

Implications of Drug Price Competition and Patent Term Restoration Act (DPCPTRA) on Indian Pharma Industry

Y Srihari † S Padmaja and G Srinivasa Rao

Aurobindo Pharma Ltd, 313 Bachupally, Qutubullapur Mandal, Hyderabad 500 072

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The Drug Price Competition and Patent Term Restoration Act (DPCPTRA), informally known as the 'Hatch-Waxman Act', introduced in 1984, modified the Patent Act of 1952 and Federal Food, Drug, and Cosmetic Act Section 21 U.S.C. 355(j) to simplify approval process of generic drugs by FDA by filing Abbreviated New Drug Applications (ANDAs). This Act also provided some incentives to innovators as well as generic companies by way of patent extension based on regulatory delays as well as 180-day exclusivity to generic companies that have the first-to-file (FTF) ANDA against patents listed in Orange Book. This paper reports the first-time generic drugs approved by FDA during 2004-08 and the number of ANDAs receiving 180-day exclusivities as well as the impact of DPCPTRA on Indian pharma industry.

Keywords: Patent, Hatch-Waxman, generic drug, Paragraph IV, FDA, ANDA, DMF, first-to-file

The 1984 Hatch-Waxman Act modified the 1952 Patent Act by creating a statutory exemption from certain claims of patent infringement and established the modern system of generic drugs.¹ Generic manufacturers may commence work on a generic version of an approved brand name drug any time during the life of the patent, so long as that work furthers compliance with FDA regulations. Although the 1984 Act provides a safe harbor from patent infringement, it also requires would-be manufacturers of generic drugs to engage in a specialized certification procedure. This Act has been described as the one of the most important pieces of legislation affecting the drug industry in the US.

Hatch-Waxman Act also amended the Federal Food, Drug, and Cosmetic Act Section 505(j) (21 U.S.C. 355(j)) which sets forth the process by which would-be marketers of generic drugs can file ANDAs to seek FDA approval of the generic. When an ANDA is filed, the application must contain a certification with respect to the patents listed in the Orange Book. There are four certification options i.e. Paragraph I certifies that there are no patents listed, Paragraph II certifies that the patent had expired; Paragraph III certifies that the patent will expire and Paragraph IV certifies that the patent is invalid or will not be infringed by the generic drug. Section 505(j) (5) (B) (iv), the so called Paragraph IV, allows 180-day

exclusivity to companies that are the FTF an ANDA against patents listed in the Orange Book.

Hatch-Waxman provides first-filing generics with a 180-day exclusivity period that can be triggered by a court decision of invalidity or non-infringement or by one of the first-filing generics entering the market. Until one of these triggering events occurs, the FDA will not grant a generic that files its Paragraph IV certification after the first filer final approval to enter the market with a generic drug. The court decision of invalidity or non-infringement can be from any case; it need not arise from litigation against one of the first-filing generics. In most Paragraph IV ANDA cases, the generic applicant is sued by the patent holder. If any lawsuit is filed against ANDA applicant, FDA is not allowed to approve the ANDA until the expiry of 30 months from the date of filing or final court decision whichever is early.

Effect of Increased Competition from Generic Drugs on Pharmaceutical Industry

Increased competition from generic drugs has affected prices and returns in the pharmaceutical industry. The pharmaceutical market has become increasingly competitive since the early 1980s, in part because of the dramatic growth of the generic drug industry. In 1996, 43% of the prescription drugs sold in the United States (as measured in total countable units, such as tablets and capsules) were generic. Twelve years earlier, the figure was just 19%. Generic

†Email: Corresponding author: srihari@aurobindo.com

drugs cost less than their brand-name, or 'innovator,' counterparts. Thus, they have played an important role in holding down national spending on prescription drugs from what it would otherwise have been. Considering only sales through pharmacies, the Congressional Budget Office (CBO) estimates that by substituting generic for brand-name drugs, purchasers saved roughly \$8 to 10 billion in 1994 (at retail prices).² Generic drugs claimed 67.3% of US prescriptions dispensed in 2007. Proportions of total expenditures on prescription drugs (Panel A) and of total prescriptions dispensed (Panel B) accounted for by brand-name drugs and by generic drugs is given in Fig.1.³

In the US, prescription drugs represent about 12% of healthcare spending. From 1995 to 2002, purchasing of prescription drugs in the US increased from \$60.8 to 160.9 billion. The introduction of generic versions of brand-name drugs increases access to these drugs by patients because they are lower priced versions of the innovator drugs. In the US, generic drugs are 30 to 80% less expensive than their brand-name counterparts.^{4,5}

North American pharma market tops global pharmaceutical sales with \$ 311.8 billion with market share of 40%. Table 1 shows the 2008 global pharmaceutical sales by region for the year ending December 2008.⁶

Competition and Contribution from Indian Industry on Generic Drugs

DMFs and ANDAs by Indian Companies

A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed

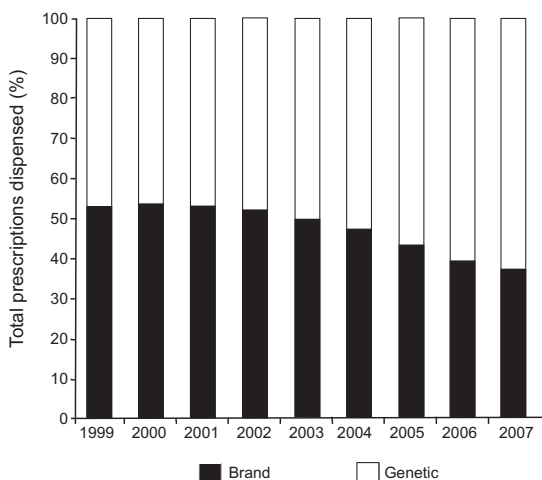


Fig. 1 — Total expenditures on prescription brand-name drugs and generic drugs

information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. There are 5 types of DMFs, Type I for manufacturing site, facilities, operating procedures; Type II for drug substance, drug substance intermediate, and material used in their preparation, or drug product; Type III for packaging material; Type IV for incipient, colorant, flavour, essence, or material used in their preparation and Type V for FDA accepted reference information.

