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MOVERS AND SHAKERS

A PHARMA MATTERS REPORT.

JULY – SEPTEMBER 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 thomsonreuters.com/business_units/scientific/pharma/generics

SECTION I: INTRODUCTION

With continuing volatility in the pharmaceutical marketplace, you'd expect the annual CPhI tradeshow, this year held in Frankfurt at the end of September, to be a lively forum of debate. And indeed, we caught conversations among both generics companies and API manufacturers about a huge number of issues, including:

- The FDA's decision to ban imports from Ranbaxy's Indian plants <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01886.html>
- The FDA's decision to open offices in India and China <http://www.dhhs.gov/news/press/2008pres/10/20081016a.html>
- The impact of the Beijing Olympics on active ingredient prices and availability
- The financial meltdown in the US and its impact on the pharmaceutical industry

This comes at a time when the pace of patent challenges shows no sign of slackening. Just like the previous quarter, *Newport Horizon Global* learned of patent challenges on seven new products between July and September 2008—four single active ingredient products and three combination products. However, the number of final approvals for generic drugs has fallen dramatically. In the previous quarter, 142 A-rated ANDAs gained final approvals. This quarter it plummeted to only 77.

First-time approvals of generic products by the FDA are also down from 11 to 8. Among these is divalproex sodium, a generic version of Abbott's blockbuster anticonvulsant Depakote. On July 29 2008, eight generic companies, including new-comer Nu-Pharm, received final approvals for divalproex sodium delayed release tablets. Two days later, a ninth generic company followed suit. You can read more about Nu-Pharm in Section IV of this report.

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?

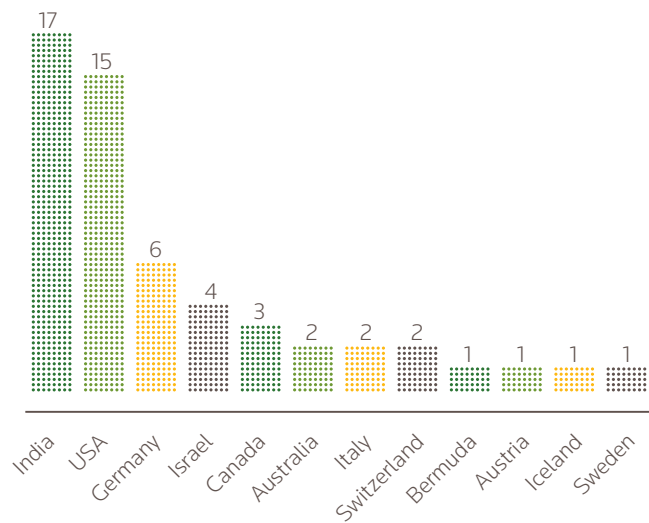
A DMF (Drug Master File) is a confidential document covering a specific manufacturing facility, process or article used in the manufacturing, processing, packaging or storing of a bulk drug. A DMF is reviewed by the FDA only if an ANDA or NDA referencing that particular DMF is filed. An ANDA or NDA will 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 JULY TO SEPTEMBER 2008

