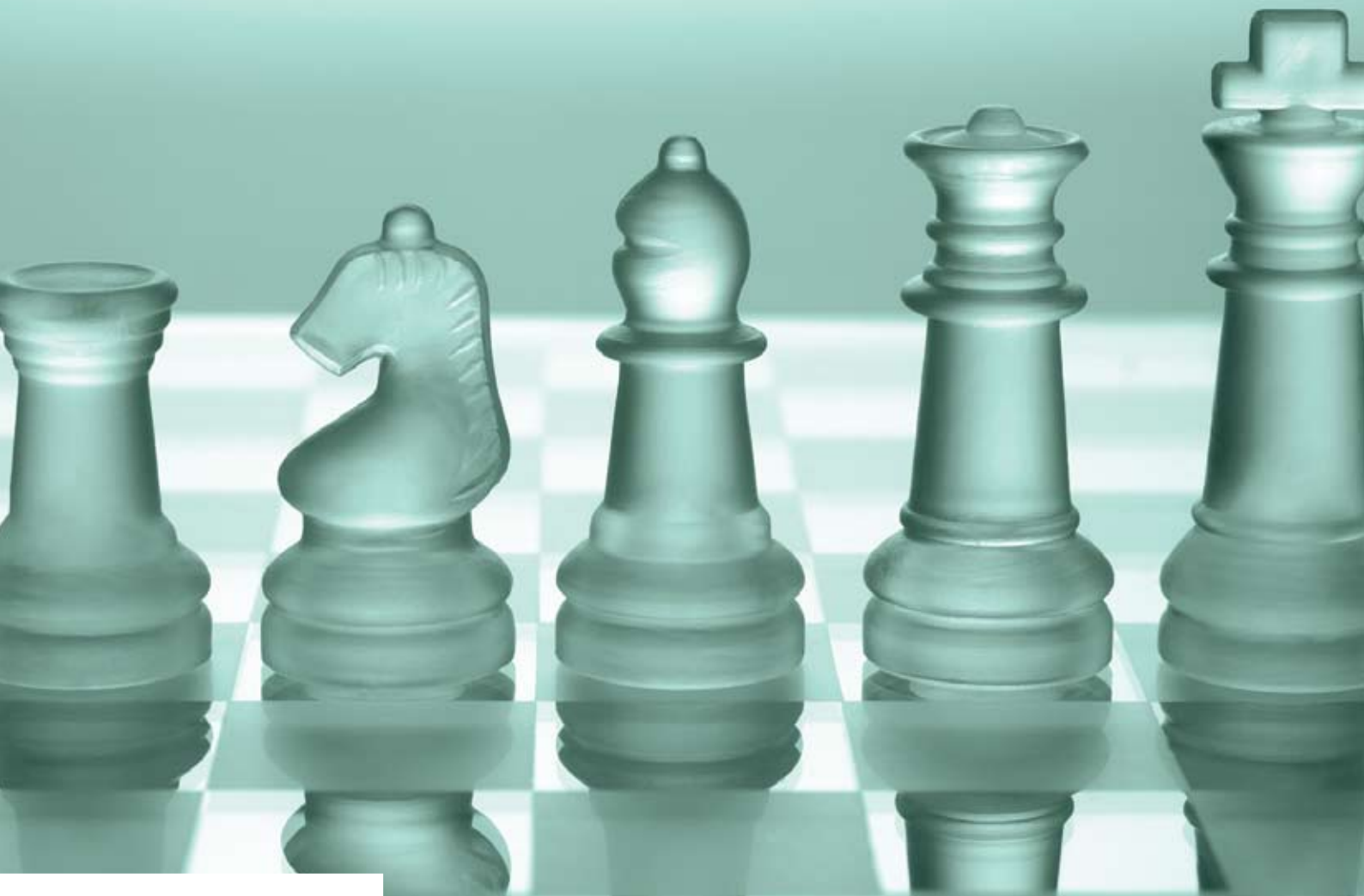


PHARMA
MATTERS

MOVERS AND SHAKERS

Thomson Scientific's 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.

Section I: Introduction

Now that the dust has settled on 2007, we can see it as a year of unprecedented competition in the US generics market, driven primarily by the number of new players entering the field.

