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MOVERS AND SHAKERS

A PHARMA MATTERS REPORT.

JANUARY – MARCH 2008

The Thomson Reuters quarterly report on the US generics industry using strategic intelligence and competitive analysis information from *Newport Horizon Premium*[™], the critical product targeting and global business development system from the industry authority on the global 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.

For more information on Thomson Reuters API Intelligence solutions, including *Newport Horizon Premium*, visit scientific.thomsonreuters.com/newport

SECTION I: INTRODUCTION

We're used to telling you about how robust the generics market has become, and highlighting the unprecedented growth in this sector. But there are problems, too. It's certain that the current boom in new generic drugs cannot last, simply because today's downturn in innovation will translate to a decline in off-patent drugs from 2012.

Equally, pharmaceutical growth is now focused on specialist therapy areas, leaving the primary care market depressed. It's not yet clear what impact these changes will have to the long-term generics business, particularly since we're going through a period of intensive globalization that is changing the whole face of the market.

Meanwhile, the boom in off-patent drugs, the rapidly expanding global market, and economies of scale are creating a new elite of 'super generic' companies such as Teva and Mylan, who themselves now rank among the top pharmaceutical organizations in the world. These are the companies that will be best able to weather future downturns, and are likely to continue to dominate the generics market as it stabilizes. We can expect a large amount of merger and acquisition activity as companies attempt to bulk themselves up for the coming drought.

Newport Horizon Premium, the competitive intelligence and sourcing solution from Thomson Reuters, is designed to address the needs of the industry, profiling and rating API companies and aiding decision-making for generic drug companies and active ingredient manufacturers alike. So let's look at the significant activity in the US market this quarter.

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").

WHAT ARE "A" RATED DRUGS?

"A" rated drugs are considered therapeutically equivalent and can be substituted for each other. "A" rated drugs are designated as AA, AB, AN, AO, AP, and AT in the Orange Book.

WHAT IS A US DMF?

A DMF (Drug Master File) is a confidential document covering a specific manufacturing facility, process or article used in the manufacturing, processing, packaging or storing of a bulk drug. A DMF is reviewed by the FDA only if an ANDA or NDA referencing that particular DMF is filed. An ANDA or NDA will not be approved until any issues with the DMF are resolved.

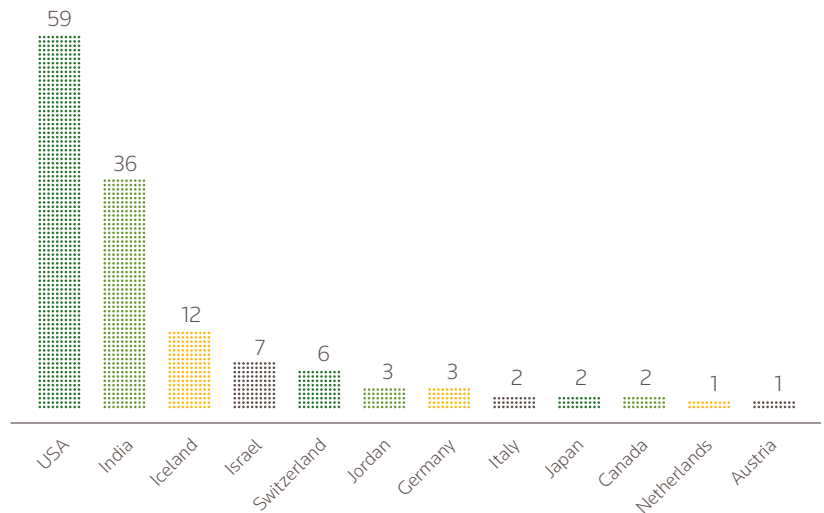
WHAT IS THE 180-DAY EXCLUSIVITY?

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.

SECTION II: ANDA APPROVALS

During the first quarter of 2008, final approvals were issued on 134 'A'-rated ANDAs, up from 108 the quarter before. Among the products that saw first generic approvals this quarter was alendronate sodium (Merck's Fosamax®), a blockbuster treatment for osteoporosis.