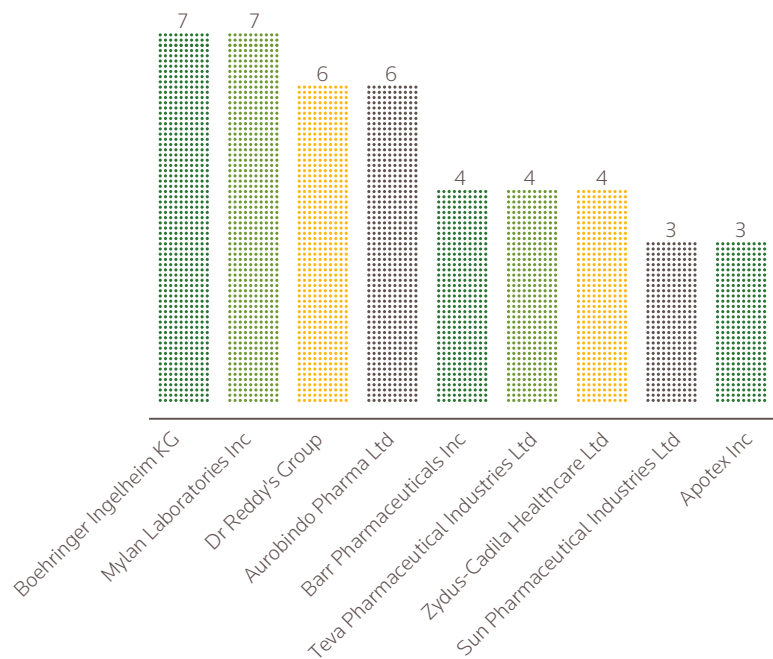


Indian groups were in first place in terms of final ANDA approvals during the third quarter of 2008, with 12 India-based groups receiving a total of 17 ANDA approvals.

This is consistent with the previous quarter, when the largest number of ANDA approvals also went to India-based groups. Between April and June 2008, 17 different groups received a total of 52 final ANDA approvals.

The second largest number of ANDA approvals this quarter went to US-based groups—11 groups received a total of 15 final ANDA approvals. Again in the previous quarter, US-based groups had been in second place in terms of final ANDA approvals, with 26 groups receiving a total of 45 ANDA approvals.

GROUPS WITH THE MOST 'A'-RATED ANDA APPROVALS FOR JULY TO SEPTEMBER 2008



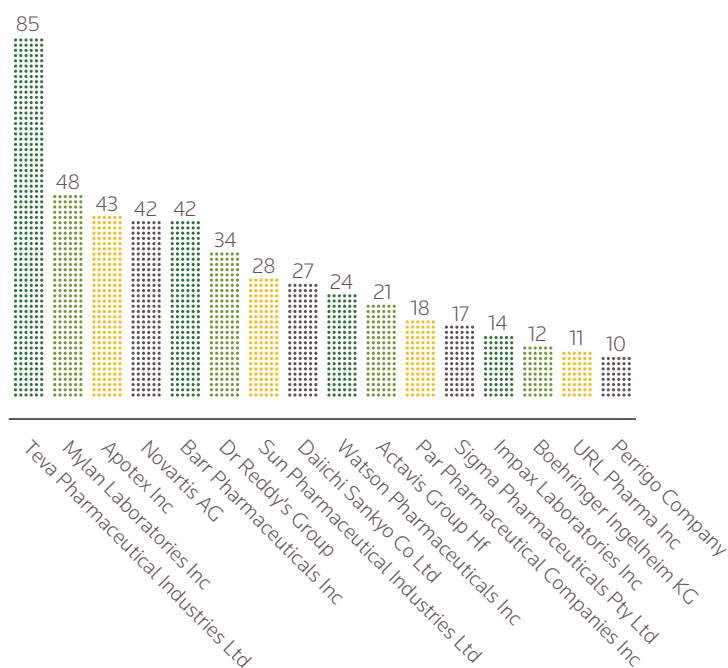
In the third quarter of 2008, Mylan of the US and Boehringer Ingelheim of Germany (through its US subsidiaries, Bedford and Roxane Laboratories) received the most final ANDA approvals (seven each). Dr Reddy's Laboratories and Aurobindo, both from India, shared third place with six ANDAs each.

Sun Pharmaceutical of India, the company with most ANDA approvals in the second quarter, had three ANDA approvals in this third quarter.

SECTION III: PARAGRAPH IV CHALLENGES

In the third quarter of 2008, we learned of first paragraph IV patent challenges on seven new products.