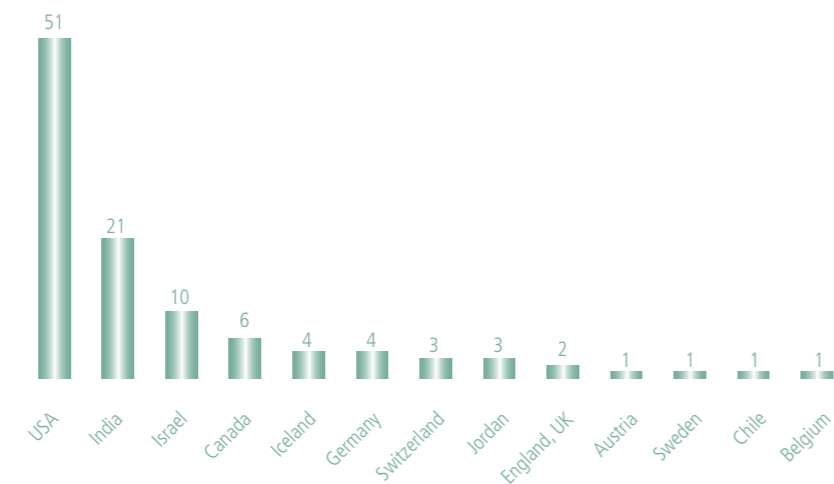
“A” rated ANDA approvals climbed to a record of more than 480, an increase from 365 the previous year. Paragraph IV patent challenges also continued at a fierce pace. At least forty different drug products were exposed to paragraph IV challenges for the first time in 2007, almost a doubling of the 24 in 2006.

It seems likely that competition will increase still further this year, meaning that early, 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 Premium* 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.

Section II: ANDA approvals

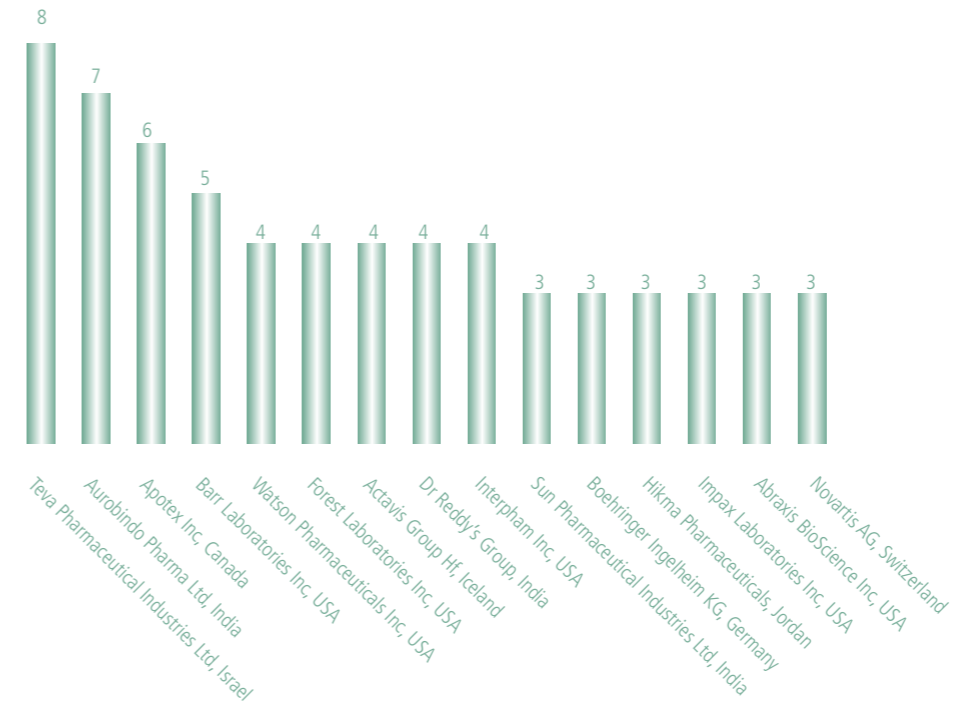
Total “A” rated ANDAs by country of origin of applicant for October to December 2007



During the last quarter of 2007, the largest number of ANDA approvals went to US-based companies. Thirty different US-based groups received a total of 51 final ANDA approvals.

In the same time period, nine India-based companies received a total of 21 approvals, putting India in second place. In the previous quarter, Indian-based companies were the leaders in terms of ANDA approvals with 51, while US-based companies received a total of 44 approvals.