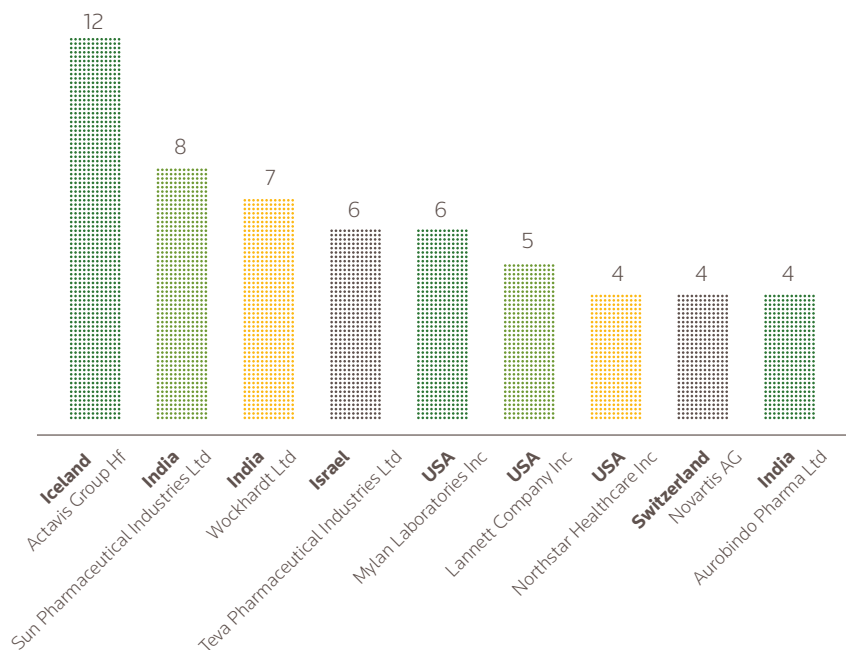
TOTAL 'A'-RATED ANDAS BY COUNTRY OF ORIGIN OF APPLICANT FOR JANUARY TO MARCH 2008



The largest number of ANDA approvals this quarter went again to US-based corporations. Thirty different US-based corporations received a total of 59 final ANDA approvals. During the previous quarter, 30 different US-based groups had received a total of 51 final ANDA approvals.

Just like the previous quarter, Indian corporations were in second place in terms of final ANDA approvals, with fourteen India-based corporations receiving a total of 36 ANDA approvals. Nine India-based companies received a total of 21 approvals in the last quarter of 2007.

GROUPS WITH THE MOST 'A'-RATED ANDA APPROVALS FOR JANUARY TO MARCH 2008



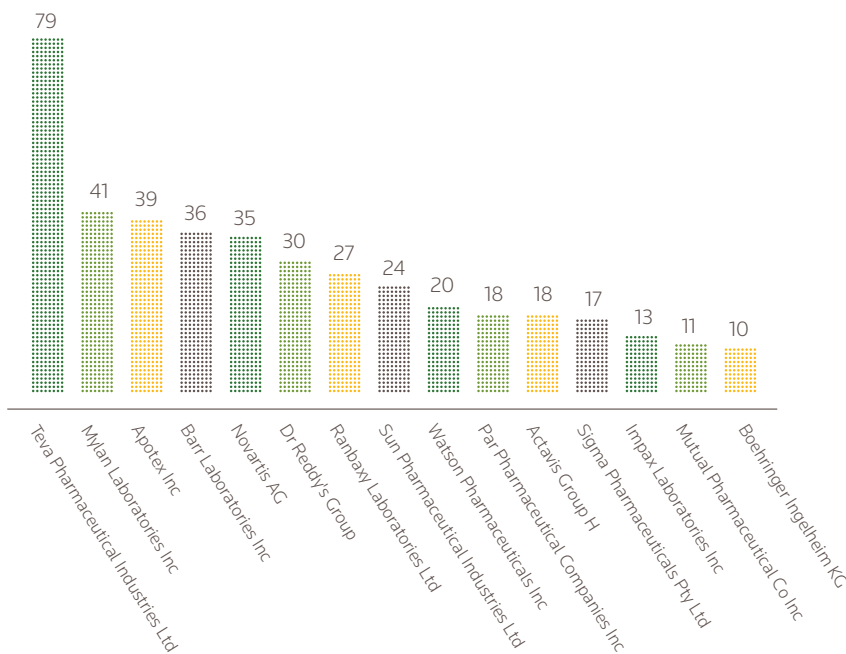
Actavis of Iceland received the most final ANDA approvals this quarter (12). Two Indian companies, Sun Pharmaceuticals with eight approvals and Wockhardt with seven approvals were in second and third place respectively.

