

PHARMA
MATTERS

MOVERS AND SHAKERS

Thomson Scientific introduces its newest quarterly report on the generics industry using strategic intelligence and competitive analysis information from *Newport Horizon Global™*, the critical product targeting and global business development system from the industry authority on the global generics market.

What's happening in the US generics market



In this quarterly report, we look at a few of the companies beginning to make their mark on the US generics market either with their finished dose product or active ingredients, and analyze trends and statistics relating to the market as a whole.

Section I: Introduction

Despite its ageing population and health provision driven by cost-cutting employer insurance schemes, the market for generic drugs in the US isn't quite as attractive as it first appears.

As more and more generic companies enter the market, especially from countries such as India, existing players fight to retain market share, lowering dose prices and squeezing margins. It is expected that the competition will become even more fierce in the next few years as Chinese companies begin to target the US market.

In order to survive in the US generic market, companies must carefully target products for development and be able to control their costs. Among the strategies that companies use for lowering costs are sourcing active ingredients from lower cost countries, moving manufacturing overseas, or entering into alliances with companies in lower cost countries.

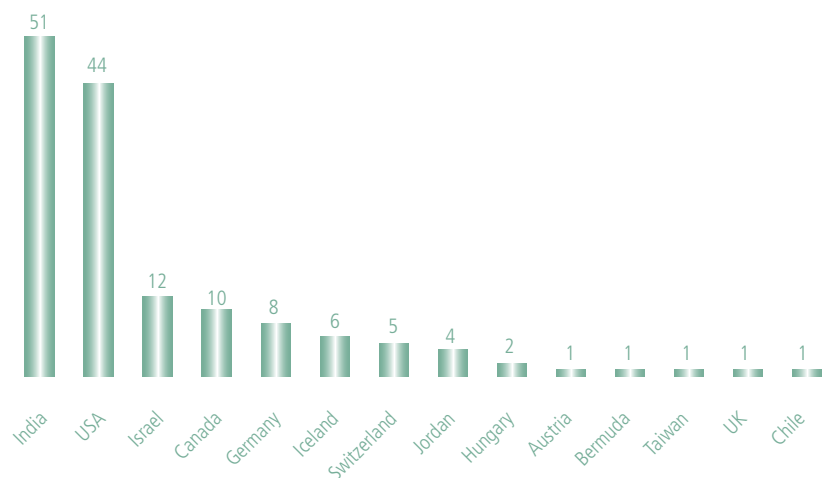
Accurate information about sources of active ingredients, potential partners, and competition is more important than ever before. Thomson Scientific's competitive intelligence and sourcing solution, *Newport Horizon Global* is designed to address exactly these information needs, profiling and rating API companies and aiding decision-making for generic drug companies and active ingredient manufacturers alike.

What is an ANDA?

An Abbreviated New Drug Application (ANDA) is the first step on releasing a generic drug in the US. It is submitted to the FDA to prove that the generic version is bioequivalent to the innovator drug in question. On approval, the generic version is added to the Approved Drug Products List ("Orange Book") and the company may manufacture and market it. An ANDA may be submitted before the patent on the innovator drug expires. However, in that case, the ANDA must include a certification indicating that the filer does not seek to market the product before the expiry of the Orange Book-listed patents ("paragraph III certification") or that the filer believes that its product does not infringe the Orange Book-listed patents or that the Orange Book-listed patents are invalid ("paragraph IV certification").