The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), and ANDA. A DMF is not a substitute for an IND, NDA, ANDA, or export application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an export application.⁷

India is now a dominant source of Active Pharmaceutical Ingredients (APIs) for the US market, either as direct supplier to US generics companies or processing the APIs in India and exporting formulations to the US.

The Indian pharmaceutical market is one of the fastest growing in the world. It contributes over 10% in terms of volume and just over 1% in terms of value of total global pharmaceutical sales. The Indian pharmaceutical industry was estimated to be around \$13.2 billion in 2006-07. Of this, domestic consumption of pharmaceuticals accounted for nearly 57% while the rest 43% was constituted by exports. In 2006, the market witnessed an accelerated growth of more than 17%, primarily on account of increased clarity on tax reforms especially the Value Added Tax (VAT) implementation. The country's pharmaceutical market is expected to maintain a healthy growth rate of 12-13% and expected to cross \$10 billion mark by 2010 and reach approximately, \$ 12 to 13 billion by 2012.⁸ The anti-infective segment remains the largest in India, accounting for 22% of the market share.

Table 1— Global pharmaceutical sales in 2008

Regions	Sales Billion dollars	Sales % Market share	% Growth 2008 (Constant dollars)
Auditedmarket 2008			
Worldwide	773.1	100	4.8
North America	311.8	40.2	1.4
Europe	247.5	32.01	5.8
Asia, Australia, Africa	90.8	11.7	15.3
Japan	76.6	9.9	2.1
Latin America	46.5	6.01	12.6

Indian pharmaceutical companies started filing DMFs in the US around the 1980s. But until the late 1990s, only a few DMFs were filed, the largest being in 1993 when 8 DMFs were filed. Since then the rate of filing has accelerated. The number of DMFs filed by Indian companies increased from 17 in 1997 to 33 in 2000, 65 in 2002, 196 in 2004, 296 in 2006 and 362 in 2008. During the quarter ending June 2006, the Indian pharma industry has filed the largest number of DMFs with the USFDA. During the quarter ending June 2006, Aurobindo Pharma Ltd topped the list of Indian pharma companies with 21 DMFs filings.⁹

In relative terms, DMFs filed from India as a percentage of total DMFs filed with the USFDA increased steadily from 18.3% in 2001 to 44% in 2006. Between January 2001 and March 2006, India has been by far the largest country, with 738 DMFs filed, way ahead of the second ranked country, China with 250 filings.¹⁰ India has displaced some of the traditional Italian and Spanish API suppliers.¹¹

Aurobindo, Cipla, Dr Reddy's and Matrix have filed more than 100 DMFs each as of March 2009. Some other top Indian companies have also individually filed a large number of DMFs (Fig. 2).^{9, 12-20}

ANDA contains data which when submitted to FDA, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

Filing an ANDA is not so simple. It involves various activities and investments by generic companies such as procurement of innovator samples, development of non infringing API as well as formulation and clinical study of formulation for bioequivalence. FDA has defined bioequivalence as,

'absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.'

Apart from the costs involved in procurement of innovator samples, as well as development of API and formulation, cost of bioequivalence studies is the major cost in developing generic drugs. There is no generalized cost statement for developing generic products; however, it depends on the complexities and time taken for development.

Until recently only a few Indian companies, particularly Ranbaxy and Dr Reddy's had ANDAs in their own names. The companies such as Cipla which also exported formulations had ANDAs in the names of their marketing partners in the US. The situation has dramatically changed in the last few years. From 161 ANDAs filed by only 4 companies - Ranbaxy, Dr Reddy's Laboratories, Wockhardt and Lupin until the last quarter of 2003, the number has gone up to 701 ANDAs filed by 17 companies by the second quarter of 2007. The number of ANDAs filed by top 12 Indian companies is 1129 as of March 2009. The number of DMFs and ANDAs filed by top 12 Indian companies during the period 2004-08 and their turnover as of December 2008 is given in Table 2.^{9, 12-20} ANDA approvals by Indian companies as a percentage of total approvals, has gone up sharply from about 7% in 2001 to 21 % in 2006.