Teva of Israel with eight ANDA approvals, Aurobindo of India with seven approvals, and Apotex of Canada with six approvals were in the top three during the previous quarter.

SECTION III: PARAGRAPH IV CHALLENGES

In the first quarter of 2008, we learned of first paragraph IV patent challenges on 11 new products (four combination products and seven single active ingredient products), among them blockbusters such as tadalafil (Eli Lilly's Cialis®). This is in comparison to the previous quarter, in which we learned of challenges on only seven new products.

GROUPS WITH THE MOST PATENT CHALLENGES ON RECORD AS OF MARCH 2008



At the time of writing this report, Teva continued to be by far the most prolific filer of ANDAs with patent challenges. We link Teva to challenges on 79 products in total. Mylan has moved to second place with links to patent challenges on 41 different products.

WHAT IS CORPORATE API RATING?

Corporate API Rating is a proprietary analytic by Thomson Reuters 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.

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.

NEW PRODUCTS FIRST EXPOSED TO PARAGRAPH IV CHALLENGES, AS REPORTED BY THE FDA BETWEEN JANUARY AND MARCH 2008

ACTIVE INGREDIENT: alendronate sodium, cholecalciferol

POSTED BY FDA: 27 Feb 2008

BRAND NAME: Fosamax® Plus D

NDA HOLDER: Merck

- At least one company has filed an ANDA with paragraph IV certification for a generic version of Fosamax Plus D tablets (alendronate sodium and cholecalciferol 70mg/2800 IU and 70mg/5600 IU). At this time we do not know which company filed the ANDA.
- At the time of the ANDA filing in November 2007, the Orange Book entry for Fosamax Plus D tablets included five patents, which have been granted pediatric exclusivity expiring between February 6, 2008 and January 17, 2019.

ACTIVE INGREDIENT: carvedilol phosphate

POSTED BY FDA: 21 Mar 2008

BRAND NAME: Coreg CR™

NDA HOLDER: GlaxoSmithKline

- An ANDA with paragraph IV certification for carvedilol phosphate 40mg and 80mg extended-release capsules (Coreg CR) was filed by at least one company: Mutual.
 - There are currently four unexpired patents covering Coreg CR listed in the Orange Book:
 - US Patent 5,902,821 expires August 7, 2016 after a six-month pediatric exclusivity.
 - US Patent 6,022,562 expires April 17, 2016 after a six-month pediatric exclusivity.
 - US Patent 7,268,156 expires December 27, 2023 after a six-month pediatric exclusivity.
 - US Patent RE40,000 expires December 7, 2015 after a six-month pediatric exclusivity.
 - *In its suit against Mutual, GSK alleges infringement of US Patent 7,268,156, which Mutual claims is invalid.*
 - At the time of the first ANDA filing in November 2007, Matrix and Wanbury held the only DMFs for carvedilol phosphate on file with the FDA. Presumably the Mutual ANDA references one of those DMFs.
-

ACTIVE INGREDIENT: doxercalciferol

POSTED BY FDA: 14 Jan 2008

BRAND NAME: Hectorol®

NDA HOLDER: Genzyme

- At least one company has filed an ANDA with paragraph IV certification for a generic version of Hectorol injection (doxercalciferol injection 2mcg/mL, 2mL ampules): Pentech Pharmaceuticals.
- Doxercalciferol injection is covered by three patents listed in the Orange Book:
 - US Patent 5,707,980, covering new use and titled "*Method for treating and preventing loss of bone mass*" expires on August 17, 2010.
 - US Patent 5,602,116, another new use patent, expires on February 11, 2014.
 - US Patent 6,903,083, covering stabilized 1alpha-hydroxy vitamin D, expires on July 18, 2021.
 - *In the suit against Pentech, the plaintiffs Bone Care and Genzyme allege infringement of US Patent 5,602,116 and US Patent 6,903,083.*
- Teva held the only active DMF for doxercalciferol at the time of the ANDA filing in October 2007.

