GENERICS bulletin
THE BUSINESS NEWSLETTER FOR THE GENERIC MEDICINES INDUSTRY

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3 February 2014

GENERICS bulletin

THE BUSINESS NEWSLETTER FOR THE GENERIC MEDICINES INDUSTRY

Actavis sells European activities to Aurobindo

Actavis has agreed to sell its generics operations in seven western European countries to Aurobindo for around €30 million (US$41 million). The deal, which is subject to antitrust and other approvals, covers commercial infrastructure, products, marketing authorisations, dossier-licensing rights and personnel in Belgium, France, Germany, Italy, the Netherlands, Portugal and Spain. The two companies will also "enter into a long-term strategic supply arrangement".

Around six months ago, Actavis announced it was considering strategic options, including divestment, for businesses in "six or seven markets" in western Europe (**Generics *bulletin***, 9 August 2013, page 1). These, the firm stated, were substitution- or tender-driven markets.

"We believe that the value created by the commercial operations in these seven markets will be better maximised by Aurobindo, which will gain scale, additional products and enhanced competitive market share position as a result of this transaction," stated Sigurdur Oli Olafsson, president of Actavis Pharma. "This transaction will permit Actavis to focus management time and resources to support accelerated investment in driving faster growth of other markets, including central and eastern Europe and south-east Asia."

Aurobindo said it would gain around 1,200 individual products and a pipeline of more than 200 drugs. The Indian firm estimated that the acquired businesses increased their net sales by a tenth last year to €320 million.

"Although these businesses are currently loss-making," the Indian group observed, "Aurobindo expects them to return to profitability in combination with its vertically-integrated platform and existing commercial infrastructure." Arvind Vasudeva, who heads Aurobindo's Formulations business, said the Indian company anticipated "a seamless integration" process, with Actavis continuing to act as "a supplier and licence provider" to the acquired operations. Stressing that Aurobindo adopted a "disciplined approach" to acquisitions and to "maintaining a prudential capital and debt structure", Vasudeva said the deal with Actavis would accelerate the Indian group's strategic goal "of becoming a significant generics player in Europe".

For further details, turn to page 22.

Two have trastuzumab approvals

Biocon and Celltrion have both received approvals for rivals to the Herceptin (trastuzumab) biologic cancer treatment marketed by Roche's Genentech. Biocon's version – developed in partnership with Mylan – has been approved in India under the name Canmab and is due to be available in early February. And Celltrion's trastuzumab – branded Herzuma – received approval from South Korea's Ministry of Food and Drug Safety (MFDS) and is scheduled to be launched in the first half of this year.

Herceptin had global sales of around US$6.3 billion in 2012, the firms claimed. Biocon said the product had Indian sales of about US$21 million in 2012, while Celltrion said the Korean market was worth around US$80 million. Both firms celebrated the approvals as "milestones" for their biosimilar development programmes.

Meanwhile, Health Canada has approved Celltrion's infliximab under the Remsima and Inflectra brand names used in Europe by the South Korean firm and its marketing partner Hospira respectively. The notices of compliance (NOCs) – effectively marketing authorisations – were obtained through the New Drug Submission (NDS) route.

For further details, turn to pages 11 and 13.

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MANUFACTURING

Fourth Ranbaxy site subject to FDA ban

Ranbaxy's Toansa active pharmaceutical ingredient (API) facility in Punjab, India has become the Indian firm's fourth plant to be subjected to certain provisions of a consent decree imposed by the US Food and Drug Administration (FDA) in January 2012. Those provisions include a ban on the Toansa site producing or distributing APIs made at the facility – or drugs containing those ingredients – for the US market.

The Indian firm recently voluntarily suspended shipments to the US from Toansa after the plant received 'Form 483' observations from the agency related to current good manufacturing practice (cGMP) violations discovered during an inspection completed on 11 January. Those observations included the company retesting raw materials, intermediates and finished APIs that failed specifications "until acceptable results are obtained", as well as failing to report any "suspect results".

"Adequate laboratory facilities are not maintained," the FDA complained. "Laboratory samples are not adequately controlled to prevent mix-ups."

Under the terms of the consent decree, the FDA has issued an order prohibiting Ranbaxy from: distributing in the US drugs manufactured using API from Toansa, including drugs made by the firm's Ohm Laboratories facility in New Jersey, US; manufacturing API at Toansa for FDA-regulated medicines; exporting API from Toansa to the US "for any purpose"; and providing API made at Toansa to other companies or Ranbaxy facilities to make "products for American consumers".

Furthermore, the Indian firm is required to hire a third-party expert to inspect the Toansa facility and to certify to the FDA that methods and controls at the site meet cGMP standards.

Last year, Ranbaxy's plant in Mohali, India was placed under import alert and subjected to certain terms of the consent decree, which also covers the company's sites in Dewas and Paonta Sahib, India (**Generics *bulletin***, 20 September 2013, page 3).

"This development is clearly unacceptable and an appropriate management action will be taken upon completion of an internal investigation," promised chief executive officer, Arun Sawhney.

BUSINESS STRATEGY

Actavis sells Chinese business

Actavis has agreed to sell its Actavis Foshan Pharma operation in China to local bulk-drugs specialist Zhejiang Chiral Medicine Chemicals for an undisclosed fee. "Actavis intends to continue further commercial operations in China in collaboration with its preferred business partners," stated the Ireland-based group, which has also just agreed to divest its generics operations in seven western European countries to Aurobindo (see front page).

A joint venture between Actavis and Foshan Chanbende Development, Actavis Foshan operates a facility in Foshan, Guangdong province, that produces antibiotics, cardiovascular and gastrointestinal drugs in a variety of dosage forms, including tablets, hard and soft-gel capsules, oral solutions, dry suspensions, ointments and liniments.

"Actavis is focused on strengthening our investment in high-growth markets where our size and scale allow us to maintain a competitive presence with the leading firms in the market," said Actavis Pharma's president, Sigurdur Oli Olafsson. "Our operations in Foshan were limited in scope. We believe their value will be better capitalised on by Chiral, which will add manufacturing and marketing capabilities."

MERGERS & ACQUISITIONS

Par pays US$490m for JHP's injectables

Par Pharmaceutical has agreed to pay US$490 million for JHP Group Holdings, the parent company of US sterile injectables specialist JHP Pharmaceuticals. Subject to antitrust clearance and other approvals, Par expects to complete the deal by the end of March.

JHP currently markets 14 injectable products in the US, including the Adrenalin (epinephrine), Aplisol (tuberculin) and Dantrium (dantrolene) brands. The New Jersey-based company also has a pipeline of 34 oncology and other drugs, half of which have already been submitted for approval to the US Food and Drug Administration (FDA).

At its 16,000 sq m sterile manufacturing facility in Rochester, Michigan – which also provides contract-manufacturing services for third parties – JHP can make both small-scale clinical and large-scale commercial batches. In 2012, the firm invested US$10 million in building a 3,700 sq m quality-control laboratory.

"The acquisition of JHP expands Par's presence into the rapidly growing market for injectables," commented Par's chief executive officer, Paul Campanelli. "With their high-barrier-to-entry products, JHP represents a perfect complement to Par's strategy and product line."

Campanelli also highlighted JHP's strong regulatory compliance record and its "well-respected and experienced management team" under chief executive officer Stuart Hinchen, who took over the role two-and-a-half years ago from Peter Jenkins, with whom he had founded the company in 2007 (**Generics *bulletin***, 15 July 2011, page 26).

Having bought the 32-hectare Rochester site from King Pharmaceuticals in 2007, Hinchen and Jenkins built up the company to employ around 450 staff. Around 18 months ago, the injectables specialist launched its JHP Generics arm with an initial portfolio of 13 stock-keeping units (SKUs) across therapeutic categories including anaesthetics, anti-infectives, gastrointestinal remedies and women's healthcare drugs (**Generics *bulletin***, 29 June 2012, page 5). JHP Generics' pipeline includes acute-care and oncology medicines.

A few months later, private-equity firm Warburg Pincus took a majority stake in JHP for US$195 million on a debt-free, cash-free basis. Around the same time, Par was bought out for US$1.9 billion by private-equity fund TPG Capital (**Generics *bulletin***, 19 October 2012, page 2).

Upon closing of the transaction – which is subject to a US$30 million termination fee – JHP will become a wholly-owned Par subsidiary. "Par has deep experience in generic pharmaceuticals and is ideally suited to drive the next stage of growth and expansion of JHP," insisted Hinchen.

BUSINESS STRATEGY

Zydus Cadila abandons Japan

Zydus Cadila has decided to discontinue its operations in Japan. "The company has recently completed a portfolio and strategy review of its business, and has decided to exit from its business in Japan," the Indian group said in a brief statement to the Bombay Stock Exchange (BSE), without revealing any other details.

The Indian company operates in Japan through a wholly-owned subsidiary that it set up more than seven years ago (**Generics *bulletin***, 22 September 2006, page 3). A few months later, it bought local generics player Nippon Universal (**Generics *bulletin***, 27 April 2007, page 1).

In the six months ended 30 September 2013, Cadila's Japanese sales fell by just over a tenth to Rs252 million (US$4.04 million).

BUSINESS STRATEGY/ANNUAL RESULTS

Lonza ponders plans for biosimilar assets

Lonza says it is still considering what to do with the assets and expertise – including intellectual-property rights – it had built up in biosimilar development through its joint venture with Teva that the two firms broke off midway through last year (**Generics *bulletin***, 9 August 2013, page 5). "The process to evaluate Lonza's accumulated investments was begun in the second half of 2013 and is in progress," the Swiss group stated.

Eliminating low-margin businesses contributed to Lonza's group turnover declining by 4.2% last year to SFr3.58 billion (US$4.00 billion). That total comprised Pharma & Biotech sales that fell by 7.9% to SFr1.43 billion – due in part to halting production to add capacity to an antibody drug conjugates plant in Visp, Switzerland – and Specialty Ingredients turnover that slipped by 1.3% to SFr2.16 billion.

Impairment and restructuring costs totalling SFr125 million that were related to closing a microbial-biologics plant in Hopkinton, US, cut the group's operating profit by a fifth to SFr253 million.

THIRD-QUARTER RESULTS

Torrent grows turnover in US

Double-digit sales growth in the US, Europe and Brazil helped Torrent Pharmaceuticals to increase its group turnover by 27% to Rs10.2 billion (US$162 million) in the group's financial third quarter ended 31 December 2013.

Torrent's total International turnover outside of India advanced by 38% to Rs6.21 billion. The Indian company said it had grown its sales by 61% in the US, and by 59% in Europe. Sales in Brazil rose by 26%.

In India – where Torrent has agreed to pay just over Rs20.0 billion for Elder Pharma's Indian Branded Formulations operation (**Generics *bulletin***, 10 January 2014, page 5) – the Ahmedabad-based group increased its turnover by 16% to Rs3.71 billion.

Torrent improved its pre-tax profit by 31% to Rs1.88 billion.

RESULTS FORECAST

Valeant sees sales exceeding US$8bn

Valeant says launching more than 300 branded generics and consolidating several acquisitions such as Bausch & Lomb should enable the group to expand its turnover by around 40% to US$8.2-US$8.6 billion this year. The group expects to report a turnover of US$5.7-US$5.9 billion for 2013, almost US$2.0 billion of which should come from emerging markets.

Chairman and chief executive officer Michael Pearson said the company would aim this year to "do at least one significant deal that creates substantial shareholder value". Valeant is looking for "tuck-in acquisitions" in emerging markets, especially in Asia, the Middle East and Russia. "We continue to pursue a merger of equals," he added.

During 2013, Pearson pointed out, Valeant had completed more than 25 transactions, typically paying between one-and-a-half and three-times sales. Buying Euvipharm had given the group a platform in Vietnam, he noted, while the US$8.7 billion takeover of Bausch & Lomb had given Valeant a strong global position in ophthalmics.

This year, Valeant expects all of its business units to grow, while it anticipates double-digit advances in central and eastern Europe, Asia, Latin America and the Middle East and North Africa regions.

The group's 2014 turnover guidance of over US$8 billion assumes an impact of more than US$200 million from generic competition to brands including Atralin (tretinoin) gel, Lotemax (loteprednol) suspension and Vanos (fluocinonide) cream, as well as to Wellbutrin XL (bupropion) tablets in Canada. A US$50 million hit to sales from divestments should be balanced by completing the acquisition of skincare devices specialist Solta Medical.

The group's gross margin is expected to be in the "low 70s". Research and development spending is set to be around US$300 million in 2014, while capital expenditure should be around US$200 million. By the end of this year, Valeant expects to achieve annual run-rate synergies from the Bausch & Lomb deal of over US$900 million.

"We intend to become one of the five most-valuable pharma companies, as measured by market capitalisation, by the end of 2016," Pearson stated. "This equates to roughly US$150 billion."

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MERGERS & ACQUISITIONS

Alvogen folds Asian operations into Lotus

Alvogen is merging its operations in Asia into Lotus Pharmaceuticals, the Taiwanese business in which it is acquiring a 67% stake for around US$200 million. The deal is expected to close by the end of June this year.

Lotus will use the proceeds from Alvogen's purchase of a private placement of 151 million new shares to acquire the US-based company's existing operations in China, India, South Korea and Taiwan. Lotus and Alvogen are also negotiating distribution rights in the Asia-Pacific region for two biosimilar monoclonal antibodies being developed by the US firm's recently-established sister company, Alvotech (**Generics *bulletin***, 6 December 2013, page 27).

"The combination of Alvogen's strong geographic coverage in the US, central and eastern Europe and Asia with Lotus' strategically important foothold in the Taiwanese market and its growing US product pipeline is expected to generate significant opportunities to drive revenue growth and margin enhancement, and to create further value for the two firms," Alvogen stated (**Generics *bulletin***, 10 January 2014, page 3).

Included in the transaction is the operation in South Korea that Alvogen gained 18 months ago by acquiring local firm Kunwha, which has a local manufacturing plant in Gongju (**Generics *bulletin***, 2 November 2012, page 3). Alvogen China promotes mainly paediatric and women's health products through a 500-strong fieldforce, while the US-based firm's Taiwanese operation holds 22 marketing authorisations, with a similar number pending regulatory approval. Alvogen India is a contract research organisation (CRO) based in Bangalore that operates under the brand Norwich Clinical Services (NCS).

Alvogen will also gain access to Lotus' high-potency and cytotoxic oral formulations facility, while the Taiwanese company will be able to utilise its US-based parent company's sales and marketing infrastructure covering more than 30 countries.

THIRD-QUARTER RESULTS

Alembic rises outside of India

Almost doubling its Formulations sales outside of India enabled Alembic Pharmaceuticals to report group gross turnover ahead by 31% to Rs4.87 billion (US$77.6 million) in its financial third quarter ended 31 December 2013.

International Formulations sales increased by 96% to Rs1.49 billion. During the quarter, the Indian company submitted one abbreviated new drug application (ANDA) in the US, taking the firm's cumulative ANDA filings to 60. One ANDA approval during the three-month period took Alembic's total to 31, including four tentative approvals.

In its domestic market, the Indian company advanced its Formulations turnover by 13% to Rs2.57 billion, led by growth from its Indian Specialty business segment.

Global active pharmaceutical ingredient (API) sales by the Vadodara-based group increased by 13% to Rs756 million as Alembic submitted two drug master files (DMFs), taking its total DMF filings to 64. Export incentives added Rs48.8 million to group turnover.

The Indian group's total Exports sales rose by 81% to Rs2.12 billion, while its Domestic turnover grew by 8% to Rs2.75 billion.

Even with research and development spending a third higher at Rs290 million, Alembic improved its pre-tax profit by 48% to Rs888 million.

MERGERS & ACQUISITIONS/DISTRIBUTION

McKesson revives takeover of Celesio

McKesson's proposed takeover of Celesio is back on, after the US pharmaceutical wholesaler agreed fresh deals with its European counterpart's two biggest shareholders.

McKesson said it would now acquire Franz Haniel & Cie's 50.01% stake in Celesio for €23.50 (US$32.16) per share, a rise from its previous offer of €23.00 per share (**Generics *bulletin***, 10 January 2014, page 6). Crucially, McKesson has also agreed a deal with Celesio's second-largest shareholder, Elliot International, to acquire for an undisclosed sum the US-based hedge fund's stake, which is in the form of convertible bonds.