GROUPS WITH THE MOST PATENT CHALLENGES ON RECORD AS OF SEPTEMBER 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 85 products. Mylan has remained in second place with links to patent challenges on 48 products, and Apotex follows closely behind with challenges on 43 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 JULY AND SEPTEMBER 2008

ACTIVE INGREDIENT:
candesartan cilexetil,
hydrochlorothiazide

POSTED BY FDA:
23 September 2008

BRAND NAME:
Atacand HCT

NDA HOLDER:
AstraZeneca

- At least one company has filed an ANDA with paragraph IV certification for a generic version of Atacand HCT 16mg/12.5mg and 32mg/12.5mg tablets. At this time, we do not know which company submitted the ANDA.
- There are five patents covering Atacand HCT currently listed in the Orange Book.
US Patent 5,705,517 contains claims to candesartan and expires on April 18, 2011. US Patent 5,196,444 claims candesartan cilexetil and has been granted an extension of 413 days, expiring on June 4, 2012.
US Patent 5,534,534 is a formulation patent expiring on July 9, 2013.
US Patent 5,958,961 includes generic claims to the combination of candesartan cilexetil and hydrochlorothiazide and will expire on June 6, 2014.
US Patent 5,721,263 includes specific claims to the combination of candesartan cilexetil and hydrochlorothiazide and will expire on February 24, 2015.
- At the time of the ANDA filing in June 2008, the FDA reported numerous DMFs on file for candesartan cilexetil and for hydrochlorothiazide.

ACTIVE INGREDIENT:
clozapine

POSTED BY FDA:
21 July 2008

BRAND NAME:
Fazaclo

NDA HOLDER:
Azur Pharma

- At least one company has filed an ANDA with paragraph IV certification for a generic version of Fazaclo 25mg and 100mg orally disintegrating tablets: Barr. Additionally, at least one company has filed an ANDA with paragraph IV certification for the 12.5mg strength.
 - The Orange Book lists four patents covering Fazaclo orally disintegrating tablets.
US Patent 5,178,878 is a formulation patent claiming a dosage form with microparticles related to CIMA's OraSolvfast dissolving drug delivery system. It will expire on January 12, 2010.
US Patent 6,024,981 and US Patent 6,221,392 concern CIMA's DuraSolv technology and will expire on April 9, 2018.
US Patent 6,106,861 covers a multi-particulate tablet formulation disintegrating in less than 40 seconds in the mouth. It will expire on December 5, 2017.
 - In their suit against Barr, patent-holder CIMA and licensee Azur Pharma allege infringement of US Patent 6,024,981 and US Patent 6,221,392.
 - At the time the ANDA with paragraph IV certification for generic Fazaclo was filed in April 2008, there were multiple active DMFs for clozapine on file with the FDA. This is not surprising since other generic clozapine formulations have been on the market for several years.
-

ACTIVE INGREDIENT: • At least one company has filed an ANDA with paragraph IV certification for a generic version of Copaxone 20mg/mL, 1mL pre-filled syringes: Sandoz.

POSTED BY FDA: • The Orange Book lists seven patents covering Copaxone, all expiring on May 24, 2014.

21 July 2008

BRAND NAME: • Teva's suit against Sandoz alleges infringement of US Patent 6,054,430, US Patent 6,620,847, US Patent 6,939,539, and US Patent 7,199,098. Yeda is the owner of those patents and Teva is the exclusive licensee.

Copaxone

NDA HOLDER: • Teva also alleges that the defendants misappropriated trade secrets that Teva disclosed to Lek Pharmaceuticals under a supply and distribution agreement reached in May 1997. Novartis acquired Lek in November 2002. Included in the material Teva made available to Lek was confidential information concerning the manufacture and characterization of Copaxone, which could serve as a blueprint for the characterization of a generic version.

Teva

ACTIVE INGREDIENT: • At least one company has filed an ANDA with paragraph IV certification for a generic version of Advicor 20mg/1000mg extended release tablets. At this time, we do not know which company submitted the ANDA.

POSTED BY FDA: • The Orange Book lists seven patents covering Advicor 20mg/1000mg extended-release tablets, expiring between September 20, 2013 and March 15, 2018.