ACTIVE INGREDIENT: drospirenone, estradiol

POSTED BY FDA: 21 Mar 2008

BRAND NAME: Angeliq®

NDA HOLDER: Bayer Healthcare

- At least one ANDA with paragraph IV certification has been filed for a generic version of Angeliq (drospirenone/estradiol 0.5mg/1mg tablets). At this time, we do not know which company filed the ANDA.
- The Orange Book lists only one patent for Angeliq. US Patent 6,933,395 concerns a process for producing drospirenone and will expire on August 11, 2017.
- At the time of the filing of the ANDA with paragraph IV certification, Schering, Gedeon Richter, and Industriale Chimica held the only active DMFs for drospirenone on file with the FDA. Schering, Pfizer, Gedeon Richter, Dr. Reddy's, and Organon held active DMFs for estradiol.

ACTIVE INGREDIENT: dutasteride

POSTED BY FDA: 30 Jan 2008

BRAND NAME: Avodart®

NDA HOLDER: GlaxoSmithKline

- At least one company has filed an ANDA with paragraph IV certification for dutasteride 0.5mg capsules: Barr.
- Dutasteride capsules are covered by three patents listed in the Orange Book:
 - US Patent 5,565,467 claims dutasteride specifically. It has been granted an extension of 766 days and will expire on November 20, 2015.
 - US Patent 5,846,976 covers methods of using dutasteride to treat androgen responsive conditions. It will expire on September 17, 2013.
 - US Patent 5,998,427 covers androstenediones and claims dutasteride generically. It will expire on September 17, 2013.
 - *In its suit against Barr, GlaxoSmithKline alleged infringement of all three patents.*
- At the time of the ANDA filing in October 2007, Dr. Reddy's Laboratories and Sterling SNIFF Italia held the only active DMFs for dutasteride API on file with the FDA.

ACTIVE INGREDIENT: tadalafil	<ul style="list-style-type: none"> At least one company has filed an ANDA with paragraph IV certification for tadalafil 5mg, 10mg, and 20mg tablets. At this time, we do not know the identity of the ANDA filer or filers.
POSTED BY FDA: 30 Jan 2008	<ul style="list-style-type: none"> Tadalafil tablets are covered by five patents listed in the Orange Book. The patents will expire between July 11, 2016 and November 19, 2020.
BRAND NAME: Cialis®	<ul style="list-style-type: none"> It appears that Matrix and Teva held the only active DMFs for tadalafil on file with the FDA at the time of the ANDA filing in November 2007.
ACTIVE INGREDIENT: lamivudine	<ul style="list-style-type: none"> ANDAs with paragraph IV certification have been filed for lamivudine 100mg, 150mg, and 300mg tablets. At this time, we do not know the identity of the filer or filers.
POSTED BY FDA: 14 Jan 2008, 11 Feb 2008	<ul style="list-style-type: none"> The Orange Book lists three patents covering Eпивir (lamivudine 150mg and 300mg tablets): <ul style="list-style-type: none"> US Patent 5,047,407 is the product patent for lamivudine. It has been granted an extension of 282 days and will expire on May 17, 2010 after a six-month pediatric exclusivity. US Patent 5,905,082 covers crystalline oxathiolane derivatives and will expire on November 18, 2016 after a six-month pediatric exclusivity. US Patent 7,119,202 specifically references the cis isomer of lamivudine. It has been granted an extension of 282 days and will expire on August 8, 2009 after a six-month pediatric exclusivity.
BRAND NAME: Eпивir®, Eпивir® HBV	<ul style="list-style-type: none"> For Eпивir-HBV (lamivudine 100mg tablets), the Orange Book lists those three patents and US Patent RE39,155. That patent covers the use of 1,3-oxathiolane nucleoside analogues in the treatment of hepatitis B and will expire on January 2, 2014 after a six-month pediatric exclusivity.
NDA HOLDER: GlaxoSmithKline	<ul style="list-style-type: none"> At the time of the first ANDA filing in October 2007, there were several active DMFs for lamivudine on file with the FDA.
ACTIVE INGREDIENT: levocetirizine dihydrochloride	<ul style="list-style-type: none"> At least one company has filed an ANDA with paragraph IV certification for levocetirizine dihydrochloride 5mg tablets: Synthron.
POSTED BY FDA: 27 Feb 2008	<ul style="list-style-type: none"> At the time of the ANDA filing in December 2007, the Orange Book listed only one patent covering levocetirizine dihydrochloride tablets. US Patent 5,698,558 describes methods for treating allergic disorders using optically pure (-) cetirizine and will expire on September 24, 2012. Sepracor is the owner of this patent and UCB is the exclusive licensee.
BRAND NAME: Xyzal®	<ul style="list-style-type: none"> At the time of the ANDA filing in December 2007, Cipla, Dr. Reddy's Laboratories, and Glochem Industries held the only DMFs for levocetirizine dihydrochloride on file with the FDA.
NDA HOLDER: UCB Pharma	

