy to comprehend, the concept of
bioequivalence is more difficult to grasp. Bioequivalence is determined by evaluation of
the area under the curve (AUC) and the maximum concentration of drug ($C_{\text{max}}$). A generic
product is considered to be bioequivalent to the pioneer product if the 90% confidence
interval (CI) of the mean AUC and the relative mean $C_{\text{max}}$ is 80% to 125%. This criterion
is the same standard used for testing the bioequivalence of branded products with
reformulation or manufacturing changes. Bioequivalence is determined by conducting
crossover studies of at least 12 patients in which half of the patients receive the generic
drug first and then the pioneer drug, with a washout period in between. The remaining
patients receive the pioneer drug first, followed by a washout period and then the generic
drug. The $C_{\text{max}}$, time to reach $C_{\text{max}}$, and AUC are determined by taking multiple blood
samples from individual patients. Based on the 90% CI, if drug levels vary by more than
10%, failure to reach FDA criteria disqualifies a drug for a bioequivalence rating. According to data for bioequivalence testing performed on 224 drugs after 1962, the mean variation in bioavailability between branded and generic drug products was approximately 3.5% (www.pharmacistsletter.com).

A common misconception in the evaluation of generic substitution relates to therapeutic equivalence. While a generic drug may be bio-equivalent to a branded drug, there is no testing to determine whether generic products are bioequivalent to each other, although it is expected that their efficacy would not differ significantly (www.prescribersletter.com).

NEW DRUG APPLICATION (NDA) APPROVAL PROCESS

Often a drug is developed to treat a specific disease. An important use of drug may also be discovered by accident. For example, Retrovir (Zidovudine) was first studied as an anti-cancer drug in 1960’s with disappointing results. It was in 1980 that the researcher found it useful for AIDS and it was granted approval by FDA in 1987 for this purpose to Glaxo.

Before a new drug can be marketed, federal law requires the submission and approval of form FDA-356h. Before the NDA is filed, an Investigational New Drug (IND) form (form FDA-1571) for the drug must be filed. The specific FDA regulations regarding INDs and NDAs are contained in 21 CFR 312 and 314. The FDA also has provided for the electronic submission of NDA’s. If the FDA does not reject the IND request within 30 days of submission, clinical testing of the investigational drug on human may begin by the IND sponsor. The IND application must include proof of pre-clinical testing of the new drug on animals to substantiate the safety of clinical testing in humans. The sponsor can be drug manufacturer, hospital, pharmacy, physician, pharmacist or anyone who submits the application.

CLINICAL TRIALS

Drug studies in human can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). The board is a panel of scientists and non-scientists in hospitals and research institutions that overseas clinical research.
Phase I of clinical investigation involves a small number of subjects (typically ranges from 20 to 80) in carefully controlled studies of the drug toxicity, metabolism, absorption, and elimination, to determine the preferred route of administration and safe dose. The goal here is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted. The emphasis in Phase I study is primarily on safety. Phase I studies have non-therapeutic objectives and normally carried out in healthy volunteers or certain types of patients.

Phase II involves use of the investigational drug on a limited number of patients for specific disease treatment or prevention, along with additional pharmacological studies on animals to further determine the drug’s safety. The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short term side effects and risks associated with the drug. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment-usually an inactive substance (placebo), or a different drug. Typically, the number of subjects in Phase II studies ranges from a few dozen to about 300.

Phase III trials evaluate whether information obtained from phase I and phase II studies can reasonably ensure the safety and efficacy of the drug or if the drug has a potential value outweighing its possible hazards. These studies gather more information about safety and effectiveness, studying different populations and different dosage and using drug in combination with other drugs. Number of subjects ranges from several hundreds to about 3000.

Phase IV involves post marketing surveillance of the approved drug after approval by FDA for marketing, to detect adverse effects or other problems that were not encountered in the three prior phases of drug testing due to the limited number of patients using the medication. FDA uses post-market requirement and commitment studies to gather additional information about a product’s safety, efficacy, or optimal use.

Informed consent of each study subject or his or her representative must be obtained in writing on ‘Informed Consent Form’ by the investigator before undertaking these studies on human being. He must also provide information about the study verbally as well as using a patient information sheet to the volunteer in the language understandable by him or her.
NEW DRUG APPLICATION (NDA)

This is a formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analysis of the data, as well as information about how the drug behaves in the body and how it is manufactured. The FDA’s Centre for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs for standard drugs no longer than 10 months after the applications are received. This period is six months for priority drugs. The review team analyzes study results and looks for possible issues with the application, such as weakness of the study design or analyses. Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. These evaluations are then considered by team leaders, division directors, and office directors, depending on the type of the application.

Traditional approval requires that clinical benefit be shown before approval can be granted. Accelerated approval is given to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments. Gleevec (imatinib mesylate), an oral treatment for patients with a life threatening form of cancer called chronic myeloid leukemia (CML), received accelerated approval. Most drugs to treat HIV have been approved under accelerated approval provisions, with the company required to continue its studies after the drug is on the market to confirm that its effects on virus levels are maintained and benefits the patient. If the studies do not confirm the initial results, the FDA can withdraw the approval.

DRUG REVIEW STEPS

1. Pre-clinical (animal) testing.


3. Phase I studies (typically involve 20-80 people).

4. Phase II studies (typically involve a few dozen to about 300 people).

5. Phase III studies (typically involve several hundred to about 3,000 people).
The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.

Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.

After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.

If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor’s research on the drug’s safety and effectiveness.

The FDA review information that goes on a drug’s professional labeling (information on how to use the drug).

The FDA inspects the facilities where the drug will be manufactured as part of the approval process.

FDA reviewers will approve the application or issue a complete response letter.

The FDA will terminate the IND approval if, during the clinical testing of new drug, the data furnished to the FDA indicate that the drug is too toxic under the criterion of the FDA’s risk/benefit ratio. The action of the FDA is not subject to court’s review or appeal. If all goes well with the clinical testing, the sponsor of the drug (usually the manufacturer or the supplier) submits a voluminous NDA (form FD-356H) to the FDA wherein the proposed labeling is contained. If approved by the FDA, the package insert will accompany the marketed product in its package.

After the NDA is approved by the FDA, the drug is marketed, but the drug manufacturer’s reporting does not end there. Periodical reporting by the manufacturer to the FDA containing samples of current labeling and advertisements, summaries of medical journal articles on the drug and information on adverse reactions is required.

**GENERIC DRUG APPROVAL PROCESS**

The process of approval of generic medicines ensures that safe and effective generic medicines are available to the American people. The Centre for Drug Evaluation and Research in the Office of Generic Drugs (OGD) is responsible in accomplishing the
task. The application (ANDA) must contain sufficient information to allow a review to be conducted in an efficient and timely manner. Pre-filing assessment of its completeness is carried out and conveyed to the applicant through 'acknowledgement letter' confirming its filing date. 'Refuse to file' letter is sent in case of missing documents or information.

The accepted application is subjected to bio-equivalence and chemistry/microbiology review process wherein it is established that the proposed generic drug is bio-equivalent to the reference listed drug based on both rate and extent of absorption of active ingredients. Under the chemistry / microbiology review the applicant's manufacturing procedures, raw material specifications and controls, sterilization process, container and closure system and stability profiles are reviewed to assure that the generic will perform in an acceptable manner.

Each facility listed on the evaluation request is evaluated individually and an overall evaluation for the entire application is made by the Office of Compliance. It is determined if the product manufacturer, the bulk drug manufacturer and any of the outside testing or packaging facilities are operating in compliance with current Good Manufacturing Practices (cGMP). Pre approval product specific inspection may be performed to assure the data integrity of the application.

The labeling review process ensures that the proposed generic drug labeling is identical to the reference listed product except for the generic characters and manufacturer’s details. The resembling names, designs, legibility or prominence of drug name as well as strength is also examined. In case of deficiency in bio-equivalence review, a deficiency letter is sent to the applicant with details of deficiencies. Similar practice is followed during the chemistry/microbiology review.

On satisfactory bio-equivalency as well as chemistry/microbiology review and pre approval inspection the application undergoes a final office level administrative approval review by all review disciplines without any further deficiencies being noted, the application can be approved. A tentative letter is issued to the applicant detailing the condition of approval, circumstances associated with the approval and delays final approval until all patent/exclusivity issues have expired. A tentative approval does not allow the applicant to market its product. A schematic diagram for the generic drug approval process is given in Figure 4.3.3.
BIOAVAILABILITY AND BIOEQUIVALENCE

Most nations require generic drug manufacturers to prove that their formulation exhibits bio-equivalence to the innovator product. In U.S., the FDA must approve generic drugs just as innovator drugs must be approved. The FDA requires the bioequivalence of the generic product to be between 80% and 125% of that of innovator product (who.int/prequel/infogeneral/document/TRS937/WHO_TRS_annex7_eng.pdf).

Bioavailability is defined as the rate and the extent to which the active drug ingredient or therapeutic moiety is absorbed from the drug product and become available at the site of drug action. Bioequivalent drug products are defined as pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either as a single dose or as multiple doses. The FDA believes that testing healthy volunteers is a strong indicator that the two tested dosage forms will behave the same under the same conditions and that even though the metabolism and absorption rate of drugs in healthy volunteers will differ from the elderly, this does not invalidate the bioequivalence test.

Bioequivalence is determined by conducting cross over studies of at least 12 patients in which half of the patients receive the generic drug first and then the pioneer drug, with a washout period in between. The remaining patients receive the pioneer drug first, followed by a washout period and then the generic drug. The Cmax, time to reach Cmax, and AUC are determined by taking multiple blood samples from individual patients. A generic product is considered to be bioequivalent to the pioneer product if the 90% Confidence Interval (CI) of the mean AUC and the relative mean Cmax is 80% to 125%.

The average difference in absorption in to the body between the generic and branded name was found to be 3.5% in a retrospective analysis comparing the generic and innovator bioequivalence measures from 2070 single dose clinical bioequivalence studies of orally administered generic drug products approved by FDA from 1996 to 2007 and were found comparable to differences between two different batches of a branded drugs (Davit, 2009).
An applicant submitting an ANDA must demonstrate pharmaceutical equivalence (PE) and bio-equivalence (BE), between generic and listed innovator product as per section 506(j) of the Hatch- Waxman Act. The purpose of bioequivalence study is to compare the bio-availability of generic and its branded counterpart and is commonly applied to oral dosage forms. During the study subject drug or its metabolite concentration-time profile is measured to determine the maximum concentration (Cmax), the time the Cmax is observed (Tmax), and the area under the concentration-time curve (AUC) up to last measurable concentration.

**ORANGE BOOK (APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS)**

The Approved Drugs Products with Therapeutic Equivalence Evaluations (the list), identifies drug products approved on the basis of safety and effectiveness by the FDA under the Federal Food, Drug and Cosmetics Act. Drugs on the market approved only on the basis of safety are not included in the publication. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. An online version of the FDA’s Approved Drug Products with Therapeutic Equivalents can be viewed on the FDA’s website at www.fda.gov/cder/ob/.

The 1984 amendment Act required the agency to, among other things, begin publishing an up to date list of all marketed drug products, OTC as well as prescription, that has been approved for safety and efficacy and for which new drug applications are required.

The list is composed of 4 parts:

- Approved prescription drug products with therapeutic equivalence evaluations;
- Approved OTC drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs;
- Drug products with approval under Section 505 of the Act administered by the Centre for Biologies;
- A cumulative list of approved products that have never been marketed, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy subsequent to being discontinued from marketing.
Drug Regulations in Various Countries

The list only identifies the holder of the approved product application in the FDA files. It does not identify the distributor or re-packager of the drug product. The FDA requirement is that every firm marketing generic drug product must have an FDA approved application on file. There is a certain degree of risk (as far as quality is concerned) involved in the use of drug products for which there is no FDA approval.

The FDA’s list entitled Approved Drug Products with Therapeutic Equivalence Evaluations is commonly referred to as “The Orange Book” due to the color of the cover of the publication. The FDA Orange Book serves as the primary source for generic equivalency information and is used by many states as the standards for determining when drug product may be substituted with generic equivalents. Under the 1984 Act manufacturer seeking approval to market a generic product must submit data demonstrating that the drug product is equivalent to the innovator drug product. This drug is referred to as the “reference listed drug” and is identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. A major breakthrough of the 1984 law is that bioequivalent drug products are therapeutically equivalent and, therefore, interchangeable.

THREAT TO GENERICS

- AUTHORISED GENERICS (PSEUDO-GENERICS)

When Congress created the US generic pharmaceutical industry in 1984, it recognized that a mechanism was necessary to ensure that brand products were not unfairly or unnecessarily protected from generic competition by inappropriate or unenforceable product patents. The complex system of brand drug patent approval is premised on what patent information brand companies submit to FDA for each brand pharmaceutical product. Recognizing that this process is not adversarial, and that a check and balance was missing from brand drug patent approval, Congress created the patent challenge process that enabled generic companies to challenge drug patents through litigation that would result in the early introduction of generic medicines if the challenge was successful.

As part of this process, Congress determined that it was in the best interest of consumers to create the 180-day generic exclusivity incentive to encourage generic
companies to challenge questionable or frivolous brand pharmaceutical patents. During the 180-day period, the generic company that successfully challenges the patent in court is exclusively permitted to compete with the brand company. Thereby, the 180-day exclusivity provision establishes a mechanism by which generic companies may recoup the significant costs of investment in product development and patent challenge litigation while also creating an incentive to undertake more patent challenges in the future. Because generic companies operate under significantly smaller margins than brand companies, the 180-day period is a critical time for a generic company.

