4 May 2018

GENERICS bulletin

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Issue No.352

Identifiable claim needed for SPC protection in EU

Active ingredients must be "specifically, precisely and individually identifiable in the wording of patent claims" to allow combination products to be covered by a European supplementary protection certificate (SPC), according to an opinion published by European Court of Justice (ECJ) advocate-general Melchior Wathelet.

Wathelet offered his opinion in a case referred to the ECJ by the UK, revolving around Gilead's Truvada (tenofovir/emtricitabine) and involving generics opponents Accord, Lupin, Mylan and Teva. The firms challenged the validity of SPC/GB05/041 on the grounds that the SPC's basic European patent EP0,915,894 does not describe the combination, meaning that Truvada is not "protected by a basic patent in force" as per the requirements of European SPC Regulation 469/2009 (**Generics *bulletin***, 20 January 2017, page 11).

"As patents often contain a range of claims varying in their degree of specificity of abstraction," Wathelet observed, "the real question which arises in the present case is with what degree of specificity or abstraction a product is 'specified' in the claims of the basic patent within the meaning of Article 3(a) of Regulation 469/2009." It was "common knowledge", he said, that claims were "often deliberately and ingeniously drafted in broad, vague, generic and stereotypical terms so that they cover multiple substances".

"To my mind," Wathelet stated, "a product is protected by a patent within the meaning of Article 3(a) of Regulation 469/2009 if, on the priority date of the patent, it would have been obvious to a person skilled in the art that the active ingredient in question was specifically and precisely identifiable in the wording of the patent claims." In the case of a combination of active ingredients, he elaborated, "each active ingredient must be specifically, precisely and individually identifiable in the wording of the patent claims". However, he clarified, "the name of the active ingredient or its chemical composition does not need to be referred to expressly in the claims, provided that the active ingredient is specifically and precisely identifiable as at the priority date of the patent". In the case of Truvada, he said, it appeared that on the '894 patent's priority date it would not have been obvious that emtricitabine was specifically and precisely identifiable in the wording of the patent claims. This was "subject once again to verification by the referring [UK] court".

US slams India and China again

China, India and Canada have all been roundly criticised by the US Trade Representative (USTR) in its latest 'Special 301' report on intellectual property (IP) rights. China was placed on the 'priority watch list' for the 14th consecutive year. Meanwhile, India remains on the priority watch list for "longstanding challenges in its IP framework and lack of sufficient measurable improvements, particularly with respect to patents", such as the "potential threat of compulsory licensing and patent revocations", and narrow patentability standards.

"USTR also downgrades Canada from the watch list to the priority watch list," the body stated, "for failing to make progress on overcoming important IP enforcement challenges", including changes following the country's Comprehensive Economic and Trade Agreement (CETA) with the European Union (EU). "The US has serious concerns about the fairness of Canada's Patented Medicines (Notice of Compliance) proceedings as amended in September 2017," the USTR stated, also adding that "Canada's long-anticipated proposal to provide for patent-term restoration for delays in obtaining marketing approval appears to be disappointingly limited in duration, eligibility and scope of protection".

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MERGERS & ACQUISITIONS

Endo eyes a deal for Somerset and Wintac

Endo is set to augment the firm's commercial portfolio and pipeline of generic sterile injectables and ophthalmic drugs, as well as bolster its manufacturing capabilities, after agreeing to acquire New Jersey-based Somerset Therapeutics and its contract development and manufacturing business, India's Wintac, for around US$190 million.

Subject to regulatory approvals in both the US and India, as well as customary closing conditions, the transaction is scheduled to close in the second half of this year. The deal includes Endo assuming approximately US$30 million of Wintac's debt.

Founded only three years ago, privately-owned Somerset Therapeutics currently has a portfolio of eight products in the US. These include generics of the Vibisone (cyanocobalamin), Robinul (glycopyrrolate), Narcan (naloxone) and Robaxin (methocarbamol) injectables, as well as the Elestat (epinastine), Patanol (olopatadine) and Tobrex (tobramycin) ophthalmic solution products. An Endo spokesperson told **Generics *bulletin*** that Somerset had just received approval for a preservative-free formulation of dexamethasone vials.

Meanwhile, according to Endo, Somerset has a pipeline of "more than 40 products", of which over 25 have been filed with the US Food and Drug Administration (FDA), significantly increasing Endo's number of sterile applications. Endo revealed to **Generics *bulletin*** there were "some first-to-market opportunities" in the pipeline.

The deal will also provide Endo access to Bangalore-based Wintac's FDA-inspected sterile manufacturing facility, which the US firm says has "proven sterile injectables and ophthalmic" capabilities.

While Somerset's office in New Jersey has a "very low number of employees", the Wintac manufacturing and research and development site has "several hundred employees", **Generics *bulletin*** was told.

Somerset was co-founded in 2015 by chairman and chief executive officer Veerappan Subramanian and general manager Ilango Subramanian. Veerappan Subramanian – who previously founded Novel Laboratories and Gavis Pharmaceuticals, before selling the businesses to Lupin in 2016 – noted Somerset and Wintac had "successfully collaborated in the past" with Endo and its Par subsidiary.

Four years ago, Par greatly expanded its sterile injectables business by paying US$490 million for JHP Pharmaceuticals, giving the firm a 16,000 sq m sterile manufacturing facility in Rochester, Michigan and marketed products including the Adrenalin (epinephrine) and Aplisol (tuberculin) injectable brands (**Generics *bulletin***, 3 February 2014, page 3). Endo bought Par from private-equity firm TPG for US$8.05 billion in September 2015 (**Generics *bulletin***, 2 October 2015, page 8).

Sales of Endo's Sterile Injectables through the firm's US Generics business climbed by 23% to US$654 million last year, in line with guidance (**Generics *bulletin***, 9 March 2018, page 7). More than three-fifths of sales, or US$400 million, came from the Vasostrict (vasopressin) 505(b)(2) hybrid injectable. Adrenalin contributed US$77 million.

Eagle Pharmaceuticals recently filed an abbreviated new drug application (ANDA) for generic Vasostrict. Endo said it was "formulating its legal strategy" to address Eagle's challenge to five Vasostrict patents (**Generics *bulletin***, 20 April 2018, page 14).

From 1 January this year, Endo has rebranded the Sterile Injectables product portfolio as a new segment named US Branded Sterile Injectables, "separating sterile products that are generally longer-duration assets from those in our US Generic Pharmaceuticals segment".

Sales of US Branded Sterile Injectables were expected to grow in the low double-digit percentage range in 2018, Endo said.

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MERGERS & ACQUISITIONS

Amneal and Impax to divest 10 to close deal

Amneal and Impax intend to conclude their merger on 4 May, after receiving approval to proceed with the deal from the US Federal Trade Commission (FTC) on condition that the pair divest 10 products. Agreements have been struck with ANI Pharmaceutical, G&W Laboratories and Perrigo for the divestments.

The announcement comes around six months after the pair first signed an agreement to merge – with Amneal acquiring interests in Impax in transactions worth a total of US$1.45 billion – to become what they claim will be the fifth-largest generics player by sales in the US (**Generics *bulletin***, 20 October 2017, page 1). Impax president and chief executive Paul Bisaro – who will be executive chairman of the combined company – had indicated earlier this year that there would be "less than a dozen products that we have to divest" (**Generics *bulletin***, 9 March 2018, page 8).

Under the terms of the agreement, ANI will acquire from Impax seven products. These include the currently-marketed felbamate tablets, ezetimibe/simvastatin tablets and desipramine tablets – which will all begin shipping to ANI's customers "immediately" once the deal closes – as well as the approved but not yet launched aspirin/dipyridamole extended-release capsules and methylphenidate extended-release tablets, which will be manufactured and supplied to ANI "under multi-year supply agreements with Amneal, Impax or pre-existing third-party contract-manufacturers". Manufacturing equipment for methylphenidate that is "currently installed at a third-party contract-manufacturing site" will be transferred to ANI.

In the case of aspirin/dipyridamole, ANI said it would "immediately commence efforts to tech-transfer [from Impax] the manufacturing of the acquired abbreviated new drug application (ANDA)" to ANI's manufacturing facility in Baudette, Minnesota. The FTC noted that Amneal was currently the only manufacturer with generic aspirin/dipyridamole extended-release capsules on the market.

Impax had received US Food and Drug Administration (FDA) approval for its aspirin/dipyridamole, but the firm's third-party manufacturer had "experienced some manufacturing difficulties", leading Impax to begin developing the means to produce the product at its own facilities. While ANI "expects to have the Impax drug on the market soon", ANI will also have the option to receive generic aspirin/dipyridamole extended-release capsules from Amneal from 1 October 2019 to 1 March 2021. If it exercises this option, ANI may have to make a milestone payment.

ANI has also acquired a licensing, supply and distribution agreement for Impax' pending application for diclofenac/misprostol delayed-release tablets. Meanwhile, the in-development product erythromycin tablets are also included in the portfolio to be acquired by ANI. In total, ANI said, the combined US market for the seven products was currently worth US$1.7 billion according to Iqvia data.

Impax' partner Perrigo will acquire full rights to azelastine 0.15% nasal spray and olopatadine nasal spray, in keeping with the firm's strategy of focusing on 'extended topicals'. And G&W Laboratories has made a deal for a single product, fluocinonide 0.05% topical cream.

In its analysis of the Amneal-Impax merger, the FTC said the proposed deal would "reduce current competition" in the markets for generic desipramine tablets, ezetimibe/simvastatin tablets and felbamate tablets. For the others, the proposed deal would "reduce further competition in seven markets in which Amneal or Impax is a current competitor and the other is likely to enter the market".

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MANUFACTURING

Three companies hit with FDA warnings

Three firms – China's Lijiang Yinghua Biochemical and Pharmaceutical, Mexico's Degasa and the US' Phase 4 Pharmaceutical – have received warning letters from the US Food and Drug Administration (FDA) concerning their manufacturing facilities. Inspections at the sites identified "significant deviations" from current good manufacturing practice (cGMP), regarding active pharmaceutical ingredients (APIs) at Lijiang, and finished-dosage forms at Degasa and Phase 4.

In October 2017, the FDA inspected Lijiang's Chinese plant in Yunnan and found that laboratory equipment used to generate analytical data for batch-release purposes by the facility's quality unit lacked restricted access. After an audit by the agency in 2015 – which cited "numerous similar cGMP deviations" – Lijiang "committed to authorising levels of accessibility to prevent electronic data from being deleted, renamed or altered", and to assign unique usernames and passwords for each staff member. However, the FDA observed in the October inspection, the firm had not implemented any of these corrective actions.

Furthermore, Lijiang was unable to provide electronic data from laboratory analyses on its 'Waters' high-performance chromatography (HPLC) system between 25 September 2011 and 5 May 2017, as the data in question "had been deleted by accident and was no longer available". The FDA placed Lijiang on import alert in February 2018.

An audit at Degasa's site in Morelos, Mexico, in September last year identified failures to implement adequate microbial testing, including for povidone-iodine antiseptic products. "Your firm was unable to provide complete raw data related to the qualification of your water system," the FDA stated. "According to your employee, half the data you generated over a year was lost." The water system was "not suitable for its intended use", as it "was not appropriately designed, controlled, and maintained to consistently produce high-purity water".

Meanwhile, the FDA inspected Phase 4's US plant in Florida from the end of April to early May 2017."Your firm receives bulk deliveries of different kinds of transdermal patches from a contract manufacturer, and you then repackage your drug products into zippered plastic bags," the agency noted. These drugs "are similar in appearance and have no identifying labels on them, which may result in product and labelling mix-ups". FDA testing of several of the firm's OTC patch products found "multiple samples to be sub-potent with no active ingredient content".