Once the transactions had been completed – which was expected "within 10 business days" – McKesson said it would exceed its stated target of holding more than 75% of Celesio's shares. A voluntary tender offer to the remaining minority holders of Celesio common shares would be launched shortly after the close of the transactions, added the US-based group, which does not anticipate requiring any approvals from antitrust authorities.

Deal appeared to have collapsed

Just two weeks earlier, McKesson's proposed tie up with Celesio appeared to have collapsed. Although Haniel had already agreed to sell its 50.01% stake to McKesson (**Generics *bulletin***, 18 October 2013, page 5), the improved US$23.50 per share offer failed to entice the company's remaining shareholders. As a result, the minimum acceptance rate of 75% was not reached by the deadline of 9 January. Media reports suggested that US-based Elliot – which had reportedly built up a 25% stake in Celesio – was sceptical about the deal's value.

Generic purchasing efficiencies are central to the US$275-US$325 million of annual synergy savings that McKesson believes it will unlock through the deal.

McKesson's chairman and chief executive officer, John Hammergren, promised "more efficient delivery of healthcare products and services around the world". "Our customers will benefit from the increased scale, supply-chain expertise and sourcing capabilities of the combined company, together with enhanced access to innovative technology and business services," he maintained.

Celesio operates in 14 countries, supplying 65,000 pharmacies and hospitals from 132 wholesale depots, while its retail operation comprises around 2,200 of its own stores and 4,100 pharmacies in partnership or banner schemes.

With an annual turnover of US$122 billion, McKesson claims to deliver a third of all pharmaceuticals used in North America.

MANUFACTURING

Lincoln opens injectables plant

Lincoln Pharmaceuticals plans to seek approval from the US Food and Drug Administration (FDA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) for the Rs270 million (US$4.39 million) injectables facility that the Indian firm has just opened near its existing operations in Ahmedabad, India.

The Indian company expects the plant – which can manufacture ampoules, vials, dry-powder injectables and liquid-syrup formulations – to add Rs500 million to its annual turnover. In the year ended 31 March 2013, Lincoln posted a turnover of Rs2.00 billion.

BUSINESS STRATEGY/THIRD-QUARTER RESULTS

Biocon prepares for progress on insulins

Biocon says it preparing "the groundwork", along with its partner Mylan, for "a global Phase III trial for our generic insulin glargine". The Indian firm already holds approvals in more than 50 countries for its generic recombinant insulin; while an insulin facility that it is building in Johor, Malaysia, is scheduled to start production within the next year or so following a US$160 million investment. Biocon has also started global trials for its IN105 oral insulin project in the US through a partnership with Bristol-Myers Squibb.

Growth from Basalog Insupen (insulin glargine) and BioMab EGFR (nimotuzumab) in India – where Biocon is poised to launch its Canmab brand of trastuzumab (see page 11) – contributed to group turnover increasing by 9% to Rs7.19 billion (US$115 million) in the firm's financial third quarter ended 31 December 2013.

Sales by Biocon's Indian Branded Formulations business rose by 15% to Rs990 million, representing just under a fifth of total Biopharmaceuticals turnover that grew by 4% as reported to Rs5.17 billion, but fell by 2% on a constant-currency basis.

"Our small-molecules portfolio is currently being optimised to balance margin accretion with growth platforms. We have seen good momentum in imunosuppressants and orlistat, while our changing product mix for statins has helped balance out headwinds in the industry," Biocon commented.

Half of the 31% sales rise to Rs1.83 billion reported by the group's Research Services business was due to exchange-rate fluctuations. Other operations contributed Rs190 million.

Lower research and development spending helped to push up Biocon's pre-tax profit by 15% to Rs1.36 billion.

BUSINESS STRATEGY

Impax is looking to acquire

Impax Laboratories is looking to acquire companies that have attractive generics development capabilities, both within and outside of the US. The debt-free, US-based firm is also looking for business-development opportunities that cover high-value solid-dose or other dosage forms, such as semi-solids and patches, as it looks to spend a cash pile of more than US$400 million.

Chief financial officer Bryan Reasons told a recent investors' conference that Impax had been relying on external partnerships for generics launches while it awaited a re-inspection of its facility in Hayward, California, that could lift a warning letter issued by the US Food and Drug Administration (FDA) two-and-a-half years ago (**Generics *bulletin***, 30 June 2011, page 5).

As an example, he cited the firm's recent introduction of a rival to Fougera's Solaraze (diclofenac) 3% gel through an alliance with Tolmar (**Generics *bulletin***, 15 November 2013, page 20).

Solaraze took to 10 the number of "alternative dosage forms" – neither standard nor controlled-release orals solids – marketed by Impax, out of a total of 47 drugs. Alternative dosage forms make up nearly a quarter of Impax' generics pipeline of 77 products pending approval or under development. Nearly half, or 37 products, are controlled-release oral solids. Impax expects to spend US$46-US$49 million on generics research and development this year.

"The majority of potential generic product launches will likely require resolution of the warning letter at Hayward," Reasons said.

IN BRIEF

ASPEN PHARMACARE is **expanding its operation in Ireland** by adding 42 new positions, taking its local workforce to around 100 within the next 12 months. Having set up a European marketing and supply-chain hub in Dublin in 2012, the South African group 18 months ago established a local "centre of excellence" for regulatory affairs, including pharmacovigilance and quality assurance (**Generics *bulletin***, 19 October 2012, page 2).

JEAN COUTU said sales by its Pro Doc generics operation **increased by 16%** to C$47.9 million (US$43.4 million) in the group's financial third quarter ended 30 November 2013. Pro Doc's operating profit, excluding amortisation, climbed by just over a third to C$21.6 million. On the same basis, the Canadian pharmacy retailer improved its group operating profit by 3.4% to C$88.0 million – "despite the deflationary impact on pharmacy sales of a strong generic drugs penetration" – on turnover that slipped back by 1% to C$713 million.

DSM reported small increases in sales and earnings before interest, tax, depreciation and amortisation (EBITDA) by its Pharma cluster to €184 million (US$251 million) and €4 million respectively, according to **preliminary figures for 2013**. The Pharma cluster now covers only the group's DSM Sinochem antibiotics joint venture, as its DSM Pharmaceutical Products drug-development arm is considered a discontinued activity after it announced a US$2.6 billion tie-up with JLL Partners, the private-equity owner of contract research organisation Patheon. DSM will own a 49% stake in the combined entity, with JLL controlling the other 51%.

CATALENT PHARMA SOLUTIONS has filed a registration statement with the US Securities and Exchange Commission (SEC) ahead of a planned **initial public offering** (IPO). The US-based drug-delivery specialist – which has yet to set details of the share offering – said it would use the proceeds to repay debt and for "general corporate purposes".

ABBOTT said turnover by its Established Pharmaceuticals division **declined by 2.9%** to US$4.97 billion last year. Growth of 1.5% to US$2.36 billion in 14 "key emerging markets" – including Brazil, China and Russia – was outweighed by a 6.5% fall to US$2.62 billion in "other" markets, such as western Europe and Japan. "In 2014," Abbott commented, "Established products will continue to focus on driving growth in key emerging markets, which currently represent approximately 50% of total sales, and are projected to grow to approximately 60% of total sales over the next several years." Key strategic priorities for the division include "building locally relevant portfolios across key therapeutic areas and tailoring local commercial activities to each market".

CFR AND ADCOCK INGRAM have admitted it is "taking longer than expected to obtain the necessary approval from the [South African] Companies and Intellectual Property Commission" to pursue a ZAR12.8 billion (US$ 1.16 billion) **takeover** of the latter by the former. CFR's shareholders have approved the deal, but the Chilean firm had extended until at least 31 January the deadline for meeting certain pre-conditions. CFR's rival suitor for Adcock, Bidvest, has set 4 February as the closing date for its ZAR70-per-share offer for up to 34.5% of the South African company's shares.

ALKALOID has invested €1.20 million (US$1.64 million) in establishing a **1,600 sq m warehouse** for finished products in Gjorche Petrov, Macedonia. The 13-metre high warehouse can accommodate more than 3,100 pallets.

RESULTS FORECAST

Stada expects sales to exceed €2 billion

Stada Arzneimittel's group turnover exceeded €2 billion (US$2.7 billion) last year, according to preliminary figures. The German group – which passed the €1 billion mark in 2005 – plans to publish its final 2013 results on 27 March.

"In reaching over two billion euros in group sales," commented executive chairman Hartmut Retzlaff, "we were not only able to exceed an important mark, we could also show that we continue to be on the growth path with our sustainable business model. Our activities in the two market regions of Commonwealth of Independent States (CIS)/ Eastern Europe as well as Asia-Pacific, and our Branded Products segment, contributed to the sales growth in particular."

"This confirms our strategic orientation by which we concentrate on furthering our business in emerging markets and focus on the expansion of our strong brands," Retzlaff added.

In 2012, Stada increased its group turnover by 7% to €1.84 billion, largely by virtue of growing its Branded Products business segment by 26% to €596 million. Generics turnover edged ahead by 2% to €1.21 billion despite a 9% slide to €331 million in the German group's domestic market (**Generics *bulletin***, 5 April 2013, page 5).

In Germany, the company's latest sales organisation, StadaVita, has begun promoting a range of consumer healthcare products, including a diabetes-care range, under the leadership of Steffen Retzlaff (**Generics *bulletin***, 18 October 2013, page 3).

CUSTOM DEVELOPMENT AND CUSTOM MANUFACTURING

Alkaloid AD – Skopje offers custom development and custom manufacturing of the following Pharmaceutical forms:

- Oral solid dosage forms
- Liquids

Both of the production sites for the above forms are EU GMP approved by the MHRA.

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MERGERS & ACQUISITIONS

Teva trumps Endo with NuPathe offer

Teva has agreed to pay US$144 million for US-based neuroscience firm NuPathe, trumping Endo's earlier takeover bid. NuPathe's board of directors has unanimously approved Teva's US$3.65 per share cash offer – which is around 28% more than Endo's upfront cash offer of US$2.85 per share made late last year (**Generics *bulletin***, 10 January 2014, page 4) – and the two firms expect to close the deal this month, subject to various conditions.

The Israeli group's offer also includes contingent payments – which match those offered by Endo – of up to US$3.15 per share, based on sales milestones for NuPathe's US Food and Drug Administration (FDA) approved Zecuity (sumatriptan) transdermal migraine treatment. Sales of at least US$100 million across any four consecutive quarters during Zecuity's first nine years on the market will see the Israeli company pay an additional US$2.15 per share, while an extra US$1.00 per share will be paid should turnover exceed US$300 million for any 12-month period.

"We believe that Zecuity is a great fit with our existing US Central Nervous System (CNS) business unit, with near-term sales and significant commercial potential," observed the Teva unit's general manager, Mike Derkacz. As the only prescription migraine patch approved by the FDA, Zecuity had been shown to relieve not only migraine headache pain, but also migraine-related nausea, pointed out Teva, which will also gain access to NuPathe's proprietary transdermal technology.

Reporting a third-quarter operating loss of US$7.59 million on no sales, NuPathe said it had teamed up with LTS Lohmann to make commercial quantities of Zecuity patches.

The Israeli group could face US generic competition for its CNS blockbuster Copaxone (glatiramer acetate) when US patents expire in May. Teva recently predicted its turnover this year could be US$500 million higher should US generics not be launched. The firm has just received US approval for a three-times-a-week, 40mg/ml formulation of Copaxone.

While NuPathe's board had unanimously approved Endo's offer, on 6 January it received an e-mail from Teva's head of global business development, Ivana Liebisch, making an unsolicited acquisition proposal. The two firms had previously been negotiating a co-promotion partnership. In that e-mail, Teva offered to pay the US$5.0 million termination fee that NuPathe would owe Endo for breaking off the deal.

Maintaining that Endo's offer had "represented fair value for NuPathe", the US firm's president and chief executive officer, Rajiv De Silva, said Endo would "look to deploy capital on other opportunities to create value for its shareholders".

MANUFACTURING

Indoco allays facility worries

Indoco Remedies has moved to allay concerns that its sterile-products facility in Goa, India, may be subjected to a warning letter issued by the US Food and Drug Administration (FDA).

Stressing that it had not received a warning letter, the Indian company said it had responded with remediation and preventive actions to a 'Form 483' list of observations issued after the FDA inspected the Goa site in August last year. "All the issues stand resolved, and the company is awaiting an establishment inspection report (EIR), which normally takes five to six months," Indoco stated.

REGULATORY AFFAIRS

GPhA disagrees over US plan on shortages

Imposing a fixed time limit within which supply-chain disruptions must be reported as part of efforts to tackle drug shortages is "not feasible" and could lead to "significant over-reporting", according to the US Generic Pharmaceutical Association (GPhA). The US Food and Drug Administration (FDA) last year invited comments on a proposal to set this limit at five business days (**Generics *bulletin***, 15 November 2013, page 14).

In a letter to the FDA, the GPhA's senior vice-president for sciences and regulatory affairs, David Gaugh, said the association "must disagree respectfully" with the time-limit proposal.

"We are concerned that in some instances it may not be feasible for the manufacturer of a drug to comply," Gaugh said, adding that the proposal also risked the "unintended consequence" of manufacturers reporting a supply interruption when they did not know whether this would lead to a disruption. Instead, Gaugh recommended the FDA to maintain the 'as soon as practicable' standard stipulated in the FDA Safety and Innovation Act (FDASIA), thus avoiding the "significant over-reporting of routine, everyday interruptions".

The GPhA also suggested the FDA should consider market dynamics. This would also avoid the reporting of supply-chain disruptions "that are not true drug shortages". A filter of 'primary suppliers' could identify those that contributed a "significant" percentage of a certain drug.

Another GPhA suggestion included adding a 60-day potential supply disruption period as the minimum for reporting, which could "avoid chances of inventory hoarding and artificial increases to market demand that ultimately undermines the intent of FDASIA". The association also urged the FDA to work with manufacturers to define more clearly the products which were used in the "severe and life-threatening conditions" referred to in the proposal.

Furthermore, the GPhA has asked the FDA to consider regulatory discretion where "medically necessary drugs" are concerned. "An available product may be impacted by a minor good manufacturing practice (GMP) deviation, but could be usable to save a patient's life," the generics association pointed out.

INTELLECTUAL PROPERTY

Accusations fly in South Africa

A row has broken out in South Africa over originators' attempts to steer a review of the country's intellectual-property laws.

Reacting to reports that health minister Aaron Motsoaledi had accused originators of "genocide" through a "satanic plot" to derail measures that would improve access to medicines, humanitarian group Médecins Sans Frontières (MSF) insisted that "to have foreign companies spending ZAR6 million (US$0.55 million) to dissuade government from pushing legislation that promotes access to more affordable medicines is outrageous".

But the Innovative Pharmaceutical Association South Africa (Ipasa) said the supposed plot was a proposal for a campaign made by a public-affairs company that it had rejected. "Ipasa supports the broad objectives of the draft national policy on intellectual property," the originators' body stated, adding that it had submitted its comments to South Africa's Department of Trade and Industry (DTI), which is responsible for finalising the policy (**Generics *bulletin***, 6 December 2013, page 19).

IN BRIEF

MHRA – the UK's Medicines and Healthcare products Regulatory Agency – has released the latest edition of its guide on European Union (EU) current good manufacturing practice (cGMP) and distribution, the **Orange Guide**. The text, which replaces the previous guidance published in 2007, includes "substantial amendments" to the Community code relating to human medicinal products.

S&P DOW JONES INDICES – a provider of financial market indices – has said that patients choosing generic alternatives over brands contributed to total **US medical costs rising by only 3.2%** in the 12 months ended August 2013, compared to the 4.8% rise reported over the prior-year period. Pointing to the falling use of brands, the managing director of S&P's Index Committee, David Blitzer, said "purveyors of branded pharmaceuticals chose to respond to price competition by increasing prices to offset declining usage". "Compared to branded [medicines], where usage is dropping by 15% annually, generics see consistent increases," he added.

US doctors are a third more likely to **prescribe branded medicines** when they are requested by a patient, despite the availability of cheaper generic rivals, according to a study authored by Eric Campbell and published in *JAMA Internal Medicine*. The study also found that 37% of doctors admitted to neglecting to prescribe generics. "That figure is probably an underestimate," Harvard professor Campbell observed, "because even though our survey was anonymous, there's still going to be a reluctance among doctors to admit doing something that would be perceived negatively."