The 180-day exclusivity provision has successfully accelerated consumer access to affordable medicines. Over the past 20 years, generic manufacturers have undertaken numerous patent challenges as a result of the 180-day exclusivity incentive. Without this incentive to challenge patents, some brand companies would have evergreen patents resulting in lack of access to affordable generic medicines for consumers for many years to come. These successful patent challenges have generated tens of billions of dollars in savings for American consumers.

Large pharmaceutical companies often spend millions of dollars protecting their patents from generic competition. Apart from litigation, companies use other methods such as reformulation or licensing a subsidiary (or another company) to sell generics under the original patent. Generics sold under license from the patent holder are known as authorized generics; they are not affected by the 180 day exclusivity period as they fall under the patent holder’s original drug application.

Authorized generics are a relatively new tactic used by the brand pharmaceutical industry to undermine this incentive and defy Congress’ intent. Authorized generics — brand products masquerading as generics — are an increasingly common brand tactic aimed at discouraging generic companies from challenging questionable brand patents. Determined to maintain their market shares at all costs, brand companies recognized that by simply changing the labels of their products, they could compete directly against the generic during the 180-day exclusivity period. Because FDA considers authorized generics to be brand products, the authorized generic is not subject to the 180-day marketing exclusivity provision. Although the practice might sound relatively benign, these products take advantage of an unintended loophole in federal law that, if left unchecked, could result in fewer affordable medicines coming to market.
An authorized generic is defined by the FDA as "any marketing by an NDA holder or authorized by NDA holder, including through a third party distributor, of the drug product approved under the NDA in a manner equivalent to the marketing practices of holder of an approved ANDA for that drug. It allows the NDA holder to market a competitive product, during the 180-day exclusivity period of the first to file Paragraph IV challenger(s) who is free to market its generic product without the competition from other generics approved subsequently. The branded manufacturer with NDA can either license its products to generic manufacturers or can market the product through an in house generic subsidiary. Thus, the authorized generics are sold under their generic names by or on behalf of brand name companies. Normally these pseudo-generics are sold a few months before any other generics enter the market, a strategy that does cannibalize higher priced brand sales (Hollis, 2005).

An authorized generic is like any other drug marketed in US in so far as it is equivalent to i.e., the same as a branded drug. The authorized generics are fully substitutable for the brand name drugs, but these are not listed in FDA's approved drug products with therapeutic equivalence evaluations (Orange book). These are sold as generics at a discount from the brand name drug.

Successful Paragraph IV ANDA applicants are facing tough competition from authorized generics during the 180-days generic exclusivity period. Keeping in view the expanding generic adoption rate the trend of acquisition of generic firms by brand name firms is on rise and they are more willing to ‘genericize’ their own brands in order to capture a share of that market (Humphries, 2005). Authorized generic versions of most of the drugs with expiring patents have appeared in the market.

The introduction of authorized generics particularly during the 180-day market exclusivity granted to the Paragraph IV challenger thwarts the generic introduction policy as it may discourage Paragraph IV patent challenge if their litigation expenses cannot be recovered through the 180-day market exclusivity period. To cite an example Apotex, a generic manufacturer was entitled to 180-day exclusivity for its version of anti-depressant drug Paxil in the year 2003. Its anticipated sales during this period of 180 days slashed to less than half because of introduction of authorized generic which crippled its sales by the brand company, i.e., GSK.
The authorized generics offer many advantages to the drug companies as well as to the patients as they are less expensive than the brand name drugs. They also provide additional revenue to the brand name companies in the shape of royalty on the sales made by its generic subsidiary. They may also help in settlement of patent infringement suit between generic and brand name firms which may provide for the sale of authorized generics years before the disputed patent is set to expire thus the patient gets early access to cheaper alternative to the brand name drug.

The introduction of authorized generics during the 180-day exclusivity period, which had traditionally been the exclusive domain of the Paragraph IV generic applicant (ANDA IV) has altered the picture by permitting two generic competitors to operate during the 180-day exclusivity period: ANDA IV and authorized generic. The ‘ANDA’ IV would normally price its product just below the brand name’s drug in order to capture tremendous profit.

Ranbaxy laboratories limited and Israel base Teva Pharmaceutical received 180-day exclusivity periods for Simvastatin after US based Merck & Company lost its patent on June 23, 2006 and started marketing of their products. Dr. Reddy’s Laboratories also marketed an authorized generic version of Simvastatin under license from Zocor’s manufacturer, Merck& Co.; some packages of Dr. Reddy’s Simvastatin even show Merck as the actual manufacturer and have Merck’s logo on the pack. The pseudo-generics lead to cost saving for the buyers-consumers, insurers and governments (Hollis, 2005).

The authorized generics practice has proven controversial keeping in view the architecture of the Hatch-Waxman Act which provides for 180-day market exclusivity to successful patent challengers. Their use may discourage Paragraph IV challenges if the litigation expenses of such challengers cannot be recouped through 180-day market exclusivity period. It is still a matter of debate as to whether the authorized generics are reducing the price of generics by encouraging competition or increasing prices by deterring Paragraph IV ANDA certifications.

- **CITIZEN PETITION ISSUES** (Tucker, 2006)

  Citizen petitions are a growing concern not only for the generic industry, but for FDA as well. Every US citizen has a constitutionally protected right to petition the federal
government. However, some brand pharmaceutical companies, their lawyers, or other representatives routinely file citizen petitions against pending generic drug applications on the eve of product approval.

Upon receipt of a citizen petition, regardless of its merits, FDA typically delays approval of the generic drug application until the issue underlying the citizen petition can be reviewed and addressed. The FDA itself has confirmed that there are examples of citizen petitions that appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application, but rather to delay approval by compelling the FDA to take the time to consider arguments raised in the petition, whatever the merits, and regardless of whether the petitioner could have made the arguments earlier.

Generic Pharmaceutical Association has been supportive of a bifurcated system in which generic drug application approvals would not be subject to delay due to pending issues raised in a citizen petition. Both FDA and Congress have recognized the inherent issues related to delaying generic competition through the abuse of the citizen petition process, and U.S. Generic Pharmaceutical Association is working with congressional and administrative leaders to ensure that this process does not delay generic competition.

- **CHALLENGING PATENTS**

Brand name companies use 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 medication, a process referred to by critics as “ever greening”. Patents are typically issued on novel pharmacological compounds quite early in the drug development process, at which time the ‘clock’ to patent expiration begins ticking. Later in the process, drug companies may seek new patents on the production of specific forms of these compounds, such as single enantiomer of drugs which can exist in both “left-handed” and “right handed” forms, different inactive components in a drug salt, or a specific hydrate form of the drug salt. If such forms are granted, these patents, “reset the clock” on patent expiration. These sorts of patents may later be targeted for invalidation (“Paragraph IV certification”) by generic drug manufacturers (http://www.fda.gov/der/ogd/#Paragraph).
FREE TRADE AGREEMENTS

The brand industry does not end its efforts to delay timely generic competition at US borders and has increasingly sought to manipulate free trade agreements as another means of obtaining its goals. Such free trade agreements contain unlimited patent extensions, greater market exclusivity, and elimination of the requirement that a brand company disclose the best mode of practicing its invention: all dramatic divergences from US law.

For example, in Canada, the brand industry is promoting eight years of market exclusivity, which is three years longer than the market exclusivity provision in the North American Free Trade Agreement. In another example, Israel raised the ire of the brand industry by approving a measure that provided for five years of market protection for novel pharmaceutical drugs, even though this very standard is adopted in the United States. In Chile, the brand industry continues to try to impede implementation of a robust generic approval process by pressuring the government to adopt a complex patent linkage system that lacks generic access provisions.

In response, the generic pharmaceutical industry has become even more active on international issues, heading off attempts by the brand industry to make changes in US patent and exclusivity laws under the guise of harmonization with trade agreements. For example, the generic industry has called for clarification of provisions of the Central American Free Trade Agreement (CAFTA) that would have made it more difficult for Central American countries to obtain access to affordable medicines. The industry is also working to prevent the establishment of such provisions in the Colombia, Ecuador, Thailand, Malaysia, Korea, and other FTA negotiations.

OTHER THREATS TO GENERIC COMPETITIONS

Another potential threat to consumers' timely access to affordable medicines is patent reform. Congress has for some time been considering legislation that could make sweeping changes to the way patents are filed and how questionable patents are challenged. Some proposals could weaken the integrity of the US patent system by increasing the length of patent monopolies on expensive, branded drugs by eliminating several defenses to patent infringement currently available to generic competitors.
Reform proposals might also eliminate the 'best mode' requirement, under which the inventor must disclose in the patent application the most efficient known method for producing the invention. Elimination of this requirement would amount to de facto patent extensions, unduly prolonging the brand's monopoly.

Generic Pharmaceutical Association has cautioned Congress on moving too quickly on patent reform and called for careful analysis to ensure that the legislation does not unintentionally harm the healthcare system. GPhA also has focused on reducing some of the red tape that slows imports of active pharmaceutical ingredients (API) and other drug products from reaching their final destinations in a timely manner. The paperwork and documentation involved in bringing API and various drug shipments into the United States has been particularly cumbersome and inconsistent in some US ports of entry. The focus of one proposal under consideration by the industry and FDA would provide assurance on the security of the shipment and prevent counterfeit materials from entering the United States. Companies would provide information on their supply chains to FDA and once FDA determined that the supply chain is authentic, secure, and unadulterated, the shipment would be considered prescreened, receive a lower risk status, and thus, be allowed to proceed without delay. The proposal would apply to both finished drug products and API.

• **A BRIGHT FUTURE, WITH CHALLENGES**

Clearly, America's generic industry is in a golden age. Opportunities to increase substitution based on cost-consciousness will expand. The large number of drugs coming off patent within the next several years will result in intense competition and substantial savings for consumers. And yet untapped opportunities for competition in biopharmaceuticals are likely to dramatically reshape the US prescription drug landscape. While GPhA and the US generic drug industry must continue to thwart efforts by brand companies to delay competition, and continue to work to educate consumers about the value of generic medicines to increase substitution rates, the future, for the next several years, is one filled with opportunities for the generic industry and its allied companies.
CONCLUSIONS

The HWA provides an expedited USFDA drug approval program for speedy generic entry and Market Exclusivity as an incentive for continued innovation. Pre-HWA those seeking to market a generic version of a branded drug also had to carry out their own safety and efficacy studies much like the branded drug companies. Post-HWA for getting the generic approval the generic drug companies are not required to conduct the costly and time consuming clinical trials and tests. The generic drug companies are allowed to rely on the clinical studies done by the branded drug manufacturer. Unlike the pre-HWA era, undue patent extension may be avoided as the generic versions may be made available as soon as the patent term of the patented product is over.

Paragraph IV filings are generally associated with litigations as the patent owner tries to maintain its monopoly by bringing in picture the de facto preliminary injunction of 30 months by commencing an infringement suit against the generic drug manufacturer who applies for the generic version of the patented drug. The HWA also has provision for the generic drug manufacturer to invalidate the patent for branded drugs or at least prove that his generic version will not infringe the patent in question. The HWA also allows for a patent term extension of a maximum of 5 years for the branded drug manufacturer to compensate for the time lost during the NDA approval by the USFDA.

The Medicare Act of 2003, an amended HWA allows only one 30-month stay and permits sharing of 180-day exclusivity by more than one ANDA applicant, if filed on the same day. It define the term ‘first applicant’ to mean all applicants who, on the first day on which a substantially complete generic application with Paragraph IV certification is filed, did themselves file similar application with Paragraph IV certification. The statute therefore, makes clear that multiple first applicants may enjoy “shared exclusivity”. Although generic substitution is allowed in US yet other generic promotional schemes like incentives for generic prescribing/ dispensing, special labeling for generics do not exist under the US laws. There are no provisions for comparative quality evaluation tests on generics and their branded counterparts.

Popularity of generics can be adjudged from the fact that more than 70% of the prescriptions are dispensed in generics in the United States. It is further expected that usage of generic would on rise in view of coming expiry of the patents.
4.4. REGULATIONS ON MEDICINES IN BRAZIL

In Latin America, due to the developing nature of its countries, access to medicines is even more challenging, as affordability plays a major role in blocking medicine purchase. Access to medicines is considered a priority by the Pan American Health Organization, which recommends developing generic drug policies as a means to increase the availability and affordability of essential medicines, and ensuring product quality and safety. Guidelines such as these reflect the common understanding that generics have to be implemented within a strict regulatory framework that goes far beyond labeling and has to include criteria to assess efficacy and safety.

Viewing pharmaceutical spending as a key cost-containment target and access to medicines as a necessary improvement for their healthcare systems, several countries in Latin America have started debating and implementing different measures related to generic medicines. Nevertheless, most of these countries sole aim is one of affordability, and they are failing to introduce a generic policy that also ensures quality. Therefore, untested copies have traditionally dominated these markets — in Brazil, for example, they are called 'similar medicines' and constitute a category apart from the generics, which are always tested for efficacy and safety. The problem of these untested copies is made even worse as some countries call them 'generics'. A closer examination will often reveal that the term is misused, with generics being understood as cheaper, international nonproprietary names (INN)-labeled copy drugs, which have no demand for tests to establish therapeutic equivalence with the innovator drugs. In fact, studies show that the terminology used around generic medicines does vary widely in the region, consequently making it difficult to draw a comprehensive comparison among Latin American countries.

