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GENERICS bulletin

GLOBAL NEWS FOR THE GENERIC & BIOSIMILAR MEDICINES INDUSTRIES

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US ruling lets originators sue wherever they please

Generics applicants in the US can be sued in any state in which they market drugs, the US Court of Appeal for the Federal Circuit has ruled in a dispute between Mylan and originators Accorda, Alkermes and AstraZeneca. Mylan had appealed against two district-court decisions allowing patent-infringement cases over Ampyra (dalfampridine), Onglyza (saxagliptin) and Kombiglyze (saxagliptin/metformin) to proceed in Delaware.

Mylan had argued the cases should be dismissed, because Delaware state and its courts could not exercise personal jurisdiction over the company under the 'due process' clause of the 14th amendment to the US Constitution, which requires states to follow fair legal practices. But two district court judges found that Mylan had sufficient links to the state to justify litigating both patent disputes in Delaware.

Writing the lead opinion, Court of Appeals Judge Richard Taranto stated: "On interlocutory appeal, we affirm, holding that Mylan is subject to specific personal jurisdiction in these cases." It was "of particular importance", he said, that Mylan planned to sell products in Delaware upon approval from the US Food and Drug Administration (FDA).

Noting that the US Supreme Court had stated that the due process clause was not impinged if the defendant had "certain minimum contacts" and "purposefully directed" activities at the forum for litigation, Taranto maintained "the minimum-contacts standard is satisfied by the particular actions Mylan has already taken – its abbreviated new drug application (ANDA) filings – for the purpose of engaging in that injury-causing and allegedly wrongful marketing conduct in Delaware".

Mylan, Taranto observed, was registered for doing business in Delaware and had litigated several ANDA cases in the state, "including some that it initiated". Furthermore, he added, "multiple lawsuits against other generic manufacturers on the same patents are pending in Delaware".

In a concurring opinion, Judge Kathleen O'Malley maintained that registering to do business in a US state amounted to giving consent to "general personal jurisdiction".

Celltrion studies support switching

Real-world studies with almost 600 inflammatory bowel disease (IBD) patients in eight countries show that patients taking Janssen's Remicade (infliximab) can be switched to Celltrion's biosimilar alternative Remsima without affecting efficacy or safety. The studies were presented, alongside post-marketing extensions to Phase III trials for Remsima, during the 11th Congress of the European Crohn's and Colitis Organisation (ECCO).

A total of 10 abstracts presented at the congress covered 593 switched patients in countries including the Czech Republic, Italy, Japan, the Netherlands, Poland, Slovakia, Spain and the UK. Extensions to Celltrion's Phase III Planetas and Planetra trials in ankylosing spondylitis and rheumatoid arthritis respectively showed that, a year after the biosimilar's launch, "there were no signs of altered efficacy, safety or immunogenicity profiles following the switch to Remsima from the originator".

A survey of ECCO delegates found that 44.4% of respondents considered biosimilars to be interchangeable with their reference drugs, compared to just 6% in a 2013 survey. The proportion of respondents who felt little or no confidence in biosimilar monoclonal antibodies sank from 61% to 19.5% over the same period.

Celltrion is marketing Remsima in Europe through a network of local partners such as Biogaran, Egis, Kern Pharma, Mundipharma, Oktal and Orion.

BUSINESS STRATEGY/ANNUAL RESULTS

Transformed Siegfried considers strategy

Swiss contract developer and producer Siegfried is currently considering its next strategic steps after doubling in size over the past 18 months through the acquisitions of injectables specialist Hameln Pharma and active pharmaceutical ingredient (API) operations from BASF. These deals helped the group to raise its turnover by 52.4% to SFr481 million (US$495 million) last year, within reach of the SFr500 million of annual sales that Siegfried set as a "critical size" goal within the 'Transform' corporate strategy that it unveiled in 2010.

Having reached critical mass in the custom manufacturing sector, established an integrated supply offering by acquiring sterile-filling capacity through Germany's Hameln and Alliance Medical Products (AMP) in the US, and achieved horizontal integration by setting up an APIs and intermediates plant in Nantong, China, Siegfried feels it has achieved the goals of the Transform strategy.

"Today, the company is significantly larger, offers a broader range of products and services and, therefore, is more robust," insisted chief executive officer Rudolf Hanko. "It is market leader in the field of exclusive synthesis and controlled substances as well as an important supplier in sterile filling and of dossiers used for generics companies."

Product group/ region	Annual sales (SFr millions)	Reported change (%)	Constant-currency change (%)
Drug Substances	333	+42.1	+43.4
Drug Products	147	+82.4	+100.0
Siegfried	**481**	**+52.4**	**+57.9**
Europe*	215	+76	–
US	154	+11	–
Switzerland	95	+97	–
Others	18	+153	–

* excluding Switzerland

Figure 1: Breakdown by product group and region of Siegfried's sales in 2015 (Source – Siegfried)

Will unveil strategy this year

"It is too soon after Transform to demonstrate the full scope of our strategy," stated Hanko. "We shall do so in the course of this year," he promised, adding that Siegfried would focus in the near term on integrating the three acquired BASF sites in France, Germany and Switzerland. The group expects to complete integration this summer, including a temporary shutdown to install a new information-technology and enterprise resource planning (ERP) platform.

Hanko told **Generics *bulletin*** that Siegfried would ensure it did not "miss the train" in a continuously consolidating industry to ensure it protected its leading position in the contract APIs industry.

Siegfried's head of strategy and mergers and acquisitions, Wolfgang Wienand, said the group was currently considering strategic steps in "development capability and new technologies, especially at the interface between API and finished dosage forms, and in specialised technologies". "In the future," he pledged, "we will continue to expand our global production network and grow by acquiring attractive business opportunities."

Excluding the effect of acquisitions and switching to a spray-drying process for enoxaparin, Siegfried said it achieved organic sales growth of around 6% last year.

As reported, turnover by Siegfried's Drug Substances product group rose by 42.1% to SFr333 million – including a three-month contribution from the BASF sites – while the firm's Drug Products sales climbed by 82.4% to SFr147 million with a full year's input from Hameln (see Figure 1).

Group earnings before interest, tax, depreciation and amortisation (EBITDA) improved by nearly a third to SFr77.1 million, but Siegfried's operating margin declined by 1.8 percentage points to 9.0%, due in part to SFr3.7 million of integration costs for the BASF takeover.

Upon closing the €270 million (US$303 million) BASF transaction last year, Siegfried said the deal would add around SFr280 million to its annual turnover and would help the group to "reach the critical size to play a leading role in the supplier market as a recognised partner" (**Generics *bulletin***, 23 October 2015, page 9).

Excluding integration costs, Siegfried expects to report EBITDA this year "in the range of SFR100 million" on group turnover that grows by at least 40% to around SFr675 million. G

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BUSINESS STRATEGY/RESIGNATIONS

Valeant admits errors and seeks new head

Valeant has begun searching for a new chief executive officer after admitting that "improper conduct" by senior executives caused the Canadian firm to misstate financial results.

Chief executive officer and board member Michael Pearson would continue to serve in the roles until a permanent replacement was appointed, the firm commented. Pearson, who only returned to Valeant at the end of February after two months' absence through illness, said he regretted the "controversies that have adversely impacted our business over the past several months".

Former chief financial officer and Valeant director Howard Schiller, who had served as interim chief executive in Pearson's absence, was named by Valeant for improper conduct. This, the firm claimed, had "resulted in the provision of incorrect information" to the firm's *ad hoc* committee – a board set up last year to review allegations about the firm's operations – and the company's auditors, and "contributed to the misstatement" of results for 2014 and the first quarter of last year.

Valeant also acknowledged that the "performance-based environment" cultivated by the firm, "where challenging targets were set and achieving those targets was a key performance expectation," may have been a contributing factor "resulting in the company's improper revenue recognition".

Schiller denied the accusations levelled against him, claiming that, "at no time did I engage in any improper conduct that relates to any restatement of revenue the company is considering".

Moreover, he assigned responsibility concerning accounting matters currently under review by Valeant – related to specialty pharmacy Philidor – to the company's former corporate controller, who was placed on administrative leave as part of "certain remediation actions" implemented by Valeant.

Schiller also became involved in a spat with Valeant's board after refusing to tender his resignation as a director in order to make way for Bill Ackman, chief executive officer of major Valeant investor Pershing Square Holdings. "As a result of the fact that I did not engage in any improper conduct," Schiller insisted, "I have respectfully declined the request from the company's board to resign."