IN BRIEF

GENOMMA LAB – the Mexican OTC and branded generics specialist – suffered a **5.5% slide in group turnover** to MXN3.03 billion (US$161 million) in the first quarter of this year. The firm's domestic sales inching up by 2.0% to MXN1.13 billion were unable to offset declines in Latin America – excluding Mexico – and in the US, where sales fell by 9.1% to MXN1.51 billion and by 11.4% to MXN390 million respectively. Genomma said that the construction of its Mexico City pilot plant "is progressing well and remains on track to begin production in the fourth quarter of 2018".

JB CHEMICALS & PHARMACEUTICALS said a **closure order** of its formulations manufacturing facility in Daman, India, made by the country's Pollution Control Committee, has been revoked by the issuing authority. The Committee had directed the closure "on the ground of alleged deviation of standards of treated waste water released from an effluent treatment plant (ETP) outlet". Noting that the firm had to "submit a compliance report within the stipulated time", JB added that the plant "shall forthwith resume operations".

INTELLIPHARMACEUTICS has filed an appeal against Nasdaq's decision to **delist the firm from the stock exchange**. "Accordingly, the delisting action referenced in the Nasdaq staff's determination letter has been stayed, pending a final written decision by the Nasdaq hearings panel," Intellipharmaceutics noted. The hearing has been scheduled for 17 May.

ALEMBIC PHARMACEUTICALS has revealed that the US Food and Drug Administration (FDA) has **completed an inspection** at its active pharmaceutical ingredient (API) facility in Panelav, India. Following an audit in April, no 'Form 483' observations were issued.

SAMSUNG BIOLOGICS has "become the first [company] in the South Korean pharma industry" to receive an **'ISO22301' business continuity management certificate** from the British Standards Institution (BSI). The certificate "represents the highest level of commitment to business continuity and disaster preparedness", Samsung BioLogics noted.

DR REDDY'S has received an **establishment inspection report** (EIR) from the US Food and Drug Administration (FDA) for its UK active pharmaceutical ingredient (API) plant in Mirfield, West Yorkshire. This closes an inspection that was conducted by the US agency in September 2017, when the US site was issued with three 'Form 483' observations (**Generics *bulletin***, 29 September 2017, page 3).

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BUSINESS STRATEGY/FIRST-QUARTER RESULTS

Biogen says it will up Samsung Bioepis cut

Biogen has confirmed plans to purchase a 49.9% equity stake in the Samsung Bioepis biosimilars joint venture between itself and Samsung BioLogics, praising the "attractive, value-creation opportunity".

"In the coming months, we plan to exercise our option," executive vice-president and chief financial officer Jeffrey Capello told investors, as Biogen reported biosimilar sales for the first quarter of 2018 that are now tracking at around US$500 million per year.

As of 31 March 2018, Biogen's stake in Samsung Bioepis sat at approximately 5%, and Samsung BioLogics' 95%, due to financings in which Biogen does not participate. However, under the firms' joint venture agreement, Biogen maintains an option to purchase up to a 49.9% share in Samsung Bioepis. This option will expire if the US-based company does not exercise it by mid-2018, at which point Samsung BioLogics will then have the right to purchase all of Samsung Bioepis' shares then held by Biogen.

Biogen says exercise of its option is based on paying for 49.9% of the total investment made by Samsung BioLogics into Samsung Bioepis in excess of what Biogen has already contributed under the joint venture agreement, "plus a rate that will represent their return on capital".

Quizzed by an investor on whether Biogen would have to integrate its profit and loss statement (P&L) or otherwise hold the equity stake "that would be worth billions of dollars", head of research and development Michael Ehlers confirmed the deal would be an equity investment and "would still be below the level that would require us to consolidate". "We would just pick up their share, or our share, of the net profits," Ehlers said.

Samsung has no plans to raise stake

Biogen's announcement comes shortly after the parent group of Samsung said there was "currently no plan" to purchase shares in Samsung Bioepis (**Generics *bulletin***, 20 April 2018, page 3). Earlier this year, Capello appeared keen on the prospect of upping Biogen's stake. "I think that would be our intent," he said (**Generics *bulletin***, 2 February 2018, page 3).

Biogen's biosimilars sales – derived from rights in certain European markets for Benepali (etanercept) and Flixabi (infliximab) – soared by 93% to US$128 million in the first three months of 2018. Almost all turnover, or US$121 million, came from Benepali, representing a rise of 85%, with the remaining US$6.6 million stemming from Flixabi, versus US$0.6 million in the first quarter of last year.

"We have seen continued steady market share gains across the large European markets following the rapid initial conversion in the Nordics," Capello commented. In addition to a "continued expected uptick for Benepali", Biogen anticipates the launch of the Imraldi (adalimumab) biosimilar in October this year – under a recent settlement with Humira (adalimumab) owner AbbVie (**Generics *bulletin***, 13 April 2018, page 13) – will be an "additional growth driver for our biosimilars business going forward".

Samsung BioLogics has also just reported the firm's first quarter sales. Turnover rose by 21.7% to KRW131 billion (US$121 million), producing an operating profit that trebled to KRW10 billion. Noting that Bioepis had so far launched three biosimilars in Europe, including Ontruzant (trastuzumab) this March, and one in the US, Samsung BioLogics said the SAIT101 rituximab biosimilar candidate it was developing through the firm's Archigen Biotech joint venture with AstraZeneca was in Phase I/III clinical trials.

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MANUFACTURING

UK accuses Indoco of falsifying GMP data

An inspection of Indoco Remedies' Goa Plant I oral-dose manufacturing facility in Verna, India, uncovered "evidence of falsification of data in good manufacturing practice (GMP) records", according to a statement of non-compliance with GMP published in the European Union's (EU's) EudraGMP database. However, the Indian company believes the audit report – which Indoco says arose out of "socio-cultural differences" – will only "have a temporary impact on our business in Europe".

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) also said "false and misleading statements were provided to the inspectors" during the inspection conducted in mid-March this year. A third critical deficiency listed was that the plant's pharmaceutical quality system was "ineffective regarding the recording, investigation and completion of actions relating to unexpected events".

Proposing that a GMP certificate that it had previously issued for the site be withdrawn and replaced by a restricted certificate that permitted making and testing medicines that were "critical to public health", the MHRA acknowledged that "there is no evidence of product having been impacted, and therefore the inspectorate does not recommend that products are recalled". National competent authorities should, the UK watchdog advises, "evaluate the criticality of products being supplied by this manufacturing site and enact measures to ensure continued supplies, where appropriate".

Indoco had already at the end of March disclosed that the MHRA's inspection on 14-16 March of its Goa Plant I – which makes tablets, capsules, oral liquids and semi-solids – had resulted in "three critical and four major" observations (**Generics *bulletin***, 6 April 2018, page 6).

Reacting to the EudraGMP publication, a company spokesperson told **Generics *bulletin*** that the Goa Plant I had successfully faced MHRA inspections since 2003 and had acted as "a preferred partner" to generics companies in Europe. "This will have a temporary impact on our business to Europe, which we will minimise by transferring products from the affected Goa I facility to our other manufacturing facilities – Goa III and Baddi I – holding valid EU GMP certification."

"It is evident from the MHRA statement that the product quality is not getting impacted and there are no recommendations for product recalls," the spokesperson insisted. "The observations, thus, are remediable and have risen out of socio-cultural differences. We are in communication with the European health authorities and are hopeful of getting an early resolution," he said.

DIVESTMENTS

Strides sells API unit to Solara

Strides Shasun's board of directors has agreed to divest Strides Chemicals, the Indian firm's remaining active pharmaceutical ingredient (API) asset in Ambernath, India, to Solara Active Pharma Sciences for Rs1.31 billion (US$19.6 million). The transaction is subject to closing conditions, including shareholder approval.

Having sold the former Perrigo plant in Ambernath – acquired in late 2016 for Rs1.0 billion (**Generics *bulletin***, 16 December 2016, page 3) – to the Solara raw-material business that it had previously spun off, Strides said it would enjoy "a 'most favoured customer' status for all drug master files (DMFs)" through a "long-term development and manufacturing agreement with Solara".

FIRST-QUARTER RESULTS

Sanofi suffers decline in European generics

Sanofi's European Generics business saw its sales slide by 6.1% to €184 million (US$222 million) on a constant-currency basis in the first quarter of this year, ahead of its proposed €1.92 billion sale to global private equity firm Advent International. Nevertheless, stronger sales in emerging markets caused global Generics turnover to increase by 0.9% to €435 million at constant exchange rates (see Figure 1). As reported, Sanofi's total Generics sales declined by 6.7%.

Emerging Markets Generics sales rose by 3.0% to €179 million in constant currencies, helping offset the European decline and Generics turnover in the US that decreased by more than a quarter – 27.0% – to €23 million on the same basis. Also bolstering the unit, Generics sales in Sanofi's Rest of the World region surged by three-fifths to €49 million in constant currencies.

In April, Advent entered into exclusive negotiations to acquire Sanofi's Zentiva European Generics business, with plans to create a "new, independent European generics leader" (**Generics *bulletin***, 20 April 2018, page 1). The US-based buy-out specialist pledged to support the Zentiva management team by investing in the company's operations, production facilities, and research and development pipeline, noting that it would "work collaboratively" with Sanofi to form a new independent operation.

Sanofi first revealed it was exploring strategic options for the business in late 2015, pointing to a changing European generic market that would require "different skills and different products, specifically differentiated generics and biosimilars, in order to grow" (**Generics *bulletin***, 20 November 2015, page 3).

Region	First-quarter sales (€ millions)	Constant-currency change (%)	Proportion of total (%)
Europe	184	-6.1	42
Emerging Markets	179	+3.0	41
US	23	-27.0	5
Rest of world	49	+60.6	11
Sanofi Generics	**435**	**+0.9**	**100**

Figure 1: Breakdown by region of sales by Sanofi Generics in the first quarter of 2018 (Source – Sanofi)

MANUFACTURING

Acino re-launches CMO unit

A "full service of best-in-class drug-delivery solutions" for oral-solid dosage forms is now being offered by Acino, following the re-launch of the Swiss firm's contract-manufacturing organisation (CMO), under the new Acino Contract Manufacturing brand.

A newly-launched set of pages on Acino's *Acino.swiss* website provide full details of Acino's contract-manufacturing offering. These span granulation/pelletisation, bulk manufacturing and primary and secondary packaging, alongside the "project-management, regulatory and sourcing services we can additionally supply".

For bulk production, Acino's focus is "on hard-to-make generics and niche-technologies", as well as suspension layering and modified-release dosage forms, and a "strong expertise" in narcotics and broad-spectrum antibiotics production. Acino revealed it had capacity in Switzerland for around 3 billion bulk units.

BUSINESS STRATEGY/FIRST-QUARTER SALES

Pfizer plots five US biosimilars by 2020

Pfizer expects to broaden its biosimilars portfolio in the US by potentially bringing five biosimilars to the market in the next two years, according to chairman and chief executive officer Ian Read.

Pfizer's current presence in the US biosimilars space is limited to the Inflectra (infliximab-dyyb) biosimilar it licenses from Celltrion, although the firm has in varying stages of development biosimilars of Humira (adalimumab), Avastin (bevacizumab), Epogen/Procrit (epoetin alfa), Neupogen (filgrastim), Rituxan/MabThera (rituximab), Herceptin (trastuzumab) and Neulasta (pegfilgrastim).

For trastuzumab, Pfizer recently received a US Food and Drug Administration (FDA) complete response letter (CRL) requesting additional technical information (**Generics *bulletin***, 27 April 2018, page 14), while the firm has also been knocked back on epoetin alfa, with a CRL, in the past 12 months.

Sales of Inflectra in the US more than trebled, from US$17 million to US$55 million, in the first quarter of 2018, with the company capturing a two-thirds share of the market in closed healthcare systems, and an approximate 6% volume share overall. While Pfizer continued to make progress with commercial health plans, Read observed: "I believe that it will take an effort by the administration to move that market, given the substantial advantage the entrenched companies have over the rebating system."