The definitions of generics in Latin America basically have in common the following criteria: same active substance, same dosage, same route of administration, same use. They vary when it comes to labeling (some countries require INN use, while some others allow brands) and efficacy/safety proofs (bioequivalence (BE)/bioavailability standards). Within such scenario, Brazil has a prominent role, being the only country that has built a true generic market based on internationally accepted scientific criteria, [i.e. pharmaceutical equivalence (PE)/BE tests and Good Manufacturing Practices (GMP) certification] used to establish efficacy and safety for copies of innovator medicines and allow full interchangeability.
GENERICS IN BRAZIL

Although there is still a degree of ambiguity over their classification, Brazil has been particularly keen to promote the use of generic medicines. For example, in public hospitals, doctors are now required to prescribe pharmaceutical products by their generic name (international nonproprietary name (INN) instead of by brand name. Although part of the approach of generics policies is to widen access to essential medicines, several government measures appear designed to directly drive down rising healthcare costs. In Brazil, generics are often priced at 60 per cent of their branded counterparts (www.bolentinformacos.org/). The official backing for generic is reflected in the nature of the approval process. The Agencia Nacional de Vigilancia Sanitaria (ANVISA) has visibly increased the number of generics applications that it has approved. The emphasis on generics has led to local manufacturers modernizing their facilities in order to compete for market share (Kermani, 2006). International companies have also taken advantage of the trend and US, Canadian, German and Indian generics companies have achieved success in the Brazilian market. For example, the Indian company Ranbaxy set itself up in Brazil in 2003 and strong sales have led it to become the fifth largest generics company in the country (www.ranbaxy.com/brazil.htm). The Brazilian government has been running a public campaign to educate patients about generics (http://www.boletinformacos.org/). A 2002 survey from the Brazilian Ministry of Health suggested that 95 per cent of Brazilians understood the concept of generics and thus it has been confident concerning uptake (http://www.boletinformaracos.org). The generics market certainly appears to be expanding rapidly in Brazil.

REGULATORY ENVIRONMENT

The Brazilian regulatory pathway for generics started in 1996, with the issue of Law 9279, setting rules for Intellectual Property and patent protection. Previous to this, any innovator drug could be copied — these copies, known as similar medicines, were granted registration by the regulatory agency without any demands for proof of therapeutic equivalence and could be marketed under a brand name or under the INN name.

Three years after rules had been set for patent protection of pharmaceutical products, another law was issued that is considered the milestone for generics in Brazil. Aimed at expanding access to quality-affordable medicines, Law 9779 was promulgated in 1999 as part of a more comprehensive health policy, whose main goals were increasing the
population's access to quality-affordable medicines and improving Brazilian sanitary legislation to a higher requirement level. Introducing tight criteria for generic registration, Law 9779 became the umbrella for a set of different Resolutions issued by Agência Nacional de Vigilância Sanitária (Anvisa; National Health Surveillance Agency) in the following years, presenting more specific guidelines on how generics should be tested, registered and marketed.

2009 marked the 10th anniversary of the Brazilian generic law that introduced the concept of unbranded generics in the country. The main objective of the law was to facilitate access to reliable medicines for a significant part of the Brazilian population who could not afford any medicines at all and to increase competition after patent expiry. February 1999 marked a turning point for unbranded generics in Brazil, with the approval of Law Decree 9787/99 known as the Generic Law, which brought together all the players involved in the issue.

Ten years after the implementation of the Generic Law, generic drug sales are around US$2 billion (14 per cent market share) and approximately 280 million units (18 per cent market share). Eighty-two pharmaceutical companies offer around 2600 products, more than 14000 presentations and have generated cost savings of around 10.3 billion reais ($ 4.12 billion) (Luciano, 2009). In Brazil, there are specific companies that perform bioequivalence studies and which are being used by the pharmaceutical industry.

Four of the six largest pharmaceutical companies in the country are Brazilian and all of them are producing generic medicines. Almost 90 per cent of the generic market is dominated by Brazilian companies, showing that the development of this sector was brought about by laws, well-qualified people and investments. Even so, the Brazilian generic market is only 18 per cent of the total pharmaceutical market so there is still room for growth (Luciano, 2009).

**THERAPEUTIC EQUIVALENCE**

Recognizing PE and BE tests as tools to prove efficacy and safety of a copy drug, ANVISA requires these tests for all generics. The Agency defines the reference products to which generics have to be therapeutic equivalent and also certifies local and international contract research organizations (CROs) through annual inspections. PE/BE tests have to be conducted by certified CROs only.
GOOD MANUFACTURING PRACTICES

The GMP certification is mandatory for generic companies. Local manufacturing plants are annually inspected by ANVISA, which verifies whether drugs are been produced within required quality standards and issues the GMP certificates. Plants abroad are also inspected and certified by ANVISA.

POST-APPROVAL PROCEDURES

In order to assure continuing product quality and performance characteristics of generic drugs, ANVISA has also set rules to control post-approval changes. All modifications introduced in the manufacturing processes must be submitted to the Agency that evaluates their impact and may require that new BE tests be performed.

MARKET MONITORING

As an extra tool for assessing generic quality, ANVISA has also established a monitoring program for generic drugs in commercialization. In coordination with INCQS — Instituto Nacional de Controle de Qualidade em Saúde (National Institute for Quality Control in Health) — the Agency takes samples of generics and their innovator counterparts from the market. Such samples are used to repeat the PE tests in the LACENS — Rede de Laboratórios Centrais dos Estados (States Central Laboratories Network), and the results are officially published.

PACKAGING

INN labeling is mandatory for generics in Brazil — brands are not allowed. Generic cartons must also display a distinctive yellow stripe with a letter G and words ‘Generico’ (generic) (Figures 4.4.1 & 4.4.2). These characteristics were introduced in order to allow a better identification of generics by consumers, and are especially important to distinguish generics from similar drugs (branded, untested products) (Valente, 2006).

PRESCRIPTION AND DISPENSING

The law enforces INN prescriptions only for the public sector — at private healthcare level, physicians are free to prescribe by brand or generic names. For generic dispensing, interchangeability is legally established as an exclusive prerogative —
pharmacists can substitute prescribed medicines for corresponding generics. The generic prescription in Brazil is very low, i.e., 20% which is because of prescribing habits of the physicians, which are slower to change.

**PRICING**

Brazilian law requires that generic prices be at least 35 per cent lower than the reference drug prices and such prices have to be pre-approved by a governmental drug committee. Owing to market competition, generic price reduction is, in fact, higher — 45 per cent in average, reaching 70–80 per cent in some cases.

**SIMILAR DRUGS REGULATION**

With the advent of generics, the situation of similar medicines (untested copies of innovator products) became a pressing issue. Such products had historically thrived under a more lenient regulatory framework, with no requirements for tests to prove their therapeutic equivalence to reference drugs. In 2003, ANVISA issued a resolution, introducing PE and BE demands for similar drugs. Products registered before 2003 have been granted an adaptation period and will have to present test results according to a schedule that goes up to 2014.

All these characteristics place Brazil in a leading regulatory position in Latin America. Mexico is also worth mentioning, with a regulation for its 'genéricos intercambiables', but, in spite of that, the country lacks a policy to stimulate generic dispensing (studies show that Mexican generics cannot be dispensed when a prescription mentions a brand name).

**GENERIC PRESCRIPTION**

As previously mentioned, physicians in the private healthcare system are not required to prescribe generics, which have a general prescription share of 16 per cent. Nevertheless, recent data indicate that INNs start to lead prescriptions for some substances, hinting on physicians growing acceptance of generics.

Even so, the market share of 18 per cent was achieved through (1) providing technical information to physicians to increase generic medicines’ prescriptions (nowadays only 20 per cent of prescriptions have the INN), and (2) promoting legislation,
which means that the reference drug may only be interchangeable with a generic medicine. Pró Genéricos conducted research among pharmacists and drugstore employees, which concluded that 67 per cent of them do not substitute the reference drug with the corresponding generic medicine, even when applicable, and that in many cases the 33 per cent that is doing it does not offer the generic medicine (Luciano, 2009).

**GENERIC-PROOF MARKET SEGMENTS**

Brazilian sanitary legislation has established some exclusion categories for generics. One such category comprises oral contraceptives and hormones, which are expected to be allowed generic registration by ANVISA in 2006. Such regulation is highly anticipated by generic companies, as contraceptives are currently the leading therapeutic class in volume and the runner-up in value, with annual sales of US$421m (Valente, 2006).

**ABSENCE OF CO-PAYMENT OR RE-IMBURSEMENT PROCEDURES**

In Brazil, Agência Nacional de Saúde Suplementar (National Supplementary Health Agency) data point to a share of 20 per cent of the population as insured by the private healthcare system, with the remaining 80 per cent relying on the public sector for health treatments. Even though both public and private healthcare providers are focused on achieving cost savings and become increasingly aware of the fact that untreated patients today may lead to higher costs in the future, the burden of medicine purchase still lies with the patients (Valente, 2006).

**THE FUTURE OF GENERICS**

The generic market is estimated to be about 750 million reais ($300 million) and the companies interested in launching these products are preparing to deliver generic medicines the day after the corresponding patents expire. It is important to remember that the generic law set a deadline of 6 months from the date that the approval is granted for launching the generic medicine, otherwise it loses its registration. It is worth mentioning that although patent owners are interested in being granted all the patent rights as set in international laws, some of them try to postpone their expiration and they use all the tools at their disposal to get such extensions. In Brazil the discussions are focused mainly on two issues: second clinical use and polymorphism (Luciano, 2009).
Since the approval of Law 9279/963 Brazil is complying with all its international obligations under the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), and all the companies are complying with the standards set in that law. Nevertheless some companies are trying to extend patent terms arguing that the products have other clinical uses than the original one and/or by developing polymorphic forms. Brazil's Industrial Property Institute (Instituto Nacional de Propriedade Industrial – INPI) had been granting the extensions for the corresponding patents. However, in 2001 the Brazilian Congress passed Law 101964 giving ANVISA a role in this process, as before a patent is granted by INPI ANVISA must now analyze and certify that such patent is rigorously and legally correct.

The Brazilian government is an important buyer of drugs and procurement is done at three levels, District, State and Federal, all of which buy reference drugs, branded drugs and generic drugs. Such drugs are used in public hospitals and Basic Health Units, which are a part of the Unified Health System (Sistema Unico de Saúde (SUS)). In some cases, the government finds differences between the prices of drugs bought through public biddings and the price charged in the private sector (national or international). In specific cases, the government resorts to the flexibility provided under Article 31 of the TRIPS Agreement. Indeed, the government may invite manufacturers to negotiate the price of drugs at competitive levels, but if the negotiations are unsuccessful the government may issue a compulsory license, as it occurred in the case of Efavirenz (Luciano, 2009).

At this time, as the international economic crisis spreads throughout the world, it is unclear whether the government and the industry will change their plans. Another way to increase drug access is through the so-called ‘Programa Farmácia Popular’ (Program of Popular Pharmacies) according to which the government pays 90 per cent of the price while the consumer pays the remaining 10 per cent. Drugs for hypertension, diabetes and contraceptives are commercialized in this way. Any private pharmacy in the country can participate and some public pharmacies have already joined the program as well (Luciano, 2009).

**CONCLUSION**

Brazil exhibits best policies for generic promotion in the country. The 1999 law was the landmark in the history of Brazil for the growth of unbranded drugs in the country.
The Brazilian law requires that generic prices to be at least 35% lower than the reference drug prices and such prices have to be pre-approved by a governmental drug committee. Owing to the market competition, generic price reduction is, in fact, higher-45 per cent in average, reaching up to 80 per cent in some cases. The doctors in public facilities are required to prescribe generic medicines only. The pharmacists can substitute prescribed medicines for corresponding generics. Even some of the categories like contraceptives are marketed exclusively as generic products.

The generic medicine carry unique identification mark for its identification and INN labeling is mandatory for generics in Brazil. ANVISA has established quality monitoring program for generics in the country. Samples of generics and their equivalent innovator counterparts are taken from the market to repeat the pharmaceutical equivalence (PE) tests and the results are officially published. In spite of the enormous generic promotional strategies the overall generic prescription is still low in Brazil (<20%). Therefore, there is ample scope for increasing generic prescription and dispensing in Brazil.

4.5 REGULATIONS ON MEDICINES IN AUSTRALIA

The objective of the Therapeutic Goods Act 1989 ('the Act') is to provide a national framework for the regulation of therapeutic goods in Australia, so as to ensure their quality safety efficacy, where appropriate, and timely availability. The regulatory framework within which the Therapeutic Goods Administration (TGA) operates is based on a risk management approach. It is designed to ensure public health and safety, while at the same time freeing industry from any unnecessary regulatory burden and minimizing the cost of medicines regulation.

Essentially therapeutic goods must be entered on the Australian Register of Therapeutic Goods (ARTG) before they can be supplied in Australia. The ARTG is a computer database of information about therapeutic goods for human use; approved for supply in, or exported from, Australia. The Therapeutic Goods Act 1989, Regulations and Orders set out the requirements for inclusion of therapeutic goods in the ARTG, including advertising, labeling, product appearance and appeal guidelines. Some provisions such as the scheduling of substances and the safe storage of therapeutic goods are covered by the relevant State or Territory legislation. The Therapeutic Goods Administration is a unit of
the Australian Government Department of Health and Ageing and is responsible for administering the provisions of the legislation.