India now has 175 manufacturing plants approved by USFDA. This is the highest number of USFDA

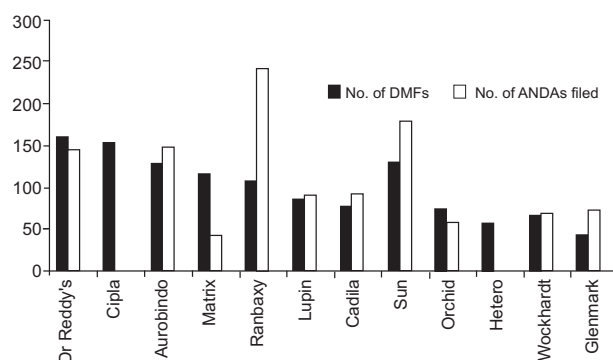


Fig. 2— DMFs/ANDA filed by Indian companies

Table 2 — DMF's and NADAs filed by top 12 Indian companies

Company	No of DMFs *	No. of ANDAs filed	Sales turnover (\$ million)
Ranbaxy Pharmaceuticals	107	241	1,510.5
Dr Reddy's Laboratories	160	144	1,447
Cipla Ltd	153		1,036
Sun Pharmaceuticals	129	179	890
Lupin Ltd	85	90	787
Cadila Healthcare Ltd	76	92	704.5
Wockhardt	66	67	748.5
Aurobindo Pharma Ltd	128	147	617.7
Matrix Laboratories Ltd	115	41	418.5
Glenmark	42	71	360
Orchid Chemicals	73	57	252.3
Hetero Drugs	57	-	NA

*As of March 2009. The sales data for Matrix, Glenmark is for the financial year 2007-08. Sun pharma includes its subsidiary Caraco

approved plants outside USA. Italy has 55 plants, China 27 and Spain 25 plants approved.²¹

Effect of Hatch-Waxman Act on Generic Entry

Caves, Whinston and Hurwitz (1991) studied thirty drugs that went off patent protection between 1976 and 1987. Of the thirty drugs, the patents of seven drugs expired before 1980, sixteen between 1980 and 1984, and seven after 1984.²²

During the period 2004-08, of the 554 first-time generics approved by FDA for 236 products with different dosage form and strength, only 46 products lost the patent protection during this period. Patents for nearly 171 products have expired before 2004 and 19 products for which patents have not expired during 2004-08 have also been approved.²³

Top molecules such as Simvastatin (Zocor), Pravastatin (Pravachol) and Sertraline (Zoloft) lost their patent protection in 2006 (Table 3). These three drugs accounted for \$10 billion in 2004, which is 2% of world pharmaceutical market.

The introduction of generics brings down the costs more than 50%. This price reduction depends on various factors including the number of generic manufactures. The authors studied few drugs which lost patent protection and their sales in the US before and after patent expiry. Sales of top drugs which lost patent protection during 2004-08 are given in Table 4.²⁴

NCE patents expired for Risperidone, Venlafaxine in June 2008 and for Divalproex in July 2008. Hence, there is not much change in sales.

Venlafaxine is approved as tablets and extended release (ER) capsules dosage form. Though NCE patent expired for Venlafaxine in June 2008, generics

have not been approved for ER capsules. Generics have been approved only for tablets, which has less market share compared to ER capsules.

Similarly, Divalproex sodium is approved in the form of delayed release (DR) tablets, ER tablet and DR capsules. Market share for delayed and extended dosage forms are equally good. The NCE patent expired in July 2008 and generics have been approved immediately for DR dosage form and generics are approved for ER dosage form in 2009.

R&D for Value Added Generics

R&D is required not only for developing the product but also to ensure that the products do not infringe on any existing patents. An innovator company usually does not obtain a patent only on the active ingredient (NCE) involved in a new drug. Other secondary patents relating to the same NCE which can be obtained are: (i) new formulations and compositions, such as new dosage forms or routes of administration; (ii) new salts, esters, etc. of existing ingredients; (iii) new uses for existing ingredients; (iv) new polymorph or solvates; and (v) new process of manufacturing the active ingredient. These secondary patents are obtained later and hence typically expire after the basic patent on the NCE expires.

Studies have shown that the innovator companies use patenting as a matter of strategy to maintain their market dominance. In fact with a number of drugs scheduled to go off-patent, they have intensified their efforts in recent years to extend the period of patent

Table 3 — Year wise patent expired products

Patent expiry year	Drugs whose patents expired
2004	Benazepril, Carboplatin, Ciprofloxacin, Fluconazole, Flumazenil, Fluticasone propionate, Halobetasol propionate. (7)
2005	Azithromycin, Clarithromycin, Zidovudine, Cabergoline, Cefprozil, Ceftriaxone, Glimepiride. (7)
2006	Finasteride, Mitoxantrone, Ondansetron, Pravastatin, Sertraline, Simvastatin. (6)
2007	Amlodipine, Balsalazide, Calcipotriene, Carvedilol, Cefdinir, Cetirizine, Didanosine, Granisetron, Ropinirole, Trandolapril, Terbinafine, Zolpidem, Cefepime. (13)
2008	Alendronate, Divalproex, Dorzolamide, Eplerenone, Galantamine, Irinotecan, Risperidone, Rocuronium, Stavudine, Venlafaxine, Zalepon, Ramipril, Metoprolol succinate. (13)

Table 4 — Sales of top drugs which lost patent protection during 2004-08

Generic drug name	Patent expiry	US retail sales before the patent expiry MAT (\$ million)	US retail sales post patent expiry MAT March 2009 (\$ million)
Pravastatin sodium	2006	1,567	159
Sertraline	2006	3,096	299
Simvastatin	2006	5,786	2,194
Amlodipine besylate	2007	2,790	2,283
Carvedilol	2007	1,606	120
Cetirizine	2007	1,425	104
Zolpidem tartrate	2007	2,491	171
Alendronate sodium	2008	2,183	606
Divalproex sodium	2008	1,751	1,406
Risperidone	2008	2,723	1,752
Venlafaxine	2008	2,941	2,987
Metoprolol succinate	2008	1,666	1,003

protection and protect the sales of their branded drugs.²⁵

Thus it is not enough to just file DMFs and ANDAs. Generic companies must be sure not to infringe the secondary patents in API processes and formulation products. In fact generic companies which can challenge the secondary patents of the originator companies can have their own patents to reap huge benefits. Apart from DMFs and ANDAs, patenting is increasingly becoming important for generic companies desiring to move up the value chain.