Ackman, who holds a 9.0% stake in Valeant, has nevertheless joined the group's board after director Katharine Stevenson voluntarily stood down. He had been unable to do so with Valeant's 14-strong board at maximum capacity.

These developments came shortly after Valeant acknowledged it was facing the possibility of defaulting on billions of dollars worth of debt after failing to file its 10-K annual report for 2015 on time.

Noting that a default would occur on Valeant's credit agreement if the firm did not file its 10-K annual report by 30 March, the group said it was "committed to filing the 10-K on or before 29 April", the 30-day window Valeant has to "cure the default". Valeant is also seeking a waiver from lenders concerning cross default provisions.

This all comes in the wake of Valeant recently slashing its full-year sales forecast for 2016 from US$12.5-US$12.7 billion to US$11.0-US$11.2 billion (**Generics *bulletin***, 18 March 2016, page 3).

Shortly before joining the board, Ackman penned a letter to investors acknowledging that the current factors surrounding Valeant's decline had "caused investors to lose total confidence in the company". This was "reflected by the current 44% decline in Valeant's stock price", he pointed out. As **Generics *bulletin*** went to press, the firm was trading on the New York Stock Exchange at US$31.14 per share, having traded at around US$260 in August last year.

MANUFACTURING

Emcure's Indian site hit by FDA warning

Operators crawling on the floor, supervisors failing to establish laboratory controls and workers falsifying evidence were among the faults that have led the US Food and Drug Administration (FDA) to issue a warning letter against Emcure's Indian facility in Hinjawadi, near Pune. This follows an inspection of the facility that took place last year, after which the FDA issued an import alert banning import into the US of drugs manufactured at the site (**Generics *bulletin***, 7 August 2015, page 2).

Highlighting "poor aseptic processing techniques" during the manufacturing process, the FDA said its inspectors observed an operator filling a cup on the floor with water collected from one unit and then using that water "to wet the mechanical assembly" of a filling line. Another employee crawled under filling equipment to perform "critical operations", according to the letter. These examples led the FDA to conclude that "facility design may represent an additional contamination risk to the products you manufacture".

Unreliable environmental and personnel monitoring were also specified by the FDA. One microbiologist claimed "work pressure" was the cause of routine false labelling of media plates which made it appear as though the plates had been submitted for incubation. The firm failed to establish and follow appropriate written procedures that were designed to prevent microbiological contamination of drug products "purporting to be sterile". Documents at the facility also recorded samples that had been taken for electronic monitoring of the zero colony forming units, but these were "not actually collected".

Failed to recognise defects

In its non-exhaustive list the FDA cited occasions when an individual had signed a quality assurance check with another person's signature despite the individual not being present nor viewing the procedure. Emcure's own inspectors at the site were also unable to correctly identify major defects such as when a vial contained particles or when it was filled to the wrong level. Emcure's standard operating procedures also allowed defects such as fragmented glass to be subjectively classified as critical or major, with no objective criteria for either distinction.

Emcure had made changes to management and engaged with consultants since the inspection, but it had not investigated "all systems and areas that may have been affected by your questionable practices", according to the FDA. The firm had acknowledged that "there have been serious gaps in management, oversight and execution of the environmental monitoring program, especially with respect to the suspected data integrity and falsification of data concerns".

However, the FDA noted, "data falsification and manipulation, and your reliance on incomplete records to release products, are repeat violations". These discrepancies were found to have previously occurred in a 2014 inspection of the facility, as well as in the 2015 investigation. Emcure's sterility issues had previously caused its partner Sagent to recall multiple product batches last year (**Generics *bulletin***, 13 March 2015, page 8).

The FDA has requested by the end of March a "comprehensive evaluation of the extent of the inaccuracy of your recorded and reported data", as well as "a detailed action plan to fully investigate the extent of deficient documentation and data-management practices" from a third party. The agency has also called on Emcure to provide a "management strategy for your firm that includes the details of your corrective action and preventative action plan".

MERGERS & ACQUISITIONS

Vectura joins up with UK firm Skyepharma

Vectura, the UK respiratory specialist that is partnering with Hikma to develop a US generic version of GlaxoSmithKline's Advair Diskus (fluticasone/salmeterol), is to merge with London-based drug delivery firm Skyepharma in a deal valued at £441 million (US$639 million).

Along with its VR315 fluticasone/salmeterol candidate, Chippenham-based Vectura is also developing with Hikma in the US VR506, an undisclosed "generic inhaled monotherapy corticosteroid" that the Jordanian firm picked up through its recent acquisition of Roxane Laboratories (**Generics *bulletin***, 4 March 2016, page 6). Hikma is also allied with Skyepharma, with the two firms partnering over an undisclosed oral formulation under the title SKP-1056.

Moreover, Vectura also acted as Sandoz' development partner for its AirFluSal Forspiro (fluticasone/salmeterol) that began rolling out across Europe and other global markets at the beginning of 2014 (**Generics *bulletin***, 10 January 2014, page 1). The two firms have also since 2007 allied over another unnamed generic inhaled combination therapy in the European Union under the banner VR632.

Vectura's chief executive officer, James Ward-Lilley, will lead the combination in the same role, while his counterpart at Skyepharma, Peter Grant, will step down "on terms to be agreed". Vectura chairman Bruno Angelici will hold the same role for the combined firms, while Frank Condella, Skyepharma's chairman, will serve as vice-chair. Also part of the executive team is Trevor Phillips, Vectura's chief operating officer, who will retain that position.

Combined the firms reported turnover of £154 million last year, generating total earnings before interest, tax, depreciation and amortisation (EBITDA) of £50.5 million. The combination hopes to realise pre-tax synergies of around £10 million by the end of 2018.

Commenting on the deal, the firms said that their respective boards "believe this is a compelling transaction that will combine complementary businesses to create an industry-leading airways-related specialty business". "The addition of Skyepharma's pressurised metered-dose inhalers (pMDIs) technology will allow the enlarged group to access the inhaled product market in its entirety," added Angelici, "and enhanced cash flow will position it better to consider attractive strategic opportunities which may emerge in the future."

Under the agreement, Skyepharma's shareholders will receive 2.7977 new Vectura shares for each share they hold, equivalent to 410.15 pence per share, giving a premium of 13.6%. The deal also includes a partial cash offer worth up to £70 million that allows Skyepharma's shareholders to receive a choice of cash, shares or a combination of both. Excluding the partial cash alternative, Skyepharma shareholders will own an approximate 41.8% share of the resulting combination "on a fully diluted basis", or 37.6% if the partial cash alternative is paid in full.

IN BRIEF

WBA – Walgreens Boots Alliance – has exercised warrants to buy almost 22.7 million shares in US wholesaler **AmerisourceBergen**. The US$1.17 billion cash transaction gives WBA a 14.97% stake in AmerisourceBergen with nearly 34.2 million shares. The two firms forged an alliance three years ago (**Generics *bulletin***, 5 April 2013, page 4). European wholesaling and retailing group WBA continues to hold warrants giving it rights to purchase another 22.7 million shares in its US partner. Rights to exercise that option begin in March 2017.

MANUFACTURING

Torrent obtains EIR for its Dahej facility

Torrent Pharmaceuticals says it has obtained an establishment inspection report (EIR) from the US Food and Drug Administration (FDA) for its major new manufacturing facility in Dahej, Gujarat, India.

Earlier this year, the Indian firm noted that increased capacity offered by the plant would "meet the needs of growth" for its US business when the facility came online scheduled for "later" in 2016 (**Generics *bulletin***, 12 February 2016, page 6). Commenting that the facility would also serve the needs of its German operation – where the plant had already received approval (**Generics *bulletin***, 6 February 2015, page 9) – Torrent noted at that time that "the initial priority right now is the US".

Moreover, the Ahmedabad-based group earlier said it expected to begin shipping "close to 10 products" out of the Dahej facility from April onwards, according to Sanjay Gupta, Torrent's executive director for international business.

Second phase of construction starting

The Indian firm said it had completed 'Phase I' of the building process for Dahej that includes capacity for 7.5 billion tablets and capsules and 25 metric tons of active pharmaceutical ingredient (API) per annum. "Construction of 'Phase II' will commence soon and once commissioned the total capacity will increase to about 14.0 billion tablets and capsules and 80 metric tons of API per year," Torrent noted.