Groups with the most “A” rated ANDA approvals for October to December 2007

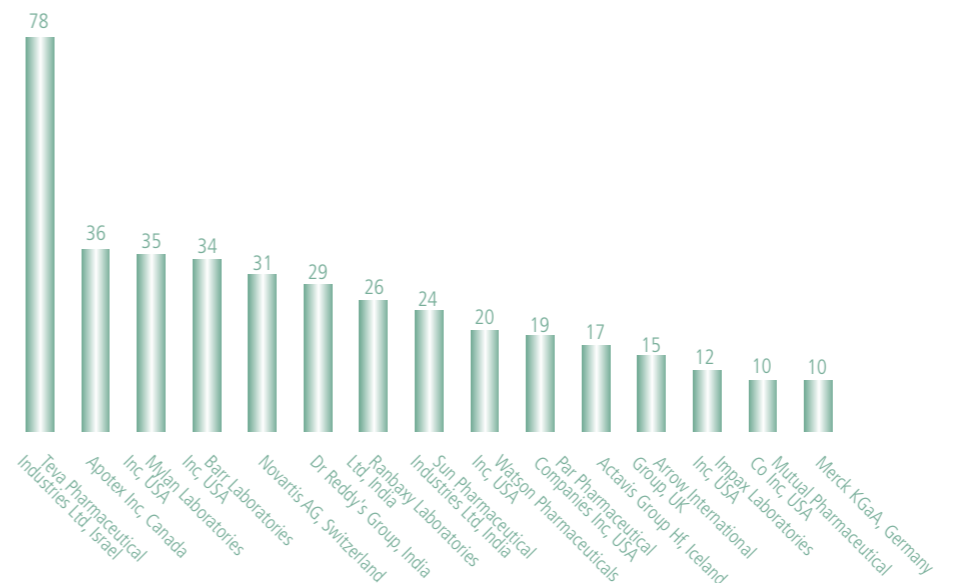


In the last quarter of 2007, Teva of Israel received the most final ANDA approvals, followed by Aurobindo of India and Apotex of Canada. During the previous quarter, Sun Pharmaceutical of India had received the most ANDA approvals (11), followed by Teva and Apotex, each with ten.

Section III: Paragraph IV challenges

In the last quarter of 2007, we learned of first paragraph IV patent challenges on seven new products, among them AstraZeneca’s blockbuster high cholesterol treatment Crestor® (rosuvastatin calcium). At the time of writing, Teva was by far the most prolific filer of ANDAs with patent challenges. We are currently linking them to challenges on 78 products.

Groups with the most patent challenges on record as of end of December 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.

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 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”).

New products first exposed to paragraph IV challenges, as reported by FDA between October and December 2007

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|---|--|
| <p>Active Ingredient: trandolapril + verapamil hydrochloride</p> <p>Posted by FDA: 19 October 2007</p> <p>Brand name: Tarka®</p> <p>NDA Holder: Abbott</p> | <ul style="list-style-type: none"> ■ At least one company has filed an ANDA with paragraph IV certification for trandolapril and verapamil HCl extended-release tablets: Glenmark. ■ The Orange Book currently lists only one patent covering trandolapril and verapamil HCl extended-release tablets. US Patent 5,721,244 covers the combination of angiotensin-converting enzyme inhibitors with calcium antagonists and will expire on February 24, 2015. Sanofi-Aventis Deutschland is the owner of US Patent 5,721,244 and Abbott Laboratories is an exclusive licensee for the manufacture, use, and sale of trandolapril and verapamil HCl combination products. ■ At the time of the ANDA filing in July 2007, multiple DMFs were on file with the FDA for both trandolapril and verapamil HCl. Glenmark held an active DMF for trandolapril and we assume it is referenced in the Glenmark ANDA. |
| <p>Active Ingredient: rosuvastatin calcium</p> <p>Posted by FDA: 2 November 2007</p> <p>Brand name: Crestor®</p> <p>NDA Holder: IPR Pharmaceuticals/AstraZeneca</p> | <ul style="list-style-type: none"> ■ Several companies have filed ANDAs with paragraph IV certification for rosuvastatin calcium 5mg, 10mg, 20mg, and 40mg tablets: Apotex, Aurobindo, Cobalt, Glenmark, Mylan, Par, Sandoz, Sun, and Teva. ■ Crestor tablets are covered by three Orange Book patents: <ul style="list-style-type: none"> - US Patent RE37314 claims both rosuvastatin and its calcium salt. It will expire on January 8, 2016. - US Patent 6,316,460 is a formulation patent that will expire on August 4, 2020. - US Patent 6,858,618 covers the use of rosuvastatin in the treatment of heterozygous familial hypercholesterolemia. It will expire on December 17, 2021. - Several ANDA filers have been sued for infringement of US Patent RE37314. ■ At the time of the ANDA filings in August 2007, six companies held active DMFs for rosuvastatin calcium: Aurobindo, Changzhou Pharmaceutical Factory, Glenmark, Lek, MSN Laboratories, and Teva. Presumably the Aurobindo, Glenmark, and Teva ANDAs reference the DMFs held by those companies. |
| <p>Active Ingredient: argatroban</p> <p>Posted by FDA: 16 November 2007</p> <p>Brand name: Argatroban</p> <p>NDA Holder: Encysive Pharmaceuticals</p> | <ul style="list-style-type: none"> ■ At least one company has filed an ANDA with paragraph IV certification for argatroban injection 100mg/mL in 2.5mL vials: Barr Laboratories. ■ Argatroban is covered by one Orange Book-listed patent. US Patent 5,214,052 is a formulation patent expiring on June 30, 2014. Mitsubishi Chemical Corporation is the owner of the patent and Encysive holds an exclusive sublicense to the patent for the United States. GlaxoSmithKline is the exclusive sublicensee of Encysive. ■ At the time of the ANDA filing in September 2007, Poli Industria Chimica and Chemwerth USA held active DMFs for argatroban. The Chemweth DMF concerns API manufactured in Germany by Chemcon. |
| <p>Active Ingredient: abacavir sulfate + lamivudine</p> <p>Posted by FDA: 10 December 2007</p> <p>Brand name: Epzicom™</p> <p>NDA Holder: GlaxoSmithKline</p> | <ul style="list-style-type: none"> ■ At least one company has filed an ANDA with paragraph IV certification for a generic version of Epzicom tablets (abacavir sulfate and lamivudine 600mg/300mg). At this time we do not know which company filed the ANDA. ■ Epzicom tablets are covered by seven Orange Book-listed patents expiring between February 2009 and November 2018. ■ At the time of the ANDA filing in September 2007, there were six companies holding lamivudine DMFs and three with abacavir sulfate DMFs on file with the FDA. Aurobindo and Matrix held active DMFs for both lamivudine and abacavir sulfate. |