NATURE BIOTECHNOLOGY has **published a joint paper** by trade association Biotechnology Industry Organisation (BIO) and research service BioMedTracker (BMT) which shows that the overall success rate for drugs moving through clinical trials to US Food and Drug Administration (FDA) approval dropped by as much as half between late 2003 and the end of 2011. Using BMT's proprietary database of close to 4,500 drugs and over 7,300 unique development paths, the two bodies showed that FDA approval slid from about one in five or six to one in 10 over the eight years.

PHARMEXCIL – the Pharmaceuticals Export Promotion Council of India – is requesting feedback from members that would be interested in making use of a **warehousing facility** that it is proposing to set up in Nigeria. The council – which plans to have premises in Lagos – is requesting information such as whether members have offices in Nigeria and neighbouring countries, and the value of their exports to those countries.

IEIS – the Pharmaceutical Manufacturers Association of Turkey – has stated that **IBSA Pharma** has joined its association. The Swiss firm has been operating in Turkey since 2007.

FDA – the US Food and Drug Administration – has announced plans to "**take enforcement action** against unapproved and misbranded oral and injectable drug products labelled for prescription use and containing codeine sulfate, codeine phosphate, or dihydrocodeine bitartrate". Some products covered by this action also included acetaminophen – known as paracetamol in other markets – at doses higher than 325mg, the agency pointed out, despite this being the upper limit allowed per dosage unit by the FDA in oral prescription products.

DANISH manufacturers, importers and distributors of active pharmaceutical ingredients (APIs) must notify the Danish Health and Medicines Authority by 1 March of any changes to their registration information that may affect the quality or safety of their APIs.

SUBSTITUTION

German deal blocks certain substitution

The immunosuppressant ciclosporin and the epilepsy drug phenytoin will be excluded from generic substitution from 1 April under the terms of a deal hammered out between Germany's statutory health insurance funds and the country's pharmacy association, the DAV. Further ingredients could be barred at a later date, based on general principles agreed by the two parties.

Triggered by a petition to exclude strong analgesics from substitution, the German government had commissioned the DAV and the funds' GKV-Spitzenverband umbrella body to draw up a list of substances that should not be substituted. After lengthy arbitration, the two bodies have now reached an agreement.

"For the first time," said the DAV, "ingredients have been defined for which prescribed medicines do not have to be switched for cheaper drugs covered by rebate contracts." The pharmacists' association believes around 20 molecules should be exempted, including cardiovascular agents, immunosuppressants and modified-release analgesics.

Arguing that undisclosed "objective criteria" that the two parties had agreed would ensure exceptions from substitution were rational, the GKV-Spitzenverband said the agreement should not affect the newly-installed German parliamentary coalition's intention to transfer responsibility for the list of exceptions to the country's federal joint committee, the G-BA.

REGULATORY AFFAIRS

ANDA filers must look ahead

Companies considering filing abbreviated new drug applications (ANDAs) in the US should be looking at drugs currently in Phase II and III clinical trials as potential targets, according to Shashank Upadhye, a partner at US law firm Seyfarth Shaw, speaking at a company seminar.

Former Apotex and Sandoz executive Upadhye said generics companies needed to be planning far ahead if they were to remain competitive. "We are seeing ANDAs being filed within two months of the reference-listed drug being approved and launched," he observed.

Competition to achieve first-to-file status, and the accompanying 180-day generic market exclusivity, was intense, Upadhye noted. At least 16 companies had filed ANDAs containing paragraph IV patent challenges for lacosamide on the first day possible, a year before UCB's new chemical entity (NCE) exclusivity for Vimpat expired on 28 October 2013, he pointed out (**Generics *bulletin***, 6 September 2013, page 24).

REGULATORY AFFAIRS

FDA aims to improve quality

Improving the "completeness and quality" of abbreviated new drug applications (ANDAs) is the goal of a public docket established by the US Food and Drug Administration (FDA). The docket is open for comments until 24 March.

"Specifically," the agency stated, "FDA is interested in hearing about any difficulties sponsors are having developing and preparing their ANDA submissions that FDA could help address, for example by providing better information." The agency is also "seeking input on how to best share suggestions for improving the quality of ANDAs".

REGULATORY AFFAIRS/INDUSTRY ASSOCIATIONS

Regulatory costs are endangering industry

Europe's generics industry must push for "significant changes to the regulatory environment" to ensure associated costs do not "become a barrier to developing and improving generic and biosimilar products, or even maintaining these products in the market", according to Beata Stepniewska, deputy director-general of the European Generic medicines Association (EGA).

Speaking at the 13th EGA Regulatory & Scientific Affairs Conference, held in London on 23-24 January, Stepniewska highlighted "huge potential" for improving the European Union's (EU's) regulatory environment. Practical steps, she argued, should include: streamlining the costs and processes of variations procedures; simplifying the decentralised procedure; improving work-sharing as a core element of the EU regulatory network; and assessing the impact of new legislation on both competent authorities and industry. Enabling single development processes for global markets would also be crucial to ensure EU firms remained competitive, she insisted.

The EGA is also concerned that new pharmacovigilance fees payable to the European Medicines Agency (EMA) have been imposed on top of similar fees due to national agencies. For drugs approved via the EU's decentralised route, this raised the risk of industry having to pay at least twice.

Furthermore, the association estimates, implementing anti-counterfeiting safety features will cost industry around €1 billion (US$1.4 billion) over the next few years (**Generics *bulletin***, 4 May 2012, page 10).

"The impact of this high burden for our industry might create a shift of generic medicines production away from Europe and a significant decrease in the availability of high-quality medicines for patients," warned the EGA's medical affairs manager, Maarten Van Baelen.

REGULATORY AFFAIRS

US agrees to restore user fees

An agreement has been reached between the US House of Representatives and the country's Senate on legislation that would restore 'sequestered' user fees paid to the US Food and Drug Administration (FDA) in the financial year ended September 2013. A group of representatives recently urged the US Office of Management and Budget that user fees – including almost US$15.3 million collected by the FDA under the Generic Drug User Fee Act (GDUFA) – should not be affected by the 5.1% across-the-board sequestration that took effect on 1 March 2013 (**Generics *bulletin***, 10 January 2014, page 15).

"The Omnibus Appropriations Act reflects the bipartisan support of members of Congress to roll back the sequester of fiscal year 2013 user fees," explained Representative Anna Eshoo. Commending the legislation, the US Generic Pharmaceutical Association (GPhA) said it "looks forward to prompt Senate approval in the coming days".

"Restoration of previously sequestered user fees, particularly those designated in accordance with GDUFA, and the Biosimilar User Fee Act (BsUFA), is a necessary and commendable step," said Ralph Neas, president and chief executive officer of the GPhA.

"Now," he added, "agency experts can get back to business, expediting site inspections and enhancing the generic-drug application and review process to ensure that savings from generic medicines are realised by patients, government, businesses and others."

REGULATORY AFFAIRS

Brazil urges input on *similares* proposals

Comments have been invited from industry stakeholders by Brazil's medicines agency, Anvisa, over proposals to allow '*similares*' drugs – which contain the same active ingredients as brands but were not approved under the same bioequivalence standards as generics – to be substituted in the same way as traditional generics.

"The determination of the equivalence of *similares* drugs is possible due to the determination by Anvisa that all products in this category prove equal to the reference medicine," the agency stated, adding that rules introduced in 2003 had set out a ten-year timetable for *similares* products to prove equivalence to their branded counterparts. "By the end of 2014, all '*similares*' products on the market will be technically equivalent to the reference products," Anvisa noted.

As part of the proposals – first mooted by Anvisa last year (**Generics *bulletin***, 15 November 2013, page 17) – *similares* drugs would all have packaging indicating their status, in a similar fashion to the yellow band used on Brazilian packs of generics.

Anvisa recently agreed a memorandum with local generics industry association Prógenéricos to foster technical and operational cooperation between the two bodies (**Generics *bulletin***, 10 January 2014, page 10).

PHARMACOVIGILANCE

Proportionality key to EU risk

Risk-management plans (RMPs) required as part of marketing-authorisation applications for generics in the European Union (EU) need not be overly burdensome to applicants, according to Peter Arlett, head of sector for pharmacovigilance and risk-management at the European Medicines Agency (EMA). Rather, he told delegates to the European Generic medicines Association's (EGA's) pharmacovigilance discussion forum in London, UK, at the end of January, RMPs should be proportionate to the product's risk.

"I know that there is concern about the requirement for generics to submit RMPs," Arlett acknowledged, "but it is a question of getting it right in terms of proportionality." The process would become more efficient as more RMPs were made public and were able to be used as the basis for future plans, Arlett predicted.

Meanwhile, Mick Foy from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) observed that the requirement to submit an RMP was still not clear to all suppliers, noting that some firms attempting to register generics had mistakenly asked the UK regulator for a "waiver" from RMPs.

LEGISLATION

India clarifies investment rules

Non-compete clauses will be allowed as part of foreign direct investment (FDI) pharmaceutical deals in India only "in special circumstances", the country's Ministry of Commerce and Industry has clarified. Stating that there was in principle no limit on greenfield or brownfield foreign investment in pharmaceuticals, the ministry said the Indian government "may incorporate appropriate conditions for FDI in brownfield cases at the time of granting approval".

REGULATORY AFFAIRS

FDA must reconsider change to label rules

Changes to rules on generic labelling being considered by the US Food and Drug Administration (FDA) should be reconsidered by the agency, according to a letter sent by a group of US congressmen to FDA Commissioner Margaret Hamburg. Under the proposed rule – opened for comment late last year (**Generics *bulletin***, 15 November 2013, page 1) – US generics firms would be able to update safety information on product labelling using the same 'changes being effected' process as originators. Current US federal law dictates that a generic's label must match that of the brand and can only be updated once brand labelling is altered.

"Allowing generic manufacturers to unilaterally change their labelling means potentially dozens of drugs that are chemically and biologically identical might nonetheless bear different safety information," the letter warns, "confusing patients and prescribers alike." The proposed rule would "conflict directly with the statute", the congressmen insist, as well as imposing "significant costs on the drug industry" that "could be in the billions".

These expenses could result from "costly, duplicative testing" due to a lack of clarity for manufacturers over labelling changes that might previously have been considered or rejected by the FDA, the letter suggests, as well as increased exposure to tort lawsuits.

Emphasising their "grave concerns" over the proposal, the congressmen "respectfully request the agency explain and reconsider this departure from more than two decades of settled practice".

The FDA recently granted a request made by the US Generic Pharmaceutical Association (GPhA) to extend the deadline for comments on the proposed rule until 13 March 2014 (**Generics *bulletin***, 10 January 2014, page 15).

PRICING & REIMBURSEMENT

German funds solicit offers

The GWQ group of 43 German funds is seeking bids for 144 active ingredients or combinations in its ninth tender round. Two-year supply contracts in the funds' ninth tender round are scheduled to start on 1 July 2014, offering access to around 7 million Germans.

In total, the GWQ is seeking bids for 163 lots, 139 of which will be awarded on an exclusive basis, with the remaining 24 to be split between three suppliers. At retail prices, the ingredients – which include acarbose, levetiracetam and valsartan, as well as those covered by the fifth GWQ tender round that expires on 30 June this year – have annual sales through the funds of around €110 million (US$151 million).

MARKET RESEARCH

GPhA points to spending drop

Healthcare spending in the US that increased by just 3.7% in 2012 marked "the fourth consecutive year of low growth", according to research by the Centers for Medicare and Medicaid Services (CMS) cited by the US Generic Pharmaceutical Association (GPhA). "This successful cost control is consistent with data demonstrating that savings from generic medicines are at an all-time high, reaching US$217 billion in 2012," the association observed.

BIOLOGICAL DRUGS

Biocon's trastuzumab is introduced in India

Biocon is launching a follow-on version of trastuzumab in India under the brand name Canmab. The product – which was developed in partnership with Mylan and is being manufactured at Biocon's plant in Bangalore, India – would be available to patients "around the first week of February", Biocon said. Roche's Herceptin original had Indian sales of about US$21 million in 2012, Biocon claimed.

Calling the launch "an important milestone for our biosimilars programme", Biocon's managing director and chairperson, Kiran Mazumdar-Shaw, said the product "demonstrates our ability to deliver on our promise of affordable innovation with a high-quality, world-class product". The monoclonal antibody would "make a significant difference in the treatment paradigm for HER2-positive breast cancer in India", Mazumdar-Shaw added. Biocon's version offered "the same level of safety and efficacy as the reference product", she insisted.

Moreover, Biocon added, "unlike the product currently available in the market, both 150mg and 440mg formulations of Canmab can be stored for one month". This was "an important offering for patients in India, as it will ensure that there is no under-dosing or wastage".

"Canmab will be available at about a 25% discount to the current list price of the reference product in India," Biocon revealed. This was "already significantly lower than its price in developed markets", the firm added. The 150mg presentation will be priced at Rs19,500 (US$317) per vial.

OPHTHALMIC DRUGS

Italian ruling upholds Xalatan abuse fine

Italy's Council of State has upheld a ruling that Pfizer abused its dominant market position for Xalatan (latanoprost) to keep generics off the market. In 2012, the country's competition authority, the AGCM, fined Pfizer €10.7 million (US$14.5 million) after finding that the originator abused its position by artificially extending protection for Xalatan (**Generics *bulletin***, 17 February 2012, page 1).

In its ruling, the AGCM had found that Pfizer "exploited the legal uncertainty" surrounding a supplementary protection certificate (SPC) based on divisional patent EP1,225,168 to prevent generics firms from launching latanoprost rivals. The SPC extended protection from 6 September 2009 – when the basic molecule patent EP0,364,417 expired – until 17 July 2011. However, a separate decision by an administrative court later concluded that Pfizer had done no more than protect its "legitimate rights and interests" (**Generics *bulletin***, 14 September 2012, page 1).

Noting that the latest ruling by the Council of State "definitively confirms the decision of the competition authority", Italy's generics industry association, Assogenerici, said the decision was an "important result" that the association would "evaluate in detail" once the full details were published. To avoid the possibility of such "delaying tactics" being used, urged Assogenerici's president, Enrique Häusermann, Italy's government should take steps to align local legislation with European rules on patent linkage.

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- The Unified Patent Court: implications for the generic medicines industry
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ALZHEIMER'S DISEASE DRUGS

Canadian companies introduce donepezil

Several of Canada's leading generics players have introduced donepezil tablets after the expiry of Eisai's Canadian patent CA1,338,808 that protected the Aricept brand marketed by Pfizer.

Ranbaxy says it conducted a 'day-one' launch of donepezil 5mg and 10mg tablets. Quoting IMS data, Ranbaxy – which is making the finished-dosage form at its Ohm facility in New Jersey, US – said Aricept achieved Canadian sales of C$154 million (US$141 million) in the 12 months ended November 2013.

Mylan – which had earlier failed to overturn the '808 patent (**Generics *bulletin***, 20 April 2012, page 13) – has also introduced donepezil tablets in Canada, as has Apotex. Other companies that have obtained notices of compliance (NOCs), or marketing authorisations, for donepezil tablets from Health Canada are Accord Healthcare, Laboratoire Riva, Sandoz and Teva.

According to Health Canada's Patent Register, the sole unexpired patent that covers Aricept is Canadian patent 2,252,806, which describes processes for producing four polymorphs of donepezil hydrochloride and expires on 6 June 2017.

ANALGESICS

Teva wins on US OxyContin

Three US low-impurity patents protecting Purdue's OxyContin (oxycodone) analgesic are invalid, a New York district judge has ruled. Judge Sidney Stein also found that an abuse-resistance patent was invalid, while another of Purdue's abuse-resistance patents was not infringed by a generic version of OxyContin developed by Teva.

Addressing the three patents describing an oxycodone salt with low levels of α,ß-unsaturated ketone (ABUK) impurities – US patents 7,674,799, 7,674,800 and 7,683,072, each of which expires on 30 March 2025 – Stein noted that Teva's extended-release tablets, which used an active pharmaceutical ingredient (API) made by Noramco, would infringe the three patents.

However, Stein decided that "the low-ABUK invention would have been obvious to a skilled artisan". Creating a low-ABUK API, as required by the US Food and Drug Administration (FDA), involved no more than "a predictable use of prior-art elements according to their established functions" as described in the landmark KSR obviousness decision.

