



IMAGE COPYRIGHT: iSTOCKPHOTO

MOVERS AND SHAKERS

A PHARMA MATTERS REPORT.

OCTOBER – DECEMBER 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 marks on the US generics market either with their finished dose products 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 go.thomsonreuters.com/generics

SECTION I: INTRODUCTION

We saw a significant amount of merger and acquisition activity in the generics sector during the last quarter of 2008. This was fueled by companies pursuing access to new markets, both in terms of new geographical markets and enlarged product portfolios, integrating API manufacturing, and finding economies of scale to weather the uncertain economic climate.

Teva strengthened its dominance of the market by acquiring Barr, Daiichi Sankyo gained a majority share (64%) of Ranbaxy (whose imports to the US, you'll remember, were banned by the FDA last quarter), and Perrigo bought up Laboratorios Diba, S.A., Unico Holdings and JB Laboratories. There was also significant 'backward integration', such as Sun's complete acquisition of Chattem Chemicals.

While the industry continued to convulse, *Newport Horizon Premium* kept its eye on all the major deals and tracked the game play as it unfolded. The talk at December's IGPA conference in Geneva, Switzerland, was on the declining sales growth of the global pharmaceutical market in key countries. While the generics market in the US has ballooned to more than \$73 billion in 2008, its growth has slowed dramatically, dropping to 3% for the 12 months ending June 2008. Just a few years ago, that growth rate was well into the double digits.

According to IMS, during the 12 months ending September 2008, generic sales actually fell for the first time ever. Only two of the top ten generic companies in the US market (Teva and Hospira) managed positive growth last year. The pressures are being blamed on rapid price erosion due to increasing competition, most notably the influx of pharmaceuticals from India. It is likely that Chinese generic imports will add even more pressure in a few years, though at the moment the abundant local market seems to be suppressing Chinese plans to expand into the US.

Looking forward further still, the IGPA speakers suggested that follow-on biologics offered substantial future opportunities for the market, but the traditional generic industry may not have the skill-set required to exploit them, including biologic manufacturing and formulation capabilities, clinical trial and marketing experience, and sufficient capital for investing. Perhaps the branded pharmaceutical companies (such as Merck, which recently announced its interest in the follow-on biologics sector) might be better equipped. Besides, though biogenerics are already available in the EU, as well as a number of other countries including Australia and Japan, US manufacturers and distributors are still awaiting a workable biogenerics bill—great hopes are pinned on the new administration, which has already indicated its awareness of the problem.

But first, let's take a more in-depth 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 for 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?

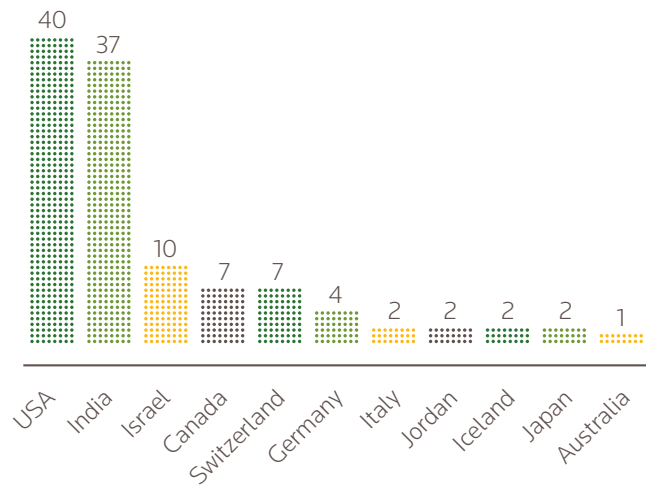
A DMF (Drug Master File) is a confidential document covering a specific manufacturing facility, process or article used in the manufacturing, processing, packaging or storing of a bulk drug. A DMF is reviewed by the FDA only if an ANDA or NDA referencing that particular DMF is filed. An ANDA or NDA will 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 non-infringing 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 FDA may not approve additional ANDAs for a period of 180 days commencing from the first commercial marketing of the first-to-file product. In cases where more than one ANDA with Paragraph IV certification is filed on the same day, the period of exclusivity may be shared.