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| <p>Active Ingredient: memantine hydrochloride</p> <p>Posted by FDA: 10 December 2007</p> <p>Brand name: Namenda®</p> <p>NDA Holder: Forest Labs</p> | <ul style="list-style-type: none"> ■ Several companies have filed ANDAs with paragraph IV certification for memantine hydrochloride tablets. Barr, Cobalt, Dr. Reddy's, Genpharm, Interpharm, Lupin, Mylan, Orchid, Ranbaxy, Sun, Teva, Upsher-Smith, and Wockhardt have filed ANDAs with paragraph IV certification for memantine HCl tablets in the 5mg and 10mg strengths. ■ Upsher Smith's ANDA for memantine HCl tablets also includes the 15mg and 20mg strengths, which are not marketed by Forest. ■ Memantine HCl tablets are covered by one Orange Book-listed patent. US Patent 5,061,703 covers the use of adamantane derivatives in the prevention and treatment of cerebral ischemia and will expire on April 11, 2010. Forest has applied for patent term restoration which, if granted, would extend patent protection until September 2013. ■ Merz Pharma is the assignee of this patent and Forest is the exclusive licensee in the United States. ■ At the time of the ANDA filings in October 2007, there were numerous active DMFs for memantine HCl on file with the FDA. Among those were DMFs belonging to ANDA filers Dr. Reddy's, Lupin, Matrix (Mylan), and Orchid. |
| <p>Active Ingredient: amlodipine besylate + valsartan</p> <p>Posted by FDA: 19 December 2007</p> <p>Brand name: Exforge®</p> <p>NDA Holder: Novartis</p> | <ul style="list-style-type: none"> ■ At least one company has filed an ANDA with paragraph IV certification for generic amlodipine besylate and valsartan 10mg/160mg tablets. At this time we do not know which company filed the ANDA. ■ Exforge tablets are covered by three Orange Book-listed patents: <ul style="list-style-type: none"> - US Patent 5,399,578 is the product patent for valsartan and will expire on September 21, 2012 after a six-month pediatric exclusivity. - US Patent 6,294,197 is a formulation patent covering solid dosage forms of valsartan and will expire on December 18, 2017 after a six-month pediatric exclusivity. - US Patent 6,395,728 covers valsartan as a component of combination and will expire on July 8, 2019. ■ At the time of the first ANDA filing in October 2007, there were many amlodipine besylate DMFs on file with the FDA. Six companies held DMFs for valsartan. Among the companies holding a DMF for both amlodipine besylate and valsartan at that time were Dr. Reddy's, Lupin, Matrix, and Teva. |
| <p>Active Ingredient: oxymorphone hydrochloride</p> <p>Posted by FDA: 19 December 2007</p> <p>Brand name: Opana® ER</p> <p>NDA Holder: Endo Labs</p> | <ul style="list-style-type: none"> ■ At least one company has filed an ANDA with paragraph IV certification for generic oxymorphone hydrochloride 5mg, 10mg, 20mg, and 40mg extended-release tablets: Impax. ■ Opana ER tablets are covered by four Orange Book-listed patents <ul style="list-style-type: none"> - US Patent 5,128,143 covers sustained-release excipient and tablet formulation and will expire on September 19, 2008. - US Patent 5,662,933 and US Patent 5,958,456 cover controlled-release formulation and will expire on September 9, 2013. - US Patent 7,276,250 covers sustained-release formulations of oxymorphone and will expire on July 3, 2022. ■ At the time of Impax's first reported ANDA filing, Mallinckrodt held the only active DMF for oxymorphone HCl. |