DEFINITION OF THERAPEUTIC GOOD

A 'therapeutic good' is broadly defined as a good which is represented in any way to be, or is likely to be taken to be, for therapeutic use (unless specifically excluded or included under Section 7 of the Therapeutic Goods Act 1989).

For the purpose of evaluation and assessment, a therapeutic good is a product for use in humans that is used in, or in connection with:

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury;
- influencing inhibiting or modifying a physiological process;
- testing the susceptibility of persons to a disease or ailment;
- influencing, controlling or preventing conception;
- testing for pregnancy; or
- Replacement or modification of parts of the anatomy.

REGULATING MEDICINES

Australian manufacturers of all medicines must be licensed under Part 4 of the Therapeutic Goods Act 1989 and their manufacturing processes must comply with the principles of GMP (Good Manufacturing Practice). Medicines assessed as having a higher level of risk (prescription medicines, some non-prescription medicines) are evaluated for quality, safety and efficacy and are registered on the ARTG. Medicines having a lower risk (consumer medicines purchased over the counter such as complementary medicines including vitamins) are assessed for quality and safety. In assessing the level of risk, factors such as the strength of a product, side effects, potential harm through prolonged use, toxicity and the seriousness of the medical condition for which the product is intended to be used, are all taken into account. Once approved for marketing in Australia, medicines are included in the ARTG and can be identified by the AUST R number (for registered medicines) or an AUST L number (listed medicines) that appears on the packaging of the medicine.
ROLE OF THE TGA

The TGA carries out a range of assessment and monitoring activities to ensure that all therapeutic goods available in Australia are of an acceptable standard. At the same time, the TGA aims to ensure that the Australian community has access, within a reasonable time, to therapeutic advances.

Overall control of medicines is exerted through five main processes:

- pre-market evaluation and approval of registered products intended for supply in Australia;
- development, maintenance and monitoring of the systems for listing of medicines;
- licensing of manufacturers in accordance with international standards of Good Manufacturing Practice;
- post-market monitoring, through sampling, adverse event reporting, surveillance activities, and response to public inquiries; and
- The assessment of medicines for export.

ROLE OF THE SPONSER

Under the Act, a 'Sponsor' is someone who: imports therapeutic goods; manufactures therapeutic goods; has therapeutic goods imported or manufactured on their behalf, or exports therapeutic goods from Australia. The sponsor of a medicine is the person or company responsible for applying to the TGA to have their medicine included in the ARTG (www.tga.au/docs/html/artg.htm).

AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

The ARTG is established under Part 3 of the Act. It includes a computer database of information about therapeutic goods for human use which are approved for supply in, or export from, Australia. All medicines manufactured for supply in Australia must be listed or registered in the ARTG, unless they are specifically exempt or excluded.

WHETHER A PRODUCT IS LISTED OR REGISTERED IN THE ARTG DEPENDS LARGELY ON THREE THINGS:

- the ingredients;
- the dosage form of the product; and,
- the promotional or therapeutic claims made for the product.
In assessing the level of 'risk', factors such as, the strength of a product, side effects, potential harm through prolonged use, toxicity, and the seriousness of the medical condition for which the product is intended to be used are taken into account.

RISK MANAGEMENT APPROACH

The TGA uses a 'risk-management' approach to regulating medicines supplied in Australia. This refers to the level of scrutiny applied to individual applications for inclusion in the ARTG. Medicines used to treat serious conditions, or which need to be used under a doctor’s supervision, are subjected to a high level of scrutiny and evaluation to determine their quality, safety and efficacy. Other products, for example many complementary medicines (such as herbal, vitamin and mineral products), are not generally subject to the same level of evaluation and are assessed only for quality and safety.

RISK ASSESSMENT

A product’s ‘risk’ is determined by a number of factors, including whether:

• the medicine contains a substance scheduled in the SUSDP;
• the medicine’s use can result in significant side effects;
• the medicine is used to treat life-threatening or very serious illnesses;
• There may be any adverse effects from prolonged use or inappropriate self medication.

Risk is not an absolute concept. It is an assessment of the potential of a product to do harm to those it is intended to help, or to others (such as children) who may come in contact with it regardless of whether the harm results from following or disregarding the directions for use.

LISTED MEDICINES

Listed medicines are considered to be of lower risk than registered medicines, so the Regulations allow sponsors to 'self assess' their products in some situations. The majority of listed medicines are self-selected by consumers and used for self-treatment. Listed medicines may only contain well known established ingredients, usually with a long history of use, such as vitamin and mineral products or sunscreens. They do not contain substances that are scheduled in the SUSDP.
Listed medicines are assessed by the TGA for quality and safety but not efficacy. This means that the TGA has not evaluated them individually to see if they work. It is a requirement under the Act that sponsors hold information to substantiate all of their product's claims. Guidelines for levels and kinds of evidence to support indications and claims are available. Most complementary medicines (e.g. herbal, vitamin and mineral products) and sunscreens are examples of listed products. The medicines, which are for export only are listed (not registered) on ARTG. All listed medicines must display an "AUST L" number on the label as proof of listing.

REGISTERED MEDICINES

Medicines assessed as having a higher level of risk must be registered (not listed). The degree of assessment and regulation they undergo is rigorous and detailed, with sponsors being required to provide comprehensive safety, quality and efficacy data. All registered medicines must display an AUS R number on the label as proof of registration and are evaluated as either 'high risk' or 'low risk' registered.

NON-PRESCRIPTION (LOW RISK- REGISTERED)

- Follow the route of evaluation described in Part 2 (non complementary), or Part 3 (complementary) of Schedule 10 of the Therapeutic Goods Regulations;
- Do not include ingredients described in Schedule 4, Schedule 8, or Schedule 9 of the SUSDP;
- Usually contain ingredients which are described in Schedule 2, Schedule 3, or sometimes Schedules 5 or 6 of the SUSDP;
- Are available without prescription;
- Examples: Mild analgesics, cough/cold preparations, anti-fungal creams.

PRESCRIPTION (HIGH RISK- REGISTERED)

- Follow the route of evaluation described in Part 1 (mainly prescription) of Schedule 10 of the Therapeutic Goods Regulations;
- May include ingredients described in Schedule 4, Schedule 8 or Schedule 9 of the SUSDP;
- Are usually only available on prescription;
- Examples: all prescription medicines; all injectables (e.g. Insulin for diabetics).
COMPLEMENTARY MEDICINES

Complementary medicines (also known as 'traditional' or 'alternative' medicines) include vitamin, mineral, herbal, aromatherapy, and homoeopathic products. Complementary medicines may be either listed or registered, depending on their ingredients and the claims made. Most complementary medicines are listed in the ARTG and some are registered.

EXEMPT OR EXCLUDED MEDICINES

All medicines manufactured for supply in Australia must be listed or registered in the Australian Register of Therapeutic Goods (ARTG) unless they are exempt or excluded.

EXCLUDED MEDICINES

Some products (mostly therapeutic devices, rather than medicines) may be unintentionally covered by the definition of a Therapeutic Good. They are therefore specifically excluded under section 7 of the Act. None of the requirements of the Act apply to excluded products. An example of an excluded good is un-medicated soap.

EXEMPTED MEDICINES

Some medicines do not need to be registered or listed in the ARTG as a result of a specific exemption or determination. However, it is important to note that all other applicable requirements under the Act and Regulations (e.g. standards and advertising or labeling) must be complied with. Examples of exempted medicines are homeopathic medicines and certain shampoos for the treatment/prevention of dandruff (http://www.tga.gov.au/docs/pdf/argemp4.pdf).

STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS (SUSDP)

The SUSDP is the document through which a uniform national approach to medicine availability, labeling and packaging is achieved. Most medicines contain substances listed in the SUSDP (or covered by its provisions), and are grouped into 'Schedules' according to the appropriate level of control required over access and availability to protect public health and safety. This classification process takes into account a substance's toxicity profile, pattern of use, indications, product formulation and dosage, potential for abuse and need for access.
Drug Regulations in Various Countries

The categories of the SUSDP which are most relevant to medicines on the ARTG are:

- Schedule 4 (S4) - prescription only medicines;
- Schedule 3 (S3) - non-prescription medicines for supply by pharmacists only;
- Schedule 2 (S2) - non-prescription medicines the safe use of which may require advice from a pharmacist;
- Schedule 8 (S8)-Controlled Drugs.

Some medicines are also included in Schedules 5 and 6 of the SUSDP, for example head lice preparations and some essential oils. Schedules 5 and 6 list substances with a low to moderate potential for causing harm, the extent of which can be reduced through the use of appropriate labeling and packaging.

The SUSDP affects the supply, labeling, packaging and availability of medicines and is given legal effect by State and Territory legislation. Medicines which are not scheduled in the SUSDP can be sold through any distribution outlet, such as a supermarket or health food store (www.tga.gov.au/ndpsc/susdp.htm). However, some unscheduled or exempt medicines may be covered by labeling or packaging requirements specified in the SUSDP (e.g. some paracetamol and iron preparations). Examples of medicines which are unscheduled include small packs of simple pain relievers, and most vitamins and minerals.

MANUFACTURING REQUIREMENTS

Australian manufacturers of therapeutic goods must be licensed under Part 4 of the Act. Their manufacturing processes must comply with the principles of GMP (Good Manufacturing Practice). The aim of these licensing requirements and standards is to protect public health by ensuring that medicines meet defined standards of quality and are manufactured in conditions that are clean and free of contaminants. GMP requirements apply irrespective of whether a good is listed, registered or exempt.

ADVERTISING AND LABELING

The Act and its associated Regulations govern the appearance and content of labels and advertising, for which there is a specific Therapeutic Goods Advertising Code.
RECENT POLICY REFORMS IN AUSTRALIA

Prescription drug sales in Australia at around US$8 billion constitute a small share of the US$800 billion global market. Yet Australia is a high income economy with strict regulatory requirements closely monitored by drug policy analysts and the pharmaceutical industry (Lofgren, 2009). Prescription medicines are subsidized by the Commonwealth (federal) government through the Pharmaceutical Benefits Scheme (PBS). The PBS is designed to ensure ‘timely access to the medicines that Australians need, at a cost individuals and the community can afford’ and forms a central component of the National Medicines Policy (http://www.health.gov.au/internet/wcms/publishing.nsf/Content/nmp-objectivespolicy.htm). Through the PBS the government exercises strong market power which has delivered, for decades, relatively low prescription drug prices. The design of the scheme precludes effective price competition and generics prices historically approximated those of originator brands. Consequently, the Australian market was until recently, the almost exclusive preserve of the big brand companies. The generics sector remains small, in both value and volume terms, by comparison with economies such as the US and the UK, though policy changes and the increasing availability in international markets of cheap generics ensure an expanding role for generics also in Australia (Bulfone, 2009; Hassali et al., 2004; Lofgren, 2004). In response to escalating health costs, and patents expiring on many big products, the Department of Health and Ageing (DoHA) had been searching for ways for tax payers and consumers to benefit, to a greater extent than hitherto, from low cost generics. The result was a major policy reorientation in 2007 aimed at driving down generics prices.

PRESCRIPTION DRUG REGULATION AND THE ROLE OF GENERICS

Australia’s system of drug regulation encompasses two major steps. Medicines must first be entered on the Australian Register of Therapeutic Goods (ARTG) following approval by the Therapeutic Goods Administration (TGA) for acceptable quality, safety and efficacy. Generic products are assessed by the TGA for bioequivalence with the originator brand through a process of rigorous scientific evaluation normally completed within 45 working days (McLachlan et al., 2007). For bio-similar, the TGA has adopted the guidelines of the European Medicines Agency (EMEA) and each submission is assessed on a case-by-case basis. Patent rights extend beyond those mandated by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) to include a
five-year data exclusivity period, precluding data submitted to the TGA relating to a pharmaceutical product from being used by another company in applying for marketing approval until five years after approval of the original product. Moreover, patent extensions of up to five years are available for pharmaceutical standard patents, under certain circumstances, to compensate for delays in the marketing approval process. Such extensions are not available in countries such as New Zealand, Canada, South Africa, China or India (Kumar, 2009). Generics can also not be produced for exports whilst patents still apply in Australia. This latter constraint "places Australian generic manufacturers at such a disadvantage, even relative to generic manufacturers located in the US, Canada or Western Europe, that global companies are actively choosing their non-Australian facilities to manufacture new products."

Following marketing approval, companies in most cases apply for PBS listing. This is normally required for sales to be commercially viable, making the prescription medicines market to all intents and purposes synonymous with the PBS. This is an uncapped scheme introduced in the early 1950s to provide all residents, irrespective of financial circumstances, with timely access to necessary medicines (Sansom, 2004). More than 70% of all dispensed prescriptions are subsidized under the PBS, at a cost to tax payers of about AUS$7 billion in 2007-08. In July 2008, 641 medicines, in the form of 2,995 branded products, were available through community pharmacies under normal PBS arrangements. The government is responsible for approximately 85% of the total cost of the PBS, with the remainder paid through patient co-payments (complemented by safety net provisions). Co-payments in 2009 were AUS$32.90 for general patients and $5.30 for pensioner and other concessional categories. Many products, particularly generics, are priced (for general patients) below the co-payment, a trend reinforced by the 2007 changes described below. In these circumstances no subsidy takes effect, which gives pharmacists discretion to determine the price to the customer (Sweeny, 2009). There are close to 5,000 community pharmacies operated as small business enterprises, which draw for most of their revenue on fees and charges, negotiated with the government, for dispensing PBS products. The pharmacy owners are represented by a politically influential lobby group, the Pharmacy Guild of Australia (PGA) (Beecroft, 2007). New PBS listings require a recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC), an independent statutory body, to the Minister of Health and Ageing. Before the listing of a new drug, a price acceptable to the government is negotiated with the supplier through the
Pharmaceutical Benefits Pricing Authority (PBPA) (Sansom, 2004). The principle of reference pricing is central to the PBS, that is, products that (in the judgment of the PBAC) produce similar health benefits are subsidized at the same level. In other words, the government subsidizes ‘each of the available brands to the level of the lowest priced brand’.