SECTION II: ANDA APPROVALS

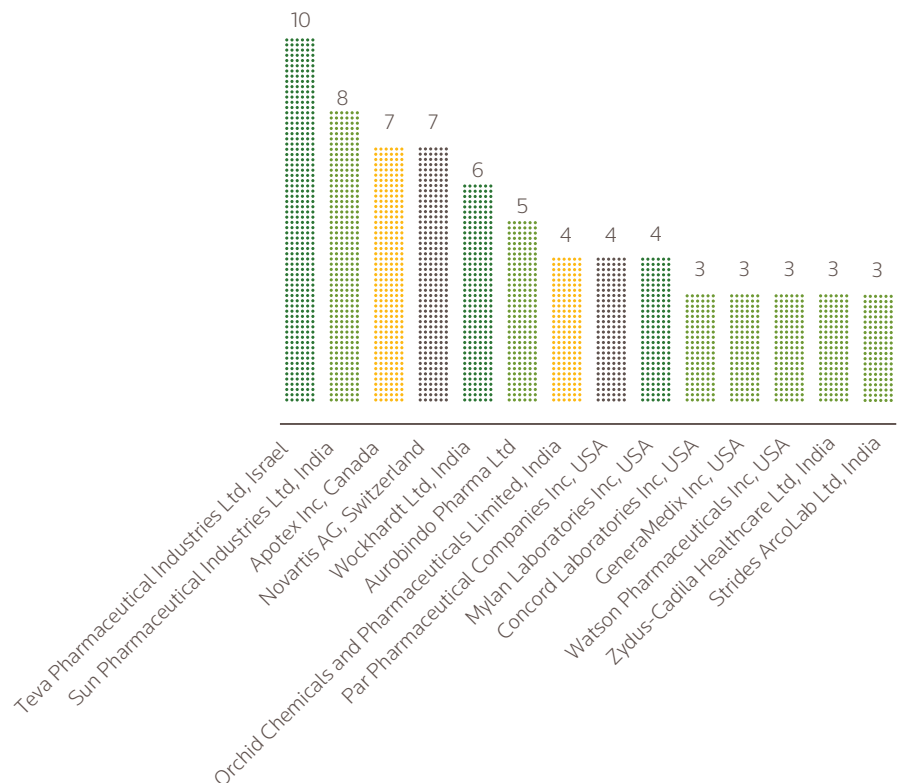
TOTAL 'A'-RATED ANDAS BY COUNTRY OF ORIGIN OF APPLICANT FOR OCTOBER TO DECEMBER 2008



During the fourth quarter of 2008, US-based companies were in first place in terms of final ANDA approvals, with 23 groups receiving a total of 40 approvals. The second largest number of approvals went to groups based in India—with 13 groups receiving a total of 37 approvals. This is a reversal of the situation during the previous quarter, when Indian groups led over US companies.

Taking 2008 as a whole, India edged out a narrow victory overall, with 151 approvals going to 21 groups. Close behind them, the US saw 148 approvals going to 40 groups. The third place went to Israel, where two groups received a total of 40 ANDA approvals.