Pfizer has filed an antitrust complaint against Remicade (infliximab) originator Johnson & Johnson for what it deems "improper exclusionary tactics", and FDA Commissioner Scott Gottlieb has responded by promising a 'biosimilars access plan', stressing the need to tackle originator rebate schemes that make biosimilar market entry "highly unattractive" (**Generics *bulletin***, 16 March 2018, page 9).

Chief operating officer Albert Bourla said Pfizer was "very encouraged by the words of the FDA". "We just wait now [for the FDA] to translate these words into tangible actions that can reverse the situation." Pointing to the disparity in biosimilar infliximab uptake between the US and Europe, he insisted "there is something wrong."

Pfizer's total biosimilar sales jumped by two-thirds as reported to US$173 million (see Figure 1), aided by 39% growth to US$75 million for the Remsima (infliximab) biosimilar in Developed Europe.

With injectable shortages, "primarily from the legacy Hospira portfolio" due to capacity constraints and technical issues, dragging Sterile Injectables sales down by 12% to US$1.36 billion, Read said Pfizer was continuing with a "comprehensive remediation plan" to upgrade and modernise facilities. "We expect additional capacity to be available in 2019," he revealed.

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	First-quarter sales (US$ millions)	Change (%)	Proportion of total (%)
Innovative Health	7,829	+6	61
Legacy Brands	*2,636*	*+1*	*20*
Sterile injectables	*1,360*	*-12*	*11*
Peri-LOE products	*737*	*-10*	*6*
Biosimilars	*173*	*+66*	*1*
Pfizer CentreOne	*171*	*-6*	*1*
Essential Health	5,077	-5	39
Pfizer	**12,906**	**+1**	**100**

Figure 1: Pfizer's sales by division in the first quarter of 2018 (Source – Pfizer)

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BUSINESS STRATEGY/FIRST-QUARTER RESULTS

Orion outlines goals after diagnostics sale

Orion's president and chief executive officer, Timo Lappalainen, says the firm is "actively evaluating late-stage in-licensing opportunities" to augment its own pipeline and "continuing to invest in research and development activities, with new clinical trials", after selling its Orion Diagnostica diagnostic test systems business on 30 April. According to Lappalainen, the Finnish company is "currently working on numerous projects that target growth in our core area of the Pharmaceuticals business".

Having discussed possible options for the unit earlier this year (**Generics *bulletin***, 2 February 2018, page 6), Orion on 21 April signed an agreement to sell Orion Diagnostica to Nordic private equity investment company Axcel Management for €163 million (US$199 million). "The sale of the division will allow us to further focus on growth and achieving our financial goals," Lappalainen had commented before the sale was complete. Orion would "monitor carefully investment opportunities", he had added.

Adjusted for the sale of Orion Diagnostica – which saw first-quarter turnover increase slightly to €14.5 million year-on-year – Orion's group turnover fell by 7% to €247 million in the first quarter of 2018. The company's operating profit declined by over a fifth to €69.8 million, including €3 million of milestone payments, following higher operating expenses and static cost of goods sold.

Specialty Products turnover, comprising generics, biosimilars and self-care products, dropped by 3% to €118 million, as the Finnish firm's domestic sales slipped by 6% to €68 million. Sales rises in Scandinavia, Eastern Europe and Russia offered some respite. Total biosimilars turnover – which makes up around a tenth of the segment – fell by 4% to €10.6 million, with Remsima (infliximab) sales sliding by 14% to €10 million due to increased competition. Meanwhile, Orion said sales had just commenced in Finland, Denmark and Sweden for Celltrion's Ritemvia (rituximab), while the biosimilar had also launched in Estonia.

Orion reiterated Remsima sales in 2018 are "expected to be materially lower" than last year, owing to the firm's failure to win national tenders in key Nordic countries (**Generics *bulletin***, 16 February 2018, page 4). "Sales development of Remsima will continue to fluctuate depending on our success in tendering competitions in the future," the firm added.

Meanwhile, despite Orion's Easyhaler product sales climbing by a fifth to €22 million, mainly due to increased sales of the budesonide/formoterol combined formulation, Proprietary Products turnover slid by 6% to €93 million, as "sales of [branded] Parkinson's drugs continued to decline steadily".

MERGERS & ACQUISITIONS

Jean Coutu deal clears hurdle

Jean Coutu, the Canadian pharmacy group that includes the Pro Doc generics subsidiary, has secured clearance from the country's Competition Bureau for the retail firm's C$4.5 billion (US$3.5 billion) acquisition by local grocery and drugstore giant Metro (**Generics *bulletin***, 13 October 2017, page 3). The C$24.50 per share cash-and-shares deal transaction is scheduled to close on 11 May, with Metro divesting rights to 10 pharmacies. "No pharmacy will close as a result of these divestitures," the companies underlined.

EVENTS – May & June

23-24 May

■ World Biosimilar Congress USA 2018

San Diego, USA

The agenda for this two-day meeting includes pricing, pharmacovigilance, bioanalytics and patent issues.

Contact: Terrapinn. Tel: +1 212 379 6320.
E-mail: enquiry.us@terrapinn.com. Website: www.terrapinn.com.

6-8 June

■ 9th Annual Biologics Formulation Development & Drug Delivery Forum

Amsterdam, Netherlands

Issues including formulation stability, manufacturing challenges, compatibility and regulatory issues will be covered at this event.

Contact: Marcus Evans Conferences. Tel: +357 22849 380.
E-mail: constandinosv@marcusevanscy.com.
Website: www.marcusevans-conferences-paneuropean.com.

11-12 June

■ EuroPLX 67

Noordwijk, The Netherlands

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

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

13-15 June

■ Joint Medicines for Europe and IGBA Annual Conference

Budapest, Hungary

This joint Medicines for Europe and IGBA three-day conference will look at the latest developments within the industry. Topics covered will include sustainability, counterfeit medicines and patient access. There will be speakers from companies including Accord Healthcare, Fresenius Kabi, Mylan, Polpharma and Sandoz.

Contact: Lucia Romagnoli. Tel: +44 7562 876 873.
E-mail: events@medicinesforeurope.com. Register online at www.medicinesforeurope.com/events.

20-22 June

■ CPhI China

Shanghai, China

Offering a range of conferences, networking opportunities and exhibitions, this event will also provide market updates and industry trends, as well as regulatory news.

Contact: UBM Asia. Tel: +852 2827 6211.
E-mail: info@ubmasia.com. Website: www.cphi.com/china.

24-28 June

■ DIA 2018

Boston, USA

This is a four-day event which will cover topics including clinical trials, the biosimilars landscape, and regulatory issues.

Contact: Drug Information Association. Tel: +41 61 225 5151.
E-mail: EMEA@DIAglobal.org. Website: www.diaglobal.org.

REGULATORY AFFAIRS/INTELLECTUAL PROPERTY

Proposed SPC waiver has to go all the way

Tangible proposals for a waiver allowing manufacturing during the term of a supplementary protection certificate (SPC) have been announced by the European Commission, in a move that has been welcomed by off-patent industry association Medicines for Europe. However, the industry group cautions, such a mechanism must allow for both manufacturing for export and stockpiling for European launch upon SPC expiry to be truly effective and workable.

A European Commission college agenda indicates that an SPC manufacturing waiver for medicines will be discussed on 23 May, after a public consultation closed at the start of this year (**Generics *bulletin***, 19 January 2018, page 9). Medicines for Europe director general Adrian van den Hoven told the association's 14th legal affairs conference in London, UK, that the subject had been the "highest priority issue" for the organisation under his leadership.

According to a report published by the Commission, he highlighted, a waiver would create 20,000 to 25,000 additional manufacturing jobs in Europe by 2025, would increase the net sales for the European Union (EU) pharmaceutical industry by between €7.3 billion (US$8.8 billion) and €9.5 billion by 2025, ensure faster generic and biosimilar entry thus improving access for patients, and enable savings in pharmaceutical spending of between €1.6 billion and €3.1 billion thanks to competition. Moreover, a further 2,000 jobs would be created in the EU active pharmaceutical ingredient (API) sector by 2030, raising API sales by between €212 million and €254 million.

However, Medicines for Europe president Marc-Alexander Mahl told **Generics *bulletin*** in an exclusive interview, "a step forward for us is only an SPC manufacturing waiver that is installed and put on track to a full extent", meaning that it would allow both manufacturing for export and stockpiling for EU launch. "Both are important," he insisted, adding that "one alone does not really do the trick".

"Only a full SPC manufacturing waiver will create the full effect" foreseen by the Commission report, Mahl explained. A compromise position of allowing export but not stockpiling would be "a poisoned compromise" he said, that would "kill the idea", discouraging localisation of manufacturing in the EU – especially for biosimilars – and having "only a minimal effect for small chemical entities".

Noting that the association was "curious to see" what form the proposal would take after the European Commission college's discussion, Mahl said industry expected that "it will take about a year to get it implemented" after passing through the EU Parliament and Council.

Speaking at the conference, Insud Pharma's associate general counsel for intellectual property, Tomos Shillingford, said he had been "surprised by the resistance put up by [European originator association] EFPIA" (**Generics *bulletin***, 23 June 2017, page 9). "The competition is going to be there anyway, wherever it is manufactured," he pointed out.

And Taylor Wessing partner Matthew Royle insisted that a 'compromise' waiver allowing manufacturing for export but not stockpiling for EU launch would be "practically very difficult".

"We are not seeking to eliminate the SPC compensation for the originator industry," van den Hoven maintained. But he said there was a "good understanding in Brussels that India, China and other jurisdictions – including Canada – have an advantage over European manufacturers as a result of the current application of the SPC", concluding that "with this modest amendment, you could restore a level playing field".

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REGULATORY AFFAIRS

Inter partes reviews must cover all claims

US *inter partes* reviews (IPRs) of patent validity conducted by the Patent Trial and Appeal Board (PTAB) within the US Patent and Trademark Office (PTO) must cover all claims challenged by the petitioner, according to the US Supreme Court. The decision came as the court also held in a case brought by SAS Institute that IPRs did not violate article III or the seventh amendment of the US Constitution (**Generics *bulletin***, 27 April 2018, page 1).

"When the Patent Office institutes an IPR, it must decide the patentability of all of the claims the petitioner has challenged," the Supreme Court stated in its decision in the SAS Institute case. However, the opinion was backed only by a slim 5-4 majority.

In that majority opinion, the court found that the wording of the IPR framework – which states that the PTAB "shall issue a final written decision with respect to the patentability of any patent claim challenged by the petitioner" – was "both mandatory and comprehensive".

"The world 'shall' generally imposes a nondiscretionary duty," the court observed. "And the word 'any' naturally carries an expansive meaning." In other words, "the agency cannot curate the claims at issue but must decide them all".

PTAB issues guidance in wake of ruling

Guidance issued by the PTO in the wake of the SAS decision states that "as required by the decision, the PTAB will institute [an IPR] as to all claims or none". "If the PTAB institutes a trial," it adds, "the PTAB will institute on all challenges raised in the petition."

For pending procedures in which a panel has instituted trial on all of the challenges raised in the petition, the panel will continue as normal. However, "for pending trials in which a panel has instituted trial only on some of the challenges raised in the petition", the panel "may issue an order supplementing the institution decision to institute on all challenges raised". "The PTAB will continue to assess the impact of the decision on its operations and will provide further guidance in the future if appropriate," it concludes.

The SAS decision followed a 7-2 Supreme Court ruling in the *Oil States* case that upheld IPRs as not violating article III or the seventh amendment of the US Constitution.

On article III, the Supreme Court found that "IPR falls squarely within the public-rights doctrine". "The decision to grant a patent is a matter involving public rights," the court observed, adding that "IPR is simply a reconsideration of that grant, and Congress has permissibly reserved the PTO's authority to conduct that reconsideration".