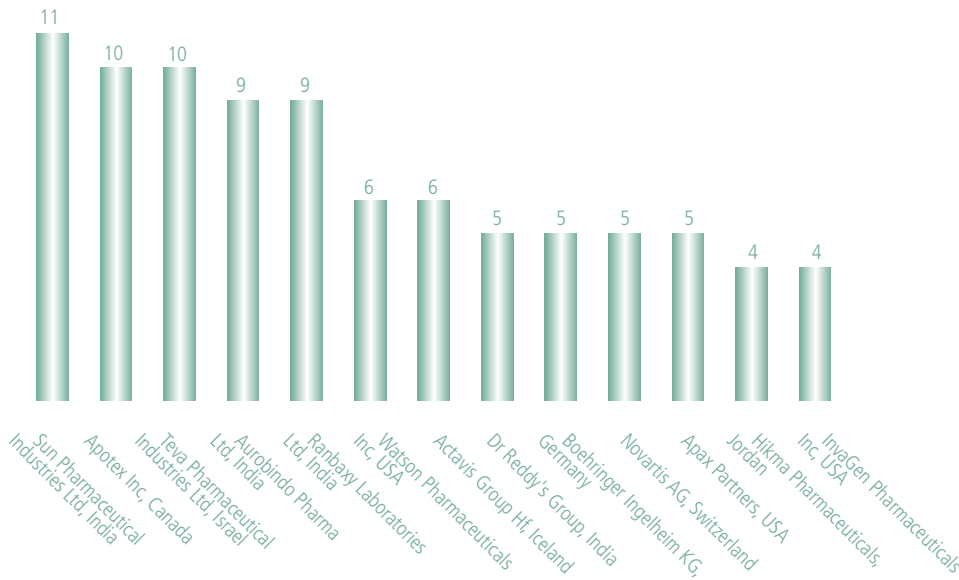
Section II: ANDA applications

Total ANDAs by country of origin of applicant for July to September 2007



From July to September 2007, the largest number of ANDA approvals went to India-based companies. Twelve different Indian groups received a total of 51 final ANDA approvals. During the same time period, 27 different US-based companies received a total of 44 approvals, putting the US in second place.

Groups with the most ANDA approvals for July to September 2007

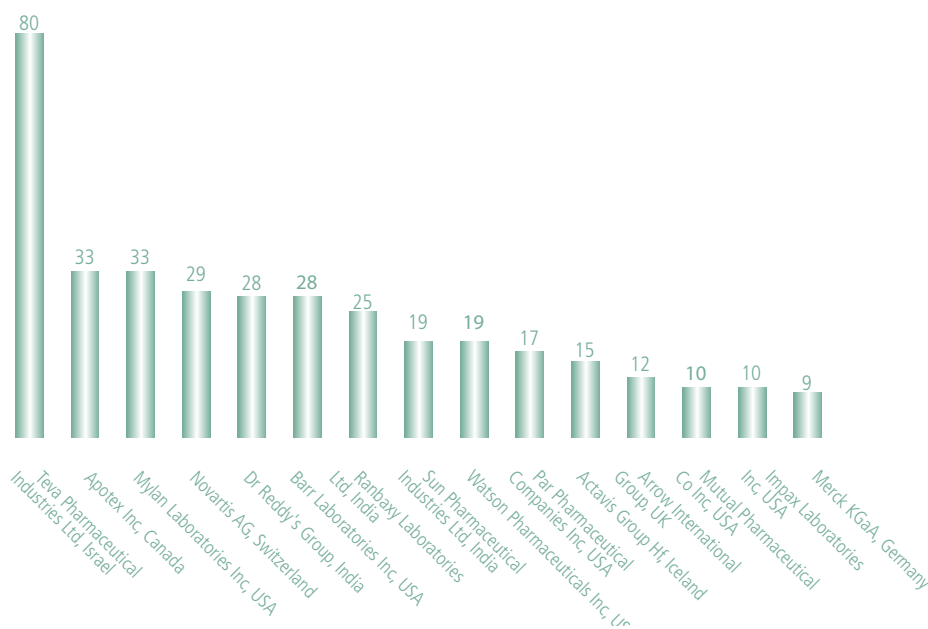


Sun Pharmaceutical of India received the most ANDA approvals between July and September 2007, with Teva (Israel) and Apotex (Canada) in shared second place. In addition to Sun, there were three other Indian companies, Ranbaxy, Aurobindo and Dr. Reddy's, in the top ten. The only US-based companies to feature were Watson with 6 ANDAs, and Apax Partners with 5 ANDAs.