GROUPS WITH THE MOST 'A'-RATED ANDA APPROVALS FOR OCTOBER TO DECEMBER 2008



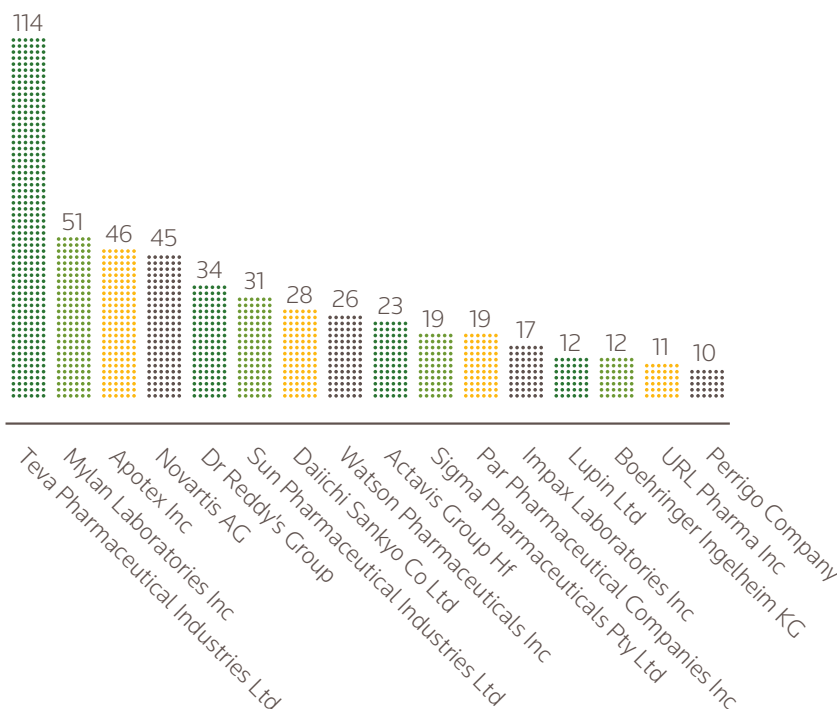
During the final quarter of 2008, Teva of Israel received 10 ANDA approvals, which put it at the top of our list. Sun Pharmaceutical of India was in second place with eight approvals. Apotex of Canada and Novartis (Sandoz) of Switzerland shared the third place with seven approvals each.

The top recipients of ANDA approvals from the third quarter—Mylan and Boehringer Ingelheim—received fewer approvals (4 and 1 respectively) in the fourth quarter.

SECTION III: PARAGRAPH IV CHALLENGES

In the fourth quarter of 2008, we learned of first Paragraph IV patent challenges on eight new active ingredients or combinations, a slight increase from the seven during the previous quarter.

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



At the time of the writing of this report, Teva continued to be by far the most prolific filer of ANDAs with patent challenges. We currently link it to challenges on 114 products, up from 85 the previous quarter. The big jump is due to Teva's acquisition of Barr, which we had linked to patent challenges on 42 products.

Mylan has remained in second place with links to patent challenges on 51 products, up from 48 the previous quarter. Apotex (46 products) and Novartis (45 products) follow closely behind.

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 OCTOBER AND DECEMBER 2008

-
- ACTIVE INGREDIENT:** desflurane
- POSTED BY FDA:** 01 December 2008
- BRAND NAME:** Suprane®
- NDA HOLDER:** Baxter
- At least one company has filed an ANDA with Paragraph IV certification for a generic version of Suprane (desflurane) volatile liquid for inhalation: Minrad.
 - At the time of the ANDA filing, the Orange Book listed only one unexpired patent covering Suprane (desflurane). US Patent 5,617,906 claims a container for a liquid anesthetic agent for supplying the agent to a vaporizer. The pediatric exclusivity associated with that patent will expire on October 8, 2014.
 - At the time of the September 2008 ANDA filing, Minrad held the only active DMF for desflurane on file with the FDA.

-
- ACTIVE INGREDIENT:** duloxetine hydrochloride
- POSTED BY FDA:** 03 November 2008
- BRAND NAME:** Cymbalta®
- NDA HOLDER:** Eli Lilly
- Several companies have submitted ANDAs with Paragraph IV certification for generic versions of Cymbalta (duloxetine hydrochloride) delayed-release capsules, including Actavis, Aurobindo, Cobalt, Impax, Lupin, Sandoz, Sun, and Wockhardt.
 - The Orange Book lists three patents covering Cymbalta delayed-release capsules.
US Patent 5,023,269 claims duloxetine specifically and its salts generically. It has been granted a five-year extension and will now expire on June 11, 2013.
US Patent 5,508,276 claims an enteric duloxetine pellet used in a delayed-release formulation. It will expire on July 18, 2014.
US Patent 6,596,756 concerns the treatment of fibromyalgia with duloxetine and will expire on September 10, 2019.
 - FDA lists many active DMFs for duloxetine HCl, including those belonging to ANDA filers Aurobindo, Lupin, Sun, and Wockhardt.