US abuse-deterrent patent 8,114,383 was invalid, Stein said, because its claims were disclosed in a prior-art application describing a hot-melt extrusion process.

BIOLOGICAL DRUGS

Janssen seeks different INNs

Biosimilars should have international non-proprietary names (INNs) that are distinguishable from their reference products or other biosimilars, according to a citizen petition submitted to the US Food and Drug Administration (FDA) by Johnson & Johnson's Janssen subsidiary. "Our own experience with Eprex/Erypo (epoetin alfa) has informed our views," Janssen said, highlighting "the importance of the ability to identify precisely which product a patient has received and the risks associated with inadvertent switching".

IN BRIEF

SANDOZ is appealing against a US decision denying the generics firm a declaratory ruling that its planned biosimilar rival to Amgen's **Enbrel** (**etanercept**) does not infringe two patents protecting the biologic brand. Late last year, a northern California district court rejected Sandoz' motion for a ruling confirming that the firm's "assertedly biosimilar product" did not infringe US patents 8,063,182 and 8,163,522 (**Generics *bulletin***, 6 December 2013, page 23).

PROSONIX – the UK-based respiratory specialist – says it has received "positive top-line results" from a Phase II dose-ranging study for **glycopyrronium bromide** suspension developed using its novel particle-engineering technology (**Generics *bulletin***, 4 October 2013, page 24). A double-blind, single-dose study of the firm's PSX1002 candidate met its primary endpoint of demonstrating improved lung function in 37 chronic obstructive pulmonary disease (COPD) patients, with "statistically significant separation from placebo for all doses" and a clear progression of effect by dose. Having identified two potential doses and a once-daily dosing interval, Prosonix plans to conduct a repeat-dose, dose-ranging study later this year.

ACTAVIS, HI-TECH, LUPIN and SANDOZ have failed to overturn five US patents protecting Allergan's **Lumigan** (**bimatoprost**) 0.01% ophthalmic solution until 13 June 2027. Texas District Judge Michael Schneider found all five patents – four of which expire in March 2025, and the other in June 2027 – were valid and infringed by the generics firms' abbreviated new drug applications (ANDAs).

AKORN has added to its ophthalmics portfolio by acquiring the US marketing authorisation and all rights to Japanese firm Santen's **Betimol** (**timolol**) 0.25% and 0.5% ophthalmic solution. The US company – which recently bought fellow US generics firm and ophthalmics specialist Hi-Tech Pharmacal for US$640 million (**Generics *bulletin***, 6 September 2013, page 1) – expects to launch the glaucoma and ocular hypertension treatment early this year.

TEVA UK has launched a rival to GlaxoSmithKline's **Malarone** (**atovaquone/proguanil**) 62.5mg/25mg and 250mg/100mg tablets under the brand name **Mafamoz**. The generics firm noted that the malaria treatment was "under certain circumstances" prescribed on the UK's National Health Service (NHS), but was typically available via private prescription. India's Glenmark has marketed a generic rival to Malarone in the UK since early last year, after successfully convincing the country's High Court to revoke the originator's patent for obviousness (**Generics, *bulletin***, 15 February 2013, page 21).

HI-TECH intends to begin shipping its generic rival to Ista's **Bromday** (**bromfenac**) 0.09% ophthalmic solution "immediately", after the US firm's abbreviated new drug application (ANDA) received final approval from the US Food and Drug Administration (FDA). Fellow US company Mylan was the first firm to launch generic bromfenac, but its ANDA was based on a discontinued formulation of a different dosing regimen that the originator marketed under the Xibrom brand (**Generics *bulletin***, 10 June 2011, page 23).

FRENCH rivals to Bayer's **Diane 35** (**cyproterone/ethinylestradiol**) 2mg/0.035mg tablets have been allowed to re-enter the market following a decision by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) that the brand and its generic alternatives are safe to use as an acne treatment (**Generics *bulletin***, 9 August 2013, page 21). France's medicines agency, ANSM, had previously suspended marketing authorisations for the products over safety concerns (**Generics *bulletin***, 15 February 2013, page 23).

BIOLOGIC DRUGS

Celltrion gets nod for Korean trastuzumab

Celltrion has received approval for a biosimilar version of trastuzumab from South Korea's Ministry of Food and Drug Safety (MFDS) under the brand name Herzuma. The firm said it expected to start marketing the product "within the first half of this year, after the completion of administrative procedures, including notification to the Ministry of Health and Welfare". Herzuma has been approved for treating "early and advanced metastatic HER2-positive breast cancer as well as advanced metastatic stomach cancer".

Claiming that trastuzumab – marketed by Roche's Genentech as Herceptin – had global sales of around US$6.3 billion in 2012, Celltrion said its domestic market for the product was worth around US$80 million. The price of Genentech's Herceptin in Korea would automatically drop by 30% as soon as the first biosimilar rival to the brand entered the market, the firm added.

Noting the MFDS approval received by Celltrion in 2012 for its Remsima (infliximab) rival to Janssen's Remicade (**Generics *bulletin***, 3 September 2012, page 16) – which was followed by European approval for the product a year later (**Generics *bulletin***, 20 September 2013, page 17) – the company said the trastuzumab authorisation "consolidates our position as a leader in biosimilar competition".

"Herzuma's approval is another major milestone for biosimilar development, as this approval marks the first approval of an oncology biosimilar monoclonal antibody (mAb) with global clinical trial results," Celltrion observed. The firm said it had conducted global clinical trials involving 558 patients starting from August 2009 to December 2011, in 115 locations across 18 countries.

"To date, there have been no biosimilar mAbs for breast cancer that have completed clinical trials in Europe or any other developed nations," Celltrion added, "which confirms Celltrion's advantageous position in the breast cancer biosimilar mAb market." When Celltrion filed its trastuzumab application with the MFDS last year (**Generics *bulletin***, 28 June 2013, page 20), the firm said its version was the "first trastuzumab biosimilar to enter the regulatory approval procedure".

Meanwhile, Health Canada has approved Celltrion's infliximab 100mg vials under the Remsima and Inflectra brand names. The notices of compliance (NOCs) – effectively marketing authorisations – were obtained through the New Drug Submission (NDS) route. Celltrion also uses the Remsima name in Europe, while Inflectra is sold by the firm's marketing partner Hospira.

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OPHTHALMIC DRUGS

Actavis fights over Allergan's Restasis

Actavis is seeking to persuade the US Food and Drug Administration (FDA) to accept for filing its abbreviated new drug application (ANDA) for a generic version of Allergan's Restasis (ciclosporin) 0.05% ophthalmic solution. Having released draft guidance on proving bioequivalence to Restasis midway through last year (**Generics *bulletin***, 9 August 2013, page 19), the FDA refused to accept receipt of Actavis' ANDA that was filed before the guidance was published. Actavis is now lobbying the agency to reconsider its position.

In mid-January, Allergan strengthened Restasis' defences against generic competition by listing a newly-issued method-of-use patent against the brand in the FDA's Orange Book. Whereas the only other listed patent – US patent 5,474,979 – expires on 17 May this year, the newly-issued 8,629,111 patent runs until 27 August 2024. Allergan said the '111 patent – which is entitled 'Methods of providing therapeutic effects using cyclosporin components' – covered "the specific formulation" of Restasis.

Actavis reacted by amending its ANDA to include a paragraph IV challenge to the '111 patent and – "to preserve its potential first-filer status" – informing Allergan of the challenge. Allergan has also asked the FDA to list in the Orange Book another method-of-use patent – 8,633,162 – against Restasis. This newly-issued patent also expires in August 2024.

Allergan – which reported Restasis sales ahead by 14.2% to US$662 million in the first nine months of 2013 – said it planned to submit a citizen petition calling on the FDA to adopt "certain approaches for demonstrating bioequivalence" when reviewing ANDAs that referenced the ophthalmic brand.

The agency's draft guidance proposes approving generics solely on the basis of *in vitro* comparative trials without human clinical trials. But Allergan challenged the legal basis for the draft guidance, raising safety and public-health concerns and arguing that the proposed non-clinical criteria were inadequate to prove bioequivalence to Restasis.

ANTIHYPERTENSIVES

Perindopril patent falls short

Servier failed to disclose the best method of carrying out the perindopril arginine innovation covered by Australian patent 2003,200,700, Federal Judge Steven Rares has decided. However, he remanded for further consideration what relief should be granted to Apotex, which had challenged the arginine salt patent.

Noting that Australian patent law required a patent's specification to disclose the best method for achieving any invention, Rares stated: "The complete specification essentially failed to disclose any detail sufficient to provide a skilled addressee with the directions necessary to perform the invention without undertaking potentially extensive trial-and-error experimentation in refining the choices of parameters and methodologies of classical salification."

Apotex – which already markets the erbumine salt of perindopril – is seeking to invalidate the patent covering the arginine salt to which Servier switched its Coversyl antihypertensive brand in 2006 after its erbumine patent expired. In March 2012, Servier had obtained an interlocutory injunction against Apotex selling perindopril arginine.

"Apotex' many other challenges to the validity of the patent have all failed, and those took up the bulk of the evidence and hearing," Rares noted. "That failure should be reflected in costs," he concluded.

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ANTIHYPERTENSIVES

Ranbaxy reacts over US valsartan rumours

Ranbaxy has fuelled speculation that it might have solved the issues holding up its US approval for generic Diovan (valsartan).

Media conjecture in India suggested that Ranbaxy had struck a deal to source valsartan active pharmaceutical ingredient (API) from "a multinational company" after the US Food and Drug Administration (FDA) found deficiencies at the firm's own API facility in Toansa, India (see page 3).

In a statement issued to the Bombay Stock Exchange, the Indian company said: "While we do not disclose individual business transactions as part of our normal course of business, Ranbaxy – as part of its strategy – evaluates alternate viable sourcing of materials from time to time." Decisions, the firm added, were based on "the best value that can be derived in the interests of the company".

Diovan lost protection in 2012

Novartis lost its main patent protection for Diovan in September 2012. While Mylan immediately launched valsartan/hydrochlorothiazide tablets with 180-day generic market exclusivity – albeit blunted by the authorised generic introduced by Novartis' Sandoz affiliate (**Generics *bulletin***, 1 October 2012, page 13) – Ranbaxy failed to secure approval from the FDA to enjoy similar exclusivity for the mono valsartan tablets.

At that time, a Ranbaxy spokesperson told **Generics *bulletin*** that the firm "believes it maintains first-to-file status" and planned to launch shortly after securing FDA approval. Mylan tried unsuccessfully to persuade a Columbia district court that Ranbaxy should forfeit its 180-day exclusivity (**Generics *bulletin***, 11 January 2013, page 17).

The FDA has approved drug master files (DMFs) for valsartan APIs from several of Ranbaxy's Indian rivals, as well as from a handful of Chinese producers. Global generics players including Apotex, Mylan and Teva also hold valsartan DMFs.

RESPIRATORY DRUGS

Sandoz' AirFluSal is launched in Denmark

Sandoz has launched its AirFluSal Forspiro (fluticasone/salmeterol) rival to GlaxoSmithKline's Seretide brand in Denmark. The Novartis subsidiary recently received a Danish marketing authorisation for both the 50µg/250µg and 50µg/500µg strengths of the respiratory drug (**Generics *bulletin***, 10 January 2014, page 1).

Meanwhile, Sandoz has also received marketing authorisations for AirFluSal Forspiro in Germany, Hungary and Sweden. Sweden approved both strengths of the respiratory drug, while the German and Hungarian approvals cover only the higher strength.

Noting that AirFluSal Forspiro combined a "novel inhaler" with a "proven combination" of ingredients, Sandoz said the Danish, German and Swedish approvals were for "the continuous treatment of patients above 12 years of age with persistent asthma or for symptomatic treatment of chronic obstructive pulmonary disease (COPD) in the same patient group". In Hungary, the wording was slightly different, covering "the continuous treatment of patients above 12 years of age with persistent asthma or for symptomatic treatment of COPD in adults".

European Union (EU) decentralised procedures had also been completed in Belgium and Bulgaria, Sandoz observed, as well as in Luxembourg, Romania and Norway. Of these, all procedures covered the higher strength, while Norway also included the 50µg/250µg form. Sweden was the reference member state. "We look forward to bringing this product to patients across these markets," Sandoz stated.

Sandoz said AirFluSal Forspiro "strengthens Sandoz' respiratory portfolio and reinforces the company's leadership in differentiated products". Developed with UK-based Vectura, the product had proved its safety, efficacy and equivalence "in multiple clinical trials", giving it "clinically-proven equivalence", Sandoz noted. Jeff George, global head of Sandoz, called the product a "key element of our strategy to introduce differentiated generic medicines".

BIOLOGICAL DRUGS

Finox gets EMA follitropin nod

Finox Biotech has received a positive opinion from the European Medicines Agency (EMA) for its Bemfola (follitropin alfa) solution as a biosimilar alternative to Merck Serono's Gonal-f fertility drug. Based on the EMA's opinion, the European Commission will now consider whether to grant Finox a centralised marketing authorisation covering all 28 European Union (EU) member states. "If approved," the Swiss group stated, "Bemfola could be available in the EU in the second quarter of 2014."

"To date, nearly 400 patients have received at least one dose of Bemfola in Phase I or Phase III studies," noted Finox, which is delivering the follicle-stimulating hormone (FSH) in disposable, once-a-day injector pens. The Phase III study had shown Bemfola to have similar safety and efficacy to Gonal-f, Finox said, based in part on "the numbers of oocytes retrieved after completing FSH therapy".

The European Commission last year approved Teva's Ovaleap (follitropin alfa) as a biosimilar alternative to Gonal-f.

The EMA's committee for human medicinal products (CHMP) also issued positive opinions for 3M's rivastigmine 4.6mg and 9.5mg patches as well as for Teva's zoledronic acid 5mg solution. But it adopted a negative opinion on Teva's Nerventra (laquinimod) multiple-sclerosis candidate, due largely to long-term cancer risks.

CONTRACEPTIVES

Lo Loestrin not obvious in US

Lupin and Amneal have failed to convince a New Jersey district court that a patent protecting Actavis' Lo Loestrin Fe (norethindrone/ethinylestradiol/ferrous fumarate) oral contraceptive is invalid due to obviousness in light of prior art. The firms' abbreviated new drug applications (ANDAs) alleged the invalidity of US patent 7,704,984, which protects the brand until 2 February 2029. They argued the patent was obvious in light of previous patents relating to the combined use of a progestin and an oestrogen for hormonal contraception.

However, Judge Joel Pisano ruled that a skilled person would neither have been motivated to make the oral contraceptive regimen described in the '984 patent, nor would have been led to the claimed sequence of administration for Lo Loestrin Fe based on previous patents. Furthermore, the originator's product "has enjoyed commercial success and fulfils an unmet need," Pisano found.

Since submitting its ANDA, Lupin had admitted infringing the '984 patent, but also asserted counterclaims against Actavis' Warner Chilcott subsidiary alleging the patent's invalidity. Amneal's ANDA had originally belonged to Actavis, but the latter firm agreed to sell the right to its ANDA, along with three others, as a condition of acquiring Warner Chilcott for US$8.5 billion last year (**Generics *bulletin***, 4 October 2013, page 5).

BIOLOGICAL DRUGS

Ranbaxy and Epirus eye Indian infliximab

Ranbaxy has signed an international licensing deal with Epirus Biopharmaceuticals for the US-based firm's 'BOW-015' biosimilar candidate being developed as a rival to Janssen's Remicade (infliximab) brand. Epirus will develop and supply the product and Ranbaxy will market it upon regulatory approval.

"The product will be introduced in India and other emerging markets," Ranbaxy said, observing that "currently, there is no biosimilar of infliximab approved in India". Having recently announced positive results from Phase III clinical trials for BOW-015 (**Generics *bulletin***, 20 September 2013, page 21), Epirus said it had in November filed for approval in India.

Noting that it would receive upfront, milestone and royalty payments under the terms of the agreement, Epirus said the deal also covered "a broad range of territories" including south-east Asia, north Africa and "selected other markets". The US firm's president and chief executive officer, Amit Munshi, said Ranbaxy had "the right focus and infrastructure in these markets to effectively bring this product to these markets". Ranbaxy would pursue registrations in other markets after launching in India, Epirus added.