Section III: Paragraph IV challenges

Due to its sheer size, the US market continues to attract attention. Companies can make a great deal of money in this market, especially if they succeed in being the first generic on the market. Many companies attempt to do this by challenging Orange Book-listed patents. The first company to file an ANDA with paragraph IV certification may be eligible for 180 days of market exclusivity if the challenge is successful. Teva is by far the most prolific patent challenger. At the time of the writing of this report, we had linked Teva to patent challenges on 80 different products.

Groups with the most patent challenges on record as of end of September 2007



What is a paragraph IV challenge?

Bioequivalent generic versions of drugs that are not protected by patents can be produced and marketed in the US by any company, subject to FDA approval. However, a generic company may obtain FDA approval before patent expiry if it certifies its product does not infringe the listed patents or the patents are invalid (paragraph IV certification). Patent holders may then sue the ANDA filer for patent infringement. If the patent holder sues the ANDA filer within 45 days of notification, the FDA may not approve the ANDA for 30 months from the date of notification. If no suit is filed within 45 days, the FDA may approve the ANDA at any time.

What is the 180-day exclusivity?

In order to encourage generic companies to develop noninfringing products and challenge invalid patents, the Hatch-Waxman act provides the incentive of 180 days of market exclusivity for the first company to file an ANDA with paragraph IV certification for a product. The 180-day period may begin from the date a company begins commercial marketing of the generic drug product, or from the date of a court decision finding the patent invalid, unenforceable, or not infringed.

Molecules first exposed to paragraph IV challenges between July and September 2007