-
- ACTIVE INGREDIENT:** emtricitabine, tenofovir disoproxil fumarate
- POSTED BY FDA:** 03 November 2008
- BRAND NAME:** Truvada®
- NDA HOLDER:** Gilead Sciences
- At least one company has filed an ANDA with Paragraph IV certification for a generic version of Truvada (emtricitabine and tenofovir disoproxil fumarate) tablets: Teva.
 - The Orange Book lists ten patents covering Truvada tablets, expiring between May 2010 and September 2021. In its suit against Teva, Gilead alleged infringement of US Patent 6,642,245 and US Patent 6,703,396. Those patents are owned by Emory University and licensed exclusively to Gilead.
 - When the first ANDA for a generic version of Truvada was filed, Aurobindo, Cipla, Hetero, Matrix, and Ranbaxy held active DMFs for both emtricitabine and tenofovir disoproxil fumarate.
-

ACTIVE INGREDIENT: fluticasone propionate

POSTED BY FDA: 03 November 2008

BRAND NAME: Cutivate®

NDA HOLDER: Nycomed

- At least one company has filed an ANDA with Paragraph IV certification for a generic version of Cutivate (fluticasone propionate) lotion, 0.05%: Glenmark Generics.
- The Orange Book lists only one patent covering Cutivate lotion, 0.05%. US Patent 7,300,669 is a formulation patent and will expire on October 20, 2019.
- When the first ANDA for a generic version of Cutivate lotion was filed in July 2008, there were multiple active DMFs for fluticasone propionate. This is not surprising because other generic products containing fluticasone propionate have been approved in the US since 2004.

ACTIVE INGREDIENT: oxybutynin

POSTED BY FDA: 01 October 2008

BRAND NAME: Oxytrol®

NDA HOLDER: Watson

- At least one company has filed an ANDA with Paragraph IV certification for a generic version of Oxytrol (oxybutynin) transdermal system 3.9mg/24hr: Barr.
- The Orange Book lists nine patents covering Oxytrol transdermal system.

In its suit against Barr, Watson alleged infringement of eight patents expiring on April 26, 2015 or April 26, 2020.

Watson did not allege infringement of US Patent 5,164,190, which covers Watson's transdermal delivery device and will expire on December 11, 2010.

- At the time of the Barr's ANDA filing, it appears that BASF Orgamol Pharma Solutions and PCAS held active DMFs for oxybutynin base. Several companies held active DMFs for oxybutynin chloride at that time.

ACTIVE INGREDIENT: paricalcitol

POSTED BY FDA: 16 October 2008

BRAND NAME: Zemplar®

NDA HOLDER: Abbott Laboratories

- At least one company has filed an ANDA with Paragraph IV certification for a generic version of Zemplar (paricalcitol) capsules: Teva.
- The Orange Book lists two patents covering Zemplar capsules. US Patent 5,246,925 claims the use of paricalcitol to treat hyperparathyroidism. It has been granted an extension of 574 days and a pediatric exclusivity expiring on October 17, 2012.

US Patent 5,587,497 is the product patent for paricalcitol. It has also been granted a pediatric exclusivity, which will expire on June 24, 2014.

- At the time of the ANDA filing in August 2008, it appears that Teva, ALP Pharm Beijing Company, and Formosa Laboratories held active DMFs for paricalcitol. We assume Teva's ANDA references the Teva DMF.