In therapeutic group (groups of non-identical drugs with similar safety and health outcomes) and multi-brand markets, companies are at liberty to charge a price higher than the lowest priced brand, with patients then paying, in addition to the co-payment, a brand or therapeutic group premium (Tatchell, 2009). A space for the generic sector was first opened up with the introduction of brand substitution by pharmacists in 1994 (Lofgren, 2004), and subsequent policy changes have progressively widened the commercial potential of consumers avoiding brand premiums by choosing a brand priced at the base rate. Where a prescription has been issued for a product with a price premium, the pharmacist can at the patient’s request dispense another brand of the same medicine, unless the prescribing doctor has specifically indicated otherwise. About 55% of all PBS prescriptions are substitutable, yet only 33% are substituted– the difference points to the potential for further generics growth through substitution (even in the absence of additional medicines coming off patents (Lofgren, 2009).

With weak incentives for prescribers and consumers to choose generics, the discounts served as an incentive for pharmacists to drive generic substitution. That the cost benefits of cheaper generics were flowing to pharmacists while PBS prices continued to approximate those of the originator brands became increasingly unpalatable to the government. This formed the context for recent changes to the PBS, which radically extend an earlier policy measure (introduced in 2005) which mandates that the first new generic brand of a medicine already listed on the PBS must be priced at least 12.5% below the current lowest priced brand. Reference pricing then ensures that the price cut flows through to other brands of the same product and to products linked in Therapeutic Groups. The keep premise of the complex reform legislation introduced in 2007 was to promote generic medicines through PBS (De Boer, 2009). The PBS was break-up in two formularies from August 2007: F1 encompassing single brand drugs, in most cases under patent and F2, comprising multiple brands (Faunce et al., 2007). Mandatory price cuts were imposed on all F2 drugs on 1 August 2008.
THE GENERICS BUSINESS IN AUSTRALIA

It is estimated, as noted, that around 30% of PBS prescriptions are dispensed with a generic, representing between 10% and 15% of the value of PBS sales (Nicholson, 2008). Several leading brand companies are also major generics suppliers, most significantly Novartis through its Sandoz division. The use of authorized or pseudo-generics is common practice, that is, products cross-licensed by a brand company to a specialized generics supplier, or marketed by an originator company by a subsidiary under a different name (Probyn, 2004). Around 20% of all generics available in Australian community pharmacies are estimated to be in this category, which includes re-packaged versions of major products such as Ventolin, Losec, Valium, Normison, Augmentin and Prozac. Repackaged is the key term – pseudo-generics are not bio-equivalent alternative brands but by definition identical to the originator product, typically from the same production line (Hess et al., 2005). The extent of this practice can be gauged from the estimate that ‘of the 300-plus products sold by Alphapharm, the nation’s biggest generic drug company, quarter is made by other companies’ (Lofgren, 2009). Pseudo-generics are the subject of legal and political controversy in the USA but in Australia it is a phenomenon yet to be systematically investigated (Chen, 2007).

CONCLUSION

The generics sector is an established and growing segment of the Australian drug market and the PBS changes initiated in 2007 will accelerate this process. Following the introduction in 1994 of brand substitution, the major impediment to the growth of the generics sector, due to small price differentials, was the absence of incentives for doctors, pharmacists and consumers to choose generics. Recent changes do not significantly address the role of prescriber and consumer incentives, but will make dispensing pharmacists more inclined to support generic substitution. However the direct cost benefits to government are arrived at through mandatory price cuts and price disclosure requirements. These steps in conjunction with coming patent expiries will significantly increase over the next decade, the market share of generics from the present level of around 30% of dispensed PBS drugs. However, the generics market is distorted by the dominance of a small group of suppliers and cross-licensing (pseudo-generic) arrangement with the major brand companies.
4.6 DRUG REGULATIONS IN CHINA

In China the Drug Administrative Law (2001) authorizes the State Food and Drug Administration (SDFA) created in 2003 by replacing State Drug Administration (SDA) to approve ‘new drug’ for marketing as ‘Licensing Authority’. Mainly there are three types of drug approval applications; new drug application; generic drug application and imported drug application. Pre-clinical as well as clinical studies are mandatory for the New Drug Approvals; however, in case if the drugs are already available in US/EU and are imported in China, such studies are not mandatory [http://www.eng.sfda.gov/]. ‘New drug’ as per Article 8 of Chapter II of the regulations refer to the drugs that have not been marketed in China. In case of change in the route of administration, type of preparation or change in indications also, it will be viewed as ‘new drug’.

Generic pharmaceuticals refer to pharmaceuticals for which the regulatory authorities has already established a technical standard, i.e., ‘drugs with existing state standard’, generally require no clinical trials. The procedure for approval and registration of both new as well as generic drugs is similar. Application for drug registration is received by the Provincial Drug Administration Authority (PDAAs) who after reviewing the application and onsite inspection send the qualified application to SDFA. The import drug registration application are submitted directly to the SDFA, which are then transferred to the Centre for Drug Evaluation (CDE) directly attached to the SDFA, which determines whether the safety and effectiveness information submitted for a new drug are adequate for marketing/manufacturing approval and send the report to SDFA, who takes the final decision about the approval and issue a certificate.

The applicant is required to provide information on patent status of the drug, its formula, manufacturing process and/or uses etc., and a statement of non-infringement. For a drug patented in China, the application can be submitted for registration two years before the expiry of the patent. The regulatory authority also allows research/ other relevant data of overseas drug research institution for registration (Zhen, 2003). While submitting application, the applicant is required to submit a statement that the application does not constitute patent infringement as per Article 11 of the patent law. The parties may settle through negotiations if any infringement dispute arises after the approval as per Article 12 or file a civil suit at the relevant authority. Further the patentee after the final favorable
judgment may file for cancellation of the approval received by the infringement party (www.kingandwood.com).

GMP compliance is mandatory in China and the SDFA has been closing down manufacturers that do not meet the GMP standards. China has established a physician licensing system, which requires them to obtain license to practice medicines. Majority of the pharmaceutical companies are generic and traditional Chinese drug manufacturers (http://en.wikipedia.org/wiki/Pharmaceutical_industry_in_China).

In China, drug administration departments are established at both central and regional governmental level. Every region has a regional drug administration department with some authority and power. Complex regulatory process induces excessive exploitation of regional administrative power. Before the revision of Chinese Pharmaceutical Law in 2001, the province drug administration was assigned with authority to streamline the process of registering a generic drug. After the allocation of authority of approval right of opening drug companies was taken down to provincial level several years ago, a sharp increase in the number of drug companies was noted. It was reported that 70 new drug production enterprises were approved to open during the first half of 2003, while only 45 similar enterprises were approved to open during the three years from 1998 to 2001.

REGULATORY AGENCIES

State Food and Drug Administration: As part of the government restructuring announced in March 1998, the Ministry of Health's Department of Drug Administration merged with the State Pharmaceutical Administration of China (SPAC) to become the State Drug Administration (SDA). As a result, SDA oversees all drug manufacturing, trade, and registration. In 2003, the SDA was restructured to become the State Food and Drug Administration.

The Chinese government's establishment of a single drug regulatory authority was an important step toward foreign access, because it eliminated the conflicting standards that prevailed among provincial government agencies, centralized the Chinese healthcare regulatory system, and made it more transparent. SFDA now oversees all medications as well as advertising and its new regulations follow FDA's model. In July 1999, as part of medical insurance reform, SFDA released its first list of over-the-counter (OTC)
medications, and in 2000, the State began to regulate OTC and prescription drugs separately. SFDA did so to encourage patients to purchase OTC medicines for less serious diseases, thereby reducing government medication expenditures and hospital visits.

In 2005, SFDA launched a regulation on drug research and supervision management aimed at enforcing GLP to investigative drugs, traditional Chinese medicine injections and biotechnology products. The regulation aims to help China’s drug research and development gain international recognition.

REGULATORY REQUIREMENTS

China quickly advanced its pharmaceutical-related regulations around the time of its December 2001 entry into the World Trade Organization (WTO). China has strengthened patent protection. In conformity with the WTO/TRIPS agreement, the patent protection structure adopted by China approaches that of Japan, Europe, and the US. Since the end of the 1990s, the government has been striving to develop a healthcare insurance system that covers 200 million Chinese. Already, 90% of the population in major cities like Shanghai, Beijing, and Guangzhou are covered, for a total of over 80 million. The Pharmaceutical Management Law was overhauled in December 2001 and various regulations were enacted from 2002-2003. Transparency in the approval process is gradually improving.

In accordance with WTO regulations, China has committed itself to cutting tariffs, liberalizing its domestic distribution practices, and restructuring its regulatory environment. China has allowed foreign enterprises to import products and engage in distribution services. Furthermore, China has also implemented new drug administration laws designed to streamline product registration and protect Intellectual Property Rights (IPR). China has agreed to six years of "data exclusivity" and has committed itself to implementing a patent linkage system. The SFDA has worked to crack down on counterfeiters but without greater resources and stricter legal consequences these actions alone have yet to be enough to curb this rampant problem.

GMP COMPLIANCE CERTIFICATION

GMP is a system to ensure products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any
pharmaceutical production that cannot be eliminated through testing the final product. A
directive circular issued by the Ministry of Health in July 95 marked the official launch of
GMP certification in China. The China Certification Committee for Drugs (CCCD) was
established in the same year. A subsidiary organization was also set up to manage the
certification program.

Currently nine government agencies are the key agencies responsible for
regulation. They are the State Food and Pharmaceutical Administration (SFDA), the State
Development and Reform Committee, the Commerce Ministry, the State Traditional
Chinese Medicine Administration, the Ministry of Labor and Social Security, the Ministry
of Health, the State Population and Family Planning Committee, the Ministry of Science
and Technology, and the State Quality and Technology Supervision Administration.

China is following and copying US rules. Chinese regulations affect nearly every
aspect of drug manufacturing, from the design and construction of manufacturing facilities
to the development of procedures and the training of operations personnel performing
them. There is only federal regulation on new drug application, but there are both local
regulation and national regulation regarding pharmaceutical expenditures of hospitals,
reimbursable drug lists, and other issues. National regulation is implemented by SFDA
and other State agencies, while local regulation is implemented by provincial agencies.
There is a mechanism for approving new drugs (from NDA filing to approval). A full
three-phase research trial takes three to five years, similar to the U.S.

PATENTS

About 10,000 patents for traditional Chinese medicines belong to Western
companies. However, some Western observers say China lacks administrative protection
for patents. In 1992, the United States and China signed a memorandum of understanding
(MOU) to allow administrative protection (AP) in China for US pharmaceutical patents
granted between 1986 and 1992. The MOU provided seven-and-a-half years of market
exclusivity, or AP rights, in China for pharmaceutical patents that were: not protected by
exclusive rights before the amendment of current Chinese laws; patent protected after 1
January 1986 and before 1 January 1993 in an MOU signatory country; not previously
marketed in China. Several Chinese government policies have prevented US industry from
realizing the intended MOU benefits. According to Article 42 of the Patent Law, the
duration of patent right for inventions is twenty years, and the duration for utility models and patent right for designs is ten years, counted from the date of filing.

The State Intellectual Property Office is responsible for enforcing patents. The intellectual property system in China was originated from and developed as a result of the policy of reform and opening-up. The State Council, the Patent Office of China, the predecessor of SIPO, was founded in 1980 to protect intellectual property, encourage invention and creation, help popularize inventions and their exploitation, and promote the progress and innovation in science and technology. In 1998, with the restructuring of the government agencies, the Patent Office of China was renamed SIPO and became a government institution under the direct under control of the State Council. The office is in charge of patent affairs and deals with foreign-related intellectual property issues (www//en.wikipedia.org/wiki/pharmaceutical_industry_inchina).

ARTICLE 18 AND 19

Chinese patent law addresses foreign companies in articles 18 and 19. Under Article 18, where any foreigner, foreign enterprise or other foreign organization having no habitual residence or business office in China files an application for a patent in China, the application is treated in accordance with any agreement between the organization's host country and China, or any international treaty to which both countries are party, or on the basis of the principle of reciprocity.

Under Article 19, where such an organization applies for a patent, or has other patent matters to attend to in China, it must appoint a patent agency designated by the patent administration department under the State Council to act as his or its agent.

The patent agency is mandated to comply with the laws and administrative regulations, and to handle patent applications and other patent matters according to the instructions of its clients. The agency bears the responsibility of keeping the contents of its clients' inventions-creations confidential. The administrative regulations governing the patent agency are formulated by the State Council.

DISTRIBUTION

The Chinese pharmaceutical distribution sector is very fragmented with about 10,000+ state-owned pharmaceutical wholesalers. Direct marketing to doctors (detailing),
which is the basic marketing activity in developed countries, complemented by advertising, is not developed in China. Chinese hospitals generate 60 percent of their revenues from the sale of prescription drugs. Hospital pharmacies are still the main retail outlets for pharmaceuticals, accounting for 80 percent of total drug sales. This situation is changing because the government is encouraging the establishment of retail pharmacies that are not associated with hospitals.

