USTR’s Special 301 Report Goes After India And China On IP

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India and China are once again featured prominently on the US Trade Representative’s priority watch list, alongside nine other countries, in the latest version of the USTR’s annual ‘Special 301’ report on worldwide intellectual-property rights and enforcement.

A total of 36 countries were identified across the USTR’s priority watch list and watch list in 2019, highlighting “trading partners that do not adequately or effectively protect and enforce IP rights or otherwise deny market access to US innovators and creators that rely on protection of their IP rights”.

India and China have regularly featured on the priority watch list in the past. (Also see “US slams India and China again” - Generics Bulletin, 4 May, 2018.) The 2019 priority watch list of 11 countries also includes Algeria, Argentina, Chile, Indonesia, Kuwait, Russia, Saudi Arabia, Ukraine and Venezuela.

This year, the USTR has indicated that it intends to take further action against countries that have consistently appeared on the priority watch list. “Over the coming weeks, USTR will review the developments against the benchmarks established in the Special 301 action plans for countries that have been on the priority watch list for multiple years,” the USTR said.

“For such countries that fail to address US concerns, USTR will take appropriate actions, such as enforcement actions under Section 301 of the Trade Act or pursuant to World Trade Organization or other trade agreement dispute settlement procedures, necessary to combat unfair trade practices and to ensure that trading partners follow through with their international commitments.”

On pharmaceuticals specifically, the USTR says it is “engaging with trading partners to ensure that US owners of IP have a full and fair opportunity to use and profit from their IP, including by promoting transparent and fair pricing and reimbursement systems.”

The USTR says it wants to promote “robust IP systems”, as well as reducing market-access barriers to pharmaceutical products and medical devices, “including measures that discriminate against US companies, are not adequately transparent, or do not offer sufficient opportunity for meaningful stakeholder engagement.”

It also wants its global trading partners to “appropriately recognize the value of innovative medicines and medical devices so that trading partners contribute their fair share to research and development of new treatments and cures.”

CHINA SUFFERS FROM ‘A RANGE OF ISSUES’

As part of this global engagement, the USTR says it has “pressed China on a range of issues affecting the pharmaceutical sector, including on the need to implement an effective mechanism for the early resolution of potential patent disputes; provide effective protection against unfair commercial use, as well as unauthorized disclosure, of test or other data generated to obtain marketing approval for pharmaceutical products; and provide a reliable and effective means of extending the patent term to compen...
Given the importance of India and increasingly China to the global generics industry, it is always interesting to see how the pharmaceutical industries of these countries interact with others on the global stage. This week saw the US yet again launch an attack on the intellectual-property regimes of both India and China – along with several other countries – as part of the US-TR’s annual ‘Special 301’ report (see front cover).

While the report is often perceived by generics manufacturers as a tool used by the brand industry to advance its own agenda, it nevertheless continues to highlight a number of areas in which mature markets and emerging markets are somewhat out-of-step on intellectual property – and prompted an immediate response from India’s government and pharmaceutical companies complaining that the USTR’s report is an attack on the generics industry (p.18).

Also this week we have seen Sandoz report slowing growth for its biopharmaceuticals segment (p.5), while Pfizer has revealed plans for launch dates of several of its biosimilars (p.9). And Australia has launched an awareness campaign that it hopes will bolster confidence in and knowledge of biosimilars, as part of a multi-year initiative (p.11).

On small-molecule generics, there have been plenty of updates in litigation around the world, including a further Indian lawsuit over Centrient’s amoxicillin (p.14), and an adverse decision for generics firms on Alimta in the US (p.19). And on the deals front, Ipca is expanding with the acquisition of API specialist Ramdev Chemical (p.7).
Sandoz, Teva and Stada Dominate German Generics And Biosimilars Market

Through various labels, Sandoz, Teva and Stada were clear leaders in the 2018 German pharmacy market for generics and biosimilars, according to IQVIA data.