And on the seventh amendment to the US Constitution – which revolves around the right to a jury trial in certain civil cases, as well as inhibiting courts from overturning a jury's findings of fact – the Supreme Court said "when Congress properly assigns a matter to adjudication in a non-article III tribunal, the seventh amendment posts no independent bar to the adjudication of that action by a non-jury fact-finder".

However, the court emphasised, "this holding is narrow", adding that it "addresses only... the precise constitutional challenges that *Oil States* raised here". "*Oil States* does not challenge the retroactive application of IPR, even though that procedure was not in place when its patent issued," the court observed. "Nor has *Oil States* raised a due process challenge."

Having issued its SAS Institute and *Oil States* decisions, the Supreme Court denied certiorari in several associated IPR disputes.

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PRICING & REIMBURSEMENT

French tender focuses on quality over price

Quality considerations outweighed price discounts in a recent French hospital tender for rituximab, Phillipe Lechat, professor of clinical pharmacology at Paris-Diderot University, told the 16th Biosimilar Medicines Conference organised by Medicines for Europe.

Noting that Biogaran's Truxima (rituximab) had triumphed over Roche's MabThera reference brand as well as Sandoz' Rixathon in the 16-month regional tender for 100mg and 500mg intravenous presentations that began on 1 February 2018, Lechat said quality attributes, such as stability before and after dilution, had constituted 57% of the selection criteria weighting. Within that proportion, the quality of associated services and information for healthcare professionals accounted for 16 percentage points. Price made up 40% of the selection criteria in the tender run by the Assistance Publique-Hôpitaux de Paris (AP-HP) group of 39 hospitals, with the remaining 3% coming from the environmental impact of competing products.

Lechat noted that France's medicines agency, ANSM, had last year published 11 biosimilar groups that could be switched for their corresponding reference products, with an aim of 70% biosimilar penetration (**Generics *bulletin***, 10 November 2017, page 11). Direct profit mechanisms, he added, had been introduced to encourage biosimilar dispensing by pharmacies for drugs initially prescribed by hospital doctors (**Generics *bulletin***, 30 March 2018, page 1).

Reflecting on AP-HP's experiences with infliximab tenders to date, Lechat said the 52% biosimilar discount to the pre-competition reimbursement price of the reference brand, Merck Sharp & Dohme's (MSD's) Remicade, had been "much more than anticipated by economists". Biogen's Flixabi had captured the latest tender in September 2017, taking over from Pfizer's Inflectra, he observed. The result, he revealed, had been a reduction by a third of AP-HP's infliximab expenditure in the three years since biosimilar competition arrived, falling from €41 million (US$49.3 million) in 2014 to €27.8 million in 2017, as biosimilars captured a 62% share by volume and 53% by value. Further savings, he added, could be expected from upcoming tenders for adalimumab, bevacizumab and trastuzumab.

MARKET RESEARCH

Net prices tend to converge

Net prices for biosimilars are tending to converge across Europe, often offering savings of 80% to 90% off the reference brand, according to an analysis conducted by market researcher Iqvia. However, it says, low net prices do not always translate into major market share.

Addressing the 16th Biosimilar Medicines Conference organised by Medicines for Europe, Iqvia's vice-president of strategic partners, Per Troein, said a case study of granulocyte-colony stimulating factor (G-CSF) had shown differing biosimilar list prices in European markets. But at a net level on hospital invoices, prices in Germany, Italy and Sweden had all converged at less than 10% of the reference brand's list price, he said, highlighting the "enormous impact" that such discounts were having on hospitals' medicines expenditure.

Biosimilars captured 4.6% of Europe's biologics market last year, but biosimilars' global share with sales of US$4.0 billion made up less than 2% of the world's US$276 billion biologics market. Thus, about 30% of the global pharmaceuticals market "has not seen the full impact of price competition".

IN BRIEF

FDA – the US Food and Drug Administration (FDA) – is currently working on measures to be **included in a biosimilar competition plan**, the agency's associate director for therapeutic biologics, Leah Christl, told Medicines for Europe's 16th Biosimilar Medicines Conference. "I can't give a [release] date, but I hope it will be shortly," Christl said, adding that the agency would aim to give "greater scientific and regulatory clarity" while making its review process more efficient. The FDA was also, she said, continuing to analyse comments on its draft interchangeability guideline. At present, she commented, it was too early to tell what commercial impact an interchangeability designation might have, especially as two of three biosimilars that had been launched in the US were not typically dispensed through pharmacies. On biologics naming, Christl said unique four-letter suffixes to international non-proprietary names (INNs) were being included in adverse reaction reports.

ACSS – the consortium of regulators from Australia, Canada, Singapore and Switzerland – could conceivably **apply its work-sharing model to biosimilars**, according to Swissmedic's head of sector for marketing authorisations, Claus Bolte. The consortium's generic medicines working group (GMWG) had, he pointed out, already completed its assessment of its first application, an immediate-release tablet submitted by Teva. Under an ACSS work-sharing trial, a reference regulatory agency reviews four common modules, while concerned regulatory agencies simultaneously consider a single country-specific module.

EMA – the European Medicines Agency – could add revising its **overarching guideline on biosimilars containing monoclonal antibodies** (mAbs) among the tasks included in the 2019 working plan of the agency's biosimilar medicines working party (BMWP), according to the party's chair, Elena Wolff-Holz. Noting that a revision had not been foreseen in the party's work plan for this year, Wolff-Holz acknowledged that the overarching guideline had come into effect at the end of 2012, before any biosimilar mAbs had been approved. Any amendments to the guideline would, she said, reflect the agency's experiences with products such as infliximab.

WHO – the World Health Organization – intends by the end of June to finalise a guideline to support its **pilot pre-qualification scheme** for assessing the quality, safety and efficacy of biosimilar, or (SBP), forms of rituximab and trastuzumab (**Generics *bulletin***, 15 September 2017, page 5). Pointing out that products pre-qualified under this mechanism would be eligible for procurement by international parties distributing drugs to low-income countries, the WHO's Francois-Xavier Levy outlined both full and abridged pre-qualification pathways. The latter option would apply, he said, where the SBP had already been approved by a 'stringent regulatory agency'.

BIOSIMILAR APPLICANTS to the European Medicines Agency (EMA) should consider taking advantage of a pilot project launched last year to offer **tailored scientific advice**, according to the agency's scientific administrator, Klara Tiitso. Running from February 2017 until six procedures have been completed, the pilot is intended to "support stepwise development of biosimilars by offering in-depth review of available quality data" (**Generics *bulletin***, 6 January 2017, page 1). Tiitso admitted that the agency had anticipated more than the two pilot-scheme requests it had validated and finalised last year out of a total 46 requests for scientific advice, but she encouraged interested companies to discuss whether their development programs were eligible for tailored advice.

PRICING & REIMBURSEMENT

England eyes £100m adalimumab saving

England's National Health Service (NHS) stands to save more than £100 million (US$138 million) per year after biosimilar competition to AbbVie's Humira (adalimumab) blockbuster enters the market later this year, believes Keith Ridge, chief pharmaceutical officer for NHS England. Anticipated biosimilar adalimumab launches this autumn – both Amgen and Samsung Bioepis have reached patent-litigation settlements allowing them to launch in Europe from 16 October – will, the NHS expects, make a major contribution to the goal of annual savings of £200-£300 million by 2020/2021 laid out in a commissioning framework last year (**Generics *bulletin***, 22 September 2017, page 5).

Ridge said adalimumab was the medicines on which the NHS hospitals spent most in 2016/17 at over £333 million. With this in mind, NHS England had formed a national adalimumab working group and was working with industry on an implementation strategy, he said.

On procurement strategy, Ridge outlined that contract specification and timing were being reviewed by a team within NHS England's Pharmaceutical Marketing Supplies Group (PMSG), supported by focused work being carried out by four regional medicines optimisation committees (RMOCs). "A timeline will be issued when this has been finalised," he revealed.

Practical issues were also being considered, Ridge stressed. "We have 59,000 patients on adalimumab receiving homecare, so we need to think carefully how to build that into the process when people might be receiving six-month prescriptions," he commented.

As NHS England sought to capitalise on the end of AbbVie's Humira monopoly, Ridge said it was drawing on its experiences and learnings from other biosimilars, such as the importance of sharing the benefits of savings and hitting uptake targets through incentives.

Such initiatives, Ridge pointed out, had been instrumental in biosimilar rituximab having in March 2018 captured a 71% market share measured by treatment days, less than a year after having entered the market (see Figure 1).

Savings from biosimilar rituximab in NHS England's 2017/2018 financial year ran to around £50 million, adding to another £60 million from etanercept and £100 million from infliximab. Monthly spending on the three molecules had decreased by 41% since 2015 to £24 million, Ridge reported, while usage volumes had risen by 16%.

In the April-November 2017 period, national biosimilar uptake in England had reached 88.3% for infliximab, 72.5% for etanercept and 57.7% for rituximab, with infliximab and rituximab shares in London exceeding 90% by February this year. "We are undoubtedly getting there," Ridge concluded.

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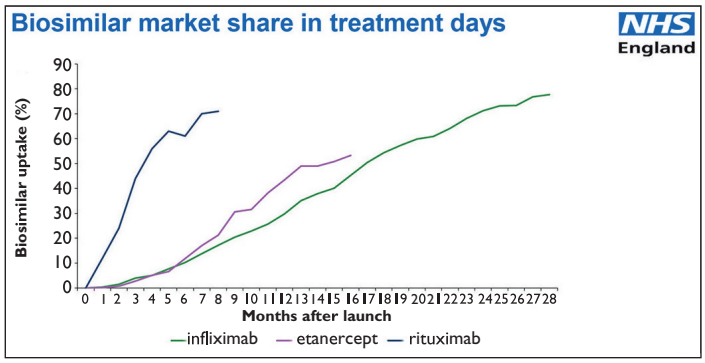

Figure 1: Uptake by treatment days of biosimilar etanercept, infliximab and rituximab by NHS England in the months after launch (Source – NHS England)

REGULATORY AFFAIRS

Clinical studies may soon be redundant

Advances in analytical techniques for biological drugs may soon render redundant large-scale Phase III clinical trials for biosimilar candidates, according to several speakers at the 16th Biosimilar Medicines Conference hosted by Medicines for Europe in London, UK. However, regulators showed some reluctance.

Justin Stebbing, professor of cancer medicine and oncology at London's Imperial College, observed that the clinical requirements of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) were closely aligned in favouring an equivalence design with strict, pre-defined margins. "Do we even need to perform clinical trials any more?" he wondered, arguing that a well-designed pharmacokinetic (PK) study in healthy subjects might suffice.

Noting that agencies were largely handling biosimilar candidates on a case-by-case basis, Stebbing believed "regulators still think the bar needs to be higher, and they still want a clinical data set for every product". "The question is," he said, "how much of a clinical data set? In two years' time, I don't think we will be seeing large studies any more, provided we do not see a nasty event occurring, like the withdrawal of a biosimilar due to immunogenicity reactions.

Independent consultant Alex Kudrin argued that expensive Phase III trials in large patient populations often lacked sensitivity and did not necessarily add much evidence on biosimilarity above that which could be gleaned from PK, pharmacodynamic (PD) and immunogenicity studies. Savings from not having to conduct large-scale trials could be invested in manufacturing and pharmacovigilance improvements, he suggested.

Avalare Health's Gillian Woollett appealed for consistency, pointing out that clinical trials were rarely required when originators made manufacturing changes to reference drugs. "Often, the originator is a biosimilar to itself, and that is OK, because the data supports it," she commented, arguing that greater regulatory harmonisation would present an "opportunity to use data cross-jurisdictionally".

But the chair of the EMA's biosimilar medicines working party, Elena Wolff-Holz, was not convinced. "I would make the case that clinical trials have their place," she said. The European agency was, she explained, still learning about which clinical and quality attributes really mattered. However, she accepted that, as the EMA gained experience with certain products, reduced-scale trials might be appropriate.