**PHARMACEUTICAL INDUSTRY IN CHINA**

The pharmaceutical industry is one of the leading industries in China, covering synthetic chemicals and drugs prepared Chinese medicines, medical devices, apparatus and instruments, hygiene materials, packing materials and pharmaceutical machinery. China accounts for 20% of the world’s population but only 1.5% of the global drug market. The domestic pharmaceutical market is highly fragmented and inefficient. Most often cited adverse factors include a lack of protection of intellectual property rights, a lack of visibility for drug approval procedures, a lack of effective governmental incentives, poor corporate support for drug research and differences in the treatment in China accorded to local and foreign firms (http://worldwatch.org/node/3923). Even so, the industry environment has been transformed for the better over the last 10 years. Entry to the WTO has brought a stronger patent system, medical insurance is now more widespread, and pharmaceutical-related regulations have been stiffened. China’s domestic companies account for 70% of the market and the top 10 companies about 20%. Since June 30, 2004, the State Food and Drug Administration (SFDA) have been closing down manufacturers that do not meet the new GMP standards.

China has established a pharmaceutical industry structure, and has become one of the largest pharmaceutical producers in the world. The Chinese pharmaceutical industry has increased in value with an annual average growth rate of 16.72% over the last few decades. However, the industry is still small-scale, with a scattered geographical layout, duplicated production processes, and outdated manufacturing technology and management structure. The Chinese pharmaceutical industry also has a lower market concentration and weak international trading competitiveness, coupled with a lack of patented pharmaceuticals developed in-house (Eliza, 2007). Investment conditions in China have improved due to the vast consumer demand for pharmaceuticals, the lower labor costs and the changes resulting from economic reform. Changes to the patenting laws in full
compliance with the requirement of the Agreement on Trade-Related Aspects of Intellectual Property Rights (or "TRIPS Agreement") and the lack of Chinese pharmaceutical R&D have also left gaps in the market.

The pharmaceutical market in China is dominated by its non-branded generic industry that operates with basic technology and simple production methods. Domestic pharmaceuticals are not as technologically advanced as western products, but nonetheless occupy approximately 70% of the market in China. Domestic companies are mainly government owned and fraught with overproduction and losses. The Chinese government has begun consolidating and upgrading the industry in an effort to compete with foreign corporations.

Around 36% of all China’s pharmaceutical enterprises are state-owned. Another 35% are privately owned domestic enterprises and the remaining 29%, foreign-funded. Synthetic drug manufacturing remains the pharmaceutical industry’s largest business in China, constituting 65% of industry sales. Another 21% of industry sales come from traditional Chinese medicine. Biotech-related medical products and medical equipment make up the rest. The pharmaceutical industry in China is still developing in view of high profit returns, unnecessary political competition among regions and excessive exploitation of regional administrative power (Yunajia et al., 2007).

**RESEARCH AND DEVELOPMENT**

With their low budget for research and development, China’s pharmaceutical makers are in a different league from the multinationals, but they do enjoy certain advantages. Many Chinese companies not only produce the dosage forms (such as tablets) but also own the pharmacies where they are dispensed, as well as the distribution networks that deliver them to the hospitals, where nearly 80% of drugs are sold. In addition, Chinese companies can produce generic versions of branded drugs for a fraction of their price.

Of the 3,000 pharmaceuticals - not including traditional medicines - manufactured in China since the 1950s, 99 percent are copies of foreign products, as are almost 90 percent of China's biotech products. Most Chinese companies - even joint ventures - compete with each other for the same generics. Many are struggling for survival. Chinese companies are not only small, but are weak in technology and often lack capital. The total R&D expenditures for Chinese-owned pharmaceutical businesses amounted to less than
that spent by a single major Western pharmaceutical company. There are presently more than 5,000 research and development (R&D) institutions in China, but only a handful of them are able to compete internationally in certain areas.

After China’s entry into the WTO, many leading pharmaceutical companies are transferring their research and development centers to China. For instance, Roche of Switzerland opened its R&D center in Shanghai recently, GSK has established its OTC research and development center in Tianjin, China, and Pfizer and Janssen Pharmaceutical (Johnson & Johnson) will carry out similar plans in the near future. AstraZeneca, Bayer, Eli Lilly, and Hoffman-La Roche, have also set up R&D or clinical trial centers in China.

During the past several years, some Chinese pharmaceutical companies began to establish R&D infrastructures largely due to internal growth needs, but their primary focus is directed toward improving existing technologies or developing generic version of new drugs.

**COMPARISON OF CHINESE AND WESTERN PHARMACEUTICAL COMPANIES**

Like its U.S. and European counterparts, the Chinese pharmaceutical business is regulated by government agencies, and competition is fierce in the business. The biggest differences include following:

i) most Chinese pharmaceutical companies are generic drug manufacturers;
ii) a large number are traditional Chinese medicine manufacturers;
iii) hospitals are still the major drug market;
iv) patent issues are the greatest weakness of Chinese producers.

When the Chinese are developing an API they try patent searches via the internet, but are limited by the scope of the available services. Few factories yet have patent attorneys on staff, but for the larger pharmaceutical groups who are seeking partnerships with large Western firms this may come soon (Dow, 2004).

**GOVERNMENTAL POLICIES**

China’s pharmaceutical industry has been a major industry that was completely directed by the State and subject to central planning, upon which transition-era reforms since the 1980s to this day have had a major impact. The pharmaceutical industry has been
shaken up following the implementation of several government-initiated structural reforms.

The main reforms included:

- Requiring all pharmaceutical manufacturers to meet GMP standards by 2004,
- Diminishing drug sales through hospitals,
- Bidding publicly for drug purchase,
- Implementing a national healthcare insurance system, and
- Strengthening intellectual property protection and SFDA supervision.

CONCLUSION

Generic pharmaceuticals refer to pharmaceuticals for which the regulatory authority has already established a technical standard, i.e. ‘drug with existing state standards.’ GMP has been made mandatory under the Chinese drug regulations for producers of medicines including generics. The generic pharmaceutical industry in China is expanding by a 10% plus annually for the last 10 years. China is designated as having “innovative capabilities” for medicine production. Most Chinese drug companies are generic drug manufacturers and Chinese medicine manufacturers. Hospitals are still the major market and patent issues are the greatest weakness of Chinese producers. The generic drug approval does not require clinical trials and the application for generic approval can be filed within two years prior to the expiration of its patent. Provisions to issue compulsory license for domestic manufacturer (where a national emergency or extraordinary state of affairs occurs, or where public interest so require) exists under the amended 1992 Law. There is great scope for exploiting the generic producing capabilities of China to make available quality affordable medicines throughout the world.

4.7 DRUG REGULATIONS IN EUROPEAN UNION

The European agency for the evaluation of medical products (EMEA) was established by council regulation (EEC) No. 2309/93 on July 1993 which is a centralized regulatory authority of the European countries which regulates market authorization, safety/efficacy of medicines, innovation and research and interstate commerce of drugs. According to the European Generic Medicines Association (EGA) a generic medicine is defined as a medicine that contains the same active substance as, is essentially similar to,
and is therefore, interchangeable with, an original brand name medicinal product. It is of the same quality, efficacy and safety as the original product and undergoes strict scrutiny before licensed and market approval. It is marketed as per patent laws and is identified either by its own brand name or by its INN name (Donovan, 2003). Often a key element for a generic drug is establishing bio-equivalency.


The Market Authorization Application (MAA) for marketing a drug within European Union should be filed in the CTD format containing 5 modules. For generic drugs, the application does not contain the module-4 and only comparative bio-availability and bio-equivalence studies in module-5 are needed. Similarly, for new indications of approved drug, quality information on module-3 is not needed (www.cma.europa.eu).

REGULATORY APPROVAL PROCESS IN EUROPEAN UNION

In European Union (EU), drug approval process is regulated by European agency for the Evaluation of Medicinal products (EMEA), which gives market authorization to market drug products in EU member countries. The European Union is a highly regulated market as far as the approval of drug products is concerned and the companies striving for the EU undergo different stages of regulatory approvals. The European Union provides four different types of filing procedures as detailed below:

- National Procedure (NP)
- Centralized Procedure (CP)
- Mutual Recognition Procedure (MRP)
- Decentralized Procedure (DCP)

The EMEA (European Medicines Evaluation Agency) at present comprises of 27 Member State of EU and 3 additional countries from the European Economic Area (EEA)-European Free Trade Association. The EMEA comprises of the following 6 scientific

- Committee for medicinal products for human use (CHMP)
- Committee for medicinal products for veterinary use (CVMP)
- Committee for orphan medicinal products (COMP)
- Committee for herbal medicinal products (HMPC)
- Pediatric Committee (PC)
- Committee for advance therapies (CAT)

NATIONAL PROCEDURE (NP)

National procedure is for that applicant who wants to restrict their marketing authorization to national level. The company approaches the licensing authority of the Member States like Medicine and Healthcare product Regulatory Agency (MHRA) in the UK, Medicinal Products Agency (MPA) in Sweden, Medicinal Evaluation Board (MEB) in Netherlands (Heads of medicines agencies URL://www.hma.eu/). The drug approval time vary between 12 to 18 months.

CENTRALIZED PROCEDURE (CP)

It is for registration of medical products derived from biotechnology, known as List A products, and for non-bio-technology products of an inventory nature, known as List B products. The CP is compulsory to the products obtained from the biotechnological process but optional for other innovative medicines. Applications are made directly to EMEA in London and are evaluated by the CHMP. On the basis of CHMP report, the European commission makes decision whether to grant a community market authorization, which will be valid throughout the EU or not. After authorization, a scientific assessment report (European Public Assessment Report) for each medicinal product is published on the EMEA website. This procedure grants a single market authorization applicable to the entire European Union.

MUTUAL RECOGNITION PROCEDURE (MRP)

It is used to obtain market authorization in several Member States only when the medicinal product in question has received a marketing authorization in any Member State at the time of application. It is based on the principle of mutual recognition of the national
authorization between Member States, and applied to the majority of conventional medicines. Applicant going through the MRP first selects Reference Member State (RMS) and files national application. RMS assesses the dossier and clarifies if there is any non-compliance. The marketing authorization is granted unless there is a serious risk to public health. After receiving the first market authorization in the community the MA holder requests the Concerned Member State (CMS) to recognize an authorization granted by the Reference Member State (RSM) by submitting an application. Within 20 days of receipt of a valid application the RMS will provide the assessment report to the CMS. Within 90 days of the receipt of these documents, the CMS shall recognize the decision of the RMS by granting a marketing authorization.

**DECENTRALISED PROCEDURE (DCP)**

In the DCP a marketing authorization is granted simultaneously for a medical product in more than one member state where the medical product has not received any national marketing authorization at the time of application. It requires 300 days. The applicant receives identical marketing authorization in all desired Member States at the same time and can launch its products simultaneously in different states.

The choice of the procedure depends on (1) the pharmaceutical company; (2) its products; and (3) the market it intends to reach. There are two routes by which a drug may be granted a product license in UK: via the European Medicines Evaluation Agency or via the Medicines and Healthcare Regulatory Agency (MHRA). MHRA was formed in 2003 from the merger of Medicines Control Agencies (MCA) and Medical Devices Agencies (MDA). Prior to the establishment of EMEA in 1995 MCA was the only route for product license in UK. Their role has changed substantially since 1995. MHRA now perform supportive role for European process.

**ROLE OF GENERIC MEDICINES IN EU**

Generic medicines play a key role in ensuring the affordability and sustainability of healthcare systems throughout Europe. Encouraging competition in the pharmaceutical market through increasing the use of generic medicines both promotes cost containment and stimulates the innovation needed to provide added value products. The European pharmaceutical market contributes nearly one forth to the global market share, representing nearly half the volume of medicines delivered to European citizens. The
European generic medicines industry is today a well-established and essential partner in European healthcare. Its role includes:

- offering front-line treatment for key chronic diseases;
- extending access to affordable quality, safe and effective medicines to more citizens throughout the entire European Union;
- creating savings on public pharmaceutical spending, thus providing budget headroom to finance innovation;
- developing generic medicines with newer formulations and methods of delivery; _etc_, which provide incremental innovative improvements for patients;
- Guaranteeing the sustainability of European healthcare systems by creating competition in the pharmaceuticals markets.

As reported by IMS health the current global pharmaceutical market worth $825 billion is expected to grow up to $975 billion by 2013 constituting nearly $ 250 billion through Western European pharmaceutical market. IMS Forecasts Global Pharmaceutical Market Growth of 4-6% in 2010; Predicts 4-7% Expansion Through 2013 (URL:http://www.imshealth.com/portal/site/imshealth/menuitem) and Western European Pharmaceutical Market To Touch $ 245.3 billion By 2012 (URL: http://www. prlog.org/10025910-western-europe-pharmaceutical-market-to-touch245-3-billion by-2012 html). The European Union is a highly regulated market in terms of drug approvals.

**GROWTH OF THE GENERIC MEDICINE INDUSTRY**

The importance of generic medicines can also be seen in the fact that in 2006 generic medicines represented nearly 75% of all new applications finalized under the Mutual Recognition Procedure, and 70% of the new decentralized applications actually finalized. European generic pharmaceutical companies are now expanding into new areas of pharmaceutical development, such as new formulations and bio-similar medicines, and are moving on to new, fast growing pharmaceutical market like China, the Middle East and Russia.