Zentiva Sale Wipes More Than A Third Off Sanofi Generics

Divesting its Zentiva branded generics business in Europe in October last year reduced Sanofi’s first-quarter 2019 Generics sales by more than a third to €282m; but on a ‘constant structure’ basis, adjusted for the divestment, Generics sales grew by 3.6% to account for just over 3% of Sanofi’s group turnover.

https://bit.ly/2V7hE5l

Manufacturing Round-Up: Sterling Gains A US Site As Normon Invests €100m

Sterling Pharma Solutions has acquired a US facility and Olon has bought a plant from Sandoz, while Normon is investing €100m in manufacturing expansions.


Global Generics & Biosimilars Awards

https://pharmaintelligence.informa.com/ggba
against unfair commercial use, as well as compulsory licensing, and protection IP reforms on long-standing issues, engaged with India to secure meaningful Meanwhile, the USTR says it has “enimbursement processes, “ the USTR says. supplemen suppliers in government pricing and requately engage with pharmaceutical latively, and inad China “also continues to impose unfair and discriminatory conditions on the effective protection against unfair commercial use, as well as unauthorized disclosure, of test or other data generated to obtain marketing approval for pharmaceutical products;” the USTR says. “China provides such protection only if the drug in question has not previously received marketing authorization outside China, which is an unfair and discriminatory condition that is unrelated to the purpose of such protection.” “Despite issuing for comment draft opinions and amendments to measures, China also has failed to establish an effective mechanism for the early resolution of potential pharmaceutical patent disputes;” the USTR highlights. “China additionally has failed to provide patent-term extensions to compensate for unreasonable delays that occur in granting a patent – a concern not limited to pharmaceutical patents – or in relation to marketing approvals.” The country “should also address delays, a lack of transparency, and inadequate engagement with pharmaceutical suppliers in government pricing and reimbursement processes;” the USTR says.

INDIA NEEDS ‘MEANINGFUL REFORMS’ Meanwhile, the USTR says it has “engaged with India to secure meaningful IP reforms on long-standing issues, including patentability criteria and criteria for compulsory licensing, and protection against unfair commercial use, as well as unauthorized disclosure, of test or other data generated to obtain marketing approval for pharmaceutical products.” In particular, the USTR points out, “Section 3(d) of the India Patents Act restricts patent-eligible subject matter in a way that fails to properly incentivize innovation that would lead to the development of improvements with benefits for Indian patients.” Moreover, “India still lacks an effective system for notifying interested parties of marketing approvals for follow-on pharmaceuticals in a manner that would allow for the early resolution of potential patent disputes.”

COMPULSORY LICENSES IN THE SPOTLIGHT Specific problems identified by the USTR across multiple territories include “actions by trading partners to unfairly issue, threaten to issue, or encourage others to issue compulsory licenses,” which it says “raise serious concerns” by undermining IP and reducing research incentives. “To maintain the integrity and predictability of IP systems, governments should use compulsory licenses only in extremely limited circumstances and after making every effort to obtain authorization from the patent owner on reasonable commercial terms and conditions;” the USTR insists. “Such licenses should not be used as a tool to implement industrial policy, including providing advantages to domestic companies, or as undue leverage in pricing negotiations between governments and right holders. It is also critical that foreign governments ensure transparency and due process in any actions related to compulsory licenses.” “The US will continue to monitor developments and to engage, as appropriate, with trading partners, including Chile, Colombia, El Salvador, India, Indonesia, Malaysia, Russia, Turkey, and Ukraine.” India’s government and the leading domestic drug manufacturers’ association have deployed the US Trade Representative office’s decision to place the country yet again on its “priority watch list” of nations that fail in Washington’s view to adequately protect intellectual-property rights, calling the move an attack on affordable generic medicines. Other “discriminatory, non-transparent, or otherwise trade-restrictive” measures criticized by the USTR include “unreasonable regulatory approval delays and non-transparent reimbursement policies”, as well as pricing and reimbursement systems that are “not market-based, or do not otherwise appropriately recognize the value of innovative medicines.” Outside of China and India, specific pharmaceutical issues highlighted by the USTR include Algeria banning “a significant number of imported pharmaceutical products and medical devices that compete with products manufactured domestically”, which the USTR describes as “a matter of paramount concern and the primary reason why Algeria remains on the priority watch list.” Meanwhile, it has urged Japan to implement “predictable and stable pricing and reimbursement policies that reward innovation and provide incentives for companies to invest in the research and development of advanced medical devices and innovative pharmaceuticals,” claiming that reforms to Japan’s reimbursement system since 2017 – including a pricing mechanism that the USTR says favors local companies – “represent a retreat from previous progress made in this area.” The USTR also attacks Turkey for lacking “efficiency, transparency, and fairness in its pharmaceutical manufacturing inspection process.” Additionally, “localization requirements for innovative pharmaceutical products and ongoing
reimbursement issues continue to act as market access barriers,” it claims. Similar concerns recently led the European Commission to bring a dispute with Turkey before the World Trade Organization.