15 August 2008

BRAND NAME: • At the time the ANDA with paragraph IV certification was filed in May 2008, numerous companies held active DMFs for lovastatin.

Advicor

NDA HOLDER:

Abbott Laboratories

ACTIVE INGREDIENT: • At least one company has filed an ANDA with paragraph IV certification for a generic version of OsmoPrep 0.398g/1.102g tablets: Novel Laboratories.

POSTED BY FDA: • The Orange Book lists only one patent covering OsmoPrep tablets. US Patent 5,616,346 is a formulation patent that will expire on May 18, 2013.

21 July 2008

BRAND NAME: • At the time the ANDA with paragraph IV certification was filed in April 2008, Mallinckrodt held an active DMF for sodium phosphate monobasic monohydrate and Chemische Fabrik Budenheim held an active DMF for sodium phosphate dibasic anhydrous. In addition, ACS Dobfar has held an active DMF for sodium phosphate dibasic since 1993.

OsmoPrep

NDA HOLDER:

Salix
Pharmaceuticals

ACTIVE INGREDIENT: voriconazole	<ul style="list-style-type: none"> • At least one company has filed an ANDA with paragraph IV certification for a generic version of Vfend 50mg and 200mg tablets: Matrix Laboratories, a subsidiary of Mylan. • The Orange Book lists four patents covering voriconazole tablets. US Patent 5,116,844 contains generic formulation and use claims for voriconazole and will expire on August 11, 2009. US Patent 5,364,938 contains generic product claims for voriconazole and will expire on November 15, 2011. US Patent 5,567,817 is the US product patent for voriconazole. It has been granted a term extension of 945 days and will expire on May 24, 2016. US Patent 5,773,443 also contains generic claims to the drug and will expire on January 25, 2011. • Pfizer did not sue Matrix or Mylan within 45-days of receiving notice of the Matrix ANDA. • At the time the ANDA with paragraph IV certification was filed in April 2008, Dr. Reddy's Laboratories and MSN Laboratories held active DMFs for voriconazole. Because Matrix is an established API manufacturer and appears in <i>Newport Horizon Premium</i> as a manufacturer of voriconazole, we speculate that Matrix included its DMF information directly in its ANDA.
POSTED BY FDA: 10 July 2008	
BRAND NAME: Vfend	
NDA HOLDER: Pfizer	

ACTIVE INGREDIENT: zoledronic acid	<ul style="list-style-type: none"> • At least one company has filed an ANDA with paragraph IV certification for generic zoledronic acid 0.8mg (base)/mL injection: Teva. • US Patent 4,939,130 is the product patent for zoledronic acid. It has been granted an extension of 1755 days by the USPTO, and will expire on September 2, 2012. The pediatric exclusivity associated with that patent will expire on March 2, 2013. It is the only unexpired patent listed in the Orange Book for Zometa and Reclast. • At the time Teva submitted its ANDAs with paragraph IV certification, there were several DMFs for zoledronic acid on file with the FDA, including one held by Teva. We assume Teva's ANDA references Teva's DMF.
POSTED BY FDA: 1 August 2008	
BRAND NAME: Zometa	
NDA HOLDER: Novartis	

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.

CIPLA LTD

One of India's largest pharmaceutical companies, **Cipla Ltd**, based in Mumbai, has been a highly visible player in the US generic market for many years, though until 2007 it did not hold any ANDAs in its own name. Its activities were through alliances with existing US companies including Watson Pharmaceuticals, Pentech Pharmaceuticals, Ivax (now part of Teva), Eon (now part of Sandoz/Novartis), Morton Grove (now part of Wockhardt), Akorn and Par. Cipla developed and supplied the generics, and the US partner registered and marketed them.

Today, Cipla holds six final approvals for five different molecules: granisetron (prevention of nausea and vomiting caused by chemotherapy and radiation in treating cancer), zaleplon (a sedative used to deal with insomnia), zidovudine (an AIDS/HIV treatment), and two ACE inhibitors, ramipril and trandolapril.