Having received the EIR for Dahej, Torrent commented that three out of its five Indian manufacturing facilities now held FDA approval, including locations in Indrad, Gujarat and Pithampur, Madhya Pradesh. The Indian firm has further plants in Baddi and Sikkim.

MANUFACTURING

UK acts against Marksans

Destroyed and deleted data records are among the data-integrity issues that have led UK authorities to withdraw a good manufacturing practice (GMP) certificate issued to Marksans Pharma's oral-dose facility in Goa, India. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) said "no further marketing authorisation should be approved naming the site as manufacturer", while only batches of products considered critical to public health should be supplied from the plant until the issues were resolved.

Among the tablets and capsules listed as made at the Goa facility in the MHRA's update to the EudraGMP database are lisinopril, metformin, propranolol, sildenafil and simvastatin, as well as OTC analgesics and allergy remedies supplied to leading UK retailers.

Having initially discovered "major deficiencies" in quality systems at the Goa plant during an inspection in March last year, the MHRA re-inspected the site in November 2015 (**Generics *bulletin***, 22 January 2016, page 3). "There was a lack of evidence to demonstrate the effectiveness of resultant corrective and preventive actions (CAPAs) taken and a lack of interim assurances to ensure that ongoing operations remain in compliance with GMP, including failures to carry out effective investigations," the agency stated.

Pointing out that it could continue to supply critical products under a restricted GMP certificate, Marksans said it was "committed to complete holistic remediation" and would prepare the plant for re-inspection to regain GMP-compliant status.

BUSINESS STRATEGY/ANNUAL RESULTS

Hikma will expand injectables in Europe

Expanding the geographic footprint of its Injectables business segment in Europe is among Hikma Pharmaceuticals' priorities as it looks to integrate and capitalise on its recent acquisitions of Boehringer Ingelheim's Bedford and Roxane generics operations.

"In 2015, we expanded our European Union (EU) registration teams and our sales and marketing capabilities in order to cover new European markets. These efforts are expected to start generating sales in 2016," the Jordanian group stated.

"We have been making good progress on the commercial front in Europe. We are looking to penetrate new European markets and have submitted over 200 files," commented Hikma's chairman and chief executive officer, Said Darwazah.

A large amount of equipment, including nine lyophilisers, had been moved from the Ben Venue US site that Hikma took over from Boehringer to the group's recently expanded injectables production site in Portugal, Darwazah explained. Having removed the useful equipment, Hikma subsequently sold the Ben Venue site to Xellia for US$30 million in cash (**Generics *bulletin***, 9 December 2015, page 5).

In November last year, the US Food and Drug Administration (FDA) issued a close-out letter, resolving a warning letter that it had issued against the Portuguese plant a year earlier (**Generics *bulletin***, 9 December 2015, page 2).

Meanwhile, Darwazah remarked, Hikma was looking to acquire additional technologies to strengthen its European injectables base.

As reported, Hikma's European Injectables sales fell by 4% to US$72 million last year. However, this equated to 15% growth at constant exchange rates, buoyed by recent launches, higher demand for certain products and new contract-manufacturing business.

Global Injectables turnover that was flat as reported, but up by 3% in constant-currency terms, at US$710 million included sales in the Middle East and North Africa (MENA) region that rose by 2% as reported – and by 14% on a constant-currency basis – to US$92 million (see Figure 1). Hikma said strong growth in Algeria, Egypt and Saudi Arabia had more than compensated for declines in Iraq and Sudan as it expanded its injectables sales and marketing team in the region.

The group has recently completed its acquisition of a controlling 97.7% stake in Egypt's EIMC United Pharmaceuticals (EUP) following a deal struck with a consortium of shareholders last year (**Generics *bulletin***, 2 October 2015, page 3). Darwazah pointed out that EUP not only strengthened Hikma's local oncology portfolio and pipeline, it also gave the group a manufacturing site near Cairo, Egypt, that could produce oral and injectable cancer treatments.

The bulk of global Injectables turnover came in the US, where sales slipped slightly to US$546 million as recent launches largely offset the impact of "increased competition on certain higher-value products".

"During 2015, we successfully launched three of the Bedford products," Darwazah commented, highlighting the introduction of caffeine citrate, phentolamine and thiotepa in the US. "This was ahead of target and reflects the excellent job the combined Bedford and Hikma research and development teams have done in transferring these products to our facilities." The group, he said, was on track to relaunch 20 Bedford drugs by 2017, including nine this year.

"Efficient management of manufacturing overheads" helped the Injectables segment to improve its gross margin by three percentage points to 63.2% and to raise its operating margin by 7.3 points to 43.8%.

The operating margin of Hikma's US non-injectables Generics segment almost halved to 29.1% as its turnover dropped by 30% to US$151 million on significantly lower sales of doxycycline and colchicine. However, the firm said, "strong volume growth" had pushed up sales of the "underlying portfolio" by 39%.

Having previously marketed a 'grandfathered' form of colchicine without formal US approval, Hikma in January 2015 introduced colchicine 0.6mg capsules under the Mitigare brand name, alongside an authorised generic. "By July, we had established a nationwide salesforce, and sales began to build gradually in the second half of this year, albeit more slowly than our initial expectations," the firm said.

Business segment	Annual sales (US$ millions)	Change (%)	Operating margin (%)
US	*546*	*±0*	–
MENA	*92*	*+2*	–
Europe	*72*	*-4*	–
Injectables	710	±0	43.8
Branded	570	+3	18.4
Generics	151	-30	29.1
Others	9	±0	–*
Hikma	**1,440**	**-3**	**26.5****

* operating loss of US$5 million
** includes unallocated corporate expenses of US$74 million

Figure 1: Breakdown by business segment of Hikma Pharmaceuticals' sales and operating margin in 2015 (Source – Hikma)

The Roxane deal announced midway through last year was completed on 29 February 2016 after Hikma had negotiated a reduced price, valuing the transaction at around US$1.6 billion (**Generics *bulletin***, 19 February 2016, page 3). "The integration of the acquisition of Roxane will be a key focus this year and will transform our non-injectables business in the US, adding complementary and well differentiated products, an attractive pipeline, proven research and development capabilities and greater overall scale," Darwazah stated, pointing out that 13 of Roxane's 57 paragraph IV patent challenges were potential first-to-file opportunities.

Darwazah said a deal for Egypt's EUP that was completed on 17 February this year had strengthened Hikma's regional presence in oncology. A first-to-market launch of the cancer treatment imatinib helped to drive 18% constant-currency growth in Egypt as total turnover by the group's Branded segment in the MENA region grew by 13% in constant currencies – and by 3% as reported – to US$570 million, including US$225 million from in-licensed brands.

"We achieved double-digit growth, on a constant-currency basis, in each of our top markets – Algeria, Egypt, the Gulf Cooperation Council (GCC) and Morocco," Darwazah highlighted. Algerian sales climbed by 54% at constant exchange rates, and 24% as reported, following recent restructuring, while turnover in the GCC, including Saudi Arabia, was 14% stronger in constant currencies.

Tight cost controls, including replacing salesforce visits with digital marketing to doctors, helped to offset negative exchange-rate shifts as the Branded segment's operating margin dipped slightly to 18.4%.

Darwazah said Hikma would soon back up its introduction of Celltrion's Remsima (infliximab) in Jordan with approvals and launches of the biosimilar in Egypt, Morocco and Saudi Arabia. "We are seeing if we can do some other business with Celltrion outside of the Middle East region," he revealed.

With adverse exchange-rates responsible for Hikma's group turnover sliding by 3% to US$1.44 billion, the group's operating profit fell by 5% to US$381 million. This year, the group expects to exceed US$2.0 billion as US Generics sales reach US$640-US$670 million, including a 10-month contribution from Roxane and divestments of products with annual sales of around US$20 million (**Generics *bulletin***, 26 February 2016, page 8). To secure antitrust clearance for the Roxane deal, Hikma has also agreed to divest its minority stake in Unimark.

INDUSTRY ASSOCIATIONS

France's Gemme sets trio of key priorities

Three key priorities have been set out by France's generics industry association, Gemme, in the wake of the organisation's first 'internal convention' in mid-March. Teva's Erick Roche, president of Gemme, said these would be the "principal areas of work" for the association in 2016 and 2017.