Active Ingredient:	Alfuzosin Hydrochloride	<ul style="list-style-type: none">■ Several companies have filed ANDAs with paragraph IV certification for alfuzosin hydrochloride 10mg extended-release tablets: Actavis, Aurobindo, Barr, Mylan, Par, Ranbaxy, Sun, Teva, and Torrent.
Posted by FDA:	21 August 2007	<ul style="list-style-type: none">■ The Orange Book lists two patents covering alfuzosin hydrochloride 10mg extended-release tablets, expiring August 22, 2017.
Brand name:	Uroxatral	<ul style="list-style-type: none">■ At the time of the first ANDA filing in June 2007, there were numerous DMFs for alfuzosin HCl on file with the FDA, including one belonging to Aurobindo. We assume the Aurobindo ANDA references the Aurobindo DMF.
Innovator:	sanofi-aventis	
Active Ingredient:	Atomoxetine Hydrochloride	<ul style="list-style-type: none">■ ANDAs with paragraph IV certification for atomoxetine hydrochloride 10mg, 18 mg, 25mg, 40mg, 60mg, 80mg, and 100mg capsules have been filed by several companies: Actavis, Apotex, Aurobindo, Glenmark, Mylan, Sandoz, Sun, Synthron, Teva, and Zydus.
Posted by FDA:	14 August 2007	<ul style="list-style-type: none">■ There is only one patent listed for atomoxetine hydrochloride in the Orange Book. It is a new use patent entitled "Treatment of attention-deficit/hyperactivity disorder" and will expire on May 26, 2017 after a six month pediatric exclusivity.
Brand name:	Strattera	<ul style="list-style-type: none">■ At the time of the ANDA filing in May 2007, there were several active DMFs for atomoxetine HCl: Cadila Healthcare, Dr. Reddy's Laboratories, Hetero, Matrix, Solmag, Teva, and Zhejiang Jiuzhou. We assume the Zydus ANDA references the Cadila DMF, the Mylan ANDA references the Matrix DMF, and the Teva ANDA references Teva's DMF.
Innovator:	Eli Lilly	
Active Ingredient:	Entacapone	<ul style="list-style-type: none">■ At least one generic company has filed an ANDA with paragraph IV certification for entacapone 200mg tablets: Wockhardt.
Posted by FDA:	23 July 2007	<ul style="list-style-type: none">■ There are five patents currently listed in the Orange Book for entacapone, which expire between November 2007 and September 2018. US Patent 5,446,194 covers the entacapone drug substance. It has received an extension of 416 days and is due to expire on October 19, 2013. On August 13 2007, Orion announced that it had been informed of an ANDA with paragraph IV certification for three of the five Orange Book-listed patents covering entacapone.
Brand name:	Comtan	<ul style="list-style-type: none">■ At the time of the ANDA filing in April 2007, there were entacapone DMFs on file with the FDA belonging to Sun, Suven Life Sciences, and Wockhardt. We assume that Wockhardt's ANDA references its own DMF.
Innovator:	Orion Pharma	
Active Ingredient:	Ibandronate Sodium	<ul style="list-style-type: none">■ ANDAs with paragraph IV certification have been filed for ibandronate sodium 2.5mg and 150mg tablets. Cobalt has filed an ANDA for a generic version of Boniva (ibandronate sodium 2.5mg tablets). Among the ANDA filers for generic versions of Boniva Once-Monthly (ibandronate sodium 150mg tablets) are: Apotex, Cobalt, Dr. Reddy's Laboratories, Genpharm, Mutual, Orchid, and Teva.
Posted by FDA:	14 August 2007	<p>Teva has submitted two separate ANDAs with paragraph IV certification for generic versions of Boniva Once-Monthly (ibandronate sodium 150mg tablets).</p> <ul style="list-style-type: none">■ The Orange Book lists three patents covering ibandronate sodium 2.5mg tablets. The product patent expires on March 17, 2012 and the two formulation patents expire on April 21, 2017 and October 7, 2019.
Brand name:	Boniva	<p>For ibandronate sodium 150mg tablets, the Orange Book lists three patents covering a new use of ibandronate sodium and expires on May 6, 2023.</p> <ul style="list-style-type: none">■ At the time of the ANDA filings in May 2007, seven companies held active DMFs for ibandronate sodium: Aurobindo, Chemi, Chongqing Shenghuaxi, Dr. Reddy's Laboratories, Natco, Orchid, and Teva. We assume that Teva, Dr. Reddy's, and Orchid reference their own DMFs in their ANDAs.
Innovator:	Hoffmann-La Roche	