ACTIVE INGREDIENT: sevelamer hydrochloride	<ul style="list-style-type: none"> • At least one company has filed an ANDA with Paragraph IV certification for a generic version of Renagel (sevelamer hydrochloride) tablets.
POSTED BY FDA: 01 October 2008	
BRAND NAME: Renagel®	
NDA HOLDER: Genzyme	

ACTIVE INGREDIENT: sumatriptan succinate, naproxen sodium	<ul style="list-style-type: none"> • At least two companies have filed ANDAs with Paragraph IV certification for generic versions of Treximet (sumatriptan succinate/naproxen sodium) tablets: Alphapharm (Mylan) and Par. • The Orange Book lists three unexpired patents covering Treximet (sumatriptan succinate/naproxen sodium) tablets. US Patent 6,060,499 and US Patent 6,586,458 concern the combination of 5HT receptor agonists with long-acting NSAIDs for the treatment of migraine. Both patents will expire on August 14, 2017. US Patent 7,332,183 is a formulation patent expiring on October 2, 2025. • At the time of the ANDA submissions, there were many active DMFs for each component of the combination. Matrix, a Mylan subsidiary, holds DMFs for both compounds.
POSTED BY FDA: 01 October 2008	
BRAND NAME: Treximet®	
NDA HOLDER: GlaxoSmithKline	

SECTION IV: OPENING MOVES

Based on our research of ANDA filings and paragraph IV challenges, we highlight some of the companies making significant game play in the US generics industry.

AKORN-STRIDES

For Akorn-Strides, this has been a significant year. At the beginning of 2008, the partnership held just one ANDA. By the time of this report, it had received 12 approvals, and boasted a product portfolio including 29 ANDAs with a total of 53 SKUs or product line offerings. Its first ANDA submission was filed in April 2006, and it generated its first product revenues in the third quarter of 2008 (from the launch of rifampin for injection).

The partnership is a joint development, manufacturing and marketing venture, funded equally, made in 2004 between **Akorn, Inc** and **Strides Arcolab Ltd**. Its purpose is to develop liquid, lyophilized and dry powder formulations of generic injectable products. In practice, this means that Strides has been charged with developing the ANDA products in its 13 world class manufacturing plants in India, Singapore, Brazil, Mexico, Poland and Italy, and Akorn with filing the appropriate submissions in the US.

Strides, formed in Bangalore in 1990, is one of India's largest exporters of pharmaceuticals, and among the world's top five soft gelatin capsule manufacturers, with 40 regulated products, a marketing presence in 55 countries and annual sales approaching \$100 million at the time of the partnership. In addition, it has formed a technical and marketing alliance with Sandoz to supply tuberculosis treatments to the Global TB Drug Facility, and a marketing deal with KV Pharmaceuticals for 10 generic products in the US and Canada, among many other agreements.

Strides is also involved with active ingredient manufacturing from its manufacturing sites in India and Italy. *Newport Horizon Premium* gives it a Corporate API Rating of 'Less Established'.

US-based Akorn has a longer track-record. Formed in 1971, it is NASDAQ listed and markets and distributes a number of generics as well as brand medicines, among them a range of ophthalmic treatments including IC-Green[®], AK-Fluor[®], Paremyd[®], Hydase[®], Fluress[®], Ful-Glo[®], and Gentak[®], and the Afluria[®] influenza virus vaccine. Its first internally-developed NDA product Akten[®], a topic anesthetic for eye surgery, was launched in October 2008.

In January 2009, Akorn announced that its President and Chief Executive Officer, Arthur Przybyl, is leaving the company. Pending selection of a new President and Chief Executive Officer, a committee of three board members will oversee operations of the Company.

ANCHEN PHARMACEUTICALS

Taiwan-based generic company **Anchen Pharmaceuticals**, a wholly-owned subsidiary of Anchen Inc, of Irvine, California, gained its first ANDA approval in November 2008, for divalproex sodium DR 500mg tablets (a generic equivalent to Abbott's Depakote® DR).