PRICING & REIMBURSEMENT

Italy sees savings of €4 billion

Savings from biosimilar competition on four biologic active ingredients – adalimumab, bevacizumab, pegfilgrastim and trastuzumab – in Italy could total over €4.0 billion (US$4.8 billion) over a decade, the country's AIFA medicines agency has calculated.

Assuming 50% discounts to the originators' prices – the highest level of discount for hospital drugs under a fast-track pricing and reimbursement procedure introduced in 2013 – AIFA's Simona Montilla forecasted potential 10-year savings of €1.43 billion from biosimilars to Humira (adalimumab), €1.40 billion from alternatives to Herceptin (trastuzumab) and €1.12 billion from rivals to Avastin (bevacizumab). Due to relatively low sales volumes in Italy, and the resulting 32% biosimilars discount, savings on Neulasta (pegfilgrastim) would be a more modest €89 million, Montilla said.

INTELLECTUAL PROPERTY

China moots changes over data exclusivity

China's Food and Drug Administration (CFDA) has released for comment a draft document detailing data exclusivity rules that propose six-year data protection for "innovative new drugs", while suggesting that "innovative therapeutic biologics" be eligible for 12-year data protection. Comments are due by 31 May.

The announcement came as the US Trade Representative (USTR) published its 2018 'Special 301' report into global trade and intellectual property (see front page). Noting that China remains on its 'priority watch list', the USTR said it plans to press the country "on a range of issues affecting the pharmaceutical sector".

This includes "providing for effective protection against unfair commercial use, as well as unauthorised disclosure, of test or other data, generated to obtain marketing approval for pharmaceutical products, as well as expediting its implementation of an effective mechanism for the early resolution of potential patent disputes". "Concerns extend not only to gaps in legal authorities and weak enforcement channels," the USTR states, "but also to investment and other regulatory requirements."

"Initial positive developments" in China last year, the report acknowledges, included concluding a three-year pilot program for specialised intellectual-property (IP) courts in Beijing, Shanghai and Guangzhou, and the CFDA's efforts to "promote the efficient resolution of patent disputes between right holders and the producers of generic pharmaceuticals". However, the USTR contends, "significant missed opportunities and troubling steps backward cast long shadows on the IP landscape in China". Last year's Special 301 report also heavily criticised the country (**Generics *bulletin***, 5 May 2017, page 1).

PRICING & REIMBURSEMENT

Tenders boost variety German funds claim

Tenders for off-patent drugs do not, as industry often claims, reduce the variety of suppliers, according to a leading group of statutory health insurance funds. Rather, research shows the range of companies providing drugs has increased since such procurement practices were introduced in 2007.

Citing an analysis of "more than 45 million ingredient-related profiles" of its members between 2006 and 2016, the AOK group of health insurance funds says the market share of the 10 largest producers by gross turnover in the off-patent market fell by five percentage points between 2006 and 2017 to 48%, while a similar decline took the top-20 players' share to 64%.

Applying the Herfindahl-Hirschmann monopoly index often employed by the European Commission, the AOK says this value has diminished from 478 to 298, suggesting a low level of market concentration.

AOK claims €4bn savings

Furthermore, the AOK argues, tenders not only saved funds €4 billion (US$5 billion) last year, they also "avoided unnecessary changes of medication". Its data shows the proportion of AOK insurees who did not have to switch their chronic treatment rose from 74% in 2006 to 85% last year.

The association of the German pharmaceutical industry, the BPI, said the research failed to recognise the dwindling number of suppliers for critical drugs such as antibiotics and vaccines that threatened to lead to shortages. Off-patent body Pro Generika criticised the AOK for not releasing its full data for scrutiny.

INTELLECTUAL PROPERTY

UK ratifies unified patent deal

The UK has ratified the agreement on a Unified Patent Court (UPC) that will handle cases related to the European single unitary patent. However, questions remain over the UK's final involvement in the framework, while it negotiates its 'Brexit' exit from the European Union (EU).

"Our ratification brings the international court one step closer to reality," the UK government said, acknowledging that for the court to come into effect, 13 EU member states must ratify the agreement. This must include France and the UK – which have ratified – and Germany, which is currently reviewing a legal challenge to ratification.

"Ratification of this important agreement demonstrates that internationally, as well as at home, the UK is committed to strong intellectual-property protections," the UK government said. However, it pointed out "the unique nature of the proposed court means that the UK's future relationship with the UPC will be subject to negotiation with European partners as we leave the EU".

Welcoming the ratification, the UK BioIndustry Association (BIA) said the framework would "provide the option for businesses to save time and money, which will be of particular benefit for small- to medium-sized enterprises (SMEs)". Emphasising that the central division of the court with responsibility for life sciences would be based in London, UK, the BIA said it was "now imperative that the government works swiftly with the other signatories to enable the UK to continue to contribute its expertise to the development of the system".

GOVERNMENT POLICIES

Sustainability key insists BGMA

Government and National Health Service (NHS) policies in the UK must ensure the local generics and biosimilars industries are sustainable, the British Generic Manufacturers Association (BGMA) has stated in reaction to a report by the King's Fund.

"The King's Fund report highlights that the optimal use of generic and biosimilar medicines results in more patients being treated for less money," the BGMA pointed out, adding that generic competition currently saved the NHS £13 billion (US$18 billion) per year. The report acknowledges how "encouraging the widespread use of cheaper generic drugs" has limited NHS England's annual drugs bill to £17.4 billion and highlights how "increasing the uptake of biosimilars" offers further opportunities to promote value for money.

"If the generics industry is to continue to make this huge contribution to the sustainability of the NHS," the BGMA argued, "the industry needs to be economically sustainable." The "lowest prices in Europe" were, the association said, made possible by a high level of generic penetration, "together with low barriers to entry and low levels of government intervention".

Faced with increased costs and uncertainties – due in part to the Falsified Medicines Directive, as well as to regulatory changes and exchange-rate fluctuations as a result of the 'Brexit' withdrawal from the European Union (EU) – the UK government and NHS should focus on "optimising the use of generics, which are frequently the gold standard for known and treatable conditions".

… Important Time-Sensitive Material – A Must Read ….

A New ANDA Holder Program Fee Approach Under GDUFA II

The new ANDA Holder Program Fee under GDUFA II is now in place! **A firm and its affiliates pay one program fee each fiscal year commensurate with the number of approved ANDAs** (both active and discontinued ANDAs) that the firm and its affiliates collectively own. The program fee is split into three tiers that represent the number of approved ANDAs held by the firms and their affiliates within the Orange Book.

The ANDA fee schedule for Fiscal Year 2018 was published by FDA on August 28th, 2017. The annual ANDA Holder Program Fee represents significant funds for some companies. And for those companies with a modest number of ANDAs, they'll be laying out cash for drug products that they don't currently market or are identified in the Discontinued Drug Product List section of the Orange Book. And YES, **discontinued ANDAs are still considered approved ANDAs for user fee purposes** unless the approval is withdrawn.

In addition, a one-time marketing status report was required to be submitted to the FDA by Wednesday, February 14, 2018, identifying the submission as "MARKETING STATUS REPORT / ONE-TIME UPDATE." While there is **no guidance as to what happens to the ANDAs identified as "not marketed"**, one scenario may be they will be either moved to **discontinued** status or have approval **withdrawn**.

FDA collects fees under the ANDA Holder Program initiative as of each October 1 as follows: small tier (1-5 ANDAs) companies pay $159,079; medium tier (6-19 ANDAs) companies pay $636,317; and large tier (greater than 20 ANDAs) companies pay $1,590,792. **For a small or medium-tier company this can be a dramatic impact in their ability to even retain the assets they worked so hard to obtain! And Fiscal Year 2019 fee rates, which will be published later this year, seem likely to rise**.

What is the **penalty** for not paying the program fee? There are three effects if an applicant fails to pay the program fee: (1) If the program fee is not paid within 20 calendar days after the due date, the parent company will be placed on a **publicly available arrears list**. (2) Any ANDA submitted by the applicant or its affiliates **will not be received**. (3) All drugs marketed pursuant to any abbreviated new drug application held by such applicant or an affiliate of such applicant shall be **deemed misbranded**.

For the second year a company called **ANDA Repository, LLC.** has successfully offered significant **user fee relief** and a solution for companies that have discontinued ANDAs, and for drug products not currently marketed. Imagine, a parking lot. The owner of a car that is not being used on a daily basis needs a parking space for that car. In exchange for that parking space (and an annual fee) the car's owner transfers title of the car to the parking lot owner. The former owner of the car can, with appropriate notice, take back ownership when he/she decides they want to use the car again. Since the parking lot owner has enough cars, this has proven to be a beneficial venture for all of the parties involved, and the cars are kept safe and secure.

In the example above, the car owner is an ANDA sponsor, and the parking lot owner is **ANDA Repository, LLC.** In exchange for its services, **ANDA Repository, LLC.** charges an ANDA sponsor an annual fee, which is significantly less than the ANDA Holder Program Fee such ANDA sponsor would otherwise pay as a small or medium size firm. **There is NO need to pay excessive fees, or to withdraw your valued assets due to short-term market conditions, capacity constraints, API supplier issues, etc.!**

Alternatively if your choice is to WITHDRAW the ANDA we may be interested in purchasing it from you!

The FY2019 GDUFA Generic Drug Applicant Program Fee is due October 1st so please contact us soon!

Phone: +1-570-261-1901 Email: info@andarepository.com

Oxybutynin prices see huge leap in April

UK trade prices for urinary and bladder treatment oxybutynin are in the spotlight this month, after steep rises – that have seen generics prices multiply three- and four-fold – prompted a swift but insufficient response from the country's Department of Health and Social Care (DHSC).

As well as a £1.11 (US$1.55) price concession for 56-count packs of oxybutynin 2.5mg tablets that has been granted by the DHSC for April (**Generics *bulletin***, 27 April 2018, page 11), the Department has also granted a further concession of £1.87 for the same pack size of the 5mg strength. However, WaveData indicates, these concessions fall far short of real average prices in the marketplace.

The £1.11 concession for the 2.5mg strength compares to an average price per 56-tablet pack that leapt by 398% to £5.12, according to a WaveData comparison of prices from 1-31 March 2018 and 1-26 April 2018. Meanwhile, the £1.87 concession for 5mg tablets compares with an average price that jumped by 327% to £6.80.

Without agreed DHSC concession prices as **Generics *bulletin*** went to press were 84-count packs of oxybutynin 5mg tablets – that saw their average price quadruple to £7.84 – and the same pack size of the 2.5mg strength, which experienced the steepest rise of all with an increase of 445% to £7.25. All comparisons were based on averages calculated from at least 30 data points.

Looking at longer-term data for 56-tablet packs of the 2.5mg strength, WaveData observed that the spike in April came after a long period of relative stability, with the average price having remained around the £1.00 mark for almost two years, and the lowest available offers in the market around a fifth below that (see Figure 1).

Examining average prices for all four presentations over the longer term, WaveData noted that the current surges marked a return to prices not seen since for almost eight years, when average UK generics prices hit a peak of more than £10.00 for 84-tablet packs of the 5mg strength in 2010 (see Figure 2).

In terms of the number of offers recorded by WaveData, all four presentations followed a similar pattern over the past two years. As Figure 3 shows, a peak in mid-2017 was followed by a decline over the next six months that led to the number of offers hitting a low at the very end of last year, before climbing gradually to the current position.

Finally, WaveData noted that the current pricing for 84 oxybutynin 5mg tablets had brought the price of the generic roughly in line with the last price recorded for Sanofi's equivalent Ditropan brand in late 2014 (see Figure 4).

According to the UK's National Institute for Health and Care Excellence (NICE), 2.5mg and 5mg oxybutynin tablets are available from a number of generics firms. These include AAH, Accord, Actavis, Alliance Healthcare, Almus, DE, Niche Generics, Phoenix, Sigma, Strides Shasun, Tillomed and Waymade.