Active Ingredient:	Morphine Sulfate	<ul style="list-style-type: none"> At least one generic company has filed an ANDA with paragraph IV certification for Avinza (morphine sulfate extended-release capsules): Actavis.
Posted by FDA:	17 September 2007	
Brand name:	Avinza	<ul style="list-style-type: none"> The Orange Book lists only one patent covering Avinza (morphine sulfate extended-release capsules): expiring on November 25, 2017. It is a formulation patent covering an oral morphine multiparticulate composition with coated particles. In its ANDA, Actavis claimed non-infringement of this patent.
Innovator:	King Pharmaceuticals	<ul style="list-style-type: none"> At the time of the ANDA filing in June 2007, active DMF holders for morphine sulfate included Mallinckrodt, Noramco, and Siegfried.
Active Ingredient:	Nisoldipine	<ul style="list-style-type: none"> At least one ANDA with paragraph IV certification has been filed for nisoldipine 40mg extended-release tablets: Mylan.
Posted by FDA:	17 September 2007	
Brand name:	Sular	<ul style="list-style-type: none"> The Orange Book lists only one patent covering nisoldipine: It is a formulation patent that will expire on June 8, 2008.
Innovator:	Sciele Pharma	<ul style="list-style-type: none"> At the time of the ANDA filing in June 2007, three companies likely to supply generics held active DMFs: Actavis, Erregierre, and Lusochemica.
Active Ingredient:	Omeprazole Magnesium	<ul style="list-style-type: none"> At least one generic company has filed an ANDA with paragraph IV certification for Prilosec OTC (omeprazole magnesium) 20mg delayed-release capsules: Dr. Reddy's Laboratories.
Posted by FDA:	9 July 2007	
Brand name:	Prilosec OTC	<ul style="list-style-type: none"> At the time of the ANDA filing, there were eight patents covering Prilosec listed in the Orange Book. These patents expire between October 2007 and November 2019.
Innovator:	AstraZeneca	<p>In its suit against Dr. Reddy's, AstraZeneca alleges infringement of US Patent 5,690,960 and US Patent 5,900,424, which expire in November 2014 and May 2016 respectively.</p> <ul style="list-style-type: none"> At the time of the ANDA filing in March 2007, the two active omeprazole magnesium DMFs on file with the FDA belonged to Dr. Reddy's Laboratories and Matrix. Presumably the Dr. Reddy's ANDA references the Dr. Reddy's DMF.
Active Ingredient:	Temozolomide	<ul style="list-style-type: none"> At least one generic company has filed an ANDA with paragraph IV certification for temozolomide 5mg, 20mg, 100mg, and 250mg capsules: Barr.
Posted by FDA:	9 July 2007	
Brand name:	Temodar	<ul style="list-style-type: none"> There is only one patent covering Temozolomide listed in the Orange Book. The term of this patent was extended through August 2013; it has, however, been granted a six-month pediatric exclusivity, which extends the patent term to February 11 2014. Cancer Research Technology is the owner of this patent by assignment and has given Schering an exclusive license under the patent to make, use, and sell temozolomide.
Innovator:	Schering-Plough	<ul style="list-style-type: none"> At the time of the ANDA filing in March 2007, Chemagis held the only temozolomide DMF on file with the FDA.
Active Ingredient:	Tizanidine Hydrochloride	<ul style="list-style-type: none"> At least one ANDA with paragraph IV certification has been filed for tizanidine hydrochloride 2mg, 4mg, and 6mg capsules: Apotex.
Posted by FDA:	17 September 2007	
Brand name:	Zanaflex	<ul style="list-style-type: none"> The Orange Book lists only one patent covering tizanidine HCl capsules, it is a formulation patent that will expire on November 28, 2021. It covers an immediate-release formulation of tizanidine that when taken with food decreases the occurrence of somnolence.
Innovator:	Accorda Therapeutics	<ul style="list-style-type: none"> At the time of the ANDA filing in August 2007, there were several active DMFs on file with the FDA. This is not surprising because generic tizanidine HCl tablets have been on the market for years.

Section IV: Opening moves

Based on our research of ANDA filings and paragraph IV challenges, we highlight some of the companies making their first steps into the US generics industry.

Dabur India Ltd

A paragraph IV challenge was filed by [Dabur India Ltd](#) for the drug [oxaliplatin](#).

Founded in 1884 and based in Uttar Pradesh, Dabur India Ltd is one of the leading consumer goods companies in India. With thirteen manufacturing units worldwide and more than 1.5 million retail outlets in India alone, the company specializes in the production of healthcare, personal care and food products, and markets its products in more than fifty countries. The company's drugs and chemicals division manufactures bulk natural compounds and formulation products, exporting APIs to Europe, Latin America, Africa, and other Asian countries.

We have assigned it a Corporate API Rating of Less Established as the company is capable of supplying APIs to regulated markets. However, it has not accumulated as much experience as its Established counterparts. We confirm 19 APIs with commercially-available manufacturing status.

Dabur holds seven active drug master files and has two API manufacturing sites; one of them has been inspected by the US FDA. Dabur also has an FDA-inspected dose facility. The company has more than 150 launched dose products in a number of countries, mostly oral, topical and parenteral forms. Its total sales for 2006 were over US \$460 million with a forecast of over US \$700 million by 2009.