However, its main strategy still seems to be to use partners in foreign markets to sell its products. Though this means it must share its profits, Cipla benefits from reduced expenses on marketing and allied costs, and hence a lower overall risk.

Biotech appears to be the company's focus in the new millennium. In 2002 and 2004, it was reported that Cipla was in tie-up talks with US biotech firm Biogenetics Inc for a marketing and manufacturing alliance. Last year, a joint venture between Cipla and Avesthagen acquired a state of the art biological company in Germany from the Siegfried Group. The reason for all this activity is clear: biopharmaceuticals are burgeoning in the Indian market, and could reach \$5 billion by 2010. Cipla hopes not only to remain dominant at home, but throughout the world. Cipla's revenues this current year were close to \$1bn which places it among the Top 25 generic companies in the world and Top 3 in India, together with Dr Reddy's and Ranbaxy.

Unsurprisingly, *Newport Horizon Premium* gives the company an Established rating. It notes 172 confirmed APIs in manufacture and 117 active US DMFs.

NU-PHARM

One of the companies involved in the paragraph IV patent challenge for Abbott's divalproex sodium delayed-release tablets in 2005, **Nu-Pharm's** ANDA was finally awarded FDA approval for the 125mg, 250mg and 500mg strengths on 29 July 2008. It was the company's first US approval.

The approval did not come without a struggle. In Abbott's May 2006 lawsuit against Nu-Pharm, a Canadian generic company

based in Richmond Hill, Abbott claimed that, although Nu-Pharm was listed as the applicant on the ANDA, it had virtually nothing to do with the ANDA or product, and that Apotex, the former owners of Nu-Pharm, was actually behind the filing. Abbott had previously won an injunction against Apotex in 2004.

Judge Posner of the District Court of Northern Illinois agreed and found Apotex in contempt, ruling that the injunction against Apotex had been violated and extending that injunction to Nu-Pharm's ANDA. In Judge Posner's opinion, Nu-Pharm was merely a "stalking horse" used by Apotex to get around the injunction.

On appeal in October 2007, the US Court of Appeals for the Federal Circuit ruled that since Nu-Pharm is based in Canada, Apotex's actions involving Nu-Pharm did not constitute contempt. Its attempts to design around Abbott's patents did not take place within the United States and did not explicitly violate the terms of the injunction. However, the court upheld the extension of the injunction to prohibit FDA approval of the Nu-Pharm ANDA until patent expiry.

Newport Horizon Premium notes that Nu-Pharm has launched more than 90 dose products in Canada, across many different therapeutic categories and in oral, nasal and inhaled forms. The company is not involved in API manufacturing.

ACCORD HEALTHCARE

Based in North Carolina, **Accord Healthcare** filed its first ANDA with paragraph IV patent challenge in September 2008. This was for AstraZeneca's quetiapine fumarate (Seroquel) extended-release tablets in 200mg, 300mg and 400mg strengths. Accord asserts that its proposed product will not infringe some claims of AstraZeneca's US Patent 5,948,437 and that other claims of the patent are invalid.

The company is a wholly owned subsidiary of Intas Pharmaceuticals Ltd, based in Gujarat, India, and part of that company's worldwide marketing and licensing-related activities that include operations in UK, Spain, Canada, Australia, South Africa, Brazil and Mexico. Accord boasts a huge marketing portfolio for products manufactured by Intas in therapy areas including oncology, biologicals, immunosuppression, cardiovascular, anti-diabetics, and osteoporosis: 1,100 live registrations in more than 55 countries, with more than 15 ANDAs in the pipeline.

In June 2008, Intas acquired California-based biotechnology corporation Biologics Process Development Inc. It has also entered into a joint venture with US-based ProGenetics to conduct clinical trials using ProGenetics' transgenic animals. Intas' revenues for the current year were nearly \$200M.