Sanofi's Ditropan original has a National Health Service (NHS) indicative price of £1.60 for the 2.5mg strength in 84-tablet packs, while generic 2.5mg tablets in 56-count packs have a Drug Tariff price of £1.00. Meanwhile, for the 5mg strength – which is also available as an authorised generic from Sanofi's Zentiva under the Cystrin name – the Ditropan original has an NHS indicative price of £2.90 for 84 tablets. Other 5mg generics have a Drug Tariff price of £1.32.

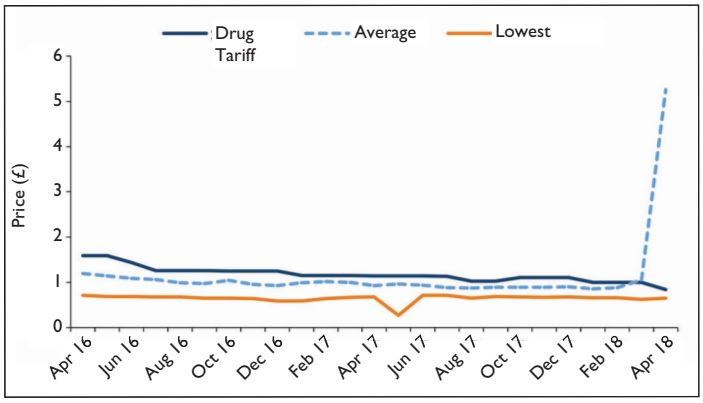

Figure 1: Average and lowest UK prices for 56 oxybutynin 2.5mg tablets between April 2016 and April 2018 (Source – WaveData)

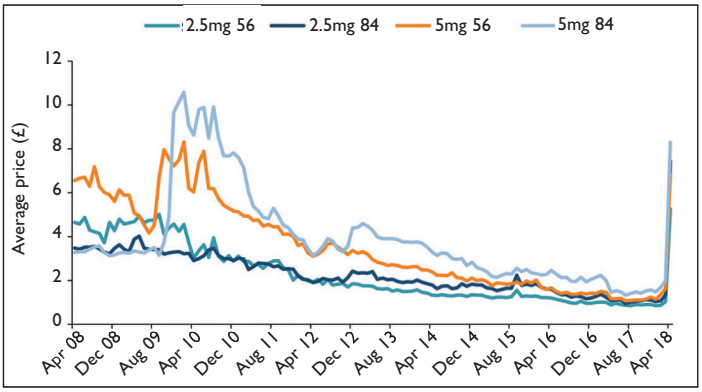

Figure 2: Average UK price trends for oxybutynin across four presentations between April 2008 and April 2018 (Source – WaveData)

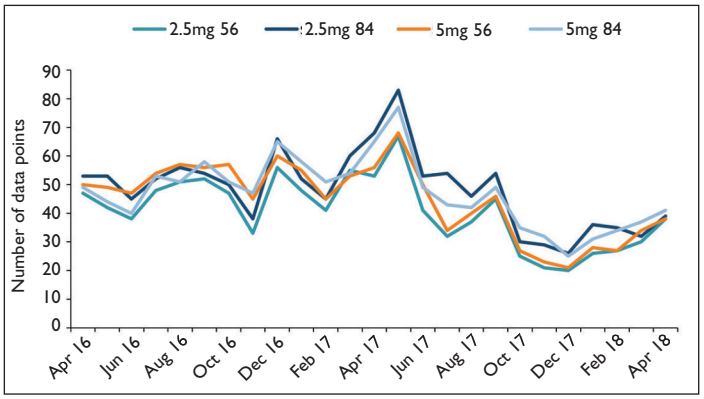

Figure 3: Number of offers observed for oxybutynin across four presentations between April 2016 and April 2018 (Source – WaveData)

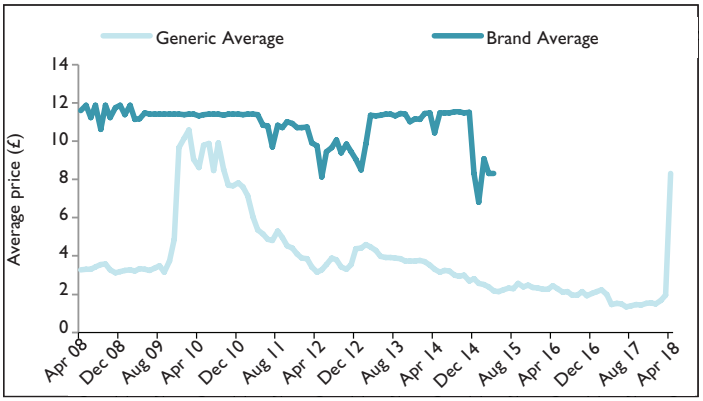

Figure 4: Average generic and brand prices for 84 oxybutynin 5mg tablets between April 2008 and April 2018 (Source – WaveData)

BIOLOGICAL DRUGS

Five biosimilars vying for a spot on the PBS

Australia's Pharmaceutical Benefit Advisory Committee (PBAC) is to consider requests for five biosimilar medicines to be subsidised on the country's Pharmaceutical Benefits Scheme (PBS) reimbursement list during its July 2018 meeting.

According to an agenda that has just been released by the committee ahead of the meeting – which will take place from 4 July to 6 July – the PBAC will consider requests for two Humira (adalimumab) biosimilars, as well as one request each for biosimilars to Lantus (insulin glargine), Neulasta (pegfilgrastim) and MabThera/Ristova (rituximab).

Amgen has requested an 'authority required' listing for the firm's Amgevita (adalimumab) 20mg/0.4ml and 40mg/0.8ml pre-filled syringes and 40mg/0.8ml pre-filled pens for all nine Humira indications currently listed on the PBS, following its approval by the Therapeutic Goods Administration (TGA) in November last year.

These are severe active rheumatoid arthritis; severe psoriatic arthritis; ankylosing spondylitis; severe chronic plaque psoriasis; severe active juvenile idiopathic arthritis; severe Crohn's disease; refractory fistulating Crohn's disease; moderate-to-severe ulcerative colitis; and moderate-to-severe hidradenitis suppurativa.

However, Merck Sharp & Dohme is seeking an 'authority required' listing for only the severe active rheumatoid arthritis indication for the Hadlima (adalimumab) 40mg/0.8ml pre-filled syringes and 40mg/0.8ml single-dose auto-injectors it licenses from Samsung Bioepis. Hadlima was registered on 24 January this year.

Meanwhile, Mylan, through the firm's local Alphapharm affiliate, has requested listings for the Semglee (insulin glargine) 100 units/ml 3ml and Fulphila (pegfilgrastim) 6mg/0.6ml pre-filled syringes, which were developed through the firm's global alliance with Biocon.

Alphapharm is requesting an 'unrestricted benefit' listing for Semglee to treat diabetes mellitus, and a streamlined 'authority required' listing under Australia's section 100 'highly specialised drug' program for Fulphila to treat chemotherapy-induced neutropenia.

Finally, Celltrion is requesting 'authority required' listings under the section 100 'efficient funding of chemotherapy' and 'highly specialised drug' programs for the Korean firm's Truxima (rituximab) 100mg/10ml and 500mg/50ml solution for intravenous infusion.

Truxima received approval from the TGA only last month, for a number of oncology and autoimmune indications, around the same time the PBAC recommended the listing of Sandoz' TGA-approved Riximyo rituximab biosimilar (**Generics *bulletin***, 27 April 2018, page 13).

Separately, the PBAC has advised that three revised considerations will be used to inform advice regarding 'a-flagging' of a biosimilar in the PBS, which allows for substitution of a biosimilar for the reference product at the pharmacy level, after acknowledging that biosimilar information "has evolved significantly over the last three years".

These revised considerations are that the TGA has determined that the product is a biosimilar as evidenced by Australian Register of Therapeutic Goods (ARTG) registration documentation; the availability of supportive data relating to the effects of switching; and "practical considerations" relating to substitution by the pharmacist at the point of dispensing.

Based on this, the PBAC has also advised that TGA-PBAC parallel processing – which enables registration and reimbursement evaluation and assessment processes for 'major submissions' to be undertaken in parallel – should not be made available for biosimilars that have not yet been approved by the TGA.

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ONCOLOGY DRUGS

Austrian appeal fails on pemetrexed patent

An Austrian appeals court has upheld a preliminary injunction previously granted by a Vienna commercial court to stop Fresenius Kabi from marketing and distributing its generic version of Eli Lilly's Alimta (pemetrexed disodium) oncology drug. Vienna's upper district court found that Kabi's version, which uses pemetrexed diacid as its active ingredient, infringed the Austrian part of Lilly's European patent EP 1,313,508 under a doctrine of equivalents.

The sole independent claim of the '508 patent – which expires on 15 June 2021 in Austria – is a Swiss-type claim covering the use of pemetrexed disodium in a combination therapy together with vitamin B12, or a pharmaceutical derivative thereof, for inhibiting tumour growth.

On appeal, Kabi – identified in the redacted ruling only by its Austrian address – argued that the commercial court had erred in last year granting an injunction against a Lilly security bond of €100,000 (US$119,865) because the '508 patent was clearly limited to pemetrexed disodium, and not to the diacid form which was contained in the generics that Kabi had been supplying to Austrian hospitals since December 2016. The German generics firm also questioned whether a skilled person, as of the '508 patent's priority date, would have regarded using the diacid form instead of the disodium salt to be equivalent.

Disodium and diacid belong to same group

But the Vienna upper district court found that the disodium and diacid forms belonged to the same group of chemical compounds and had the same effect in the human body. The first-instance commercial court had, it said, been justified in finding infringement under the doctrine of equivalents.

Having considered Kabi's sales figures for the period between December 2016 and June 2017, the appeals court described the generics firm request to increase the size of Lilly's security bond pending full proceedings from €100,000 to €850,000 as "reasonable".

OPHTHALMIC DRUGS

Formycon trials ranibizumab

Formycon says it and licensee Bioeq have achieved an "important milestone" for their FYB201 proposed biosimilar rival to Lucentis (ranibizumab) after reporting Phase III study results that show "comparable efficacy between FYB201 and Lucentis" in patients with neovascular age-related macular degeneration.

Noting that the data meant that the "primary endpoint of the global Phase III study [has been] achieved", Formycon added that the final patient in the 48-week trial was expected to complete treatment by the end of June.

"Data from the Phase III study will be part of the application for marketing approval with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)," the company confirmed, noting that the confidence interval for the study data "lies within the pre-defined equivalence limits" and had shown "no abnormalities" with regard to safety and immunogenicity.

As Bioeq – which holds exclusive global marketing rights for the biosimilar – "intensifies out-licensing discussions" with "interested parties", the licensee said it was aiming to launch the first biosimilar rival to Lucentis in the US in 2020, and in European Economic Area (EEA) countries in 2022.

ONCOLOGY DRUGS

Amgen beats lawsuit on Mvasi launch date

Amgen has successfully beaten off a US legal challenge from Genentech over launch plans for its Mvasi (bevacizumab-awwb) biosimilar rival to Avastin, after a Delaware district court denied Genentech a declaratory judgement over Amgen's 'notice of commercial marketing'.

Having in early 2017 entered into the 'patent dance' information-exchange process set out by the Biologics Price Competition and Innovation Act (BPCIA), Amgen and Genentech identified 27 patents over which "a claim of patent infringement could be reasonably asserted". Of these, Amgen challenged 19 as invalid, unenforceable or not infringed. It told Genentech that it did not intend to begin marketing Mvasi before 18 December 2018, after the remaining eight patents expired.