ERECTILE DYSFUNCTION DRUGS

England plans more sildenafil

Restrictions on prescribing sildenafil in England on the National Health Service (NHS) should be removed from 1 May now that low-cost generics have entered the market, following patent expiry for Pfizer's Viagra original in June last year, the Department of Health has proposed. "The Department estimates that these cheaper generic products are affordable on NHS prescription and their availability can bring health benefits for patients," states a consultation paper that is open for comment until 21 March.

According to the Department, Drug Tariff reimbursement prices for four-tablet packs of sildenafil 50mg fell by around 93% following Viagra's patent expiry, falling from £21.27 (US$35.34) in June 2013 to £1.45 in November. This steep price fall justifies making generic sildenafil more widely available on the NHS, it believes, although restrictions on the Viagra brand, tadalafil and vardenafil will remain in place.

IMMUNOSUPPRESSANTS

Zydus has sirolimus headstart

Zydus Cadila has claimed 180-day generic marketing exclusivity for sirolimus 0.5mg tablets in the US. The Indian company said the 0.5mg strength accounted for US$11.7 million of all US sirolimus sales totalling US$204 million last year. Zydus' approval came immediately upon expiry on 7 January of a six-month paediatric extension to US patent 5,100,899 protecting Pfizer's Rapamune brand.

Last year, Actavis failed to convince a Delaware district court that the '899 patent was invalid due to obviousness (**Generics *bulletin***, 15 February 2013, page 23). Rapamune is also covered by US patent 5,989,591, for which a paediatric extension ends on 11 September 2018.

Zydus has also secured tentative approval from the US Food and Drug Administration (FDA) for sirolimus 1mg tablets.

IN BRIEF

PAR has strengthened its affiliation with **IntelGenx** by striking a deal for two of the Canadian firm's **oral products**. Under terms of the agreement, Par will gain exclusive rights to sell the drugs in the US in exchange for undisclosed upfront and milestone payments to IntelGenx, as well as a share of profits. The two firms previously collaborated on a **buprenorphine/naloxone** sublingual film. Par has also struck a deal with Covis Pharma to distribute US authorised generics of **Lanoxin** (**digoxin**) 0.125mg and 0.25mg tablets.

ALPHAPHARM must provide AstraZeneca with copies of common technical document (CTD) modules, its drug master file (DMF) and batch records, an Australian federal court has ruled in a dispute over the Mylan subsidiary's **Noxicid** (**esomeprazole**) rival to Nexium. However, the court refused the originator's request for samples of Alphapharm's capsules and tablets. AstraZeneca had argued that it lacked sufficient information to determine whether Alphapharm's formulation infringed its Australian patent 722,839 covering esomeprazole magnesium trihydrate. According to court papers, Alphapharm intends to launch its capsules after AstraZeneca's Australian 'purity' patent 676,337 expires on 27 May this year.

IMB – the Irish Medicines Board – has published lists of interchangeable brands of **amoxicillin/clavulanic acid**, **losartan** and **simvastatin**. Consultations on drawing up lists of interchangeable **rabeprazole**, **anastrozole** and **candesartan** run until 7, 12 and 17 February respectively.

APOTEX has won a judicial review of Health Canada's refusal to accept for filing the firm's abbreviated new drug submission (ANDS) for **telmisartan**. Noting that Health Canada had approved other generic versions of Boehringer Ingelheim's **Micardis** (telmisartan) reference brand, Federal Judge Catherine Kane found that Health Canada had acted inconsistently by refusing Apotex' ANDS for the antihypertensive because it used excipients including potassium hydroxide. What was key, she said, was not the potential formation of salt forms, but that generics contained an identical amount of telmisartan to the reference brand.

PERRIGO has begun shipping with 180-day generic market exclusivity its rival to Medicis' **Vanos** (**fluocinonide**) 0.1% cream. Under the terms of a settlement with Valeant's Medicis over US patents 6,765,001 and 7,220,424 – that protect the dermatoses treatment until December 2021 and January 2023 respectively – Perrigo was able to launch from 15 December last year (**Generic *bulletin***, 1 May 2009, page 14).

ACTAVIS has introduced three strengths of **telmisartan/ hydrochlorothiazide** tablets in France. They are equivalent to Boehringer Ingelheim's **MicardisPlus** antihypertensive. The generics firm has also launched rivals to Janssen's **Pariet** (**rabeprazole**) 10mg and 20mg enteric-coated tablets in France.

AMNEAL has persuaded the US Patent and Trademark Office (USPTO) to conduct *inter partes* reviews of the obviousness of three US patents protecting Supernus' **Oracea** (**doxycycline**) antibiotic.

MYLAN has launched US rivals to Novartis' **Myfortic** (**mycophenolic acid**) 180mg and 360mg delayed-release tablets, with 180-day exclusivity for the higher strength. Apotex also holds approval for the 180mg version of the immunosuppressant. Mylan has also introduced cabergoline 0.5mg tablets, and joined Actavis, Aurobindo, Paddock, Sandoz and Unichem in securing US approval for repaglinide tablets once Caraco's 180-day exclusivity for generic Prandin expired.

MULTIPLE SCLEROSIS DRUGS

Teva calls for trials for Copaxone rivals

Rivals to Teva's Copaxone (glatiramer acetate) multiple sclerosis treatment should be subjected to clinical trials, according to a study published in online scientific journal *Plos One*. "Data demonstrates key genes respond differently to Copaxone versus a purported generic glatiramer acetate," Teva explained, noting that the generic version used in the study was marketed by Natco Pharma in India. The "significant differences in biological and immunological effects" had "potential clinical ramifications", the Israeli firm insisted.

Citing "a significantly different and irregular impact" on "key immune-response cells" by the "purported generic", Teva said the study "suggests a distinct potential difference in the impact of a purported generic glatiramer acetate on the immune system of patients, with possible implications on efficacy and safety". The firm's chief scientific officer and president of global research and development, Michael Hayden, insisted: "Teva believes the only way to truly understand the impact of these differences is by conducting a full battery of clinical studies."

Generic shows 'inconsistency'

The study – written in part by Hayden, and commissioned and funded by Teva – "shows that Copaxone has a more consistent biological impact across batches than the purported generic", the Israeli firm noted. "A high degree of consistency was found across 34 samples from 30 difference Copaxone batches", compared to "a high level of inconsistency across only 11 samples representing just 5 different batches of the purported generic glatiramer acetate".

Noting "higher variability in gene expression following activation by generic" compared to Copaxone, as well as "significant differences in impact on key biological processes", the study found that the differences "raise questions for physicians and regulators seeking safe and effective treatments for multiple sclerosis patients". It concluded that "clinical studies are warranted, using appropriate safety and efficacy endpoints" to compare generics with the brand.

"This extensive analysis indicates, in my view, a concerning lack of consistency and predictability by the purported generic glatiramer acetate's effect on key elements of the murine immune system," said one of the study's co-authors, Ben Zeskind, chief executive officer of the Immuneering Corporation. Such variability "raises the possibility that patients may not receive the same treatment effect with each dose", he warned.

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CHOLESTEROL-LOWERING DRUGS

More sued in Japan over Livalo patent

Three more Japanese generics companies – Kotobuki Pharmaceutical, Nichi-Iko Pharmaceutical and Sagami Chemical – have been sued by Kowa and Nissan Chemical for alleged patent infringement.

Suits filed in a Tokyo district court on 15 January allege that generic versions of Kowa's Livalo (pitavastatin) cholesterol-lowering brand – for which the generics firms secured National Health Insurance (NHI) price listings on 13 December last year – infringe Nissan Chemical's patent covering a crystalline form of pitavastatin.

The two originators had previously sued seven other generics players – Daito, Kaken, Kobayashi Kako, Meiji Seika, Mochida, Towa and Tsuruhara – for infringing the same patent (**Generics *bulletin***, 10 January 2014, page 19).

Kowa and Nissan said annual sales of Livalo in Japan were around ¥51 billion (US$489 million). The two firms promised in future to "bring similar actions against any other entities as soon as their infringement upon our intellectual-property rights has been confirmed".

SEDATIVES

FDA ponders Precedex patent

Firms that have filed abbreviated new drug applications (ANDAs) for generic rivals to Hospira's Precedex (dexmedetomidine) injectable sedative have been invited to submit initial comments on issues resulting from Hospira changing the use code for the sole unexpired patent listed against the brand.

While Hospira had in May 2004 listed the US method-of-use patent 6,716,867 – which expires on 1 October 2019 – with the use code 'Intensive care unit sedation', the FDA on 8 January this year acted on the originator's move to amend the use code to 'Intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures'.

"Does the breadth of the new use-code description for the '867 patent foreclose ANDA applicants from gaining approval for any of the approved indications [of Precedex] before the '867 patent expires?" the FDA enquires.

The agency is also inviting comments on whether Hospira missed a 30-day window for changing the use code, and whether it was relevant that Hospira did not change the code until after another Precedex patent with a similar use code expired.

ERECTILE DYSFUNCTION DRUGS

Apotex wins sildenafil appeal

A summary judgement of invalidity and non-infringement that Apotex had won against Pfizer's Canadian patent 2,163,446 has been upheld on appeal. The '446 patent covers Pfizer's Viagra (sildenafil) erectile-dysfunction brand until 13 May this year.

No error was found in an earlier court ruling that the '446 patent was invalid because of insufficient disclosure that sildenafil was useful in treating erectile dysfunction. That Federal Court ruling was based on the Supreme Court of Canada's verdict in favour of Teva in a patent-linkage case over Viagra (**Generics *bulletin***, 23 November 2012, page 17).

Treanda filings will test patent strategies

As the US generics industry has grown more competitive, the number of companies pursuing patent challenges has risen as players seek early entry into the market. Intended as an incentive to challenge weak patents and bring low-cost generics to consumers more quickly, the Hatch-Waxman Act provides the potential for 180 days of market exclusivity for the first applicant to file an abbreviated new drug application (ANDA) containing a paragraph IV certification of patent invalidity, unenforceability or non-infringement.

The US Food and Drug Administration (FDA) may accept submissions of ANDAs with paragraph IV certifications exactly one year before the expiration of the reference drug's new chemical entity (NCE) exclusivity. This is the so-called 'NCE-1' date on which several applicants may file as they seek to obtain the 180-day exclusivity. Recent examples include Pfizer's Toviaz (fesoterodine fumarate) extended-release tablets, which drew as many as eight ANDA filers on the first day possible, and UCB's Vimpat (lacosamide) tablets, which attracted at least 16 applicants. However, Cephalon's Treanda (bendamustine) powder for injection shows that heavy competition is not limited to products challenged on the NCE-1 date.

The NCE exclusivity for bendamustine expired on 20 March 2013, giving an NCE-1 date for generic versions of Treanda of 20 March 2012. The FDA reports that the first ANDA with a paragraph IV certification was filed on 4 June 2013 (see Figure 1), more than a year after such a submission was first possible. Typically, when there is a delay in filing paragraph IV ANDAs, challenges appear spread out over time, since there is no specific submission target date to lure applicants seeking the first-to-file exclusivity. Potential competition for those products builds over time as ANDAs are filed and patent-infringement litigation follows. Treanda has not followed that pattern.

Eagle chose to follow 505(b)(2) route

In September 2013, Teva's Cephalon received notice of Eagle's 505(b)(2) new drug application (NDA) for a 100mg/4ml liquid concentrate of bendamustine hydrochloride. A 505(b)(2) application allows the sponsor to rely, at least in part, on the FDA's findings of safety and efficacy for a previously approved drug. The resulting drug may differ in significant ways from the reference product and is not necessarily automatically substitutable upon approval. Like ANDA applicants, a 505(b)(2) filer must certify to the patents listed against the reference product in the FDA's Orange Book. Eagle's NDA included a paragraph IV certification to the patents listed against Treanda, and Cephalon filed an infringement suit against Eagle in October.

In November 2013, Cephalon received notice of bendamustine 25mg and 100mg vial ANDAs filed by Accord, Agila, Dr. Reddy's, Glenmark and Hetero, as well as by Hospira, InnoPharma, Sandoz, and Sun. Descriptions of the generics in Cephalon's complaints varied, citing terms such as 'powder for infusion' or 'intravenous infusion'.

A month later, Cephalon filed infringement suits against all of the ANDA applicants. In litigation concerning ANDAs from Accord, Agila, Hospira, InnoPharma, Sandoz and Sun, Cephalon alleged infringement of US patents 8,445,524 and 8,436,190. But the complaints against Eagle, Glenmark and Hetero alleged infringement of only the '524 patent, which includes claims directed to crystalline forms of bendamustine, processes for their preparation, compositions containing them, and their use. The '190 patent includes claims covering lyophilised formulations of bendamustine. US patent 8,609,863 was subsequently issued on 17 December last year and was listed against Treanda in the Orange Book. This was after the ANDAs had been submitted. It has not been asserted in any of the litigation thus far.

"It is unclear which of the many ANDA filers was the first to file and may be eligible for 180-day exclusivity," comments Thomson Reuters, which compiles a database of paragraph IV challenges and resulting litigation. "The cluster of paragraph IV notification letters sent to Cephalon in November suggests that the FDA accepted the ANDAs for filing at around the same time." Once an ANDA is accepted for filing, the sponsor may send the paragraph IV notification letter that usually triggers the litigation.

"Notably, while Eagle's 505(b)(2) product may not be automatically substitutable for Treanda, it will also not be subject to any 180-day exclusivity awarded to the first ANDA filer and may compete for market share during the first-filer's period of exclusivity. Given the number of ANDAs, it appears that the competition will only increase once any exclusivity expires," Thomson Reuters observes.

KEY DETAILS: TREANDA

Brand:	Treanda
Active ingredient:	Bendamustine hydrochloride
Delivery form:	25mg and 100mg vials
Brand owner:	Cephalon (Teva)
First paragraph IV filing submitted to FDA:	4 June 2013
Known paragraph IV filers:	Accord, Agila, Dr Reddy's, Glenmark, Hetero, Hospira, InnoPharma, Sandoz, Sun. Eagle filed a 505(b)(2) NDA.
Patents at issue –	8,445,524 – 26 September 2029* 8,436,190 – 26 April 2031*
Other patents –	8,609,863 – 12 July 2026*
District court location:	Delaware
Litigation reference:	Cephalon vs Accord – 1:13-cv-02095 Cephalon vs Agila – 1:13-cv-02080 Cephalon vs Dr Reddy's – 1:13-cv-02082 Cephalon vs Eagle – 1:13-cv-01738 Cephalon vs Glenmark – 1:13-cv-02093 Cephalon vs Hetero – 1:13-cv-02046 Cephalon vs Hospira – 1:13-cv-02094 Cephalon vs InnoPharma – 1:13-cv-02081 Cephalon vs Sandoz – 1:13-cv-02104 Cephalon vs Sun Pharma – 1:13-cv-02096

* includes six-month paediatric extension

Figure 1: Paragraph IV challenges to Cephalon's Treanda (bendamutine hydrochloride) powder for injection (Source – Thomson Reuters)

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ANTIRETROVIRALS

Hetero and Apotex get US lamivudine

Hetero Drugs and Apotex have secured US Food and Drug Administration (FDA) approvals to market lamivudine 100mg tablets. The approvals came immediately upon a six-month paediatric extension to US patent RE 39,155 expiring on 2 January this year. The FDA's Orange Book also lists against GlaxoSmithKline's Epivir-HBV original US patent 5,905,082, for which a paediatric extension runs out on 18 November 2016. Apotex immediately launched the antiretroviral in bottles of 60 film-coated tablets with a suggested average wholesale price (AWP) of US$966.66.

A few days later, Hetero – which operates in the US under the Camber and InvaGen brand names – obtained FDA approval for lamivudine 150mg and 300mg tablets. Apotex and Aurobindo already held since late-2011 similar approvals for the Epivir tablets in these two strengths marketed by Viiv Healthcare.

Unlike the 100mg version, the 150mg and 300mg strengths of Epivir are protected by just the '082 patent in the FDA's Orange Book.

In the first nine months of last year, Viiv Healthcare reported US Epivir sales that were ahead by a fifth at constant exchange rates to £7 million (US$12 million).

ANTIHYPERTENSIVES

Roxane rivals Actavis' launch

Roxane Laboratories has launched a US authorised generic of parent group Boehringer Ingelheim's Micardis (telmisartan) tablets. The move came in response to Actavis introducing the first generic rival to Micardis with 180-day generic market exclusivity.