**CANADA MOVED BACK TO REGULAR WATCH LIST**

In its 2019 report, the USTR has moved Canada back from the priority watch list to the regular watch list, having previously ‘downgraded’ the country to the priority watch list last year.

“The most significant step forward taken by Canada is its agreement to important IP provisions in the US-Mexico-Canada Agreement (USMCA),” the USTR observes. These include “provisions to ensure that national-level government processes for the listing and reimbursement of pharmaceutical products and medical devices are transparent, provide procedural fairness, are non-discriminatory, and provide full market access for US products.”

Nevertheless, the USTR still has some complaints with Canada, citing “serious concerns about the fairness of Canada’s Patented Medicines (Notice of Compliance) proceedings as amended in September 2017.”

“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,” the USTR adds.

It also cites “significant concern” over proposed changes that would ‘dramatically reshape the Patented Medicine Prices Review Board evaluates patented pharmaceuticals and sets their ceiling prices. If implemented, the changes would significantly undermine the marketplace for innovative pharmaceutical products, delay or prevent the introduction of new medicines in Canada, and reduce investments in Canada’s life sciences sector,” the USTR says.

“The US urges Canada to appropriately recognize the value of innovative medicines in both the private and public markets, to ensure its decisions are made transparently, and to contribute fairly to research and development for innovative treatments and cures.”

**Slowing Biopharmaceuticals Puts A Dent In Sandoz’ Sales**

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A relatively weak performance from its Biopharmaceuticals unit led Sandoz to report first-quarter turnover down by 8% to $2.33bn, although the drop in constant currencies was a less severe 2%. Nine percentage points of price erosion, mainly in the US, outweighed seven points of volume gains.

The Novartis division – which will see Richard Saynor take over from interim head Francesco Balestrieri in the third quarter of this year – achieved global Biopharmaceuticals sales from biosimilars, its Glatopa (glatiramer acetate) generic of Teva’s Copaxone and contract-manufacturing activities ahead by 5% as reported, and by 11% on a constant-currency basis, to $351m.

However, this marked a notable slow-down from the Biopharmaceuticals constant-currency growth of 24% and 29% recorded in the full year and fourth quarter of 2018. As reported, the rises were 27% and 26%.

Asked by an analyst to comment on the relatively weak first-quarter Biopharmaceuticals sales, Novartis CEO Vas Narasimhan commented: “On Sandoz Biopharmaceuticals, globally we saw very strong growth, really driven by Europe.”

“Europe is performing well, with the recent launches of Rixathon, our rituximab biosimilar, and Erelzi, our etanercept biosimilar,” Narasimhan insisted. “And we are now preparing for what we hope is a [US] approval of our pegfilgrastim biosimilar relatively soon to build on what is arguably the broadest portfolio of biosimilars in the market.”

Sandoz secured a pan-European authorization for its Ziestenzo pegfilgrastim biosimilar in November last year.

“Any softness we have seen is in the US, where we have seen additional competition both on Glatopa, our Copaxone generic, as well as on filgrastim, where we have additional entrants coming to that product line,” he acknowledged.

Narasimhan maintained that restoring Biopharmaceuticals growth in the US would be dependent on further launches “to replenish the biosimilars portfolio”. Referencing the recent resubmission of the firm’s dossier for its LA-EP2006 pegfilgrastim candidate after the US Food and Drug Administration issued a complete response letter (CRL) in 2016, he said this had started a six-month review
clock towards approval of the treatment for chemotherapy-induced neutropenia.

**ETANERCEPT ENTRY IN US DELAYED BY LITIGATION**

Narasimhan also noted that Sandoz held FDA approval for its Erelzi etanercept biosimilar to Amgen’s Enbrel, but had not launched as patent litigation continued.