ACTIVE INGREDIENT: miconazole nitrate

POSTED BY FDA: 27 Feb 2008

BRAND NAME: Monistat® 1 Combination Pack

NDA HOLDER: Johnson & Johnson

- At least one company has filed an ANDA with paragraph IV certification for the Monistat 1 Combination Pack (miconazole nitrate 1200mg suppository and 2% cream): Perrigo. Other miconazole nitrate products have been available generically for years.
- At the time of the ANDA filing in December 2007, the Orange Book listed two patents for the Monistat 1 Combination Pack.
 - US Patent 5,514,698 is a formulation patent covering antifungal vaginal cream composition and will expire on March 21, 2014.
 - US Patent 6,153,635 covers methods and kits for treating vulvovaginal candidiasis with miconazole nitrate and will expire November 28, 2020.
 - *In its suit against Perrigo, McNeil-PPC alleges infringement of US Patent 6,153,635. Perrigo has challenged the validity of all claims of the patent and asserted non-infringement of claims 1-7 and 11.*
- At the time of the ANDA filing in December 2007, there were several DMFs for miconazole nitrate on file with the FDA.

ACTIVE INGREDIENT: polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid

POSTED BY FDA: 21 Mar 2008

BRAND NAME: MoviPrep®

NDA HOLDER: Salix Pharmaceuticals

- An ANDA with paragraph IV certification has been filed for a generic version of MoviPrep (Polyethylene Glycol 3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate, and Ascorbic Acid for oral solution) by at least one company: Novel Laboratories.
- The Orange Book lists only one patent for MoviPrep. US Patent 7,169,381 concerns colon cleansing compositions and methods and will expire on September 1, 2024.

ACTIVE INGREDIENT: risedronate sodium, calcium carbonate

POSTED BY FDA: 27 Feb 2008

BRAND NAME: Actonel® with Calcium

NDA HOLDER: Procter & Gamble

- At least one company has filed an ANDA with paragraph IV certification for a generic version of Actonel with Calcium tablets (risedronate sodium 35mg and calcium carbonate 1250mg, equivalent to 500mg elemental calcium): Teva.
- At the time of the ANDA filing in December 2007, the Orange Book entry for Actonel with Calcium tablets included seven patents, expiring between November 21, 2011 and August 14, 2018.
 - In its suit against Teva, Procter & Gamble alleges infringement of only US Patent 5,583,122. This patent was the subject of related cases concerning Teva's proposed generic risedronate sodium tablets. On February 28, 2008, the court issued an opinion in one of the related cases, finding specific claims of US Patent 5,583,122 valid, enforceable and infringed by Teva's proposed risedronate sodium tablets.
- At the time of the ANDA filing in December 2007, several DMFs for risedronate sodium were on file with the FDA, including one belonging to Teva.

SECTION IV: OPENING MOVES

Based on our research of ANDA filings and paragraph IV challenges, we highlight some of the companies who made opening moves in the US generics industry toward the end of 2007 and at the beginning of 2008.

INDICUS PHARMA LLC/USV LTD

In December 2007, [Indicus Pharma LLC](#) and [USV Ltd](#) received their first ANDA approval, for minocycline hcl in 50mg, 75mg and 100mg tablets. Their ANDA for glycopyrrolate 1mg and 2mg tablets was approved in March 2008.

Indicus is a niche generic product manufacturer focusing on its home US market. Established in 2005, the partners in the company claim to have experience with over 90 ANDA filings, including paragraph IV and first-to-file submissions. The company specializes in oral controlled-release formulations. It is also involved in new molecule research.