It was a busy month for the company. At the same time, its parent company launched Bupropion HCl ER 150mg tablets, the generic equivalent of GlaxoSmithKline's depression treatment Wellbutrin® XL. And the same month, Anchen Inc settled with Wyeth over a US patent infringement case pertaining to its proposed generic capsule formulation of the antidepressant Effexor® XR. Under the terms of the settlement, Wyeth has granted Anchen a license to launch its generic capsule formulation no earlier than June 1, 2011 (with the possibility of a limited earlier launch no earlier than January 1, 2011), and with the condition of FDA approval for the ANDA. Anchen will pay Wyeth royalties on sales of its generic version.

Anchen focuses on developing and marketing extended release and niche generic products, and has participated in a number of Paragraph IV challenges (for bupropion hydrochloride, divalproex sodium, pseudoephedrine sulfate, desloratadine, venlafaxine hydrochloride, and zolpidem tartrate).

Anchen Pharmaceuticals holds two plants in Taiwan—a research unit in Taipei, formerly owned by Empax Pharma Inc, with which the company merged in 2006, and a production unit in Chung-Li. It is working with two universities in Taiwan to research an integrin protein inhibitor as a possible treatment for cancer.

CYPRESS PHARMACEUTICAL INC

With more than 160 prescription and over the counter (OTC) pharmaceutical products already under its belt, **Cypress Pharmaceutical Inc**, formed in the US in 1993, has announced that it will continue to expand its product portfolio through the execution of an ANDA strategy. Although the company has a large number of products in its portfolio, the first ANDA approval in its name (for granisetron HCl solution) was granted in February 2008. In the last quarter of 2008, Cypress received final approval of ANDAs for cetirizine HCl syrup (prescription and OTC) and calcium acetate tablets. The company also boasts a large number of ANDA products in various stages of development—more than 35 at last notice.

The company is also going after patent challenge opportunities. Through the end of December 2008, we had linked the company with one Paragraph IV patent challenge, for ranitidine, a generic equivalent of Glaxo's Zantac® syrup. In January 2008, Cypress reached an agreement with GlaxoSmithKline to resolve the dispute surrounding ranitidine. Under the terms of the agreement, Glaxo would not assert its patent against the Cypress alcohol-free formulation of its generic ranitidine syrup. Since then we have learned that Cypress has informed Allergan and Boehringer Ingelheim of its patent challenge on epinastine HCl ophthalmic solution, 0.05%, a generic version of Elestat®.

Cypress outsources its manufacturing to a network of contractors in the US and Canada. In January 2008, Cypress entered into a multiple generic product development and marketing agreement with Standard Chem & Pharm Co Ltd of Taiwan, which gives Cypress exclusive rights to market Standard's generic drug products in the US.

The company also holds a specialty branded business, Hawthorn Pharmaceuticals, to market its own products in the US. We noted total company revenues of more than \$100 million in 2005.

To sign up to our Pharma Matters range of publications visit:
scientific.thomsonreuters.com/forms/matters/

THE ONES TO WATCH

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 Reuters, 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.

ABOUT THOMSON REUTERS

Thomson Reuters is the leading source of intelligent information for professionals around the world. Our customers are knowledge workers in key sectors of the global economy. We supply them with the intelligent information they need to succeed in fields that are vital to developed and emerging economies such as law, financial services, tax and accounting, healthcare, science and media.

Our knowledge and information is essential for drug companies to discover new drugs and get them to market faster, for researchers to find relevant papers and know what's newly published in their subject, and for businesses to optimize their intellectual property and find competitive intelligence.

NOTE TO PRESS:

To request further information or permission to reproduce content from this report, please contact:

Sue Besaw

Phone: +1 215 823 1840

Email: susan.besaw@thomsonreuters.com

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

Scientific Regional Head Offices

Americas

Philadelphia +1 800 336 4474
+1 215 386 0100

Europe, Middle East and Africa

London +44 20 7433 4000

Asia Pacific

Singapore +65 6411 6888
Tokyo +81 3 5218 6500

For a complete listing of Scientific offices, visit:
scientific.thomsonreuters.com/contact