Similarly, the development of bio-similar medicines can be seen as a form of ‘economic innovation’. High priced biopharmaceutical products currently represent approximately 25% of pharmaceutical sales and 50% of all new marketing applications.
As a result, bio-similar medicinal products will soon become a necessary component of future healthcare management policies as even a 20% price reduction on six off-patent biopharmaceutical products would save the EU some €1.6 billion each year. Already today, Europe can be seen as the world centre for research, development and production of bio-similar medicines.

**COMPOSITION OF THE GENERIC MEDICINE INDUSTRY**

The generic medicines industry is a highly diverse and competitive sector, ranging from global players represented in most European countries to local players represented in no more than one or two. The penetration of generic medicines varies between EU Member States from as little as 10% by volume in countries such as Italy and Spain, to over 50% in Scandinavia, the UK and Eastern European countries. Variations in the level of generic penetration is significant, due not only to different historical and economic backgrounds, but also to the public policies employed to promote them, *i.e.*, whether governments choose to take a more or less interventionist approach to their respective markets to create a more sound environment to ultimately facilitate the advancement of generics in these markets.

**HURDLES FOR GENERIC MEDICINES INDUSTRY**

As is the case with the prices of patented pharmaceuticals, prices of generic medicines differ from Member State to Member State as a result of varying healthcare systems and functioning of the distribution chain, such as differences in pharmacists’ and wholesalers’ margins. Significantly, average ex-factory prices of generic medicines are lower in Europe than in the USA. This is despite lower volume share, ‘higher operating costs,’ more IP hurdles, and the lack of a single market environment for generic companies in European markets. Comparative analysis of the generic markets in USA and European Union is given in Table 4.7.1.

Moreover, the European generic medicines industry is currently operating under increasing cost pressures as a result of higher regulatory requirements for bioequivalence, added GMP requirements, and stricter pharmaco-vigilance rules. At the same time, the generic medicines industry is constantly facing price reductions and increased competition from outside Europe, where more flexible labor, tax and environmental conditions offer competitive advantages over European producers. In contrast to the European research
based industry, governments and European institutes provide no incentives to encourage development and production of generic medicines.

MARKET BARRIERS TO COMPETITION FROM GENERIC MEDICINES

i) Lost Savings Due to Inefficient Pricing and Reimbursement Policies:

The potential for savings through competition from generic medicines is not being maximized in Europe. Generic medicines still provide over 40% more savings to European healthcare budgets. For the full potential of savings and headroom for innovation to be realized, it is essential to develop a strong, sustainable European generic medicines industry. In 2006, a study from the University of Leuven pointed out that: “Generic medicines create major savings for healthcare providers and stimulate innovations. But, the European Union is not maximizing its full potential in generic medicines. Added savings of 27-48% could be attained if the appropriate measures were taken by EU countries.”

The Leuven University study also emphasizes that:

“The ability of the (European) generic medicines industry to deliver competitive prices can only be achieved and sustained if it is assured a high volume of the pharmaceutical market. High volume is dependent on demand side measures.”

In order to obtain the potential savings for a sustainable healthcare system within the 27 EU Member States, the study recommends several policy measures including: encourage price differentiation/competition within the existing regulatory frameworks, remove financial disincentives for pharmacists to dispense generic medicines, provide incentive to patients to demand generic medicines and provide incentives for physicians to prescribe generic medicines (Simoen et al., 2006).

ii) The Need for Automatic Price Approval for Generic Medicines to Increase Competition and Access

Substantial savings for healthcare systems, insurers and patients are lost as a result of unnecessary pricing and reimbursement procedures applied to generic medicines. Although the need to review the application for the price and the reimbursement level of a new originator product can be justified by the necessity to assess its cost-benefit advantages, no such procedure is necessary for generic medicines which have well-known
properties and profiles. Consequently, generic products which have been granted a Marketing Authorization (MA) should be given automatic pricing and reimbursement approval and substitution status to avoid delaying the availability of cost-effective generic medicines. Competition from generic medicines is immediate in countries such as Denmark and the UK, where price controls do not exist. However, generic products often experience delays in countries where price controls are practiced. For example, a generic medicine approved through the same European procedures is typically launched one year earlier in the Netherlands than in Belgium due to Belgium’s long timelines for price and reimbursement approvals (http://www.egagenerics.com/doc/ega_Future_Pharmaceuticals.pdf).

iii) **Price Linkage between Reference Product and Generic Alternatives**

Similarly, once a medicine is off patent, the price of its equivalent generic medicines should be set independently from the off-patent reference product and from other generic formulations. For example, linking the price of generic medicines to a constant set percentage of the originator product (for example, always 25-50% lower than the originator) is anti-competitive and endangers the security of supply of generic medicines. Such linkage enables originators to force generic medicines competitors off the market by constantly lowering prices to the point where generic medicines (forced to sell at a fixed percentage below the originator) can no longer afford to enter in to or to stay on the market.

Examples of free competition in Member States such as Sweden, Denmark and the UK show that free pricing encourage competition, which results in lower prices and higher savings. Indeed, there should be no need for complicated cost containment measures such as tendering or comparative price baskets. Instead, the pharmaceutical market should be driven by free competition.

**REGULATORY BARRIERS TO COMPETITION FROM GENERIC MEDICINES**

i) **Disharmonized implementation of the new pharmaceutical legislation**

European generic medicines companies currently have to deal with the problem of dishonrmonized implementation of the new pharmaceutical legislation in different Member States. The disparity in implementation causes late approvals of Marketing Authorization and additional administrative hurdles, which delays competition from generic medicines.
ii) Lack of resources

Of key concern to the generic medicines industry is the lack of resources available to the national competent authorities to run the Marketing Authorization process efficiently and to meet the timelines of the relevant procedures. The significant delays for obtaining a date for submitting an application to start the DCP procedure, the important delays for updating Assessment Reports to start a Repeat Use (RU) MRP, and the limited availability of the national medicines agencies to serve as the RMS constitute an important barrier to the introduction of generic medicines onto the market. The increasing number of variations, including the approval process of those which are not related to public health protection, demands significant recourses from the authorities and of industry which might otherwise be used to better effect. The lack of flexibility in handling administrative changes, like a change in company address, must be dealt with in the revised variations regulation.

iii) Second Medical Use Patents

Second Medical Use Patents [includes i) different new indications, ii) different patient groups iii) same indications, same patient groups but different functional effect, iv) different mode of administration] also constitutes new barriers to the registration of generic medicines and particularly of bio-similar medicines under the centralized procedure (CP). Since second medical use patents differ from country to country, and since it is not permitted to carve out the infringing parts from the product information before marketing at national level, access to the single market through the CP is seriously hampered. This constitutes a competitive disadvantage especially for the biotechnology industry as derived bio-similar medicines can only be approved centrally. The proposal to submit duplicate applications in order to provide access to indications not covered by a used patent in certain Member States will place additional administrative and financial burden on drug industry. A change in the legislation is desperately needed to allow the approval of full summary of Product Characteristics and the removal of the infringing product information only in the markets covered by the used patents.

iv) Lack of appropriate implementation of Bolar Provision

Article 10.6 of Directive 2001/83 as amended — known as the ‘Bolar Provision’ — has not been properly implemented in all Member States, and certainly not in a
harmonized manner. Consequently the EU does not as yet constitute a safe harbor for developing generic and bio-similar medicinal products. In order to attract more clinical trials to the EU drug industry needs a harmonized and safe environment for all tests and trials in view of the applications for a marketing authorization in the EU and worldwide. This will additionally help to secure the EU’s worldwide leadership in regulated bio-similar medicines development.

**IP BARRIERS TO COMPETITION FROM GENERIC MEDICINES**

**Innovation, Ever-greening and the Patent & Pricing Systems**

The European generic medicines industry heartily endorses pharmaceutical innovation, and fully recognizes incremental as well as breakthrough innovation. The European generic medicines industry is, however, concerned that certain product changes which claim to bring innovation in reality offer little added benefits to patients and are, in fact, rendered less advantageous to patients by their higher prices. Such products are actually designed to prolong the life cycle of the originator product and to hinder competition from generic alternatives.

Partial blame for this problem lies with the patent system, which may not always show sufficient rigor when assessing patent applications. The current patent granting process and the weak application of the inventive step principle leads to ‘false’ or ‘weak’ patents leading to ‘ring-fencing’ against competition. This situation has produced an environment of increasing litigation within the pharmaceutical industry due to dubious secondary patents, frivolous litigation and the generous issuance of injunctions. A strong patent system requires rigorous application of solid criteria. Limited or marginal changes to existing medicines designed to obtain extensions to existing patents — a practice known as ‘ever-greening’ — should not be rewarded in the pricing and reimbursement system so as to allow for improved economics throughout the healthcare system by increased competition from generic medicines. Patents, which should always have an incentive step in technical terms, do not always measure added therapeutic value. In all cases innovation is only of value if it can demonstrate added therapeutic benefit to patients (compared to therapeutic alternatives), *i.e.* relative efficacy.

Countries are generally clustered in three groups according to their market shares (Perry, 2006):
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- Less than 10 per cent market share by value: Austria, Belgium, Finland, France, Ireland, Italy, Portugal, Spain;
- Between 10 and 40 per cent market share by value: Denmark, Estonia, Netherlands, Slovak Republic, Slovenia, Sweden, Turkey, the United Kingdom;
- Greater than 40 per cent market share by value: Croatia, Czech Republic, Germany, Latvia, Lithuania, Hungary, Poland.

A range of factors can affect generics markets within Europe. Businesses, for example, in an effort to simplify the market, are seeking to harmonize pharmaceutical registration processes as well as product packaging, marketing strategies and branding. Governments, concerned with the rising cost of pharmaceuticals within their national healthcare budgets, are striving to promote the use of generics over high-priced originator products. Reference-based pricing regimes are increasingly being implemented that benchmark not only products, but also countries.

Indeed, the European pricing and reimbursement map is very complex. Each Member State deploys its own regime, adapted to its own economic and healthcare needs. Governments worldwide continue to search for the ideal system, elusive as it may be. In the meantime, pricing and reimbursement agreements play an important role in regulating supply and demand in healthcare systems. Their objective is to achieve the savings that generics can provide relative to the costs of originator products, while ensuring a fair rate of return to manufacturers and others in the supply chain. It is ultimately a question of creating an economically sustainable healthcare system and ensuring access to affordable medicines to all patients.

For a full understanding of the pricing and reimbursement mechanisms in place, therefore, it is important to look beyond market penetration figures to investigate the following key points:

- How pricing for generic medicines is established;
- How reimbursement systems for generic medicines are established and managed;
- The role of patient co-payment in healthcare systems;
- The public's general attitude towards the use of generic medicines;
- The prescribing behavior of physicians with regard to generics medicines, and how they are assisted in their generic prescribing;
• The regulations governing the dispensing of generic medicines, and how pharmacists are remunerated;
• The delays to market caused by the post-market authorization procedures for establishing price and reimbursement status.

**GENERIC PRICING AND REIMBURSEMENT**

European pharmaceutical pricing systems are either (i) a generic free-pricing system or (ii) a generic price-regulated system. Countries with a price-regulated system typically deploy a reference pricing system based on criteria that differs from market to market.

In countries boasting price-regulated systems, prices are regulated and are established according to: (a) an average of selected European Union (EU) countries, (b) a percentage below the originator price, (c) a maximum price (price index), (d) a negotiable price (price/volume) or (e) some other measure.

The second internal EGA survey of European generics markets (Perry, 2006) found that, in terms of pricing and reimbursement systems in Europe, 82 per cent of the countries surveyed have implemented price-regulated systems. In 36 per cent of these countries, price levels are set at a predetermined percentage below the originator price, whereas in 21 per cent price levels are based on the average price of pharmaceuticals in a selection of countries Figure 4.7.1.

These reference pricing systems were introduced in 71 per cent of European countries as a tool to reduce pharmaceutical expenditure. Reference pricing systems are, therefore, a significant aspect of healthcare systems and cost containment efforts across Europe.

In a reference pricing system, medicines are categorized into groups with identical or similar active ingredients, the so-called 'reference groups'. Three ways of classifying similarity between medicines are used by national health authorities: (1) chemical, (2) pharmacological and (3) therapeutic equivalence. The authorities will then determine a maximum reimbursement price (reference price) for each reference group. The internal EGA survey 2006 verified that the majority of European countries (63 per cent), which use a reference pricing system, establish their reference prices based on the active substance Figure 4.7.2.
National health authorities also take into account the prices of existing medicines in the relevant reference group when determining the reference price. Thirty-two per cent of the European countries surveyed currently base their reference price on the lowest-priced medicine; 16 per cent of countries base their reference price on the lowest-priced generic Figure 4.7.3.

PATIENT CO-PAYMENT

In publicly funded healthcare systems, it is important to highlight the role of patient co-payment in financing a country's healthcare system as it can strongly influence the patient's ultimate decision on the medicine he or she will take. Patient co-payment is common practice in all European countries with the exception of Ireland and Malta. Even so a great deal of variation exists in how these regimes are actually implemented.

In most EU countries, the patient's role in contributing towards the total cost of medicines (co-payment) is very limited. Patients are generally concerned with the outcome of the therapy prescribed and their participation in the cost. Patients may become more involved as their contribution increases. Patient co-payments are typically charged according to one of the following four mechanisms:

- Fixed fee per prescription (per item, per prescription, or according to pack size);
- A percentage of cost of the medicines prescribed (partially reimbursed);
- The difference above the reference price (reference price is equal to the maximum reimbursed price);
- A combination of the above usually comprised of a fixed fee and a percentage of the cost of medicines prescribed.