However, after Mvasi received US Food and Drug Administration (FDA) approval (**Generics *bulletin***, 22 September 2017, page 11) Amgen told Genentech in a letter dated 6 October 2017 that it would "begin commercial marketing of Mvasi... no earlier than 180 days from the date of this letter", or 4 April 2018. Genentech therefore sought a declaratory judgement to "enforce Amgen's earlier representation that it would not launch Mvasi until the later December date".

Amgen insisted that there was "no cognizable legal theory that would grant Genentech the relief it seeks from the commercial marketing claim". But Genentech said its claim was "based on a private-right action arising under the BPCIA itself".

Describing Genentech's argument as "a novel legal theory not yet addressed by any court", the district court said there was "no need to delve into this uncharted territory at this time". "It is unclear whether Amgen will actually launch Mvasi before 18 December 2018," the court pointed out. "Genentech points to no evidence of an actual controversy other than the notice of commercial marketing." Moreover, the court added, "the parties are currently engaged in discovery and appear interested in co-operating".

"The court is left with the impression that the commercial marketing claim is not of 'sufficient immediacy' to warrant the issuance of a novel declaratory judgement," the district court concluded. However, it noted, "if this claim ripens into an actual controversy, where Amgen launches Mvasi before 18 December 2018, there will be an opportunity for Genentech to seek a temporary restraining order or a preliminary injunction at that time".

ANTICOAGULANTS

Rovi reports enoxaparin sales

Laboratorios Farmacéuticos Rovi has reported that sales of its biosimilar rival to Sanofi's Lovenox (enoxaparin) amounted to €4.1 million (US$4.95 million) in the first quarter of 2018. Reiterating its previous full-year sales estimates of €20-€30 million for enoxaparin, the Spanish firm noted that enoxaparin "represents an excellent growth opportunity for us" as it is rolled out in other markets.

Last month, Rovi signed a licensing agreement with Hikma to exclusively distribute and market the deep vein thrombosis and pulmonary embolism treatment across 17 Middle East and North Africa (MENA) markets (**Generics *bulletin***, 27 April 2018, page 10). In March, Rovi began marketing enoxaparin in the UK, having launched the drug in Germany in September 2017.

ONCOLOGY DRUGS/ANALGESICS

EU passes carmustine and sufentanil filings

Obvius Investment has secured a positive opinion from the committee for human medicinal products (CHMP) within the European Medicines Agency (EMA) that recommends granting a pan-European marketing authorisation for the firm's generic version of Bristol-Myers Squibb's Carmubris (carmustine).

Carmustine Obvius – which is used to treat brain tumours, non-Hodgkin's lymphoma and Hodgkin's disease – will be available as 100mg powder and solvent for solution for infusion. Observing that the drug was "administered intravenously and is 100% bioavailable", the CHMP noted that a bioequivalence study against reference product Carmubris was not required.

Meanwhile, the committee also recommended authorising FGK Representative Service's hybrid medicine Dzuveo (sufentanil) 30µg sublingual tablets, which are used to treat pain. The CHMP noted that Dzuveo contained the same active substance as the reference drug, Janssen's Sufenta injectable, "but is given in a different way".

The European Commission typically decides within 67 days whether to convert the committee's positive opinions into pan-European centralised marketing approvals.

Including new medicines, orphan drugs, biosimilars and generic, hybrid and informed-consent applications, the CHMP has to date in 2018 offered 21 positive opinions on new medicines, of which three came in April.

IN BRIEF

STRIDES SHASUN AND ZYDUS CADILA have each obtained US approvals for **cinacalcet hydrochloride** 30mg, 60mg and 90mg tablets equivalent to Amgen's **Sensipar**. Strides is making the tablets at its oral-dose facility in Puducherry, India, using an active pharmaceutical ingredient (API) supplied by Solara Active Pharma Sciences, while Zydus – which has also secured US approval for methylprednisolone 4mg, 8mg, 16mg and 32mg tablets – is manufacturing its Sensipar rival at a plant in Ahmedabad, India.

MHLW – Japan's Ministry of Health, Labour and Welfare – has granted a two-year market exclusivity extension for Lundbeck's **Lexapro** (**escitalopram oxalate**) that runs until 21 April 2021.

BEXIMCO PHARMACEUTICALS has introduced its third product in the US by starting exports of generic **Robaxin** (**methocarbamol**) 500mg and 700mg tablets. The muscle relaxant follows the Bangladeshi firm's earlier US launches of **carvedilol** and **sotalol**. The group's manufacturing site in Bangladesh was approved by the US Food and Drug Administration (FDA) in June 2015.

SEVERAL GERMAN GENERICS FIRMS – including affiliates of Aurobindo, Krka, Intas, Sandoz, Stada and Teva – have seized upon the local expiry of a supplementary protection certificate (SPC) protecting Merck Sharp & Dohme's (MSD's) **Ezetrol/Zetia** (**ezetimibe**) brand to introduce ezetimibe 10mg tablets (**Generics *bulletin***, 23 March 2018, page 10). Other entrants include the local operations of Dr Reddy's, Glenmark, Mylan, Sanofi and Torrent.

ARGENTUM says it has reached a settlement with Cosmo over its *inter partes* review petition challenging US patent 9,320,716 listed against the originator's **Uceris** (**budesonide**) treatment for ulcerative colitis. The '716 patent is currently the subject of US patent litigation involving Lupin and Sun Pharma, as well as Mylan.

CLARIFICATION. In the 20 April 2018 edition of **Generics *bulletin***, we reported on a European marketing authorisation for Medac's **Metoject** (**methotrexate**) 15mg pre-filled pen (**Generics *bulletin***, 20 April 2018, page 14). Medac has asked us to point out that the authorisation covers 10 strengths, ranging from 7.5mg to 30mg.

MYLAN has extended its range of oral contraceptives in the US with an alternative to Bayer's **Yaz** (**drospirenone/ethinylestradiol**) 3mg/0.02mg tablets. The company now offers "more than 20 generic birth-control medicines in multiple dosage forms".

BIOSIM – the US company "building a portfolio around hard-to-copy generic drugs and biologics" – has selected CPC Scientific to supply the bulk peptide for its '**ACTH**' prospective rival to Mallinckrodt's **H.P Acthar** (**corticotropin**) gel. "CPC Scientific's advanced purification plant enables it to meet all anticipated needs of BioSim in a more timely manner, and BioSim will no longer require its previous synthetic supplier for this portion of the ACTH gel manufacturing supply chain," explained the Seattle-based firm, which expects to capture over half of the Acthar market.

TEVA does not need judicial leave to change its statement of opposition to the Irish part of Boehringer Ingelheim's European patent EP1,379,220 covering **inhalation capsules**, High Court of Ireland Justice Max Barrett has decided. Noting that Boehringer had applied to amend the claims of the '220 patent, but the court had been asked in the first instance to address Teva's revocation action on the basis of the unamended claims, Barrett said the Israeli firm had sought a court order "in an abundance of caution".

ONCOLOGY DRUGS

Alvogen is first with Revlimid rival in EU

Alvogen is claiming the first approvals in "several European countries" for its generic version of Celgene's Revlimid (lenalidomide) capsules, after its Lotus Pharmaceuticals affiliate "successfully concluded multiple registration procedures" for the oncology drug. Lotus' lenalidomide has been approved in European markets in seven strengths: 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg capsules.

Noting that Iceland acted as the reference member state (RMS) in the decentralised marketing-authorisation procedure, Lotus said its European application for lenalidomide had been approved around a year after the filing was accepted. Observing that the drug achieved annual European sales of around US$1.81 billion, Lotus added that it had "already obtained approvals in Taiwan for some strengths".

The drug – which was "fully developed in-house" – was a "key asset for the group", Lotus chairman Andrew Lin insisted, stating that lenalidomide formed "a critical part of [the firm's] comprehensive portfolio of solid-oral dosage oncology drugs". "Launch of the product in Europe will occur once relevant and valid patents expire," the Taiwanese firm added.

Lin noted that the company was "carefully manoeuvring through" a lawsuit in the US, which was triggered by Lotus' abbreviated new drug application (ANDA) filing for lenalidomide. In September last year, Alvogen was sued by Celgene in a New Jersey district court after Lotus filed a paragraph IV challenge to patents protecting the originator's Revlimid (**Generics *bulletin***, 12 September 2017, page 12). The suit – which triggered a 30-month stay on final approval for Alvogen's generic – alleges infringement of 16 US patents that protect the drug through to April 2027.

TOPICAL DRUGS

FDA issues transdermal report

Further research on transdermal delivery system (TDS) products is needed so "additional tools and techniques" can be developed, the US Food and Drug Administration (FDA) contends in a science and research report recently published by the agency.

This may include "new methods to control advanced manufacturing processes for TDS products and transdermal gels, studies to better understand how different transdermal gel packaging and TDS designs and/or formulations may need to be controlled, and techniques to ensure the stable performance of a transdermal product throughout its shelf life".

The FDA said the goal of such research was to "develop generally applicable bioequivalence approaches and supplementary regulatory standards for all types of transdermal products". These may involve "rational combinations of *in vitro*, *in silico*, and/or *in vivo* evidence that collectively support an efficient and compelling demonstration of bioequivalence, as well as of all the supplemental quality and performance requirements for a generic transdermal product".

"The methods and tools that result from this ongoing research would become valuable resources for the pharmaceutical and regulatory community to efficiently advance transdermal drug development, provide increased certainty in regulatory decision making, and ultimately, enhance patient access to high-quality generic transdermal products," the FDA insists.

PIPELINE WATCH

Enfuvirtide shows Greece plays differently

In Greece, a supplementary protection certificate (SPC) covering Roche's Fuzeon (enfuvirtide) HIV-fusion inhibitor expires in early May this year. The injectable HIV treatment already lost SPC protection in much of Western Europe – specifically in Austria, Belgium, Denmark, France, Ireland, Italy and Luxemburg, as well as in the Netherlands, Portugal, Spain, Sweden, Switzerland and the UK – last month, according to an analysis conducted by IQVIA using its Ark Patent Intelligence Expiry Database (**Generics *bulletin***, 23 March 2018, page 10).

While the SPCs granted for enfuvirtide throughout the European Union (EU) are based on the same European patent – EP0,774,971 entitled 'Synthetic peptide inhibitors of HIV transmission', which expired in 2014 – IQVIA notes that the expiry dates for those SPCs vary slightly depending on national interpretation of the EU's SPC Regulation EC469/2009.

Some EU countries such as Sweden and the UK – as well as non-EU member Switzerland under its national SPC rules – apply a typical SPC term of five years minus one day, or 15 years from the market authorisation date minus a day, IQVIA explains. This means that the UK SPC/GB05/026 for enfuvirtide expired on 29 April 2018, 15 years minus a day after the first marketing authorisation in Switzerland on 30 April 2003.

SPC expiries in May	
INN	**Country**
Enfuvirtide	Greece

Figure 1: Molecules for which supplementary protection certificates (SPCs) expire in certain markets in May 2018 (Source – Ark Patent Intelligence)

Data exclusivity expiries in May	
INN	**Country**
Alglucosidase alfa	Switzerland
Catumaxomab*	Canada
Dabrafenib	US
Denosumab**	European Union
Etravirine	Switzerland
Fluocinolone acetonide	Turkey
Fluticasone furoate/Umeclidinium bromide/Vilanterol	US
Fluticasone furoate/Vilanterol	US
Micafungin	Australia
Pertuzumab	Australia
Pixantrone	Turkey
Remestemcel-L*	Canada
Trametinib	US
Umeclidinium bromide/Vilanterol	US
Vedolizumab***	US
Vismodegib	Australia

* 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.
** This will be followed by three years of market exclusivity, where a generic will not be placed on the market
*** This will be followed by eight years of biosimilar application approval exclusivity, during which a biosimilar will not be approved

Figure 2: Molecules for which data exclusivity expires in certain markets during May 2018 (Source – Ark Patent Intelligence)

Other EU member states interpret the SPC Regulation as convey protection for an extra day, such that Fuzeon enjoyed a monopoly in several countries up to 30 April this year. "Greece has a SPC term of normal extension of five years plus one day, or 15 years from the market authorisation date plus one day," IQVIA points out. Thus, the local SPC protection for enfuvirtide stretched up to 1 May (see Figure 1).