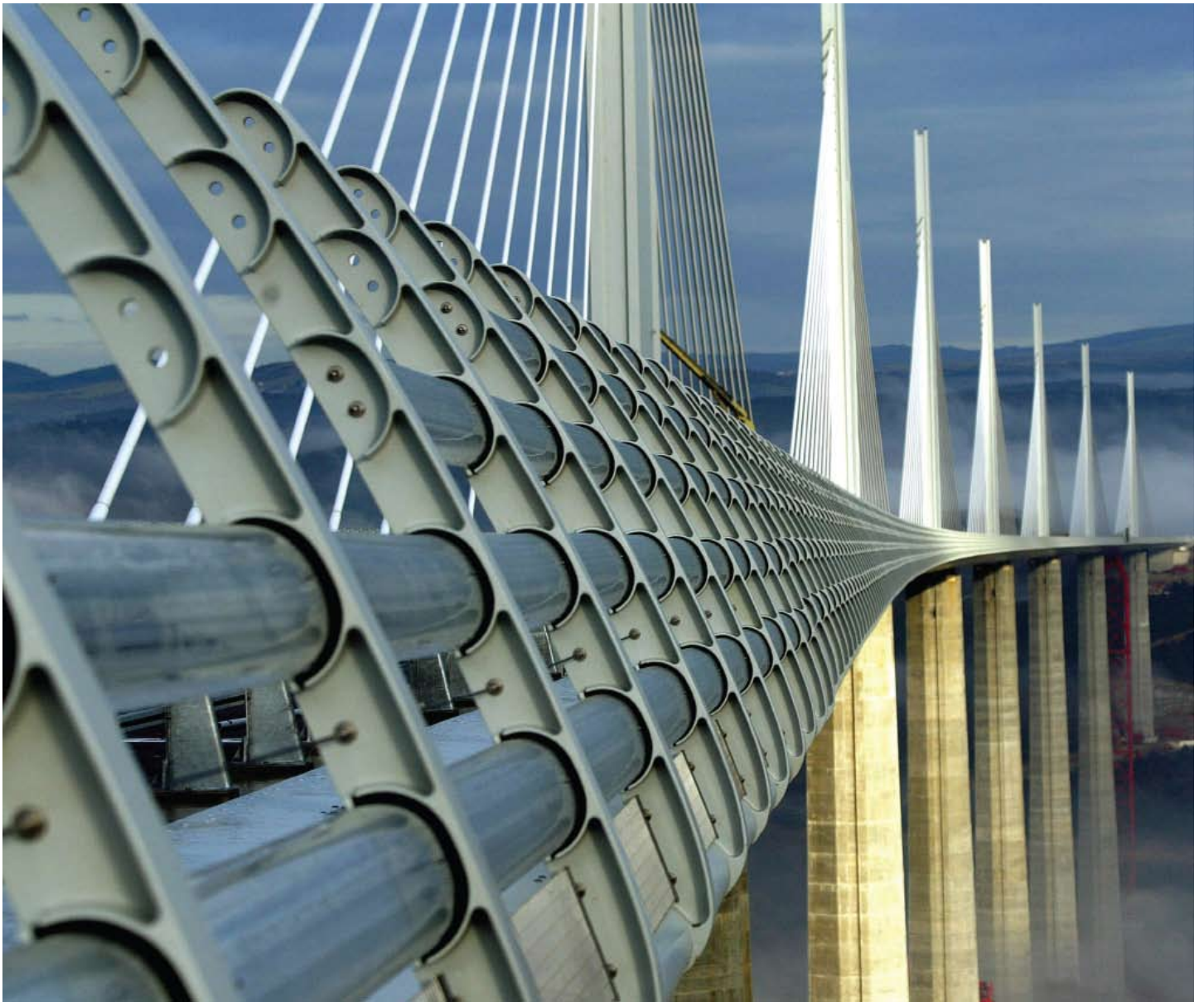


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THE ONES TO WATCH

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.

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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