The three key tenets set out by Gemme are: "improving the image and ensuring the recognition of generic and biosimilar medicines as economic and good-quality therapeutic alternatives"; "enhancing the predictability and stability of the economic model of generics and biosimilars in France so that industry can continue to invest and play its role in the economy"; and "bringing together all stakeholders around the issues of sustainability and solvency of our healthcare system".

Noting that Gemme had in recent months welcomed new members such as Accord, Mylan and Zentiva, as well as 'corresponding members' Helm, Macors and Synerlab, the association said it now represented "more than 92% of generic medicines sold in France" – by value and by volume – and almost two-thirds of biosimilars.

"The environment in which Gemme is evolving is constrained both by weak growth in the use of generics and by price cuts repeatedly imposed on medicines, notably generics," Gemme said, calling these cuts "excessive". It urged the French government to rapidly proceed with its "national plan of action to promote generic medicines" announced last year (**Generics *bulletin***, 10 April 2015, page 1).

REGULATORY AFFAIRS

FDA costs climb for biosimilars activities

A significant rise was seen in the most recent US financial year for costs incurred by US Food and Drug Administration (FDA) activities relating to biosimilars, according to a three-year report published by independent auditor the Eastern Research Group. The Biosimilar User Fee Act (BsUFA) requires the agency to "contract with an independent consulting firm to study the workload".

In the year ended September 2015, costs relating to the FDA's biosimilars activities reached US$32.7 million, compared to US$23.5 million and US$26.0 million in the previous two financial years. Measuring the workload by full-time equivalents (FTEs), the report found that total FTEs for the 2015 financial year came to almost 127, compared to nearly 82 FTEs in the 2014 financial year and just over 86 in the year ended September 2013.

Basing its estimates on several sources – including employee interviews, e-mail requests for time estimates, BsUFA financial reports, and Center for Drug Evaluation and Research (CDER) data – Eastern Research Group acknowledged "several complexities that could result in the actual hours being higher or lower than the value we used in our calculations". "There is most likely a learning curve that could result in initial biosimilars work being performed in 2013 taking longer to complete compared to work being performed in 2014 and 2015," the report acknowledges. "On the other hand, the work has grown more complex over the three fiscal years we considered."

Spiriva SPCs expire throughout Europe

March brings the expiry in major European Union (EU) member states of six-month paediatric extensions to supplementary protection certificates (SPCs) protecting Boehringer Ingelheim's Spiriva (tiotropium bromide) asthma treatment. France, Germany, Italy, Poland, Spain and the UK are among the countries in which SPCs linked to European patent EP0,418,716 are no longer valid (see Figure 1).

The '716 patent was filed in 1990, and granted in 1993 with the title 'thienylcarboxylic acid ester of aminoalcohols, their quaternary products, their preparation and use of the compounds'. However, points out Ark Patent Intelligence, other European patents protect Spriva Respimat dry powder and solution for inhalation, and may constrain generic competition beyond the term of the '716 molecule patent.

Spiriva capsules patent invalidated in UK

In the UK, Teva recently convinced the Patents Court that two key claims in the UK part of European patent EP1,379,220 were invalid due to lack of inventive step. The two claims in the '220 patent relate to hydroxypropylmethylcellulose (HPMC) capsules with specified moisture content to be used in a tiotropium bromide dry-powder inhaler.

Justice Paul Morgan found that at the '220 patent's priority date of 1 June 2001 it would have been "obvious to try" HPMC capsules "with a high prospect of success". He cited in particular a 1998 'Ogura' article by Japanese producer Shionogi Qualicaps promoting the "naturally low moisture content" of HPMC capsules (**Generics *bulletin***, 9 December 2015, page 21).

Boehringer claims Spiriva is the world's "most prescribed maintenance therapy in chronic obstructive pulmonary disease (COPD)". Even though global sales fell by 8.9% to €3.24 billion (US$3.66 billion) in 2014 "as a result of price pressure" in the US, the respiratory drug remained by far the German group's best-selling drug.

"The last of Abbott's SPCs for its antiretroviral combination Kaletra (lopinavir/ritonavir) for treating HIV-AIDS expire during March in the Netherlands and Spain," Ark observes. And throughout much of Europe, SPCs expire this month for Eisai's Targretin (bexarotene) antineoplastic agent for treating cutaneous T-cell lymphoma.

Looking at data exclusivity, Ark notes that an eight-year period in which generics firms in the EU have not been able to refer to data on Boehringer's Pradaxa (dabigatran) anticoagulant blockbuster ends in March. This will be followed by a two-year window in which generics will not be able to enter the market (see Figure 2).

"However, the dabigatran molecule patent, which has been extended via SPCs until 2023, is likely to further constrain generic entry beyond the expiry of data exclusivity," Ark highlights.

March also sees the end of a post-marketing surveillance period in South Korea for Bristol-Myers Squibb's Orencia (abatacept) rheumatoid arthritis treatment. However, Ark believes, local patents are likely to constrain market entry until 2022 for Korea's vibrant biosimilars industry. With Celltrion having led the way on biosimilar infliximab, Samsung Bioepis scored another first for the country with EU approval earlier this year for its Benepali (etanercept) biosimilar rival to the Enbrel original that Pfizer markets in Europe under licence from Amgen (**Generics *bulletin***, 22 January 2016, page 1). In Korea, the joint venture between Samsung Biologics and Biogen is marketing biosimilar etanercept in partnership with Merck, Sharp & Dohme.

SPC expiries in March

INN	Country
Alendronic acid	Latvia
Bexarotene	Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden
Diclofenac	Italy
Ferucarbotran	Austria, Belgium, Denmark, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland
Lopinavir/Ritonavir	Netherlands, Spain
Sirolimus	Sweden
Sulfur hexafluoride	Austria, Belgium, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, UK
Tiotropium bromide	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Poland, Romania, Slovakia, Spain, Sweden, UK

Figure 1: Molecules for which supplementary protection certificates (SPCs) expire in certain markets in March 2016 (Source – Ark Patent Intelligence)

Data exclusivity expiries in March

INN	Country/Region
Abatacept	South Korea
Alglucosidase alfa	European Union
Asenapine	Australia
Cinacalcet	South Korea
Dabigatran	European Union**
Eltrombopag	Turkey
Gadobutrol	US
Gamithromycin	Canada*
Saxagliptin	Australia
Sorafenib	Switzerland
Thiotepa	Turkey

* This will be followed by a no-marketing period of two years during which a notice of compliance will not be granted to a generic manufacturer. In addition, a further six months data protection will be added to the 8-year term for studies of gamithromycin in paediatric populations.

** This will be followed by two years of market exclusivity, where a generic will not be placed on the market.

Figure 2: Molecules for which data exclusivity expires in certain markets in March 2016 (Source – Ark Patent Intelligence)

LEGISLATIVE AFFAIRS

GPhA praises Senate over restrictive deals

The US Generic Pharmaceutical Association (GPhA) has praised the country's Senate for its criticism of voluntary restricted agreements utilised by certain companies to "thwart" generic market entry. In a hearing by the Senate special committee on aging, chairman Senator Susan Collins criticised companies that put drugs "in a closed distribution system, or special pharmacy, which gives the company a monopoly".

"Misuse of restricted-distribution agreements, intended to deny generic and biosimilar manufacturers' access to product samples needed to conduct bioequivalence studies that are required for FDA approval, only serves to extend market monopolies at the expense of patients," agreed the GPhA.

Ranking member Senator Claire McCaskill cited Retrophin and Turing as a "new breed of pharmaceutical company" which prevent "generic companies from competing in the market". McCaskill called these actions "a market failure", and said the committee would take steps to prevent these actions "for the sake of the patients". The committee also revealed that it would be examining Valeant in more depth at its next investigative hearing.

Recognising the importance of mandatory US Food and Drug Administration Risk Evaluation and Mitigation Strategies (REMS), but also warning that there had been abuses of REMS, the GPhA was "pleased the committee paid needed attention to the abuse of voluntary restricted distribution agreements" that were self-imposed.

REGULATORY AFFAIRS

FTC hits settlements even if lawsuit is live

A Pennsylvania district court was wrong to conclude that the 'rule of reason' analysis of reverse-payment settlements established in the US Supreme Court's landmark *Actavis* decision should not apply in cases where such a deal allows the underlying litigation to continue, according to the US Federal Trade Commission (FTC).