Micardis achieved US sales of US$274 million during the 12 months ended 30 September 2013, according to IMS Health data.

Actavis' final approval for, and market entry with, telmisartan 20mg, 40mg and 80mg immediate-release tablets followed the expiry on 7 January of US patent 5,591,762. The Micardis antihypertensive brand is also protected by US patent 6,358,986, a polymorph patent that expires on 10 January 2020.

Alembic and Glenmark currently hold tentative approvals from the US Food and Drug Administration (FDA) for telmisartan immediate-release tablets in multiple strengths.

BIOLOGICAL DRUGS

Washington mulls biosimilars

Draft legislation that would impose conditions on substituting biologic drugs with their biosimilar counterparts has been introduced in the US state of Washington.

Welcoming the proposals, brand industry association the Biotechnology Industry Organization (BIO) said the requirement to "communicate prescription changes to patients and physicians" would help to "maintain a consistent and complete medical record".

Acknowledging that the US Food and Drug Administration (FDA) was still developing a national biosimilars pathway, BIO nevertheless insisted that there was "still a major role for states to play in ensuring substitution practices remain transparent and physicians remain engaged in the process".

ANTIRETROVIRALS

Teva triumphs over Atripla in Canada

Teva has convinced a Canadian federal court that its generic version of Bristol-Myers Squibb's (BMS') Atripla (efavirenz/emtricitabine/tenofovir) fixed-dose antiretroviral does not infringe a local crystalline patent that expires on 2 February 2018.

Federal Judge Robert Barnes said the case revolved around whether the efavirenz form used by Teva would convert into the patented Form I "in some measure" during Teva's tablet-manufacturing process.

"In the absence of grinding or prolonged exposure to temperatures exceeding those used by Teva, 'Form Teva' did not convert," Barnes observed. And pestle-and-mortar grinding used by BMS' expert during tests was not "a reliable surrogate" for Teva's production process, he concluded in finding that the originator had not met its burden of proving infringement of Canadian patent 2,279,198.

OSTEOPOROSIS DRUGS

UK dismisses Aclasta appeal

Novartis has lost its UK appeal against a High Court ruling that the local part of European method-of-use patent 1,296,689 – covering the firm's Aclasta (zoledronic acid) 5mg/100ml solution – was invalid. The Court of Appeals upheld the ruling, dismissing the originator's assertion that the '689 patent was entitled to priority from an earlier submitted 'PD2' patent application in the US.

Last year, Mylan and Hospira secured a High Court invalidity ruling against the '689 patent (**Generics *bulletin***, 5 April 2013, page 13). But the originator was later granted an injunction barring Hospira from launching a generic after Novartis launched an appeal (**Generics *bulletin***, 28 June 2013, page 18).

"The issue, in essence, is whether PD2 discloses the subject matter of claim 7 of the patent," stated Judge Christopher Floyd. This claim covers the intravenous administration of a zoledronate medicine to treat osteoporosis with a dosage range of around 2mg to 10mg at intervals of around once per year.

Novartis insisted that the PD2 application contained a "clear and unambiguous disclosure of the use of 2mg to 10mg of zoledronate once a year". The originator said the judge in the High Court ruling had been "led into error by failing to read the document as a whole", arguing that he had read the passage on dosage size and intervals "in isolation".

However, Floyd insisted that the PD2 passage "tells the skilled reader nothing about dosage range for any particular method of administration" or for "any particular condition, such as osteoporosis".

"If it were possible to read the '2mg to 10mg once a year' passage as disclosing that particular dosing regimen for intravenous administration for the treatment of osteoporosis," Floyd acknowledged, "then I think one would conclude that the patentee was teaching that the regimen would be effective." However, he concluded, "without that disclosure, the argument does not get off the ground".

IN BRIEF

HOSPIRA is recruiting patients for US long-term safety studies for its proposed intravenous and subcutaneous forms of **epoetin**. The trials form part of its Anemia Management with Epoetin (AiME) programme (see page 24).

FEBRUARY

19-21 February

■ GPhA 2014 Annual Meeting

Orlando, USA

This three-day meeting of the US Generic Pharmaceutical Association (GPhA) will look at regulatory issues and the challenges and opportunities for the generics industry. There will also be networking opportunities.

Contact: GPhA.
Tel: +1 202 249 7100.
E-mail: JNguyen@gphaonline.org.
Website: www.gphaonline.org.

MARCH

18-19 March

■ 10th EGA Legal Affairs Forum

Brussels, Belgium

This two-day European Generic medicines Association (EGA) event will look at issues including intellectual property, litigation, regulatory matters, patent settlements and the European unified patent court.

Contact: Lucia Romagnoli, GPA Conferences.
Tel: +44 7562 876 873.
E-mail: events@egagenerics.com.
Register online at www.egagenerics.com or www.gpaconferences.com/laf.htm.

24-27 March

■ BDP Week

San Diego, USA

Conference tracks at this four-day event on biopharmaceutical development and production (BDP) will include viral safety, contract manufacturing and technology transfer, manufacturing efficiencies and raw materials/supply chain.

Contact: IBC USA.
Tel: +1 941 554 3500.
E-mail: reg@ibcusa.com.
Website: www.ibclifesciences.com/BDPWeek.

25-27 March

■ DIA 26th Annual EuroMeeting

Vienna, Austria

Issues covered at this three-day meeting of the Drug Information Association (DIA) will include clinical research, regulatory topics, active substances, drug development and globalisation.

Contact: DIA.
Tel: +41 61 225 5151.
E-mail: diaeurope@diaeurope.org.
Website: www.diaeurope.org.

31 March – 1 April

■ EuroPLX 54

Lisbon, Portugal

This event provides a forum for business-development decision makers to discuss and negotiate collaborative agreements, in-licensing, marketing and distribution of patented medicines, generics, biosimilars, OTC products, medical devices and food supplements.

Contact: Raucon.
Tel: +49 6222 9807 0.
E-mail: meetyou@europlx.com.
Website: www.europlx.com.

APRIL

1-4 April

■ World Generic Medicines Congress Europe 2014

London, UK

This four-day conference will be co-located with the Biosimilar Drug Development World event. The conference will look at topics including intellectual-property developments, commercial strategies and building market share, and will provide global policy updates.

Contact: Health Network Communications.
Tel: +44 207 608 7055.
E-mail: customerservices@healthnetwork communications.com.
Website: www.healthnetwork communications.com.

3-4 April

■ 12th EGA International Biosimilar Medicines Conference

London, UK

This meeting, organised by the EGA, will look at the latest industry developments and regulatory issues for biosimilars, as well as business opportunities, global development and pharmacovigilance.

Contact: Lucia Romagnoli, GPA Conferences.
Tel: +44 7562 876 873.
E-mail: events@egagenerics.com.
Register online at www.egagenerics.com or www.gpaconferences.com/bios.htm.

7-8 April

■ Biosimilars & Biobetters USA

New Jersey, USA

This conference will provide networking opportunities and will cover issues including innovation, legislation, pharmacovigilance, biosimilar development and pricing.

Contact: SMi.
Tel: +44 207 827 6000.
E-mail: events@smi-online.co.uk.
Website: www.smi-online.co.uk.

MAY

20-23 May

■ 5th Annual Biosimilars Asia

Shanghai, China

Looking at strategic challenges and innovations in the development of biosimilars, this four-day event will be preceded by a workshop covering clinical development. Key topics to be covered will include regulatory updates.

Contact: IBC Asia.
Tel: +65 6508 2401.
E-mail: register@ibcasia.com.sg.
Website: www.biosimilarsasia.com.

JUNE

3-4 June

■ GPhA CMC Workshop

Maryland, USA

This two-day workshop will provide information on CMC regulatory requirements and meeting the challenges of first cycle approval. The event will detail the US Food and Drug Administration's (FDA's) expectations for regulatory filings.

Contact: GPhA.
Tel: +1 202 249 7100.
E-mail: JNguyen@gphaonline.org.
Website: www.gphaonline.org.

25-27 June

■ 20th EGA Annual Conference

Madrid, Spain

The EGA's three-day annual conference will look at topics including the current regulatory environment.

Contact: Lucia Romagnoli, GPA Conferences.
Tel: +44 7562 876 873.
E-mail: events@egagenerics.com.
Register online at www.egagenerics.com or www.gpaconferences.com/ega14.htm.

19-21 November 2014

■ 17th IGPA Annual Conference

Miami, USA

This three-day conference is being organised by GPhA and is the global event of the worldwide generics industry. It is the annual joint meeting of the Canadian, European, Japanese, South African and US generics industry associations, the CGPA, EGA, JGA, NAPM and GPhA.

Contact: Jennifer Nguyen, GPhA. Tel: +1 202 249 7127.
E-mail: jnguyen@gphaonline.org. Website: www.gphaonline.org.

Category M prices trim pharmacy margins

Three products launched in 2013 were added to category M of the Drug Tariff of pharmacy reimbursement prices in January 2014. For the first time, reimbursement prices of memantine, raloxifene and rizatriptan were based on their historical prices in the marketplace.

Since their launch as generics, they had mostly been reimbursed at the trade price of their equivalent branded product – Lundbeck's Ebixa, Daiichi Sankyo's Evista, and Merck, Sharp and Dohme's Maxalt. For most of 2013, all three had been classified in category C and had been reimbursed at the equivalent brand price. In December, however, both memantine and rizatriptan were moved to category A. Based on the list prices of Actavis and Teva, as well as the two leading wholesalers, the category A reimbursement price for 28-tablet packs of memantine 20mg was slightly lower than a month earlier, falling from £69.01 (US$113.64) to £68.32, but three-tablet packs of rizatriptan 10mg were unchanged in reimbursement price at £13.37.

The new year brought tumbles in the reimbursement prices of all three products, which in turn did similar damage to pharmacists' dispensing margins. Launched in February 2013, 28-tablet packs of raloxifene 60mg slipped from a reimbursement price of £17.06 in December to £14.15 in January 2014, a modest fall of 17% (see Figure 1). Both the lowest and average market prices increased, however, as the reimbursement price declined, with the result that pharmacists saw their average dispensing margin drop from 28% to 9%. Similarly, the best margin obtainable on the lowest price in the market dipped from 56% to 44%.

Launched in May 2013, memantine 20mg was worse news for dispensers last month, as its Drug Tariff price slid by 38% to £42.27 (see Figure 2). The best margin available in December had been 74%, but last month this was reduced to 57%. The product's average trade price rose in January, reducing the average margin from 53% to 21%.

The most shocking change was reserved for rizatriptan 10mg, as its Drug Tariff price was slashed to almost the product's lowest trade price, and well below its average market price (see Figure 3).

Some volatile pricing in the short time since the product's August launch had apparently been misinterpreted by the Department of Health. Companies like Actavis, Aspire and Waymade had put their prices up after launch in October, while others including AAH, Cavendish and Lexon, had reduced theirs. By January, the average market price of rizatriptan 10mg had recovered to £7.63 from as low as £4.72 immediately after launch in September. The lowest price available had also improved from £0.89 in the same month to £1.49. Pharmacists had been reimbursed £13.37 for dispensing the product, but this was cut by 88% to just £1.58 last month.The best pharmacists could have made in January was £0.09 on each transaction, but on average they would have made a £6.05 dispensing loss.

As can be seen in Figure 4, the numbers of price offers made to independent pharmacists and dispensing doctors were slow to pick up for rizatriptan 10mg, which would indicate a sluggish market and little downward pressure on prices. Even in January, there were only 33 recorded by WaveData for rizatriptan 10mg, compared with about 50 for the other two products. G

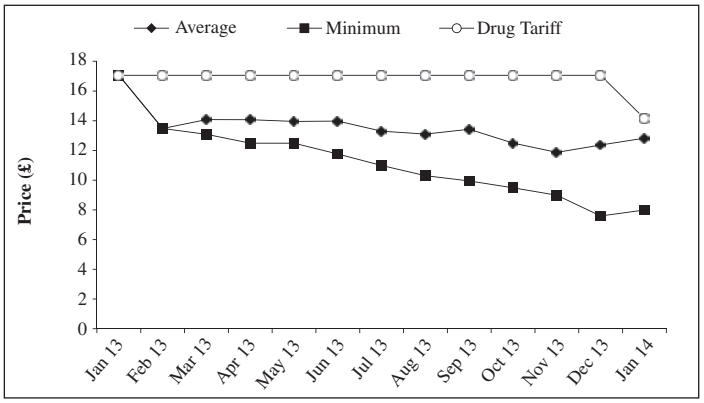

Figure 1: Monthly changes since launch in the trade and Drug Tariff reimbursement prices for 28-tablet packs of raloxifene 60mg (Source – WaveData)

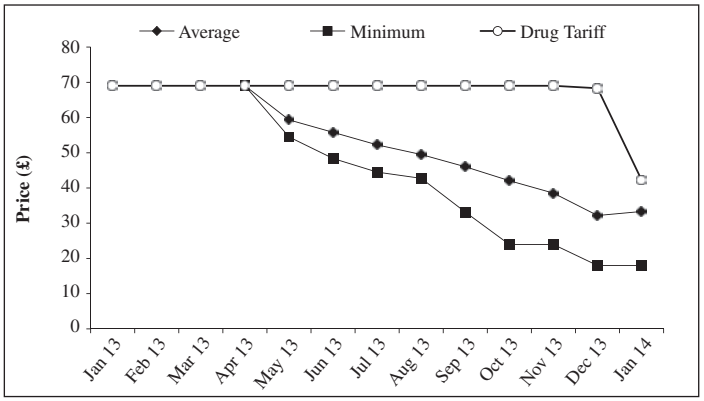

Figure 2: Monthly changes since launch in the trade and Drug Tariff reimbursement prices for 28-tablet packs of memantine 20mg (Source – WaveData)

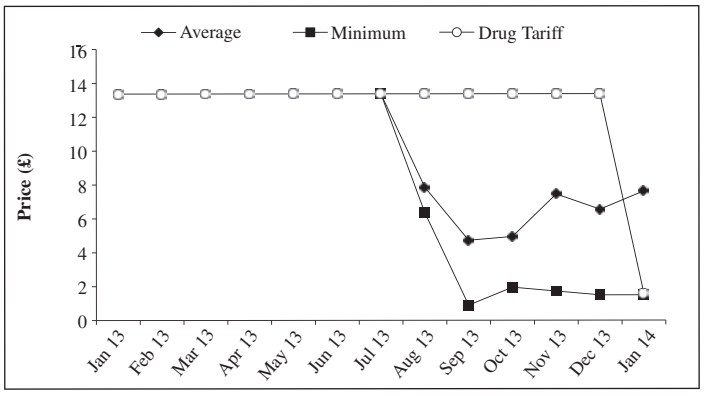

Figure 3: Monthly changes since launch in the trade and Drug Tariff reimbursement prices for three-tablet packs of rizatriptan 10mg (Source – WaveData)

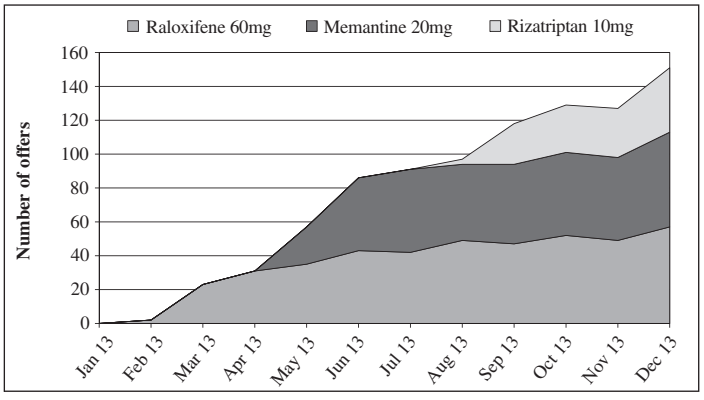

Figure 4: Price offers made to independent pharmacists and dispensing doctors for raloxifene 60mg, memantine 20mg and rizatriptan 10mg (Source – WaveData)

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■ **For further information** see www.bppi.co.uk. Alternatively, contact Charles Joynson at WaveData Limited, UK. Tel: +44 (0)1702 425125. E-mail: cjoynson@wavedata.co.uk.