The company's development and manufacturing process is located at USV's facility in India. USV owns approximately 90% equity in Indicus, which it hopes will increase its penetration of the US market. According to its managing director, the company has a "mixed bag" of 25 generic products under development.

Newport Horizon Premium gives USV a corporate API rating of Established, meaning that it has a history of supplying APIs to regulated markets such as the US.

NAVINTA LLC

Based in Ewing, New Jersey, [Navinta LLC](#) received its first ANDA approval in March 2008, for fomepizole 1.5gm per 1.5ml. The company is also linked to at least one patent challenge, for Abraxis's ropivacaine hydrochloride monohydrate.

The company's Chief Executive Officer, Dr Mahendra Patel PhD, is of some note in the pharmaceutical industry. With over 30 years of experience, he was co-founder and partner of generics company Invamed (now part of Novartis) and chief scientific officer of Sandoz. He's held senior management positions in R&D at both Bristol Myers Squibb and Lederle, and currently also sits on the boards of Zydus Pharmaceuticals USA Inc and Emcure. Dr Patel holds 30 patents to his name.

Navinta focuses on novel routes of synthesis of new and existing drug molecules, novel formulations of liquid dosage form, novel oral dosage form, novel injectable dosage form and implantable drug delivery devices.

In August 2007 it entered into an exclusive worldwide licensing agreement with Tikvah Therapeutics Inc, a biopharmaceutical company focused on new treatment options to better manage central nervous system diseases. This agreement encompasses unique solution formulations including a proprietary formulation

of sodium phenylbutyrate and methods of use and treatments of a variety of neurodegenerative disorders including spinal muscular atrophy, amyotrophic lateral sclerosis and multiple sclerosis.

Navinta's challenge to ropivacaine hydrochloride monohydrate, covered by an Orange Book-listed patent, has resulted in a 30-month stay that prevents FDA approval of its generic ropivacaine products until mid-2009, unless it prevails in its litigation with Abraxis before then.

Newport Horizon Premium shows that Navinta holds eight active DMFs and at least 5 patents filed or approved in the US. In several cases, it relies on Indian manufacturers to do the API manufacturing. The company filed two manufacturing applications for controlled substances (fentanyl and sufentanil) in 2004, but as far as we know these applications have not yet been approved.

SYNTHON PHARMACEUTICALS INC

During the second half of 2007, *Synthon Pharmaceuticals Inc* achieved a number of ANDA approvals. The company is also linked to several recent ANDAs with paragraph IV patent challenges, including levocetirizine (Xyzal®) for the relief of symptoms associated with allergic rhinitis and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

Synthon is a research, development and production company founded in 1991 in the Netherlands. It introduced its first generic product two years later, dobutamine, and its best-selling product simvastatin in 2003. The company has factories in Barcelona and San Lorenzo, and produces more than 40 drugs for the European market. Active ingredients are produced in the Czech Republic and Argentina, and the dosage forms are formulated in Spain. The medicines are then packed in Spain or the US — keeping the entire process under Synthon's quality control.

In April 2004 Synthon launched Pexeva®, a formulation of paroxetine mesylate, for the treatment of depression in the US. Legal action from GlaxoSmithKline, whose Paxil® uses paroxetine hydrochloride, was settled in December. Synthon also has approval to market the anti-depressant fluvoxamine (Luvox™) but has not yet placed it on the market.

In 2007, the company announced that it was abandoning entirely its plans to make branded drugs in the US, choosing to focus on its existing generics business.

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Focuses on the latest phase changes in the pharmaceutical pipeline.

MOVERS AND SHAKERS

Unravels the most significant game-play in the US generics market.

WHO IS MAKING THE BIGGEST SPLASH

Reviews the leading sources of information on medical research.

ABOUT NEWPORT HORIZON PREMIUM

Newport Horizon Premium 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.

Newport Horizon Premium offers all the benefits of our existing industry-standard *Newport Horizon Global™* solution — the same ease-of-use, its comprehensive data and outstanding features — but it also incorporates significant new content including kilogram and International Unit API consumption data from IMS and routes of synthesis information from Prous Science, a Thomson Reuters business.

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