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 in 2007.

Torrent Pharmaceuticals Ltd

In 2007, [Torrent Pharmaceuticals Ltd](#) of India received four ANDA approvals. It expects to make an additional 14 ANDA and nine DMF filings in 2008.

In common with a number of other players in the generics industry (including among them Teva Pharmaceutical Industries Ltd, Apotex Inc and Mylan Laboratories Inc), Torrent has filed an ANDA with paragraph IV certification for sanofi-aventis's alfuzosin hydrochloride 10mg extended-release tablets. In response, sanofi-aventis issued a patent infringement lawsuit in September 2007.

Torrent has a strong presence in its domestic pharmaceutical market in India, focusing on treatment for chronic lifestyle conditions, particularly in the cardiovascular and central nervous system segments. It also has significant presence in gastro-intestinal, diabetes, anti-infective and pain management. Domestic business accounts for slightly more than half its revenues. We note more than 1000 product registrations and 430 launched dose products.

The company has two major manufacturing plants. In 2006 its API and formulations facilities at Indrad gained FDA approval. Here it produces both formulations and bulk drugs for export to more than 50 countries, including Europe, China, Brazil, Central America, Russia and the Far East.

In addition, it is in the process of building a dedicated formulation and packaging facility for insulin to supply exclusively to Novo Nordisk, and has acquired German generic company Heumann Pharma GmbH & Co Generica KG from the Pfizer Group. This latter division has had a troubled past, making heavy losses, but Torrent intends to turn around its fortunes by introducing new products and expects it to break even in 2009.

Torrent has several discovery projects in the pipeline, including new drugs for diabetes and obesity.

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.

US WorldMeds LLC

Louisville, US-based specialty pharmaceutical company [US WorldMeds LLC](#) was established in 2001, partly through sizeable grants from the Vogt Invention & Innovation Fund (it was the inaugural winner) and Kentucky Science & Technology Corporation. Its first ANDA was approved in July 2007.

This was for dantrolene sodium for injection, the first available generic equivalent of Proctor and Gamble's Dantrium® IV for malignant hyperthermia. It is manufactured for US WorldMeds under a multi-year commercial supply agreement with DSM Pharmaceuticals at that company's site in Greenville, North Carolina.

US WorldMeds also holds the US license to lofexidine hydrochloride, manufactured by Britannia Pharmaceuticals for the treatment of opiate addiction. The drug, administered in pill form, is an alpha-2-adrenergic antagonist which works by blocking withdrawal symptoms and has more than a decade of prescription in the UK to commend it. US WorldMeds hopes to repeat the success with opiate addicts in the US, which may number as many as 10 million.

Technofarma SA

In December 2006, Canadian company QLT sold its generic dermatology and manufacturing business to Argentina-based pharmaceutical company [Technofarma SA](#). Technofarma hoped the acquisition would help it to break into the US market, as well as giving it additional manufacturing capabilities.

The result was Tolmar Inc, which entered the US market for the first time in 2007. Its activities are focused on three distinct areas: contract manufacturing of pharmaceutical products, generic dermatological products and generic dental drugs. Six products are approved in Orange Book. It plans to develop its own proprietary products within the next four to six years, funded by continuing generic activity.

Technofarma was founded in Paraguay in 1974 to provide cancer treatment in Latin America. It now employs 4,000 workers and has five manufacturing plants exporting more than 200 generic drugs throughout Central and South America.

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.

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.

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