The development of generics also encourages the research activity. Many Indian companies compete with other global generic companies in filing patent applications on various API processes, polymorphs, formulation etc. This results in enrichment of intellectual property of generic companies. Few examples of Indian companies which benefited from developing intellectual property are:

Alembic has developed ER compositions of Levetiracetam and filed patent applications. UCB, the innovator of Keppra®(Levetiracetam) has licensed the patents owned by Alembic laboratories. Alembic will get \$11million as milestone payment for Levetiracetam.²⁶

Similarly, Lupin has earned 20 million Euros (equivalent to \$31 million) by selling patent rights of its hypertension drug, Perindopril to France-based Laboratoires Servier.²⁷

Ranbaxy had outlicensed its Novel Drug Delivery System (NDDS) drug, Ciprofloxacin to Bayer of Germany for \$ 65 million.²⁸

Unlike in other countries, USA has different system, where innovator companies after getting such secondary patents usually list them in the Orange Book together with the basic patent, which claims new molecule. The types of patents that can be listed in the Orange Book are product patent (basic patent), formulation, process, polymorph, method of treatment etc. However, as per the revised FDA regulations metabolite or intermediate patents are not eligible for listing in the Orange Book. As per DPCPTRA, when any patent listed in the Orange Book, the generic companies, based on their intentions to market the products, have to provide certification with any of Paragraphs II, III or IV under Food Drug and Cosmetic Act.

Challenging Patents

By listing patents in the Orange Book, the innovator companies can delay the entry of generics.

When an ANDA is filed with Paragraph IV application, in most of the cases, the generic applicant is sued by the patent holder. The ANDA applicant with FTF will be awarded 180-day exclusivity in certain instances. Patent litigation is a high-risk-high-gain strategy. A failure means a loss of several years of hard labour and huge legal expenses. Any successful FTF Paragraph IV ANDA can bring immense returns to the company as per the experience of Dr Reddy's Laboratories. Dr Reddy's was the first Indian company to get the 180-day exclusivity for marketing Fluoxetine (Eli Lilly's Prozac) 40 mg capsule in August 2001.²⁹

However, some times the revenues of generic companies might be hindered by the launch of authorized generics. Authorized generics are prescription drugs produced by brand pharmaceutical companies and marketed under a private label, at generic prices. Authorized generics compete with generics on price, quality and availability in the generic marketplace, and are marketed to consumers during and after the 180-day exclusivity period.

In July 2009, Federal Trade commission (FTC) issued an interim report that examined the effects of authorized generics on competition in the prescription drug market. The 180-day period of marketing exclusivity granted to certain generic 'first filers,' however, does not preclude competition from authorized generics. As per FTC report, it has become increasingly common for brand-name drug makers to begin marketing authorized generics at the same time the generic firm is beginning its 180-day marketing exclusivity period.

According to the FTC report, drug prices are lower when authorized generics are marketed against a single generic drug than when they are not. With authorized generic competition during the 180-day marketing exclusivity period, retail drug prices are on an average 4.2% lower than the pre-generic branded price, and wholesale drug prices are on an average 6.5% lower than the pre-generic branded price,

The report also found that the impact of an authorized generic on first-filer revenue is sizable, the ability to promise not to launch an authorized generic is a huge bargaining chip the brand company can use in settlement negotiations with a first-filer generic.³⁰ Few examples of authorized generic launches which impacted the sales of generic companies are:

- Macrobid (nitrofurantoin) during Mylan's exclusivity period.³¹

- Paxil® (paroxetine hydrochloride) by Par Pharmaceuticals during Apotex's exclusivity period.
- Zocor® (Simvastatin) and Proscar® (Finasteride) by Dr Reddy's during Teva's exclusivity period.

In the case of antidepressant drug, paroxetine, omeprazole generic approvals were delayed with listing of secondary patents in the Orange Book. The basic NCE patent for paroxetine expired in mid-1990s. But GlaxoSmithKline could delay the entry of generics by obtaining several secondary patents such as crystalline paroxetine hydrochloride hemihydrate with expiry date of June 2007 and several other polymorph patents. Apotex has filed ANDA with Paragraph IV certification and has been sued by Glaxo. Apotex successfully challenged the hemihydrate patent and had been awarded approval in July 2003 with shared exclusivity of 180 days.³²

The basic NCE patent for omeprazole expired in 2001. However, several secondary patents such as formulation and polymorph are listed in the orange book by AstraZeneca that delayed the entry of generics. First generic for Omeprazole has been approved in November 2002 with shared 180-day exclusivity for Genpharma and Andrx for 10mg and 20 mg capsules. However, Andrx ANDA could not get approval in 2002 and received approval on 30 May 2008. Genpharma's commercial marketing has triggered the exclusivity period for 10 mg and 20 mg capsules. Andrx has been awarded 180-day exclusivity for 40 mg capsules on 30 May 2008.³²

Similarly, for Finasteride three patents are listed in the Orange Book such as Finasteride Form II and method of treating secondary indications. Eight patents are listed in the Orange Book for Alendronate (Fosamax) tablets, other than product patent such as formulation, dosage regimen. Innovator for alendronate, Merck, has filed infringement action against the first generic filer and lost case, which led to the approval of generic soon after the expiry of product patent in 2008. In this case, the first filers Teva and Barr both received 180-day exclusivity from FDA which expired on 4 August 2008.^{33,34}

Apart from secondary patents, innovators are developing secondary dosage forms to avoid competition i.e. developing alternate dosage form and discontinuing the earlier dosage forms. For example, Carvedilol was approved in the form of tablets in September 1995. The NCE patent for Carvedilol expired in September 2007. Just before expiry, ER

capsule dosage form of carvedilol phosphate was approved by FDA in October 2006. Patents are listed in the Orange Book for this dosage form. The sale of ER capsules for the year ending March 2009 is \$ 440 million with an increase of 62%. The sales of carvedilol tablets decreased from \$ 1,305 million to 120 million.