In an *amicus* brief filed with the US Court of Appeals for the Third Circuit, the antitrust regulator insists that the Eastern Pennsylvania District Court made "four fundamental legal errors" in its application of the 'rule of reason' approach set out by the Supreme Court in 2013 (**Generics *bulletin***, 28 June 2013, page 1).

The district court's decision involved a deal struck by generics firms Anchen and Teva and originator GlaxoSmithKline (GSK) over Wellbutrin XL (bupropion) extended-release tablets.

Anchen had filed a paragraph IV abbreviated new drug application (ANDA) for a rival to Wellbutrin XL, but was sued by GSK for patent infringement. A ruling of non-infringement was then appealed, but while this appeal was pending, Teva – through a deal with Anchen – started selling a 300mg version of the drug. The FTC noted that Teva and Anchen subsequently entered into a deal with GSK to not sell a lower 150mg strength 'at risk' for more than a year unless Anchen won the patent appeal before then. GSK agreed not to market an authorised generic.

In its *amicus* filing, the FTC said the district court had "incorrectly concluded that the 'rule of reason' analysis prescribed by the Supreme Court's 2013 decision does not apply in this case, because, unlike in *Actavis*, the parties' agreement allowed the underlying patent litigation to continue, even though it precluded generic entry until the litigation was resolved".

"The relevant antitrust harm identified in *Actavis* is the brand-name company's sharing of monopoly profits with the generic through a reverse payment to prevent the risk of competition," the FTC pointed out. "This harm arises whether the generic company drops its patent challenge entirely or simply agrees not to enter during the pendency of that challenge."

No requirement to prove delay

Moreover, the FTC said, "the district court also incorrectly held that to show an antitrust violation, the plaintiffs had to prove that the reverse-payment settlement resulted in delayed entry into the market for the antidepressant drug Wellbutrin XL". According to the regulator's *amicus* brief, "the relevant consideration under *Actavis* is whether the nature of the restraint is likely to harm competition, and there is no 'rule of reason' requirement to show delayed entry or an injury to a specific party".

The district court further erred, the FTC said, when it failed to require an explanation of "how the claimed pro-competitive benefits were attributable to the reverse payment". "Indeed, it is implausible that Teva would have required a payment to accept beneficial terms, or that GSK would have paid Teva to accept such benefits."

Finally, the FTC believes that the Pennsylvania district court was wrong to find the agreement lawful "based in part on a provision that entitled the parties to abandon their deal if the FTC objected to it". But the court "mistook that provision as an effective grant of veto power to the FTC", the *amicus* brief maintains. Under the 'rule of reason', the antitrust authority insisted, "such provisions are not relevant, because they shed no light on the likely competitive effects of the alleged restraint".

REGULATORY AFFAIRS

GPhA's Liang urges action on biosimilars

Swift action is needed by the US Food and Drug Administration (FDA) to enable the US biosimilars framework to achieve its full potential, according to Pfenex' chief executive officer Bertrand Liang, chairman of the Biosimilars Council within the US Generic Pharmaceutical Association (GPhA). "Biosimilars must be a top priority" on the US agency's agenda for 2016, he insisted.

"Interchangeability guidance is a key facet eagerly awaited by the biosimilars industry," Liang stated, noting that the potential for biosimilar substitution was "a crucial element for patient access". Interchangeability "realises the full potential of biosimilars by bolstering competition, lowering prices, and increasing availability for patients", he observed, insisting that "each day of delay of the issuance of guidance around achievable activities to create interchangeable biosimilars increases the time until these important therapeutic options can be made available to patients, with corresponding cost savings".

While Liang – who was recently reinstated as chair of the Biosimilars Council for a second term (**Generics *bulletin***, 4 March 2016, page 16) – acknowledged that the FDA's approval of the first US biosimilar, Sandoz' Zarxio (filgrastim-sndz), last year was "a momentous step forward" for the country's biosimilars pathway, he emphasised that it was "just that – a single step". "This singular US approval in 2015, though significant," he pointed out, "is dwarfed by the progress of other geographies such as Europe, which already has more than 20 approvals for biosimilars and is reaping the benefits of significantly improved patient access and healthcare savings afforded by such prescience."

"The FDA reports that there are currently close to 60 [biosimilar] development programmes for 16 reference products at the agency, with a significant backlog of development-stage meetings to advance these programmes with regulatory advice," Liang stated. "So why the backlog?", he queried.

While the agency had admitted that "the number of qualified reviewers within its ranks is insufficient to meet the unanticipated demands previously forecasted", Liang said, it was also significant that "critical guidances are absent, necessitating each FDA review team to move incrementally at best when working with biosimilar developers".

As well as interchangeability, biosimilars guidance is awaited on extrapolation and labelling. FDA Commissioner Robert Califf recently confirmed that key biosimilars guidelines were "very close" to completion, giving assurances that the agency was working "as quickly as it can" (**Generics *bulletin***, 11 March 2016, page 8).

Liang acknowledged that the FDA's agenda for 2016 was looking to add new guidance documents for bioimilars and "renegotiate five-year user fee agreements, with the [second] Biosimilar User Fee Act (BsUFA) on the docket". But while it was "important the FDA implement processes and regulations allowing for a more transparent and timely biosimilar approval process", he said, "simply addressing the backlog is insufficient".

"The FDA must also create, with industry, stakeholder education efforts around biosimilars to facilitate uptake, very much as it did with the generics industry," Liang stated. "FDA has noted that the pathway to licensure does not affect the determination of safety and efficacy of a product," he observed.

"We in industry encourage the FDA to move expeditiously in this effort," he urged, concluding that industry would "stand ready to partner with the agency to provide increased access to patients for these important therapeutic alternatives".

REGULATORY AFFAIRS

EDQM applications get revised roadmap

Paper submissions will no longer be accepted by the European Directorate for the Quality of Medicines & Healthcare (EDQM) for any kind of application from June 2016, under a revised 'roadmap' for certification of suitability (CEP) applications that the regulatory body says "represents a major change to current practices".

"Procedures for the electronic submission of CEP applications have been in place since 2007," the EDQM observed. Although "the number of e-submissions has increased regularly", paper applications still represent "around 10% of applications received".

While the EDQM has so far accepted several electronic formats – including PDFs, the electronic common technical document (eCTD) and the non-eCTD electronic submission (NeeS) – "the majority of applications received are in PDF, which is the most basic electronic format". But the Directorate said it intended eventually to make the eCTD the "single format for submission of data", except for transmissible spongiform encephalopathy (TSE) only submissions – for which PDF will remain the standard – and for veterinary submissions. Currently, the EDQM said, eCTD submissions represented "less than 20%" of the formats received.

Moreover, the Directorate has "decided to use the Common Electronic Submission Platform (CESP) as the preferred way to receive e-submissions", despite Dropbox currently being most popular. By January 2017 the EDQM Dropbox will be discontinued and the eCTD will be the only format accepted for new CEP applications – except for TSE-only and veterinary submissions – with this rubric expanded to all applications and renewals, barring TSE-only and veterinary submissions by January 2020.

PRICE WATCH ..... UK

Metronidazole prices double

Average prices for metronidazole 200mg tablets in 21-count packs more than doubled in mid-March, according to the latest UK figures provided by WaveData.

Comparing UK trade prices between the periods 1-29 February 2016 and 1-21 March 2016, the average trade price to UK independent pharmacies grew by 141% to £1.94 (US$2.79), despite the lowest available offer dropping very slightly to £0.23.

For similar size packs of metronidazole in a 400mg strength, the rise was less steep, with the average price per pack growing by just over two-fifths – 41% – to £0.62, based on averages calculated from at least 25 data points.

Meanwhile, the UK's Department of Health granted a price concession of £2.50 for bumetanide 1mg tablets in a 28-count pack, as the average price of the product rose by almost half – 49% – to £2.12. The lowest available price jumped by 18% to £1.07.

A price concession was also granted for 60-tablet packs of cimetidine in a 400mg strength. This came as the average price of the heartburn and ulcer treatment increased by a third to £17.61. At £10.02, the lowest available price was 18% higher than in February.

GASTROINTESTINAL DRUGS

Ferring fails in US to force data exclusivity

Ferring has failed to obtain a summary judgement from a Columbia district court that would have forced the US Food and Drug Administration (FDA) to retrospectively grant five-year data exclusivity to its Prepopik (sodium picosulfate/magnesium oxide/anhydrous citric acid) fixed-dose combination for cleansing the colon.