WaveData

Aurobindo bets on beating Actavis units' cost of goods

Using its Indian manufacturing base to cut cost of goods is central to Aurobindo's strategy for capitalising on its purchase of Actavis' generics operations in western Europe. Aidan Fry reports.

By any standards, €30 million (US$41 million) represents a relatively modest sum in the context of generics industry consolidation. For that sum, Aurobindo Pharma is set to acquire operations from one of the world's largest generics players in some of the world's largest and fastest-growing generics markets.

Through the deal – which is subject to adjustment for cash and net working capital position at closing – Aurobindo is set to gain Actavis' generics operations in seven western European countries: Belgium, France, Germany, Italy, the Netherlands, Portugal and Spain. The Indian firm estimates that these businesses increased their combined net turnover by more than 10% to €320 million last year, rendering the agreed purchase price less than one-tenth of sales.

The rationale for such a modest price for a portfolio of 1,200 products containing more than 450 different molecules – along with a pipeline of over 200 products poised for launch over the next few years – lies in the target businesses' weak or non-existent profit margins.

"These businesses are currently loss-making," the Indian group observed. "Aurobindo will leverage its industry-leading manufacturing economies of scale and ability to source low-cost active pharmaceutical ingredients (APIs) to significantly improve profitability of the businesses in the coming several years," it promised. "Aurobindo's vertically-integrated platform provides the target businesses with a unique opportunity to materially lower cost-of-goods-sold (COGS) and enable their return to profitability."

"With our cost competitiveness and group structure, we can significantly capitalise on Actavis' strong market position in these western European countries and improve profitability, thereby accelerating our strategy of becoming a significant generics player in Europe," maintained Arvind Vasudeva, who heads Aurobindo's Formulations business segment.

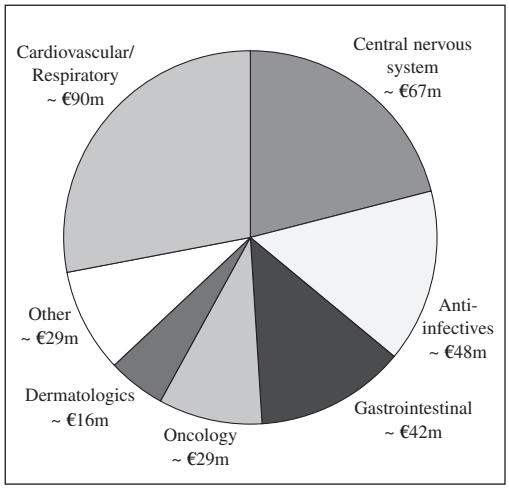

Figure 2: Breakdown by therapeutic category of the €320 million of annual sales by the businesses in seven western European countries that Aurobindo is acquiring from Actavis (Source – Aurobindo)

Aurobindo intends either for a "significant number of molecules" to pursue production-site transfers or to replace Actavis' portfolio with drugs that the Indian company manufactures itself.

In its domestic market, the Indian firm operates a wide range of API and intermediates facilities covering sterile and non-sterile bulk drugs, including betalactam, cephalosporin, penam and semi-synthetic penicillin antibiotics. Several of the company's Indian sites produce solid-dose and liquid oral products, while it also makes antibiotic injectables in India. Furthermore, the 60% share in Celon Laboratories – since renamed Eugia – that Aurobindo acquired last year (***Generics bulletin***, 6 September 2013, page 3) has given the group capacity to make hormonal and oncology injectables.

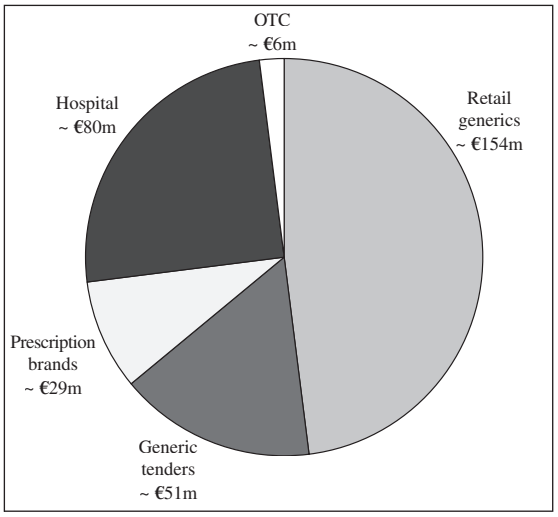

Figure 1: Breakdown by sales channel of the €320 million of annual sales by the businesses in seven western European countries that Aurobindo is acquiring from Actavis (Source – Aurobindo)

Through the Eugia hormones and oncology facility and its AuroNext penam antibiotics plant, as well as its Unit IV non-betalactams and Unit XII semi-synthetics sites, Aurobindo plans to supply from India injectable products for marketing in western Europe.

The Indian company highlighted the "ready-made hospital salesforce infrastructure for Aurobindo to launch its own injectables and specialty portfolio across western Europe". It noted that "the target businesses provide a front-end infrastructure in five segments, covering retail generics, off-patent brands, OTC products, hospital products and generics tenders".

As can be seen from Figure 1, sales through the hospital channel account for a quarter, or around €80 million, of the estimated €320 million of turnover generated by the Actavis generics operations covered by the planned transaction. Retail generics represent almost half of the portfolio, tender-driven generics 16%, and prescription and OTC brands just over a tenth.

"The [Actavis] hospital portfolio includes a number of attractive injectables, including oncology, pain-management and anti-infective therapies," Aurobindo pointed out. As Figure 2 shows, antineoplastic oncology drugs account for nearly a tenth by value of the portfolio that Aurobindo will pick up through the deal. Cardiovascular and respiratory drugs make up 28% by value, central nervous system medicines just over a fifth, and anti-infectives another 15%.

Viewed by dosage form, tablets comprise almost three-fifths by sales value of the portfolio to be acquired, and capsules another 14% (see Figure 3). Liquid products account for 16% by value, and powders 8%, while the portfolio also includes a handful of other presentations.

In general, Aurobindo believes it can make more

effective use of Actavis' current sales and marketing platform in continental western Europe by "channelling a larger portfolio of marketed and pipeline products through the front-end infrastructure".

"The acquisition will enable Aurobindo to achieve critical mass in western Europe with a top-10 position in several key markets," the Indian company stressed. "Aurobindo will become one of the leading Indian pharmaceutical companies in Europe."

By taking over Actavis' western European operations, Aurobindo will "establish a strong foothold in France through the 'Arrow Génériques' brand", and will also gain entry into the local generics markets in Belgium and Italy. Furthermore, the Indian group will complement its existing presence in Germany, the Netherlands, Portugal, and Spain.

Via the generics operation that Actavis acquired through its acquisition of Arrow, Aurobindo will immediately achieve "critical mass" in the large and growing French generics market. The Indian firm said the acquired portfolio of almost 400 drugs would rank it seventh in France, based on retail and tender sales.

France is expected to account for 44%, or around €141 million, of the targetted businesses' combined sales of €320 million in 2013 (see Figure 4).

Even with just 1%, or about €3 million, of the combined sales – from 14 marketed products – Aurobindo said the acquired Belgian operation would rank it among the country's top-10 retail and tender generics players. On the same basis, the Indian firm expects to rank eighth in Italy with annual sales from 137 marketed drugs of around €26 million, or 8% of the combined total.

Germany makes up 22% of the value of the targetted businesses. A portfolio of nearly 200 drugs places the local operation sixth in a local generics market increasingly dominated by tenders. In the Netherlands, Aurobindo said it would gain the third-largest generics player, with 236 products marketed by the legacy Actavis operation, generating an annual turnover of about €35 million.

In Portugal, Aurobindo expects the transaction to establish it among the "top-five pharmaceutical companies". On a standalone basis, the acquired Portuguese operation will provide 128 products and annual sales of about €16 million, ranking it tenth in the local generics market. A similar ranking in Spain will come from Actavis' local portfolio of almost 100 products generating annual sales of around €29 million.

"The target businesses' European infrastructure is highly complementary to Aurobindo's critical mass in the UK," the Indian group said. Actavis has retained its generics and OTC operations in the UK and Scandinavia.

Buying Milpharm in the UK in 2006 marked Aurobindo's first acquisition in Europe as the Indian group advanced from being an APIs supplier to marketing its own finished dosage forms around the world (**Generics *bulletin***, 17 February 2006, page 5).

A year later, Aurobindo acquired Pharmacin in the Netherlands (**Generics *bulletin***, 12 January 2007, page 3), and then 12 months further on picked up a range of marketing authorisations and other intellectual property in Italy from Tad Pharma (**Generics *bulletin***, 2 April 2008, page 1). In Germany, Portugal and Spain, the group pursued organic growth by selling its own drugs.

In the first half of Aurobindo's financial year ending March 2014, the company increased its formulations sales in Europe and the Rest of the World region – including countries such as Australia, Brazil and Canada – by a third to Rs5.48 billion (US$88.6 million). US formulations and APIs each contributed around Rs13.6 billion to group turnover of Rs37.0 billion. Finished-dose antiretrovirals added another Rs4.25 billion.

By the end of calendar 2016, Aurobindo plans to have more than doubled its annual global formulations sales to US$1.30 billion, while its APIs and contract research and manufacturing services (CRAMS) business is to grow at 15% per year to reach US$700 million.

Commenting on the Actavis transaction – which has been approved by Aurobindo's board, but requires antitrust clearance and completion of employee-consultation processes – Venugopalan Muralidharan, the Indian group's senior vice-president of European operations, said: "We have been clear about our intention to focus on growth initiatives in Europe and international markets." "This transaction," he continued, "will complement our strategy of pursuing organic growth along with value-creating acquisitions within our served markets and adding complimentary growth platforms to provide scale and revenue diversity."

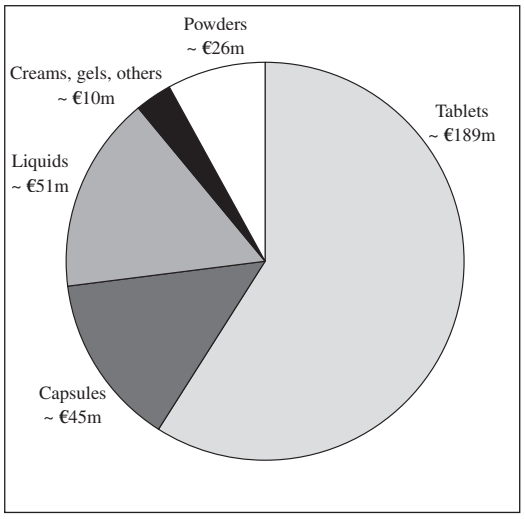

Figure 3: Breakdown by dosage form of the €320 million of annual sales by the businesses in seven western European countries that Aurobindo is acquiring from Actavis (Source – Aurobindo)

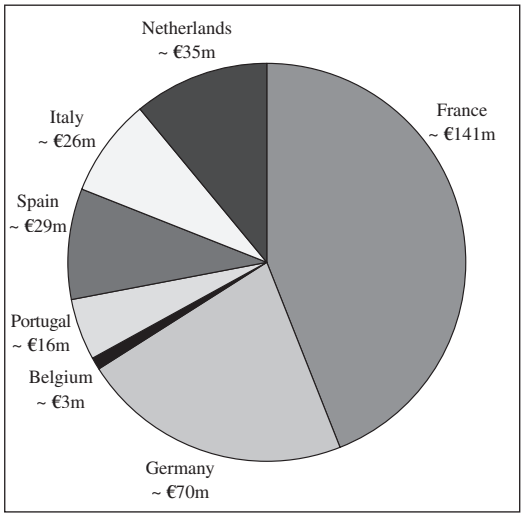

Figure 4: Breakdown by country of the €320 million of annual sales by the businesses in seven western European countries that Aurobindo is acquiring from Actavis (Source – Aurobindo)

Aurobindo – aided by financial advisor Jefferies – and Actavis had been negotiating a deal since September last year, shortly after the latter revealed it was reviewing strategic options for its generics operations in "six or seven" western European countries. The two firms have formed a joint steering committee to oversee the transition, and Actavis will continue to support the transferred businesses as a supplier and licence provider.

"We decided we were undersized in some of our western European markets, and that made for a bad business plan," Actavis' chairman and chief executive officer Paul Bisaro told investors shortly before the deal with Aurobindo was announced. Rather than invest in inorganic growth to build critical mass, Actavis had chosen to sell its commercial operations in the seven countries and to redeploy its capital in markets with higher growth potential.

Bisaro said the company was keen to expand its commercial presence outside of the US, including in Japan, Australia, South America and south-east Asia. "We will continue to look to support our businesses in Russia and the Commonwealth of Independent States (CIS)," he remarked.

Hospira starts to see fruits of global biosimilar project

Having established itself in Europe and Australia, Hospira says it is close to becoming a global biosimilars player. Aidan Fry reviews the company's pipeline.

With annual European sales from its biosimilars now exceeding US$100 million, Hospira has established itself as one of a triumvirate of market leaders, alongside Sandoz and Teva.

Having partnered with Germany's Stada to bring Retacrit (epoetin alfa) to market following European Union (EU) approval in December 2007, Hospira followed up in 2010 by securing approval for its Nivestim (filgrastim) rival to Amgen's Neupogen. And a few months ago, the US-based injectables specialist – along with its South Korean development partner, Celltrion – achieved a landmark by gaining clearance for the EU's first biosimilar monoclonal antibody, its Inflectra (infliximab) alternative to Janssen's Remicade (**Generics *bulletin***, 20 September 2013, page 17).

Hospira's chief executive officer, Mike Ball, noted that the firm was currently celebrating five years of offering biosimilars in the EU. During that time, he said, the company had shipped more than five million doses. Noting that the company also marketed Nivestim in Australia, Ball pointed out the EU Inflectra approval included all the indications granted to Remicade.

While Ball acknowledged the US biosimilar regulatory framework was less advanced than in the EU, he told investors that Hospira had completed enrolment for Phase III US trials for its biosimilar erythropoeitin (EPO). The company planned to submit a dossier to the US Food and Drug Administration (FDA) later this year or early in 2015, he said, ensuring that Hospira would be ready to launch upon market formation.

Globally, Ball pointed out, the biological drugs market was worth around US$127 billion and was growing at 9% per year. However, more than half of those biologics by value – US$67 billion – would lose patent protection by 2020. "We are taking dead aim at US$40 billion of that value through our [biosimilars] research and development pipeline," he stated.

"Up to 2018," observed chief scientific officer Sumant Ramachandra, "there is anywhere from US$1 billion to US$5 billion going off exclusivity every year. There has not been this kind of value creation ever in the speciality injectables market."

Looking at the US$127 billion global biological drugs market, Ramachandra said almost half of that figure – US$60 billion – was generated in the US, while more than a quarter, or US$35 billion, came from Europe. Hospira, he said, was focusing on highly-regulated western markets and was aiming to create biosimilars of originals, rather than improved 'biobetter' versions.

Noting that biosimilar regulatory guidelines were now in place "in all major markets", Ramachandra said Hospira was spending US$100-200 million on developing each molecule. "The risk is really in the regulatory and commercial sphere," he maintained.

To mitigate such risks, Hospira last year struck a financing deal whereby investment company NovaQuest is contributing up to US$150 million towards developing Hospira's EPO for marketing in the US and Canada, filgrastim in the US and pegfilgrastim on a global basis (**Generics *bulletin***, 17 May 2013, page 17). In return, Hospira will make milestone payments on sales.

"By getting NovaQuest in, we were able to accelerate some opportunities," Ramachandra explained. Even if pre-clinical analysis had demonstrated a level of similarity to the reference biologic that was likely to satisfy regulators, he asserted, conducting Phase III clinical studies would "help with market acceptance".

At present, Hospira's biosimilars pipeline – including products that it is developing in partnership with Celltrion – covers 11 molecules (**Generics *bulletin***, 10 January 2014, page 23). The pipeline focuses on three therapeutic areas: dialysis and kidney disease; oncology and supportive care; and immunology.

As Figure 1 shows, Hospira has molecules in all three therapeutic focus areas currently undergoing Phase III clinical trials. Studies for the immunological agent infliximab and the oncology drug trastuzumab are being conducted through the firm's alliance with Celltrion. In both cases, the programmes are intended to support filings in the US, Canada, Australia and New Zealand, while the trastuzumab project also covers Europe.