Paragraph IV and 180-Day Exclusivities

In the years from 1984 to 1998, only three ANDA applicants qualified for 180-day exclusivity. Since the *Mova* decision in 1999, over 40 ANDAs have received 180-day of exclusivity.³² The district courts in *Mova Pharmaceutical Corp v Shalala*, held that 180 days of marketing exclusivity should be granted to the first ANDA applicant who files a Paragraph IV certification, regardless of whether the applicant is subsequently sued for patent infringement. This decision has been affirmed by the appeals court.³⁵

In the past, Dr Reddy's Laboratories and Ranbaxy were the two companies from India which have been very active in challenging patents in order to be the first to enter the generics market. These Indian two companies have been the FTF Paragraph IV ANDAs in several cases. Now, many Indian companies are willing to have the taste of fluoxetine made by Dr Reddy's.

Figure 3 shows the trend of ANDAs filed with Paragraph IV. It is clear that all ANDAs are not filed with Paragraph IV certification.³⁶⁻³⁸ One of the reasons for this might be that there are no patents listed in the Orange Book for these products or the patent(s) might be expiring in near future by the time

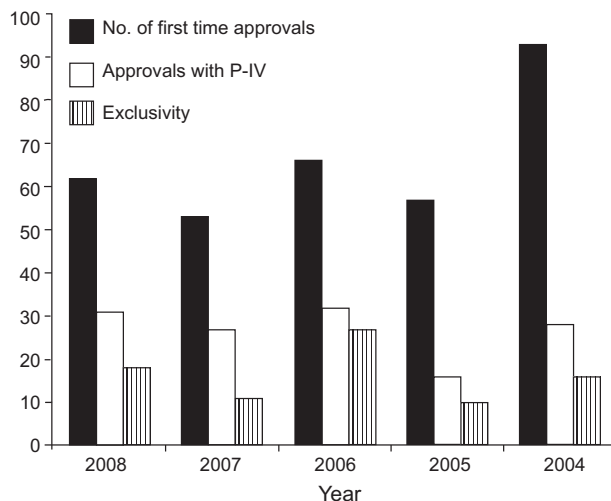


Fig. 3 — Trend of ANDAs filed with Paragraph IV

generics file ANDAs to avoid unnecessary 30 month stays or only one patent is listed which might be difficult to overcome/challenge by generics. Of the 554 first-time generics approved by FDA during 2004-08, 134 ANDAs are filed with Paragraph IV certification. Of the 134 ANDA approvals with Paragraph IV certification, 94 ANDAs have been granted 180-day exclusivity by FDA during the year 2004-08. In some cases multiple 180-day exclusivities have been granted for the same product. For example, 180-day exclusivity has been granted for Simvastatin to Ranbaxy and Teva. As Teva was first to file ANDA with Paragraph IV certification for 10 mg, 20 mg and 40 mg tablets, Ranbaxy was the first to file ANDA with Paragraph IV certification for 80 mg tablets. This resulted in multiple 180-day exclusivities for Simvastatin tablets. Similarly, Glenmark, Sun Pharma and Roxane have been granted 180-day exclusivity for Oxcarbazepine tablets on 9 October 2007. In this case, there are no patents listed in the Orange Book at the time of NDA approval and ANDAs have been filed soon after the expiry of NCE exclusivity. US Pat No 7,037,525 claiming particle size of Oxcarbazepine is listed in the Orange Book and all ANDA applicants filed Paragraph IV certification with respect to this patent on the same day, which resulted in multiple 180-day exclusivities for Oxcarbazepine tablets. As per the FDA regulations, 180 days exclusivity will be granted to the first applicant who files ANDA with Paragraph IV certification. If multiple generic applicants file ANDA

applications on the same day, exclusivity will be granted to all applicants.

Even though numbers of products for which patents have expired are less in 2006 compared to other years, 180-day exclusivities have been granted for more ANDAs than the rest.

Of the 554 first-time generic ANDA approvals by FDA during 2004-08, 83 ANDAs are approved for Indian companies. Ranbaxy with 19 approvals stands first followed by Dr Reddy's with 13. Fig. 4 shows the first-time generic approvals by Indian companies for the years 2004-08.³⁹

During 2004-08, 33 companies have received 180-day exclusivities. Of these, Teva is in first place with 15 ANDA approvals with 180-day exclusivities. Fig. 5 shows the number of 180-day exclusivities