The relatively weak Biopharmaceuticals performance in North America was offset by “continued strong double-digit growth from Rixathon, Hyrimoz (adalimumab) and Erelzi” in Europe. “Launch roll-outs in Asia, Africa and Australasia also contributed to growth,” Novartis commented.

Biopharmaceuticals accounted for 15% of Sandoz’ total turnover in the first quarter as Retail Generics sales declined by 9% as reported, and by 3% on a constant-currency basis, to $1.850bn. This came on a 16% Retail decline in the US that was slightly lower than Sandoz’ overall 17% sales fall in the US to $590m, “mainly due to continued industry-wide pricing pressure”.

The global Retail Generics total included $204m from finished-dosage Anti-Infectives sold under the Sandoz label. The division’s turnover from Anti-Infectives supplied to third parties for marketing under their own name fell by 11% to $125m, equivalent to a 6% slip at constant exchange rates.

On a geographic basis, the proportion of its turnover that Sandoz derived from the US slid to one quarter, from 28% in the prior-year period. And that proportion is set to decline further once Novartis completes the sale of Sandoz’ US oral-dose and dermatology franchises to Aurobindo Pharma for around $800m in cash plus potential earn-outs. Novartis believes the transaction, which is subject to antitrust clearances, could be completed in the third quarter of this year.

**US SALE TO AUROBINDO SCHEDULED FOR THIRD QUARTER**

Through the transaction, India’s Aurobindo will obtain a portfolio that includes around 300 products plus additional development projects, as well as a dermatology development center and manufacturing facilities in Wilson, North Carolina, and in Hicksville and Melville, New York. Novartis said that in 2018, the Sandoz operations it was divesting generated sales of $1.174bn, producing an adjusted ‘core’ operating profit of $294m.

Excluding the US, Novartis said Sandoz’ global sales were down by 4% as reported, but up by 4% in constant currencies.

Europe made up just over half of Sandoz’ total turnover with sales that fell by 4% as reported, but grew by 5% in constant currencies, to $1.241bn. A reported 2% slip to $318m in Asia, Africa and Australasia represented a 3% constant-currency rise, while the reported 9% slide to $177m in Canada and Latin America was a less severe 1% dip at constant exchange rates.

Countries that Novartis deems to be established markets made up almost three-quarters of Sandoz operations despite sales falling by 9% as reported, and by 4% in constant currencies, to $1.695m. Turnover from ‘emerging growth markets’ was down by 5% as reported, but up 5% at constant exchange rates, to $631m.

A favourable geographic and product mix, as well as “ongoing productivity improvements”, lifted Sandoz’ gross margin by just over a percentage point to 48.0%. The division reduced its selling, general and administrative expenses by 7% to $562m, and it cut research and development spending slightly by 3% to $194m.

**OPERATING PROFIT DECLINED BY A THIRD**

Nevertheless, Sandoz’ operating profit tumbled by a third as reported, and by a quarter on a constant-currency basis, to $273m. This depleted the division’s operating margin by 4.5 points to 11.7%.

Novartis said Sandoz’ margin decline was “mainly due to lower divestment in-
come, higher net changes in legal provisions, higher net restructuring expenses and lower sales, partly offset by continued gross margin improvement.”

On an adjusted ‘core’ basis excluding $188m of total charges – including $79m of amortization, $13m of impairments, $52m of restructuring expenses and $45m of legal expenses – Sandoz’ margin stabilized at 19.8%.

Novartis confirmed its full-year sales outlook for Sandoz as being broadly in line with 2018 at constant currencies, excluding any impact from divesting the US portfolio to Aurobindo. The group forecast of mid-single-digit growth assumes no Gilenya (fingolimod) generics are launched at-risk this year, but factors in generic competition to Afinitor (everolimus), Exforge (amlodipine/valsartan) and Exjade (deferasirox), as well as potentially to Sandostatin LAR (octreotide acetate).

India’s Ipca Laboratories has announced its third acquisition in two years with a deal to buy manufacturer Ramdev Chemical Ltd for INR1.1bn ($15.7mn). Ipca said the acquisition would allow the company to “grow its active pharmaceutical ingredient (API) business by adding new molecules in its products basket, with the possibility of forward-integrating such products in its dosage formulations business for the world market.”