In the US, the Orange Book maintained by the US Food and Drug Administration (FDA) does not list any unexpired patents or data-exclusivity periods against Fuzeon. Nevertheless, the agency says it has not approved any generic alternatives to Roche's HIV brand.

End of exclusivity in Switzerland

Looking at data exclusivity (see Figure 2), IQVIA's Ark Patent Intelligence Expiry Database shows during May the end of protection periods in Switzerland for both Sanofi Genzyme's Myozyme (alglucosidase alfa) and Janssen's Intelence (etravirine).

Due to Switzerland lying outside of the EU, and having an independent medicines and therapeutic products regulatory agency in the form of Swissmedic, intellectual-property protection periods in the country can differ to those in much of the rest of Europe, IQVIA observes. This, it says, is because a separate marketing authorisation application (MAA) has to be filed in Switzerland, and the date of that Swiss filing is used to calculate the duration of any local term of data exclusivity.

In the case of alglucosidase alfa, Sanofi-Genzyme already surrendered EU data exclusivity for its Myozyme infusion-based treatment for Pompe disease in March 2016 (**Generics *bulletin***, 25 March 2016, page 8). Conversely, EU data exclusivity for Janssen's Intelence oral HIV treatment does not expire until September this year, several months after the comparable Swiss protection period ends.

Sanofi reported European sales of Myozyme – which forms part of the French group's Rare Disease franchise – ahead by 14.6% on a constant-currency basis to €93 million (US$112 million) in the first quarter of this year. This contributed to global sales of the brand that grew by 4.3% as reported, but by 11.0% at constant-exchange rates, to €170 million, "supported by naive-patient accruals".

In the EU, May also brings the end of an eight-year data exclusivity period for Amgen's Prolia/Xgeva (denosumab) that will be followed by a two-year period of market exclusivity during which no biosimilar of the bone-cancer and osteoporosis treatment can be placed onto EU markets. In July 2011, Amgen announced that it had secured an additional one year of data and market exclusivity for Xgeva on the basis of having secured approval for another indication offering a significant clinical benefit – preventing skeletal-related events in adults with bone metastases from solid tumours.

While Amgen says a European Prolia/Xgeva patent covering the medical use of RANKL antibodies has just expired, the originator says the brand benefits from two RANKL antibody patents – one including epitope binding, and the other sequences – that expire in February 2021 and June 2022 respectively. Furthermore, the US biotech giant claims it has secured SPCs covering denosumab until 2025 in EU member states including France, Italy, Spain and the UK.

VALUE ADDED MEDICINES IN BRIEF

OREXIGEN THERAPEUTICS has entered into an agreement to **sell "substantially all" of its assets** to Nalpropion Pharmaceuticals, a newly-formed entity created by investors including Pernix Therapeutics. The proposed deal includes obesity specialist Orexigen selling global rights to its **Contrave** and **Mysimba** (**naltrexone/bupropion**) extended-release and prolonged-release formulations, along with certain other assets, for US$75 million in cash. However, the transaction is "subject to higher and better offers" up to 21 June.

ELI LILLY said US sales of its **Basaglar** (**insulin glargine**) rival to Sanofi's **Lantus** diabetes drug, approved through the hybrid 505(b)(2) regulatory pathway, were almost six-times higher in the first quarter of 2018 at US$127 million. The US firm – which collaborated on Basalgar with Boehringer Ingelheim – attributed an increase of US$12.3 million over US sales of US$114 million in the fourth quarter of 2017 to "increased demand due to Medicare Part D formulary access, partially offset by lower realised prices due to changes in estimates of rebates and discounts". As of March this year, Lilly said Basaglar had captured 14% of total, and 27% of new-to-brand, prescriptions for basal insulin in the US. Lilly's International Basaglar sales totalling US$39.3 million in the first quarter of 2018 comprised US$26.5 million in Europe and US$6.8 million in Japan. Global sales climbed by 261% to US$166 million.

ORAMED says it has "begun screening patients in its 90-day, dose-ranging pivotal Phase IIb HbA1c clinical study of its oral **insulin** capsule, **ORMD-0801**". The US-based company claims that, in a previous Phase II study, "a statistically significant improvement in HbA1c glycated haemoglobin – a long-term gauge of blood-glucose control – was observed in just 28 days of treatment". The 90-day dosing study in around 240 patients with type-2 diabetes in the US is, it explains, "a prerequisite to Phase III confirmatory studies under the US Food and Drug Administration's (FDA's) biologic license application (BLA)".

DOUGLAS PHARMACEUTICALS has linked up with the University of Western Australia to develop **immunotherapy treatments** for cancer. The New Zealand-based company will work with academic teams to develop drug combinations that may have "far greater activity than the use of a single drug on its own", with the aim of "progressing into a clinical trial in 2019".

BORMIOLI PHARMA claims its **AccuRec** dual-chamber packaging system for oral drugs "solves two industry challenges", making it "ideal for drug-stability challenges and value-added medicines". "Pre-dosed solvent and drug powder are stored in separate chambers in a tamper-evident and child-proof package; a simple twist releases the powder into the solvent at the time of dosing," the US-based packaging specialist explained.

UCB has expanded its epilepsy pipeline by acquiring a **midazolam** nasal spray candidate from Proximagen. The USL261 nasally-administered midazolam, which is intended as a rescue treatment for acute repetitive seizures (ARS), has already "demonstrated strong results" in a Phase III clinical development program and been granted orphan drug designation with fast-track status by the US Food and Drug Administration (FDA). UCB intends to file a new drug application (NDA) later this year.

ACELRX PHARMACEUTICALS has published a pharmacokinetic study on **sufentanil** 15µg and 30µg sublingual tablets that the firm says provides evidence that the formulation provides "the opportunity to non-invasively and rapidly treat moderate-to-severe pain".

AUTOIMMUNE DISEASES TREATMENTS

German expiries aid access to biologicals

The anticipated arrival of biosimilar alternatives to AbbVie's Humira (adalimumab) in Germany later this year is likely to broaden access to the biological treatment for autoimmune diseases, according to an analysis of patient data for two competing tumour necrosis factor alpha (TNF-α) inhibitors, etanercept and infliximab.

Based on anonymised medication records for 47 million patients, market researcher Insight Health observed that between the period of Biogen's Benepali (etanercept) offering competition to Pfizer's Enbrel original in February 2016 and January this year, the total number of German patients receiving the rheumatoid arthritis and psoriasis treatment increased by a fifth from 10,000 each month to over 12,000.

In January 2018, the market researcher said, Enbrel had clung onto just over half of the market with 6,725 patients, compared to 5,260 for Benepali. Sandoz' Erelzi biosimilar, which entered the German etanercept market midway through 2017, attracted 797 patients in January, equivalent to a market share of a little over 6%. "Thus, after 22 months, biosimilars account for almost half the etanercept market," Insight Health commented.

Looking at how the etanercept biosimilars had captured market share, Insight Health noted that Benepali had already by October 2016 surpassed Enbrel in attracting 563 patients who were naive to treatment, compared to 527 for the original. "In the following months," it said, "an increasing number of patients received Benepali first, taking this value by the end of 2017 to around 900 new patients per month." By contrast, the number of new patients taking Enbrel sank from 843 in March 2016, immediately after biosimilar entry, to just 222 in January 2018.

"As the number of switches from Enbrel to Benepali each month only reached around a quarter of the number of new starts, naive patients are the main driver of biosimilar uptake," Insight Health concluded. By contrast, switches played a more significant role for Erelzi, with 161 patients in January moving over from other etanercept products, along with 254 naive patients starting on Sandoz' biosimilar.

Turning to infliximab, the market researcher observed that usage volumes had climbed by around 80% over three years, from 5,550 per month to almost 10,000. For the first two years after biosimilar market entry in February 2015, Merck Sharp & Dohme's (MSD's) Remicade reference brand held steady, but from the third quarter of 2017 it dropped from around 5,000 patients per month to 4,000.

At around the same time, Pfizer's Inflectra (infliximab) biosimilar "passed the milestone of 2,000 initiated patients", rising to around 3,300 by January 2018. Mundipharma's competing Remsima biosimilar had by January this year narrowly overtaken Remicade in terms of naive patient starts, while Biogen's Flixabi was gradually picking up new starts and switches.

Of 839 naive German patients started on infliximab in January 2018, Insight Health pointed out, 313 were given Inflectra, 230 Remsima, 210 Remicade and 86 Flixabi.

"Doctors appear increasingly to be taking account of recommendations by funds to choose less expensive biosimilars, especially for first-time prescriptions," the market research observed.

Given that Humira was the most costly drug for Germany's statutory health insurance system, with annual retail sales of €1.04 billion (US$1.25 billion) and prescriptions up by 11% between 2015 and 2017, Insight Health predicted "a market expansion once biosimilars are available".

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LITIGATION

Teva US settles with Apotex on collusion

Teva and Apotex have settled litigation in the US over allegations Teva's former senior director of regulatory affairs for US generics, **Barinder Sandhu**, misappropriated trade secrets and shared them with Apotex' erstwhile chief executive officer **Jeremy Desai** while the pair were in "a romantic relationship".

According to Teva's initial complaint, filed last July, the Israeli firm learned in 2016 "through a former Apotex employee" that Sandhu had provided Desai with a copy of a US Food and Drug Administration (FDA) complete response letter, relating to an in-development Teva product, at the time Sandhu "resided and/or cohabited" with Desai in Pennsylvania (**Generics *bulletin***, 14 July 2017, page 16). Sandhu was also said to have e-mailed confidential documents to Desai, shared files through a cloud-based drive, and copied data containing trade secrets to USB flash drives.

"Apotex and Desai used and continue to use Teva USA's trade secrets and other confidential information to benefit Apotex' own competitive product development," Teva's filing claimed, "thereby allowing Desai and Apotex to improperly profit at Teva's expense." Sandhu's employment with Teva was terminated in October 2016.

In late January, certain claims in the case were dismissed, while others proceeded (**Generics *bulletin***, 9 February 2018, page 16). Shortly beforehand, Desai had resigned from Apotex "to pursue other opportunities" (**Generics *bulletin***, 2 February 2018, page 1).

APPOINTMENTS

Barcelos leaves Teva for Sandoz Belgium

Senior director of Teva Generics in the UK, **Bruno Ultra Barcelos**, has been appointed as head of Sandoz Belgium.

Having joined the Israeli firm in 2004 as general manager of Teva's operation in Portugal – following previous stints with Schering-Plough and Pharmis Biopharmaceuticals – Barcelos held a variety of senior roles in Europe over the next 14 years, including in Zagreb, Croatia, Amsterdam, the Netherlands, and Paris, France.

Before his most recent role with Teva, which Barcelos took on in July 2016 he managed Teva's retail pharmacy business in Paris.

Barcelos' move from Teva to Sandoz comes as the Israeli firm announced its board of directors was proposing to slim down from 13 to 11 members, ahead of Teva's annual meeting on 5 June.

Teva revealed **Galia Maor**, **Gabrielle Sulzberger** and **Dan Suesskind** have decided not to seek re-election to the board, while Teva's board has recommended that shareholders vote for the appointment of **Ronit Satchi-Fainaro** on a three-year term. Current board members **Rosemary Crane** and **Gerald Lieberman** have also been backed for re-election until 2021.

Along with chairman **Sol Barer**, president and chief executive officer **Kåre Schultz** and Satchi-Fainaro, Crane and Lieberman, Teva's 11-strong board is set to comprise **Amir Elstein**, **Murray Goldberg**, **Jean-Michel Halfon**, **Roberto Mignone**, **Perry Nisen** and **Chemi Peres**.