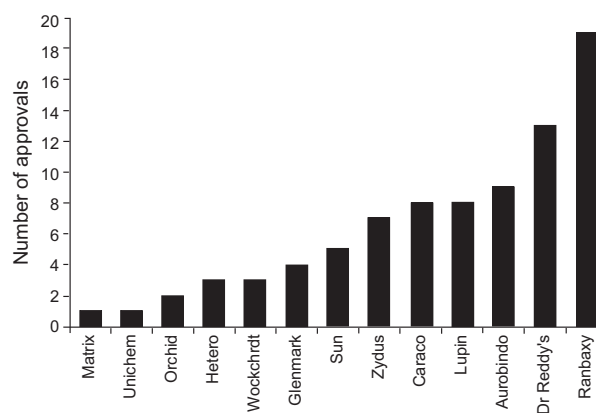


Fig. 4 — ANDA approvals received by Indian generic companies

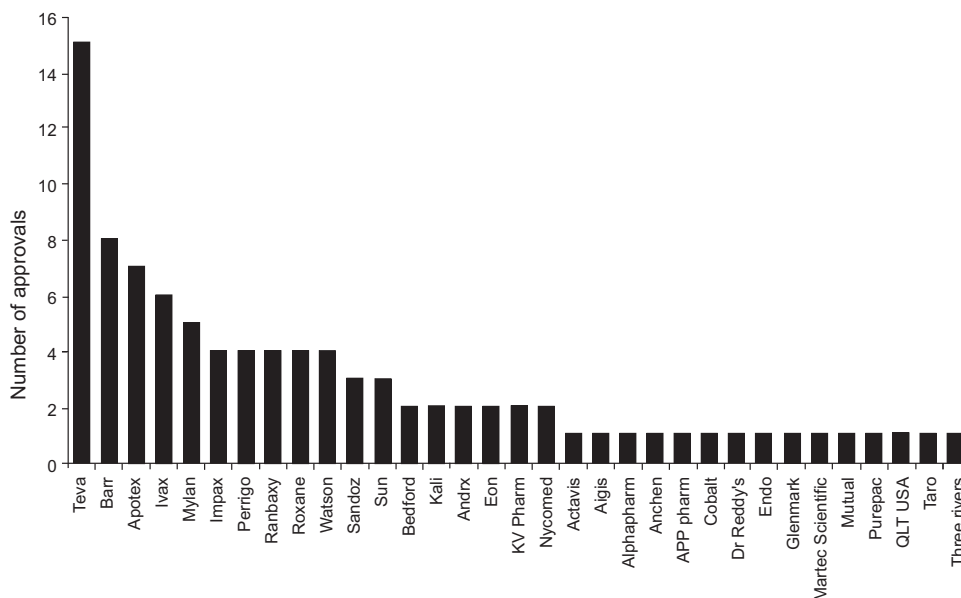


Fig. 5— 180-day exclusivities received during the period 2004-08

Table 5— 180-day exclusivities to Indian companies

S. No.	Generic drug name	Company	Approval date	Brand product annual sales
1	Ondansetron hydrochloride tablets, 4 mg (base), 8 mg (base), and 24 mg (base)	Dr Reddy's	26 Dec 2006	\$ 639 million
2	Loperamide hydrochloride and simethicone tablets, (otc) 2 mg/125 mg		6 Sept 2006	\$ 25.3 million (IRI - MAT: June 2006)
3	Pravastatin sodium tablets 80 mg	Ranbaxy	23 April 2007	\$ 1.19 billion (MAT: December 2006). 80 mg alone is \$ 209 million (MAT - Dec. 2006).
4	Quinapril tablets, 5 mg, 10 mg, 20 mg, and 40 mg		15 Dec 2005	\$ 555 million
5	Simvastatin tablets usp, 80 mg		23 June 2006	\$ 4.6 billion, 80 mg strength accounted for \$ 513 million (MAT: March 2006).
6	Amifostine for injection usp, 500 mg/vial		14 March 2008	\$ 80 million
7	Pantoprazole	Sun	10 Sept 2007	\$ 2.3 billion
8	Oxcarbazepine tablets, 150 mg, 300 mg, and 600 mg		10 Sept 2007	\$ 640 million
9	Oxcarbazepine tablets, 150 mg, 300 mg, and 600 mg	Glenmark	10 Sept 2007	

received by each company during the period 2004-08.^{39,40}

Of 94 ANDAs granted with 180-day exclusivity, four Indian companies have received 180-day exclusivities. The products and their sales for which Indian companies have received 180-day exclusivity are given in Table 5.^{13,17,19,20}

Post Hatch-Waxman Act Effect on Top Indian Pharma Companies

The authors studied the ANDA approvals by top 12 Indian companies during the years 2004-09 including first-time generics, number of 180-day exclusivities and the impact of these approvals on the sales as well as prospects of these companies. Fig.6 shows the few first-time generic products with patent expiry during 2004-08 and Indian companies share.^{39,40}

Indian companies are advancing in filing ANDAs with Paragraph IV with FTF status in the recent past. For example, Indian companies are the first to file ANDAs with Paragraph IV for 4 products out of 15 products by sales. Table 6 shows the top 15 US pharmaceutical products by sales and the FTF generic company which filed the ANDA and the likely possibility of 180-day exclusivity.

Of the 10 top products under litigation, Ranbaxy is the FTF for top three products and Sun pharma is FTF among others for Abilify.

Dr Reddy's filed first ANDA in 1997 and became the first Indian pharmaceutical company to obtain a 180-day exclusive marketing rights for a generic drug in the US market with the launch of Fluoxetine 40 mg capsules on 3 August 2001. Fluoxetine sales of \$ 68.5 million contributed 21% of the total turnover in 2001-02.

For the year 2006-07, revenues touched \$ 1041.6 million. Dr Reddy's obtained second 180-day marketing exclusivity with the launch of Ondansetron hydrochloride tablets in the last week of December 2006, which contributed \$ 60.2 million in revenues during the year 2006-07. The exclusivity for this product expired on 22 June 2007.