The EGA survey 2006 has found that the majority of countries in Europe calculate patient co-payment either as a percentage of the cost of the medicine (36 per cent), or as the difference above the reference price (34 per cent), as illustrated in Figure 4.7.4.

GENERIC PRESCRIBING

The prescription process is an essential source of efficiency in healthcare systems. This is particularly true when prescribing generic medicines as a means to reduce costs to payers. Therefore, it is important to understand (i) what factors influence doctors to
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prescribe generic medicines; (ii) what format doctors use to prescribe generics and (iii) under what conditions they prescribe generics. According to the EGA survey, doctors are encouraged to prescribe generics in only 50 per cent of the countries reviewed, and generic prescribing is compulsory in only 7 per cent Figure 4.7.5.

Doctors prescribe medicines according to both a patient's therapeutic needs and the financial implications. There are few restrictions on the prescribing of medicines, but not all medicines are reimbursed. Consequently, national governments develop guidelines to inform and aid doctors in their prescribing. In general, guidelines exist on therapeutic considerations, available budgets and cost efficiency, as well on as how to write prescriptions to allow more efficient dispensing.

A significant factor affecting the way medicines are dispensed and/or substituted is the format the doctor uses in the prescription, that is, whether it is prescribed using a brand name or the International Non-proprietary Name (INN). In the UK, medical students are taught to prescribe using INN, although it is not compulsory by law, and pharmacists are obliged to dispense exactly as written on the prescription. In countries where INN prescribing is compulsory, only in Portugal are physicians obliged to do so for all medicines when a generic product is available, and in Lithuania doctors must use the INN only for those products that are reimbursed.

**GENERIC SUBSTITUTION**

Where generic substitution is allowed, a doctor prescribes a specific product and the pharmacist is either free or is obliged to substitute it with a less expensive generic product. Generic substitution is used as a means to promote cost-effective prescription and rational dispensing in healthcare systems. Ultimately, generic substitution is a key issue for all generic pharmaceutical manufacturers as it can provide an effective boost to the dispensing of generic medicines, consequently providing room for growth in the generics market. Substitution, of course is not always a necessity if doctors are prescribing generic medicines adequately. The UK, for example, has high generic volume but no need for substitution because of the general prescribing practice. But for national governments where generic prescribing is insufficient, generic substitution translates into cost-savings in pharmaceutical expenditure and into access to quality affordable medicines for patients. Generic substitution has been adopted in 71 per cent of the European countries. However,
rules governing generic substitution in markets where it is allowed often vary from
country to country and according to the different circumstances surrounding the actual act
of dispensing in the pharmacy.

MARKETING AUTHORISATION

Europe is a complex market in terms of transparency, hence making it difficult to
assess how long it will take for generic manufacturers to obtain their price and
reimbursement status after receiving MA. Although delays for price approval have
improved in part due to the European Commission's recommendations and the EU Price
Transparency Directive, the time delays for reimbursement status remain an obstacle to a
competitive generic medicines industry in Europe.

Market access conditions for generics constitute a core issue for generic medicines
manufacturers as these tend to differ from country to country in Europe. The variables
affecting market access generally include: (a) the need for the MA holder to apply for
price, (b) the delay between the MA grant and price approval, (c) prevention of generic
MA due to Supplementary Patent Certificate (SPC) period, (d) naming of the generic
product, (e) delays in approving the generic reimbursement and/or substitution status, (f)
conditions for a generic medicine to be determined therapeutically interchangeable and
thus apt for substitution.

CONCLUSION

EMEA is a central drug regulatory authority for regulation of marketing approvals,
safety/ efficacy of medicines, innovations, research and development, and interstate
commerce of medicines in the entire European Union. Bio-equivalency establishing is
must for generic drugs. The Marketing Authorization (MA) within Europe is filed in the
CTD format containing 5 modules. For generic drug applicants the application does not
require module 4 and only comparative bio-availability and bio-equivalence studies in
module 5 are required. The marketing authorization process involve National Procedure,
Centralized Procedure, Mutual Recognition Procedure and Decentralized Procedure
depending upon the pharmaceutical product (s), its marketing company and the market it
intends to reach. The generic penetration varies from Member State to State in EU, i.e.,
from 10%-over 50% in Scandinavia, UK, etc. Price controls in certain EU members create
hurdles in the launch of generics, after its market authorization. Free medicine pricing
system in Sweden, UK, Denmark, etc., result in lowering of the generic prices and higher saving for the consumers. Generic prescription is only in 50% of the EU countries and it is compulsory in only 7% countries. INN prescription is not compulsory except in Portugal where INN prescription is must. In Lithuania doctor must use INN only for those products that are reimbursed. The generic substitution is not of much importance in UK because of general prescribing practices of physicians. However, generic substitution has been adopted in 70% of EU countries; still there is wide scope for expanding the growth of generics in European Union.

4.8  REGULATIONS ON MEDICINES IN CANADA

Every drug sold in Canada must be approved by the Health Protection Branch, which is part of Health Canada. The approval process ensures that the medicines are safe & effective and meets the mandatory standards set by the government. The Patented Medicines (Notice of Compliance) Regulations were passed by the government in 1993 specific only to patent disputes in the pharmaceutical industry. The regulations allow a brand name company to stop Health Canada approval of generic drugs simply by alleging patent infringement (automatic 24 month injunction). Even the brand company is not required to obtain a preliminary injunction from the courts to stop generic product approval and same is kept in abeyance till decision of the court. The brand companies strategically list a numbers of additional patents on a single drug in order to prolong the litigation under the Regulations and keep competition off the market. The practice is called “ever-greening” or layering. Even when the generic manufacturer wins, the generic drug is still kept off the market through lengthy and costly litigations—often for years past the expiry of original patent. Bill C-91 also passed in 1993 by the Mulroney government extended the pharmaceutical patent in Canada from 17 to 20 years.

Recently, federal government has proposed major changes to the Regulations governing approval of generic drugs, similar to the Hatch-Waxman Act providing a drug company to register a patent list for each drug approval by Health Canada. A generic manufacturer wishing to obtain market approval for a counterpart drug must either agree to await expiry of every patent on the patent list, or commence a legal proceeding to establish either (i) that the patent listed are invalid or (ii) its product does not infringe any of the patents. The legal proceeding triggers a 24 month stay of generic drug approval. Unfair listing of patents subsequent to the approval of first original patent by the brand
companies to keep the generic away from competition by getting repeated 24 month stay has been taken care of in the proposed amendments.

In Canada, a ‘new drug’ has been defined in Section C.08.001 of the Food & Drug Regulations as a drug which contains a substance which has not been sold in Canada for a sufficient time and in sufficient quantity to establish its safety and efficacy. Thus, ‘new drug’ includes both novel products as well as drugs that are not novel but are ‘new’ in the sense that the particular version of the drug has not been previously marketed (as in case of a competing or a generic version of a drug that has the same properties). Under Canada’s Food & Drugs Act, the Therapeutic Products Program (TPP) of the Federal Department of Health (Health Canada) is responsible to ensure that “new drug” meet health and safety requirements.

Both generic as well as patented products are treated as ‘new drugs’ by the Food and Drug Regulations because generic is equivalent, and not identical, to the patented product it replicates. The major difference between submission for a patented and a generic product is the data required to establish the safety of new drug and its clinical efficacy. For a generic drug comparative studies to establish pharmaceutical and bioequivalence with another, usually innovator’s product, i.e. “Canadian Reference Product” identified in section C.08.001.1 of the Regulations is required while extensive pre-clinical, toxicity studies in animals, clinical studies and pharmacokinetic studies to establish safety and efficacy of new drug is must. The generic drug must be demonstrated to deliver the same amount of active ingredient at the same rate as the original.

The generic manufacturer files an Abbreviated New Drug Submission (“ANDS”) with Health Canada while an innovator would file a New Drug Submission, since it must provide full pre-clinical and clinical data to establish safety and efficacy of the drug in question. For an innovator, it takes about 8-12 years (out of 20 year patent term) to develop and receive regulatory approval while it takes 3-6 years in case of generics. ANDS reviews will lead to the grant of a Notice of Compliance (NOC) subject to litigation under the Patented Medicines (Notice of Compliance) Regulations enacted pursuant to section 55.2(4) of the Patent Act which prohibits issuance of NOC in respect of ‘patent- linked’ drugs. NOC is not issued to a generic manufacturer where the patentee alleges patent infringement. Thus, like H.W. Act 1984 in US, the PM (NOC) Regulations in Canada link the generic approval to the patent status of the original product. Canada’s
Drug Regulations in Various Countries

Patent Act includes ‘Bolar Provisions’ which allows research and development of a generic product prior to patent expiry as well as application submission for regulatory approvals (www.cgpa.com).

The Canadian Generic Pharmaceutical Association (CGPA) represents Canada’s generic drug industry – a dynamic group of companies that specialize in the production of high quality, affordable generic medicines and fine chemicals and in conducting the clinical trials required for governmental approvals. The generic companies have provided quality medicines at affordable prices saving for nearly 40 years. These provides on an average 40-50% savings when compared to their brand equivalents, and play a vital role in keeping prescription drugs affordable in Canada. The generics are dispensed to fill about 50% of all prescriptions but accounts for less than 20% of the Canadian prescription market.

POLICY OPTIONS TO PROMOTE GENERICS

*Removal of NOC Linkage Regulations*- The regulations allow brand name companies to lengthen market monopolies by delaying Health Canada’s approval of generic drugs simply by alleging, not proving, patent infringement. Their removal will speed up generic entry and reduce the costs to the provincial government, private insurer and the Canadian public.

*Improvement in time of approval process at the TPP of Health Canada* - There is a major shortage of resources at the Therapeutic Product Program of Health Canada which is responsible for evaluating the safety effectiveness and quality of drugs. Currently the approval times for generic drugs are double TPP’s own performance targets.

*Harmonization between federal and provincial governments* - The ability to interchange generic and brand name drugs varies from province to province, which leads to unequal access to less expensive bio-equivalent generic drugs. Similarly reluctance of some provinces to accept the TPP’s Declaration of Bio-equivalence often leads to duplication of work and unnecessary delay in generic approvals.

*Direct to consumer advertisement by pharmaceutical companies* - The direct to consumer advertisement leads to higher drug costs and more physician visits. The brand
name companies lobbying to the government to lift the ban on such advertisement would add to the sky-rocketing prescription drug costs.

Provisions for Humanitarian aid to ailing world by CGPA—Presently, Canadian patent law does not allow providing life saving medicines to peoples in poor and developing countries. The federal government can amend the patent law to allow manufacture and shipment of such medicines by generic companies which are still under patent protection on humanitarian grounds.

The government on October 18, 2006 published a package of regulatory amendments to Canada’s patent rules necessary to comply with Canada’s international trade obligations. As per these rules, the government provided brand name companies with an eight year ban on generic competition regardless of whether there are relevant patent on their products. These new rules are the government response to lobbying from brand name companies and pressure from United States Trade Representative (USTR) to strengthen data exclusivity provisions.

Ontario based Apotex became the first generic company to reach sales of more than $1 billion in Canada and forth largest pharmaceutical manufacturer in Canada behind brand name companies Johnson & Johnson Astra Zeneca and Pfizer. Sales of generic medicines grew 13.6% in 2006 twice the rate of branded sales. As more and more patent are expected to expire over the coming year the generic industry is poised to benefit.

CONCLUSIONS

Canadian drug regulations provides for filing of Abbreviated New Drug Submission (ANDS) and New Drug Submissions (NDS) on the pattern of USFDA for generic and innovator drug approvals. The definition of ‘new drug’ also includes generics in Canadian definition of new drug, which makes it different from the definition in USFDA. For a generic drug, comparative studies to establish pharmaceutical and bioequivalence with Canadian Reference Product is required. The generic drug must be demonstrated to deliver the same amount of active drug at the same rate as the original. Canadian drug regulations allow a brand name company to stop approval of generic drugs by Health Canada, simply by alleging patent infringement. Like H.W. Act of US the PM (NOC) Regulations in Canada link the generic approval to the patent status of the innovator. Canadian Patent Act includes ‘Bolar Provisions’ which allows research and
development of generic product prior to patent expiry as well as application for generic approvals to Health Canada. However, the brand to generic change regulations varies from province to province as far as generic uptake and their promotional policies are concerned. British Columbia with generic prescription exceeding 40% provides for incentives to pharmacists for generic substitution. Further, the Government provides brand name companies with an eight year ban on generic competition regardless of whether there are relevant patent on their products indicating their anti-generic policies.

It can be safely concluded after extensive studies of drugs regulation of various overseas countries that they are aimed at promoting generic utilization to provide affordable treatment to the mankind. USA followed by Brazil provided the best policy in the world to promote generic by adopting various strategies in this contest. Even countries like China, Japan etc. have initiated number of generic promotion policies. The recent policy adopted by Australia under its popular PBS system which provides for reduced prices in first timer generics is commendable. In spite of the tremendous growth of pharmaceutical industry in India and also the fact that the country is known world over for producer and supplier of quality generic medicines at affordable prices, yet it lacks appropriate generic promotion policies / regulations for making essential medicines affordable to its own countrymen. Generic promotion schemes like generic substitution, generic prescription, generic price approval, incentives to pharmacists for generic, identification mark for generic etc. practiced world over must be adopted in India to promote generic and to provide relief to the millions who lacks access to essential medicines.