The originator argued that it merited five-year exclusivity because sodium picosulfate had never previously been approved in a new drug application (NDA). But because Prepopik's other two ingredients had previously been approved, the FDA denied five-year exclusivity under its interpretation of the relevant statute at the time of Ferring having filed an NDA (**Generics *bulletin***, 15 February 2013, page 23). When the FDA subsequently changed its view of the statute, the agency refused to apply its revised, more generous position retroactively to combinations such as Prepopik, and denied citizen petitions on the issue filed by Ferring, Bayer and Gilead.

FDA's interpretation was reasonable

Columbia District Judge Rudolph Contreras found that "the term 'drug' as used in the five-year exclusivity provision is ambiguous and that the FDA's prior interpretation was a reasonable one". "The agency has thoroughly explained both its prior and its new position, and thus there is no reason to avoid deferring to either," he commented.

Contreras described both parties' arguments on whether the FDA's revised, more generous stance on exclusivity for combination drugs should be applied retroactively as "thin on legal citations". He instructed Ferring and the FDA to file renewed motions for summary judgement "that more fully address the retroactivity issue".

ANTIRETROVIRALS

Teva rivals Kivexa in Canada

Teva claims its is the "first generic supplier in Canada" of abacavir/lamivudine combination tablets that are bioequivalent to Viiv Healthcare's Kivexa antiretroviral agent.

On 14 March this year, Health Canada approved dossiers for abacavir/lamivudine 600mg/300mg tablets submitted by both Teva and Apotex. On the same date, the agency also approved Apotex' generic version of GlaxoSmithKline's Ziagen (abacavir) 300mg tablets. The Canadian company lists both products as available on its website, along with a combination of abacavir, lamivudine and zidovudine.

Referring to IMS Brogan data for 2015, Teva said Kivexa had annual sales in Canada of C$68.4 million (US$52.3 million).

Last year, both Teva and Apotex obtained an appeals court ruling that a patent covering the hemisulfate salt of abacavir – Canadian patent 2,289,753 that expires in May 2018 – could not be listed against Kivexa in the country's patent register (**Generics *bulletin***, 8 May 2015, page 18). Two other patents listed against Viiv's brand in the register expire this year. All three patents are listed against Ziagen in the register.

Meanwhile, Teva Canada has been awarded costs after Janssen failed to convince Federal Judge Alan Diner that the issues of Teva's patent-linkage damages over bortezomib and the originator's counterclaim for infringement of four patents should be bifurcated into separate trials. Diner said a prothonotary had properly weighed various factors, including the complexity of the case, the link between liability and damages, and the potential to save time and money.

BIOLOGICAL DRUGS

Mexico's Pisa joins Biocon for US insulin

Biocon has formed an agreement with Mexico's Laboratorios Pisa to develop and commercialise recombinant human insulin (rh-insulin) for the US market. India's Biocon will be responsible for clinical development, regulatory approvals, and commercialisation of the product in the US. The partnership will also leverage "Pisa's drug product facilities in Mexico" and take advantage of Pisa's "proximity to the US market and Mexico's North Atlantic Free Trade Agreement (NAFTA) membership".

This agreement is an extension of Biocon's "long-standing relationship of over 10 years with Pisa, who has a dominant position in insulins in Mexico". The two firms received approval from Mexico's Cofepris for biosimilar insulin glargine last year, through the country's bio-comparable approvals pathway defined in 2012 (**Generics *bulletin***, 24 April 2015, page 21).

Biocon insisted that its "global clinical development experience with insulin glargine for the US will be a useful precedent in developing rh-insulin for the US market". The Indian firm is currently developing insulin glargine with Mylan, which has two global Phase III clinical trials for the diabetic treatment underway (**Generics *bulletin***, 22 May 2015, page 19). The collaboration with Pisa is part of Biocon's strategy to address the "large demand for generic rh-insulin in the US", which has a market worth US$2 billion, according to the Indian biotech firm.

Kiran Mazumdar-Shaw, Biocon's chairperson and managing director observed: "This collaboration will enable us to manufacture the rh-insulin product at Pisa's facilities in Mexico and commercialise it under the Biocon brand in the US market, which has a huge diabetes burden with over 1.4 million people diagnosed with diabetes every year."

Pisa chairman and president Carlos Alverez Bermejillo commented that the agreement "represents a major milestone in Pisa's strategy to enter the US sterile injectables market". He went on to add that Pisa had marketed insulin products based on Biocon's high-quality active pharmaceutical ingredient (API) for many years and this collaboration was "the natural progression of a strong relationship between the two firms".

OSTEOPOROSIS DRUGS

Atelvia's claims are obvious

Asserted claims in two US patents protecting Allergan's Atelvia (risedronate) are obvious in light of prior art, the US Court of Appeals has ruled in upholding a New Jersey district court's decision from a year ago (**Generics *bulletin***, 13 March 2015, page 21).

The Court of Appeals found no error in the New Jersey court's finding that claim 16 of US patent 7,645,459 and claim 20 of US patent 7,645,460 were obvious. Both claims cover formulations of about 35mg of risedronate sodium and 100mg of disodium ethylene-diaminetetraacetic acid (EDTA) and form part of patents that expire in January 2028.

The claims' only addition to the content of a Brazilian patent application was "pharmaceutically effective absorption", the Court of Appeals noted. Linking that phrase to "fed/fasted absorption" described in the patents' specifications, the court said defendant Teva had proven it was obvious to "use a chelating agent [such as EDTA] to bind calcium ions to mitigate the food effect for risedronate and thereby achieve similar fed/fasted absorption".

BIOLOGICAL DRUGS/ONCOLOGY DRUGS

Taiwan's Genovior will produce for Velit

Taiwanese company Genovior Biotech will produce both active pharmaceutical ingredients (APIs) and finished dosage forms of the biological drugs ranibizumab and somatropin, as well as of the oncology agents azacitidine, bortezomib and pemetrexed, under the terms of a technology-transfer agreement struck with Austria's Velit Biopharmaceuticals. No financial details were disclosed.

Velit – which recently said its ranibizumab candidate had "reached pilot-plant level" (**Generics *bulletin***, 4 March 2016, page 10) – will have access to the API and finished products manufactured by Genovior, while the Taiwanese company will have rights to sell both bulk and finished products in its domestic market and certain "large territories".

The partners expect contract manufacturer Genovior to begin production later this year at its plant in Zhunan, Taiwan, that the firm anticipates achieving Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) status next year. Genovior plans to apply for European and US good manufacturing practice (GMP) certification later this year or early in 2017. A sterile-products facility that the firm is building in Tainan, Taiwan, is scheduled to start operating next year.

BIOLOGICAL DRUGS

Benepali adds a multipack

Samsung Bioepis has got regulatory clearance from the European Medicines Agency (EMA) to offer its Benepali (etanercept) biosimilar in 'multipacks' of 12 pre-filled pens or syringes, each containing 50mg of etanercept. Variations to the firm's centralised marketing authorisation allowed the company to amend product labelling and the summary of product characteristics (SmPC) for its biosimilar rival to Enbrel beyond its initial authorisation as packs of four pens or syringes.

Biogen – which holds marketing rights to the biosimilar in Europe – recently began rolling out Benepali, with an initial launch in Europe to be followed soon by introducing the rheumatoid arthritis treatment in Denmark, Germany, the Netherlands and Norway (**Generics *bulletin***, 26 February 2016, page 1).

PARKINSON'S DISEASE DRUGS

Orchid's rasagiline approved

Orchid has received final approval from the US Food and Drug Administration (FDA) for its rival to Teva's Azilect (rasagiline) 0.5mg and 1mg tablets, which it intends to launch in the first quarter of next year. The firm claims its rasagiline product represents "a first-to-file application with a shared 180-day exclusivity for Orchid" in conjunction with Apotex.

Both Alkem and Mylan also have tentative approvals for rasagiline. Targeting a market size of over US$300 million and with "limited generic competition" for the Parkinson's treatment, Orchid stated it "hopes to garner a decent market share from this product launch".

Four patents are listed against Azilect in the FDA's Orange Book. One expires in September this year, and another in February next year, but the other two run until 2026 and 2027.

EVENTS – April, May & June

18-19 April

■ 4th Annual Biosimilars & Biobetters Congress

London, UK

Topics including market access and opportunities and commercial challenges will be addressed at this two-day event.