Dr Reddy's is first company to file ANDA with Paragraph IV certification for Finasteride 1mg tablets sold as Propacia by Merck. Merck filed lawsuit against DRL and later on settled the case. As part of the settlement, DRL became authorized generic for Simvastatin and Finasteride 5 mg tablets of Merck after the expiry of NCE patent.

Revenues from Paragraph IV ANDA products before exclusivity/settlement and after exclusivity / settlement period are given in Table 7.⁴²

Dr Reddy's was one of the first companies to file ANDA with Paragraph IV for sumatriptan succinate tablets and has been sued by Innovator Glaxo. Later,

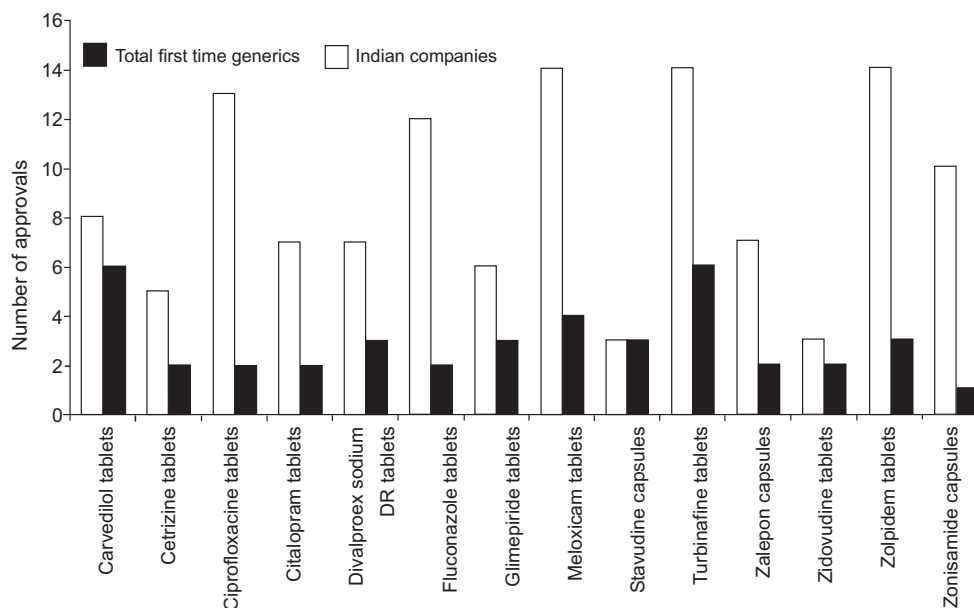


Fig. 6— First-time generic products with patent expiry during 2004-08 and Indian companies share

Table 6— Top 15 US pharmaceutical products by sales

Drug name	2008 sales in \$ billion ⁴¹	FTF generic company	180-day exclusivity possibility
Lipitor	7.8	Ranbaxy	Yes
Nexium	5.9	Ranbaxy	Yes
Plavix	4.9	Apotex	-
Advair diskus	4.4	No Para IV	-
Seroquel	3.9	Teva	No
Singulair	3.5	Teva	No
Enbrel	3.4	No Para IV	-
Neulasta	3.1	No Para IV	-
Actos	3.1	Ranbaxy, Mylan	Yes
Epogen	3.1	No Para IV	-
Prevacid	3.1	Teva	No
Abilify	3.1	Barr, Synthron, Sandoz, Sun	No
Remicade	3.1	No Para IV	-
Effexor XR	3.0	Teva	Yes
Lexapro	2.7	Teva	Yes

Dr Reddy's and Glaxo settled the lawsuit which allowed the launch of authorized generic version of sumatriptan succinate tablets in December 2008 that has contributed to \$ 150 million for the fiscal year 2009.⁴³

Dr Reddy's has 69 pending approval as of date. Of which, 30 ANDAs are filed with Paragraph IV including 18 FTFs. These products address innovator sales of \$ 46 billion.⁴⁴

Of these, Dr Reddy's is the FTF for Desloratadine, Rivastigmine, Ibandronate, Memantine, Zafirlukast, Omeprazole Mg OTC. DRL has settled Rivastigmine,

Desloratadine+ Pseudoephedrine, Desloratadine ODT with innovator companies.

Ranbaxy received first ANDA approval in 1997. Ranbaxy achieved global sales of Rs 7,250 crores (equivalent to \$ 1,682 million), a growth of 4% for the year 2008. Ranbaxy became the second Indian company to receive 180-day exclusivity with the approvals of Simvastatin, Pravastatin, and Quinapril.

From the ANDAs pending approval, Ranbaxy believes potential FTF opportunity on 19 products, valued at an innovator market size of around \$ 27 billion. During the year 2008, US market contributed sales of Rs 1,794 crores (equivalent to \$ 390 million).⁴⁵

Few FTF products of Ranbaxy are Atorvastatin, Esomeprazole, Valacyclovir, Pioglitazone. In Atorvastatin, Ranbaxy has challenged the NCE patent and lost the case with Pfizer. Subsequently, Pfizer and Ranbaxy have settled the case. Under the terms of the agreement, Ranbaxy will have a license to sell generic versions of Atorvastatin and the fixed-dose combination of Atorvastatin-Amlodipine besylate in the United States effective 30 November 2011 with 180-day exclusivity.^{20,46} Similarly, Ranbaxy has also settled Esomeprazole litigation with AstraZeneca.