Dabur is among India's market leaders in anti-cancer drugs and is setting up a strategy for long-term growth of its pharmaceutical business by becoming a vertically-integrated global oncology player. In 2007, Dabur ended its sales and distribution agreement with Hospira and set up its own subsidiary company in the US, which is responsible for sales, marketing, and distribution of cancer drugs in the US.

The company has received FDA approval to market its generic anti-cancer drugs carboplatin, epirubicin and paclitaxel. On May 10, 2007, it notified sanofi-aventis of its patent challenge for oxaliplatin by filing its ANDA with paragraph IV certification.

Dabur has a strong research and development organization, having filed numerous patents for formulation, new use, process and product (derivative), mostly in the neoplasm therapy areas. It is currently developing new products and delivery systems for oncology products.

What is Corporate API Rating?

Corporate API Rating is a proprietary analytic by Thomson Scientific designed to indicate how capable a corporate group is of supplying bulk materials to regulated markets, such as North America and Europe. The rating values are:

Established

An experienced source with a history of supplying APIs to regulated markets.

Less established

A moderate track record in supplying APIs to regulated markets, either in terms of the number of years, or the number of products supplied. They are still considered capable of supplying regulated markets.

Potential future

The group has an interest in supplying regulated markets, but so far has no known performance.

Local

Locally focused only (non-regulated markets).

Big Pharma

Large innovator company.

Zhejiang Huahai Pharmaceutical Group Co Ltd

In July 2007, Zhejiang Huahai received tentative approval for nevirapine 200mg tablets under the President's Emergency Plan for AIDS Relief (PEPFAR) program. This was the first FDA approval of a finished dose product manufactured by a Chinese company.

PEPFAR offers an expedited review process for antiretroviral drugs, regardless of the existence of valid patents or market exclusivity in the US. Though Zhejiang Huahai's product meets all safety, efficacy, and manufacturing quality standards necessary for the US, it cannot be marketed there because of existing patent protection. It can be purchased only for distribution under the PEPFAR program. The tablets will be eligible for final FDA approval and in May 2012, upon patent expiry.

Established in 1989, Zhejiang Huahai focused initially on cardiovascular drugs, but has since expanded its portfolio to other therapeutic categories. It has a formulation workshop and 13 API workshops at its facility in Linhai in Zhejiang Province and currently holds 17 US drug master files, at least one European drug master file, and four active COS (European certificates of suitability).

The company has experienced dramatic growth in the past few years, almost tripling its sales between 2002 and 2006 to \$74 million — analysts expect it to reach \$143 million in 2009. We have assigned it a Corporate API Rating of Established.

GeneraMedix Pharmaceuticals Inc

Since April 2007, GeneraMedix Pharmaceuticals has received FDA approval to market methotrexate sodium preservative free, carboplatin, fluorouracil, and ampicillin-sulbactam combination product.

Based in Liberty Corner, New Jersey, GeneraMedix Pharmaceuticals produces generic parenteral products for hospital and specialty markets in the US, focusing on medicines that are difficult to formulate or have limited sources of raw material supply. To do this, the company is establishing strategic alliances with raw material suppliers, drug development companies, and final dosage manufacturers.

Carboplatin, fluorouracil and methotrexate sodium were the first products to result from a long-term relationship with India-based Intas Pharmaceuticals Ltd in which Intas developed the products and provides the commercial supplies.

The company has developed other partnerships. It signed a manufacturing contract with HollisterStier Contract Manufacturing to develop a process for compounding and lyophilizing a number of generic products and entered into a development and supply agreement with MN Pharmaceuticals, based in Turkey. The first product to result from this agreement is the ampicillin and sulbactam combination product.

About Newport Horizon Global

Newport Horizon Global is the critical product targeting and global business development system from Thomson Scientific, the industry authority on the global generics market.

Created specifically for generic pharmaceutical companies and strategic API manufacturers, it can help you to identify and evaluate product opportunities worldwide, ensuring you'll be first to find the generic product and niche opportunity, first to make the deal, and first to get to market.

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