Contact: Oxford Global Conferences. Tel: +44 1865 248455.
E-mail: info@oxfordglobal.co.uk. Website: oxfordglobal.co.uk.

28-29 April

■ 14th EBG Biosimilars Conference

London, UK

This conference will cover issues including market access, regulatory issues, the evolving landscape and scientific developments.

Contact: Lucia Romagnoli. Tel: +44 7562 876 873.
E-mail: events@egagenerics.com. Register online at www.egaevents.org/bios/egabios2016reg.htm.

17-18 May

■ GPhA CMC Workshop

Maryland, USA

This interactive workshop will provide up-to-date information regarding CMC regulatory requirements and the challenges of approval.

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

8-10 June

■ Joint EGA and IGBA Annual Conference

Dubrovnik, Croatia

For 2016, the European Generic and Biosimilar medicines Association (EGA) and the International Generic and Biosimilar Medicines Association (IGBA) will join forces for their annual conferences.

Contact: Lucia Romagnoli. Tel: +44 7562 876 873.
E-mail: events@egagenerics.com. Register online at www.egagenerics.com or www.egaevents.org.

13-14 June

■ EuroPLX 61

Valetta, Malta

This meeting provides an opportunity to discuss and negotiate agreements, in-licensing and marketing and distribution.

Contact: Raucon. Tel: +49 6221 426296 0.
E-mail: meetyou@europlx.com. Website: europlx.com.

13-14 June

■ 7th Annual Summit on Biosimilars

New York, USA

Issues to be discussed at this event include interchangeability and labelling as well as litigation strategies, naming and substitution.

Contact: American Conference Institute. Tel: +1 212 352 3220.
E-mail: customercare@americanconference.com.
Website: americanconference.com.

26-30 June

■ 52nd DIA Annual Meeting

Philadelphia, USA

Topics covered at this event will include innovation, development, life cycle management and regulatory issues.

Contact: Drug Information Association. Tel: +1 215 442 6162.
E-mail: dia@diahome.org. Website: www.diaglobal.org/DIA2016.

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Divestments allow Aspen to sharpen its global focus

Selling assets in Australia and South Africa will allow Aspen Pharmacare to turn greater attention to areas where the most value can be added, the South African firm believes. Dean Rudge reports.

While many players across the global generics industry continued to use acquisitions to expand their capabilities, capacities and geographies in 2015, South Africa's Aspen Pharmacare opted to go in the opposite direction.

Fuelled by a strategy of "lessening complexity" and "decreasing bureaucracy", the South African firm last year completed two large divestments, providing the opportunity to better focus attention in areas where Aspen believes "the most value can be added". These are in Asia, Aspen's export-driven finished dose-formulation and active pharmaceutical ingredient (API) manufacturing business in South Africa, and the US.

In May last year, Aspen agreed to sell for around ZAR1.6 billion (US$105 million) a "broad portfolio" of around 60 branded and generic injectables and established products – including pain, anti-infective, cardiovascular and other specialty drugs – in South Africa to Endo's local Litha Healthcare affiliate (**Generics *bulletin***, 22 May 2015, page 4)

This deal was followed shortly after by Aspen selling generics operations in Australia – covering a basket of approximately 130 products, along with an "extensive range of non-prescription pharmacy products" – in a transaction worth around A$265 million (US$202 million) to India's Strides Shasun (**Generics *bulletin***, 5 June 2015, page 3).

In a separate deal with Strides, Aspen also sold six Australian brands for US$92 million. In total, the group reduced its stock keeping units (SKUs) in the country from around 2,100 to "less than 600", while "retaining over 80% of profitability". Earlier, in 2014, Aspen had slimmed down in the region by divesting to Perrigo its Herron OTC range in Australia and New Zealand (**Generics *bulletin***, 21 March 2014, page 19).

"The completion of the divestments marks an important step in achieving increased focus in the South African and Asia-Pacific businesses," Aspen insisted. While the firm has actively targeted these two areas for expansion, chief executive officer Stephen Saad last year described the US as the "next big frontier" for the company (**Generics *bulletin***, 2 October 2015, page 6).

"Further meaningful advances in the implementation of Aspen's strategic objectives have been made," Aspen said, noting that it now had a "solid foundation for the next growth phase".

Underpinning this foundation were two large acquisitions that were both completed by Aspen on the last day of 2013. From GlaxoSmithKline (GSK), the firm picked up for £700 million (US$1.01 billion) the global marketing rights to the Arixtra (fondaparinux) and Fraxiparine (nadroparin) deep-vein thrombosis injectable brands – excluding in China, India and Pakistan – along with a related manufacturing plant in Notre-Dame-de-Bondeville, France (**Generics *bulletin***, 28 June 2013, page 5).

Aspen then picked up 11 original products in a US$1.0 billion tie-up with Merck & Co, covering a "diverse range of therapeutic areas" and including the fractionated heparin Orgaran (danaparoid) brand. Aspen also obtained Merck's API business in the Netherlands that it operates under the Aspen Oss and Aspen API names (**Generics *bulletin***, 12 July 2013, page 3).

Moreover, further bolstering to its global anticoagulants presence, the firm a year ago acquired the rights to Novartis' Mono-Embolex (certoparin sodium) injectable for US$142 million (**Generics *bulletin***, 27 February 2015, page 27).

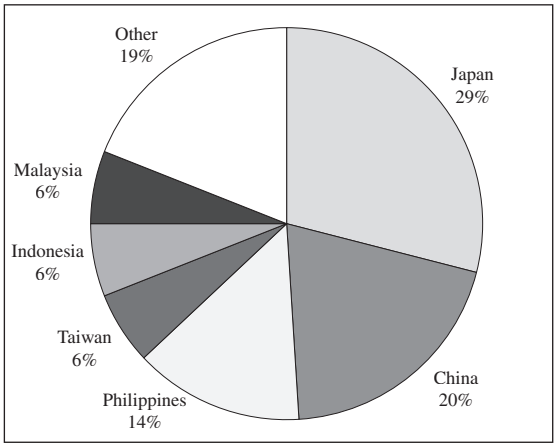

Figure 1: Breakdown by market of Aspen's sales in Asia that increased by 41% ZAR889 million in its financial first half ended 31 December 2015) (Source – Aspen)

Divestments are logical

Addressing investors discussing Aspen's expansion plans in Asia, South Africa and the US, Saad reiterated the group's overall view that the advantages of the divestments were "logical" but "not immediately apparent" from a financial perspective.

"There are hard decisions you have to make, to have a bit of an earnings hiccup for six months, or a year. We have made calls," he observed. "We got the big transactions right," he stated, commenting that Aspen had over the last several years evolved from a "regional player" to a "global multinational player".

In Asia, Saad stressed that, "in order to be successful in the region you need to be successful in Japan, and you need to be successful in China". Aspen had, he commented, "learnt a lot about" the market from earlier excursions in the Philippines and Taiwan.

Aspen announced its intention to enter Japan early in 2014 (**Generics *bulletin***, 21 March 2014, page 6), and later that year formed an alliance with GSK targeting the market. Under the Aspen Japan venture – in which GSK holds a 25% stake – Aspen agreed with the originator to invest ¥2.5 billion (US$22.4 million) in the entity to market both the South African group's portfolio and a basket of off-patent brands and authorised generics provided by GSK (**Generics *bulletin***, 17 October 2014, page 7).

Having begun trading in Japan from 1 July last year, Aspen said that the operation had "exceeded targets". Launch preparations for authorised generics were underway, Saad said, following recent approvals for its initial marketing authorisations.

Acknowledging that there had been a "lot of infrastructure costs" in Japan, Saad noted that Aspen had ultimately "yielded results quicker than we had hoped for". "Of all the territories in which we operate the Japanese market is best suited to the Aspen product offering," he observed.

As Figure 1 shows, Japan contributed 29% – or approximately ZAR258 million – of Aspen's total Asian sales that advanced by two-fifths to ZAR889 million in its financial first-half ended 31 December 2015. Meanwhile, in China, the firm said that establishing a dedicated affiliate in the country was "under consideration". Chinese sales made up a fifth of Aspen's sales in Asia during the period, and included supply of anticoagulants to GSK, Aspen pointed out.

In the rest of Asia, and through its other affiliates in the region, including in Indonesia and Malaysia, Aspen insisted it had "posted strong results in a challenging environment".