Phase III trials in Hospira's EPO development programme for the US and Canada – funded, in part, through the NovaQuest agreement – are scheduled to be completed later this year. The firm's internal development of filgrastim in the US, and pegfilgrastim on a global scale, are at the Phase I stage.

Two internal Hospira development programmes overlap with Celltrion's own pipeline. These are a biosimilar of Rituxan (rituximab) that is poised to enter Phase I trials following pre-clinical work, and a rival to the Avastin (bevacizumab) oncology brand that is at the cell-line and process-development stage.

Also covered by the development agreement that

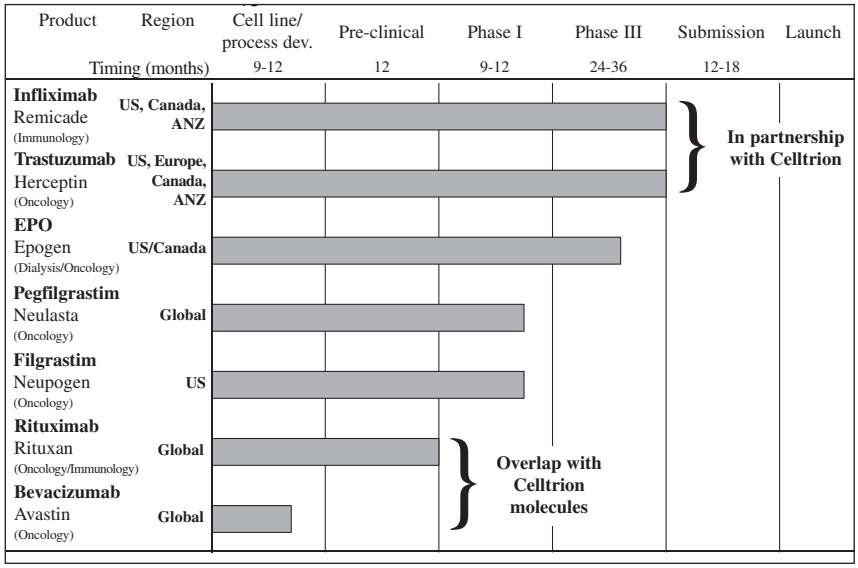

Figure 1: Stages of development for selected molecules within Hospira's pipeline of 11 biosimilar molecules currently under development (Source – Hospira)

Hospira struck with Celltrion more than four years ago (**Generics *bulletin***, 16 October 2009, page 13) are biosimilar versions of the anti-tumour necrosis factor (anti-TNF) drug Enbrel (etanercept), the bowel-cancer treatment Erbitux (cetuximab), the arthritis drug Humira (adalimumab) and the Synagis (palivizumab) treatment for paediatric respiratory syncytial virus.

Addressing Hospira's North American EPO development programme, Ramachandra said the firm was building on the "excellent foundation" provided by its Retacrit biosimilar in the EU. "We recently met primary and secondary end-points of our US phase I EPO study," he revealed, adding that Phase III studies in two modes of administration were underway under the banner of Anemia Management with Epoetin (AiME).

"Being the only biosimilar EPO product to have two major studies evaluating modes of administration in the US provides us with a competitive market advantage," Ramachandra believed.

Hospira's AiME-01 Phase III study is comparing the safety and efficacy of intravenous delivery of the firm's EPO compared to Amgen's Epogen original in 564 haemodialysis patients. At the same time, 288 patients are enrolled in the AiME-13 subcutaneous trial.

Ramachandra said the company expected to have completed the AiME-01 and AiME-13 trials by the second or third quarter of this year, paving the way to submitting a dossier via the FDA's '351k' biosimilars pathway during the second half of this year or early next year. Assuming a first-cycle approval within the 10-month window envisioned by the Biosimilar User Fee Act (BsUFA), FDA approval would follow in 2015 or 2016. "We are aiming to be the first with biosimilar EPO in the US," he stated.

EPO in US shares Retacrit's cell line

While the US EPO candidate shares a cell line with the EU product Retacrit, Hospira's studies compare the drug to the US Epogen reference product. The injectables specialist has enlisted GlaxoSmithKline's facility in Maryland, US, as its manufacturing partner. Hospira also has biosimilar production partnerships with Celltrion, Stada and Rovi in Spain, augmenting its own capabilities in Australia, Croatia and the US.

Chief commercial officer Richard Davies insisted Hospira's experience of marketing both Retacrit and its Nivestim filgrastim brand in Europe would prove crucial as it prepared to market biosimilars in the US. "As I have talked to physicians, payers and providers in the US about Hospira's biologic capabilities, it has surprised me how much they have asked about our European experience," he stated.

Describing lessons from Hospira's EU experiences, Davies said: "Prescribers really want to see the data demonstrating the safety and efficacy of our biosimilars." Potential savings needed to be clearly communicated to payers, while legislators had to be pushed to support biosimilar uptake and market formation. "Our ability to explain data to clinicians and negotiate competitive contracting with payers is going to be of paramount importance," he acknowledged, stressing Hospira's strong relationships with hospital group purchasing organisations (GPOs) and formulary committees.

"What we have seen in Europe is that the initial competition comes from a communication standpoint," commented Davies, who joined from Amgen two years ago. "Competition on price has been relatively small."

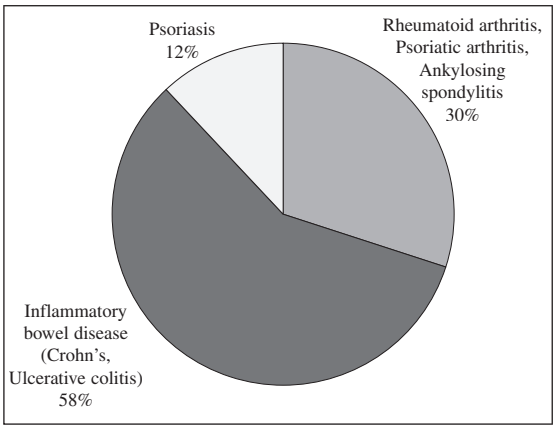

Figure 2: Breakdown by therapeutic indication of sales of Janssen's Remicade (infliximab) monoclonal antibody (Source – Hospira)

"We are really pleased on how we are doing with Retacrit and Nivestim," he continued. "We are in a solid number-two position across both medicines in Europe."

Retacrit, Davies said, was continuing to gain share in the short-acting EPO market and was tracking close behind Sandoz' Binocrit. "Nivestim is now the second-largest brand of biosimilar granulocyte-colony stimulating factor," he claimed, adding that Nivestim had overtaken Teva's Ratiograstim/Tevagrastim by volume, even though it had been launched around 18 months later. "With our newly expanded manufacturing capacity in Croatia, we have sufficient volumes to continue this growth."

Hospira's launch schedule for Inflectra in Europe is largely dictated by the intellectual-property landscape. Whereas Remicade was off-patent in much of central and eastern Europe, Davies noted, patent protection meant launches would follow from 2015 in the larger western markets that represented around 90% of the sales opportunity in the region.

Where Inflectra reached the market, it would have the same indications as Remicade, Davies stressed. Hospira submitted data from a Phase I trial in patients with ankylosing spondylitis and a Phase III trial in patients with rheumatoid arthritis (RA). Based on these rheumatology studies, the European Commission – on the advice of the European Medicines Agency (EMA) – also approved indications for psoriasis and psoriatic arthritis, as well as for Crohn's disease and ulcerative colitis in both adult and paediatric populations.

As Figure 2 shows, inflammatory bowel disorders (IBDs) such as Crohn's disease and ulcerative colitis account for almost three-fifths of Remicade's sales, while arthritic complaints make up another 30%. The remaining 12% of sales are due to psoriasis prescriptions.

As Hospira's clinical data focused on rheumatic complaints, the company anticipates some initial resistance from IBD physicians. But any resistance from prescribers would create tension with payers, Davies forecasted. "As governments and payers understand the savings they can achieve by using Inflectra to treat their IBD and RA patients, we should start to see the share of infliximab, driven by Inflectra, start to grow in the anti-TNF market," he predicted.

Noting that many of Hospira's initial launches of Inflectra would be through local distributors, Davies welcomed Celltrion's plans to market its own version under the Remsima brand name. "It is going to take more than one company to cut the trail on this," he stated. G

"We are aiming to be the first with biosimilar EPO in the US"

APPOINTMENTS/BUSINESS STRATEGY

Actavis picks leaders for its Specialty units

Actavis has restructured its US Specialty Brands division into four independent business units, following the firm's recent acquisition of women's health and urology specialist Warner Chilcott. The firm has hired two new staff and promoted another from within to lead the new Women's Health, Urology & Gastroenterology and Business Operations divisions respectively, while it is "actively engaged" in finding a head for its Dermatology & Established Brands unit.

Leading the Women's Health division is Bayer's former vice-president of marketing and commercial operations for women's healthcare, **Herm Cukier**, while Aptalis Pharma's **Charles Sabino** heads Actavis' Urology & Gastroenterology business. Former vice-president of sales and operations for Actavis' US Specialty Brands business, **Thomas Griffin**, will oversee Business Operations.

The four business unit leaders will report to **Tim Callahan**, senior vice-president of commercial operations, who in turn reports to Actavis' president of its Specialty Brands business, **Fred Wilkinson**.

IN BRIEF

AMNEAL has named **Rochelle Fuhrmann** as chief financial officer. Prior to joining the US firm, Fuhrmann held senior financial roles at Actavis subsidiary Warner Chilcott.

APPOINTMENTS

Pfizer's Gulfo named Mylan strategy head

Mylan has appointed **Adele Gulfo** to become the US firm's vice-president of global collaboration and strategic operations. Commenting on the appointment, Mylan's chief executive officer, Heather Bresch, said Gulfo's expertise would "support many of our key growth drivers".

These, Bresch indicated, included the firm's expansion into Latin America, and the development and expansion of Mylan's Speciality franchise as well as strategies for upcoming global launches in the biologics and respiratory areas.

Prior to joining Mylan as a member of its executive leadership team, Gulfo worked at Pfizer as regional president of Latin America in the originator's Emerging Markets unit, having previously been general manager of Pfizer's US Primary Care division after nine years with AstraZeneca. Gulfo, according to Mylan, was earlier in her career "instrumental" in the launch of Pfizer's blockbuster Lipitor (atorvastatin) cholesterol-lowering agent.

IN BRIEF

EXPRESS SCRIPTS has appointed **Cathy Smith** as chief financial officer. Smith had served in the same role at US retail corporation Walmart for four years.

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IN BRIEF

HETERO EUROPE has appointed **Bjarni Baerings** as vice-president in charge of the firm's pharmaceutical business. The appointment follows the departure of the firm's former president, **Michael Winstrøm**, to "pursue new challenges outside the firm". Baerings, 39, has served Hetero since 2010 in business-development roles. Previously, he worked for Actavis, AstraZeneca and Genepharm.

STADA's chief financial officer, **Helmut Kraft**, has had his contract extended with the German group by four years. Kraft, who succeeded Wolfgang Jeblonski four years ago (**Generics *bulletin***, 13 November 2009, page 27), will now continue his financial duties with Stada until 31 December 2018.

SHANGPHARMA has named **Mitchell Reff** as chief biologics officer of the contract research organisation (CRO). Reff held a number of senior development roles at former employer Biogen Idec during his 21-year tenure with the company.

AMGEN's chief financial officer, **Jonathan Peacock**, is stepping down from his position "to pursue broader career opportunities", the US company has confirmed. Although Peacock has been replaced by **Michael Kelly**, the company's former chief accounting officer, in an acting role, he will remain with Amgen until May to "assist with the transition".

CIPLA says it has strengthened its "world-class leadership team" by appointing former GlaxoSmithKline (GSK) Consumer Healthcare executive, **Sameer Goel**, as head of its operations in India. Goel enjoyed numerous senior international roles with GSK, serving as general manager of the UK firm's Consumer Healthcare business in India, in addition to senior sales roles with GSK across Africa and Asia. The Indian firm recruited another former GSK executive, **Frank Pieters**, to head its respiratory business in Europe two years ago (**Generics *bulletin***, 13 July 2012, page 27).

TAKEDA has named **Christophe Weber** as chief operating officer and a candidate to become the firm's next chief executive officer (CEO). Weber, who will join the Japanese company "by April 2014", previously served as president of GlaxoSmithKline's Vaccines business. At the same time, the firm's current president and CEO, **Yasuchika Hasegawa**, is expected to be named chairman and CEO. Meanwhile, Takeda has also appointed **Arie Kramer** as country manager for the firm's newly-established subsidiary in Israel. The former AbbVie finance and strategic commercial planning head will oversee operations from the unit's headquarters in Tel Aviv, where Takeda will market products from its existing pipeline with an initial focus on oncology products.

AMRI – Albany Molecular Research Inc – has appointed **George Svokos** to the newly-created position of senior vice-president of sales and general manager for active pharmaceutical ingredients (APIs). He reports directly to AMRI's chief executive officer, Bill Marth (**Generics *bulletin***, 20 September 2013, page 27). Svokos, who has served at Teva since 1979, is currently senior vice-president of the Drug, Chemical & Associated Technologies Association (DCAT) and will become president next year.

USP – the United States Pharmacopeial Convention – will from 1 February be headed by **Ron Piervincenzi**, who joins the organisation as chief executive officer and chair of USP's Council of Experts. Piervincenzi, who will replace outgoing chief executive **Roger Williams**, was previously leader of McKinsey's global pharmaceutical and medical product practice for 12 years.

APPOINTMENTS

Vigodman selected to take lead at Teva

Teva has announced that **Erez Vigodman** will become president and chief executive officer (CEO) of the Israeli firm from 11 February, replacing **Eyal Desheh** who is currently serving in an acting capacity. The appointment follows the departure last year of Teva's former president and CEO, **Jeremy Levin**, following differences with the board over how best to pursue the firm's strategy (**Generics *bulletin***, 1 November 2013, page 1). Desheh will return to his role as executive vice-president and chief financial officer.

Vigodman, 54, will leave his current post as president and CEO of Makhteshim Agan Industries (MAI) – which Teva described as "the world's leading generic agrochemical company" – on 6 February, having led the firm since 2010. Before working for MAI – where former Teva chief Shlomo Yanai also served as president and CEO before taking the lead at Teva between 2007 and 2012 – Vigodman was president and CEO of global food and beverages firm Strauss Group.

"As a member of the Teva board since 2009," said the firm's chairman, Phillip Frost, "Erez has a deep understanding of the company and the industry in which it operates, putting him in a strong position to hit the ground running."

Amir Elstein, vice-chairman of Teva's board, said Vigodman "stood out due to his impressive track record in transforming global and complex corporations", having "led the expansion of MAI into emerging markets across Asia and Latin America."

Elstein also cited Vigodman's "proven ability to execute restructuring programmes". Teva recently announced plans to slash around 5,000 jobs – more than a tenth of its global workforce – by the end of 2014 in a bid to produce annual cost savings of US$2.0 billion by 2017 (**Generics *bulletin***, 18 October 2013, page 1). "I understand the challenges facing Teva and I am confident that, together with the management team, we can address these challenges," Vigodman insisted.

At the same time, Frost said Teva was reviewing the "size and composition" of its management board as part of a "broader review of Teva's governance" following "constructive input" from shareholders over the past few months. Noting that the firm planned to add "new board members with global healthcare experience", Frost said Teva was "currently in the process of identifying appropriate candidates".

Meanwhile, Teva has appointed **Doug Sommerville** to lead its operations in Canada as senior vice-president and general manager. Having joined the Israeli firm's Canadian subsidiary in 2005, Sommerville has served in numerous senior roles, including as general manager of its Specialty Products business. Sommerville's predecessor, **Barry Fishman**, had served in the position since 2008.

APPOINTMENTS

Kent's Broeer chairs BGMA

Kent Pharmaceuticals' managing director, **Thomas Broeer**, has been elected as chair of the British Generic Manufacturers Association (BGMA) on a two-year term. He replaces **Kim Innes**, who will serve for 12 months as the association's vice-chair alongside her duties as commercial director for Teva's UK business. Former vice-chair **Peter Ballard** vacated his role with the BGMA after departing from Genus Pharmaceuticals in October.

Prior to joining his current employer, Kent, Broeer held senior management roles with US firm Mylan in the UK and Germany.

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