Sun Pharma launched 3 products with 180-day exclusivities. However, launch of Pantoprazole and Amifostine are at risk, since the out come of the court litigations are still pending. Sun Pharma is the first Indian company to launch Pantoprazole product in the

Table 7— Revenues from Paragraph IV FTF ANDA products by Indian companies

Drug	Fiscal year ending 31 March 2007		Fiscal year ending 31 March 2008	
	Sales in \$ million	% Share	Sales in \$ million	% Share
Ondansetron	60.2	8.7	10.0	2.7
Simvastatin	289.5	41.8	5.3	3.5
Finasteride	39.8	5.8	35.8	9.7

% Share is percentage of total revenues from generics sales throughout the world.

US at risk. Sun Pharma filed 12 ANDAs with the US FDA in 2003-04, making it the first Indian company with the largest number of filings in the very first year. Of the, pending ANDA approvals, Sun Pharma is FTF for Alfuzosin, Atomoxetine, Desloratadine, Duloxetine, Gemcitabine, Levocetirizine, Pregabalin, Memantine, Rosuvastatin.⁴⁷

Glenmark's turnover in 2000 turnover was \$ 38.4 million and for the year ending March 2007, the turn over increased to \$ 498.81 million. There are four potential FTF Paragraph IV applications filed by Glenmark for products Desloratadine, Ezetimibe, Trandolopril+verapamil, Fluticasone Propionate 0.05% Lotion.

Aurobindo filed first ANDA in November 2003 and received approval in October 2004. The FTF Paragraph IV products include Atomoxetine, Alfuzosin, Rosuvastatin, Duloxetine.

Lupin entered the US generic pharmaceutical market in 2003 with the ANDA approval for Cefuroxime Axetil. Lupin is the first Indian company successfully invalidated molecule patent on Ramipril. However, Lupin could not get 180-day exclusivity, since Cobalt was FTF ANDA with Paragraph IV certification for Ramipril capsules and awarded 180-day exclusivity. Lupin believes that it has the FTF on Fortamet ER (Metformin extended release tablets) and Antara (Fenofibrate tablets). The total tally of FTF stands at 8.

Zydus has received 44 product approvals so far. Zydus has launched Simvastatin and Meloxicam following patent and exclusivity expiries. The FTF Paragraph IV products include Aripiprazole, Desloratadine, Divalproex ER tablets.

Matrix has been acquired by Mylan in June 2006. Matrix has filed its first FTF ANDA for Olmesartan.

Wockhardt is the only company to file ANDA with FTF for Entacapone and its combination with Carbidopa+Levodopa and is eligible for 180-day exclusivity. Orion has filed the first lawsuit in the US in 2007 and settled the lawsuit.⁴⁸

Orchid has made the first ANDA filing in 2004 and received the first approval for Cefazolin in 2005 in just 12 months from filing. Total ANDA filings as of December 2008 are 57. This includes 7 Paragraph IV FTF filings.

Recent ANDA Filings with FTF Paragraph IV and the Indian Companies Share

However, the trend of filing ANDA with FTF has been changing in the recent past. For example, 10 companies have filed ANDAs on the same day for Atomoxetine and Alfuzosin to have FTF status. Among the 10 companies, Glenmark, Sun, Aurobindo, Zydus for atomoxetine and Aurobindo, Ranbaxy, Sun, Torrent, Wockhardt for alfuzosin are Indian companies among others.⁴⁹

Thirteen companies have filed ANDAs on the same day with Paragraph IV certification to have FTF status for Memantine and Desloratadine in 2008. Of these Lupin, Orchid, Wockhardt, Dr Reddy's, Ranbaxy and Sun for Memantine and Orchid, Caraco, DRL Zydus, Glenmark, Lupin and Sun for Desloratadine are Indian companies among others.⁵⁰

Similarly, 8 companies have filed ANDAs on the same day with Paragraph IV certification to have FTF status for Duloxetine in 2008 and Pregabalin in 2009 including Aurobindo, Lupin, Sun and Wockhardt for Duloxetine and Lupin, Sun and Wockhardt for Pregabalin from India.^{51,52}

Conclusion

Though Hatch-Waxman Act was introduced in 1984, Indian companies made entry into the US generics market in 1997 with first approval by Ranbaxy. Since, then the number of companies as well as the number of ANDAs by Indian companies is increasing tremendously. Indian companies are competing with companies in other countries as well among themselves to launch the generic product on the day one soon after the expiry of the product patent. Most of top Indian companies reported herein have their major turnovers from US market.

In terms of DMF filings and manufacturing plant approvals, India now has 175 manufacturing plants approved by USFDA with highest number of DMFs. The cumulating DMFs filing by top 12 Indian companies itself is 1191. Of the 554 first-time generic ANDA approvals by FDA during 2004-08, 83 ANDAs are approved for Indian companies. Ranbaxy with 19 approvals stands first followed by Dr Reddy's with 13. The number of ANDAs with 180-day exclusivity by Indian companies is also increasing at a steady rate. The first being in 2001 for Dr Reddy's; followed by another one in 2005, 2 in 2006, 3 in 2007. As of date 4 Indian companies have received 180-day exclusivities.

However, there are many ANDAs filed with Paragraph IV certification pending approval by FDA with possible 180-days exclusivities. Indian companies have filed FTF ANDAs with Paragraph IV for top 4 products out of 15 products by sales. Recent trend also shows that Indian companies are aggressive in filing ANDAs with Paragraph IV to have FTF status for top selling products like Memantine, Rosuvastatin, Duloxetine, Pregabalin, Atomoxetine, Desloratadine etc.

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