Turning to the US, Saad emphasised that the "globally-strong positions in niche areas" that Aspen had gained through its acquisitions had given the firm the necessary platform to stake a claim. "It is a market we really want to be in," Saad insisted. Aspen noted that building a "niche business based on supply of specialised APIs and finished-dose formulations" represented a significant opportunity for the company.

"We are not rushing. We have not gone in because we have not had the right intellectual property," Saad insisted. "We have no delusions, to say Aspen will be in the US what it is in South Africa. But we do have some excellent APIs, which we think we can leverage. And we now want to acquire finished-dose formulations, and are in the process of doing so."

Exemplifying Aspen's caution, the firm in September 2014 sold its US sales, marketing and intellectual-property rights for Arixtra – as well as an authorised generic – to Mylan in a deal worth US$300 million, claiming a "lack of knowledge of the US generics sector".

But going forward, Saad pointed out that the firm had acquired US rights to hydroxyprogesterone caproate, was the sole supplier of the API, and "hoped to launch the product" during Aspen's current financial year ending June 2016.

Working with distributor in US

"We will work with a very strong distributor," he commented, adding that additional agreements that would have "material effects on profitability in the next couple of years" were to follow. Such effects were however "hard to quantify", Saad admitted.

Moreover, Aspen had also recently "sat down with the US Food and Drug Administration (FDA)" to discuss a process to introduce the firm's danaparoid anticoagulant, Saad revealed.

Commenting on Aspen's export-driven South African contract-manufacturing business, Saad insisted: "This is a very big opportunity, and a very big opportunity for growth. It is certainly something that could drive South African growth into the future."

	First-half sales (ZAR millions)	Change (%)	Proportion of total (%)
Europe/CIS	*6,130*	*+21*	*35*
Latin America	*1,343*	*+1*	*8*
North America	*510*	*+2*	*3*
Middle East, North Africa	*413*	*+7*	*2*
Brazil	*382*	*-8*	*2*
Venezuela	*41*	*-95*	*–*
International	8,819	+3	50
Private Sector	*2,480*	*+1*	*14*
Public Sector	*787*	*-4*	*4*
Manufacturing	*510*	*+25*	*3*
Consumer	*402*	*+15*	*2*
South Africa	4,179	-3	24
Australia, New Zealand	*3,127*	*-22*	*18*
Asia	*889*	*+41*	*5*
Asia-Pacific	4,016	-14	23
Sub-Saharan Africa	1,635	+11	9
Eliminations	-1,136	±0	-6
Aspen Pharmacare	**17,512**	**-3**	**100**

Figure 2: Breakdown by region of Aspen Pharmacare's sales in its financial first half ended 31 December 2015 (Source – Aspen)

With sales ahead by a quarter to ZAR510 million during the financial first half (see Figure 2), Saad pointed out that the manufacturing business had benefited from a weaker rand. Quizzed on whether Aspen had any further plans to divest assets in South Africa, Saad insisted "absolutely not", reiterating that it remained a key area of growth for Aspen.

Going forward in its domestic market, Aspen said that expansion projects were continuing, including at its Port Elizabeth finished-dosage manufacturing site, as well as at its 'Fine Chemicals' API manufacturing site in Cape Town.

"In Port Elizabeth, the building of the high-containment facility is in the qualification process," the firm revealed, adding that construction of an additional specialist sterile manufacturing facility at the site was "progressing to plan". Meanwhile, "much of the construction at Fine Chemicals is complete", the firm announced, adding that further expansion and upgrade projects "remain underway".

On top of Aspen's growth plans, the firm also remains focused on a broad plan revealed last year "aimed at delivering synergies from recent acquisitions, targeting an additional ZAR2.5 billion in earnings before interest, tax, depreciation, amortisation (EBITDA) from these synergies" by the firm's financial year ending June 2019.

Building a "niche business in the US" was just one element of the plan, Aspen noted, reiterating that this was a "significant opportunity". Further aspects included: lowering the cost of goods for the anticoagulant portfolio; improving margins in its infant nutritionals business; bringing new manufacturing capacity and technologies on-line; building its third-party API business; and leveraging acquired intellectual property.

"Significant progress has been made over this past period in regard to the realisation of these synergies and Aspen is confident that this target will be achieved and exceeded," the group insisted.

> "The completion of the divestments marks an important step in achieving increased focus in the South African and Asia-Pacific businesses"

APPOINTMENTS

Weininger takes lead for Eris in Australia

Australia's Eris Pharma has appointed the chairman of its board, **Oren Weininger**, to become chief executive officer of its Australian business, replacing **Panos Athanasiou**. Weininger also currently heads Eris' Switzerland-based parent company Fair-Med Healthcare as chief executive officer, a position he has occupied since 2014 (**Generics bulletin**, 5 September 2014, page 31).

Previously, Weininger had held senior business-development and sales and marketing roles at Israeli firm Dexcel, which he left after eight years in 2013 (**Generics *bulletin***, 6 September 2013, page 31).

Eris said Weininger's immediate role in Australia would be to "align Eris more with its parent company" and "capitalise on the solid base on which the Australian business is set to grow". Almost a year ago, Eris declared that it was becoming a "significant generic pharmaceutical company in Australia" after acquiring Aurobindo's Australian and New Zealand business for an undisclosed sum (**Generics *bulletin***, 24 April 2015, page 3).

Weininger has also been charged with "searching for a permanent general manager for the Australian business". He insisted that "Eris remains focused on delivering exceptional service to Australian pharmacies and wholesalers alike", adding that "our commitment to the market sees us poised to cement our place as one of Australia's top-10 generics companies".

APPOINTMENTS

Austrian head is EMA chair

The European Medicines Agency (EMA) has named **Christa Wirthumer-Hoche**, head of Austria's Medicines and Medical Devices Agency, to become chair of the EMA's board for a three-year term. She succeeds **Sir Kent Woods**, who stepped down as chair in December. Wirthumer-Hoche has served as vice-chair of the EMA's board since last year, when she replaced **Walter Schwerdtfeger** of Germany's federal institute for drugs and medical devices, BfArM, in the role (**Generics *bulletin***, 10 April 2015, page 27).

She is also co-chair of the European Union (EU) network training centre launched in January 2015, and has served as chair of the EMA's active substance master file working group.

IN BRIEF

MARKSANS says that its chief operating officer and whole-time director **Balwant Shankarrao Desai** has resigned from the role with immediate effect. **Vinay Gopal Nayak** has been appointed as whole-time director – "designated as executive director" responsible for the entire technical operations – for a three-year period.

CAMBREX has appointed **Claes Glassell** to its board of directors, to serve on the board's audit and regulatory affairs committees. His appointment increases the size of the board to 10 members, although **William Korb** plans to retire following the active pharmaceutical ingredients (APIs) and intermediates specialist's April 2016 annual stockholders meeting. Glassell in the past spent more than eight years as president and chief operating officer of Cambrex.

BAFNA's chief financial officer, **MR Ramachandran**, has resigned from the company with immediate effect.

SANOFI has appointed **Ameet Nathwani** as group chief medical officer and member of the French firm's executive committee from 1 May. Nathwani will be responsible for "enterprise-wide medical, patient safety and medical quality assurance and will ensure the highest standard of transparency and compliance in Sanofi's interactions with healthcare providers, patients and medical organisations". He succeeds **Paul Chew** who has served as chief medical officer since January 2013 and plans to retire later this year.

MOMENTA has named **Jose-Carlos Gutiérrez-Ramos** to the firm's board of directors. Gutiérrez-Ramos currently serves as chief executive officer and president of Synlogic and was formerly group senior vice-president and global head of biotherapeutics research and development at Pfizer. Momenta president and chief executive officer Craig Wheeler said Gutiérrez-Ramos' experience would be "invaluable to the company as we advance our biosimilar and novel drug candidates through development and toward commercialisation".

PAMPLONA CAPITAL MANAGEMENT has made **Mark Pacala** an operating partner "with a focus on healthcare". Pacala has "more than 20 years' experience working in the healthcare industry".

MOODY DIRECT – the UK-based process parts supplier to the pharmaceutical industry – has recruited **Roy Taylor** as sales manager in connection with a sole distribution deal that Moody Direct has just signed with Romaco Kilian and Romaco Innojet in the UK and Ireland. The deal includes Innojet granulation and powder-coating systems and Kilian tablet presses.