Ipca will purchase 100% of shares in Ramdev, which is based in the Palghar district of the western Indian state of Maharashtra. The firm employs 170 staff and manufactures and markets advanced drug intermediates, fine chemicals, custom synthesis molecules and APIs. The 20-year-old company exports its products to various countries such as the US, UK, Japan, Germany and Canada and its clients include major Indian pharmaceutical companies as well as several multinational companies.

For its most recent financial year, Ramdev clocked a net profit of INR30.1m on revenue of INR759m. Ramdev’s manufacturing facility, which includes a fully equipped R&D centre, is inspected by the US Food and Drug Administration (FDA) and the European Directorate for the Quality of Medicines & HealthCare (EDQM), among other bodies. Ipca noted the acquisition faces no governmental or regulatory hurdles to proceed.

The acquisition meshes with Ipca’s business model. Around three-quarters of Ipca’s total sales are generated from its formulations business. Of this, domestic formulations contribute around three-fifths, with export formulations generating the remainder. Ipca is also one of India’s largest suppliers of bulk APIs which contribute around a quarter of sales. In total, the company makes over 350 formulations and 80 APIs for different therapeutic segments and operates in 110 countries and worldwide.

The purchase is the latest in a string by Ipca, which last year bought an 80% stake in US drug marketing firm Bayshore Pharmaceuticals for $10.23m. That deal was aimed at commercializing its generic drugs in the US.

Also in 2018, Ipca acquired a manufacturing plant in Indore from Alpha Labs for $12m. And back in 2015, the company bought a 19% stake in Hyderabad-headquartered Krebs Biochemicals & Industries Ltd.

Ipca Is On An Upswing
Ipca’s purchase comes as its financial performance has been on the upswing amid rising market optimism about an end to the US regulatory troubles which have been buffeting the company. Ipca’s revenues were growing by a robust 21% CAGR between 2009-2014. Then, Ipca’s
We offer relief to ANDA Holders, especially small and medium firms, through a PROVEN GDUFA II Program Fee approach

The ANDA Holder Program fee schedule for Fiscal Year 2019 was published by FDA in August 2018, and the fees increased by 17% from the previous year. Fees were as follows:

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<td>Small</td>
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This is a significant expense for many firms. Those with a modest number of ANDAs will again be paying substantial fees for products they may not even currently market or are identified as Discontinued in the Orange Book. For a small- or medium-tier company this can be a dramatic hurdle simply to retain the assets they worked so hard to own.

Discontinued ANDAs are still considered approved ANDAs for user fee purposes unless the approval is withdrawn. And once withdrawn, ANDAs become virtually impossible to reactivate. Your asset may be gone forever. Further, no one yet knows what will happen to the ANDAs identified as “not marketed” from last year’s one-time marketing status report as submitted to the FDA.

A PROVEN Solution

Now in its third year, ANDA Repository, LLC. offers significant user-fee relief and a solution for companies with discontinued ANDAs or drug products not currently marketed. Like with a parking lot, car owners need space for their cars, whether in use or not. At ANDA Repository, in exchange for the space to park (and a fee), car owners transfers title of the cars to the parking lot owner. The former car owners can, with appropriate notice, resume ownership when they choose to use the car again. Since the parking lot owner has enough cars, this venture benefits for all the parties involved, and the cars remain safe and secure.

In the example above, the car owner is an ANDA owner, and the parking lot owner is ANDA Repository, LLC. which charges ANDA owners an annual fee significantly less than the GDUFA II ANDA Holder Program Fee the FDA charges small- or medium-sized firms. There is NO need to pay excessive fees or be forced to withdraw your valued assets due to short-term market conditions, capacity constraints, API supplier issues, etc!

And check with us before WITHDRAWING your ANDAs...we may be interested in purchasing them!

The FY2020 GDUFA Generic Drug Applicant Program Fee is due October 1, 2019, so please act now!

Phone: +1-570-261-1901           Email: info@andarepository.com
The purchase is the latest in a string by Ipca, which last year bought an 80% stake in US drug marketing firm Bayshore Pharmaceuticals.

Announcing the purchase of Ramdev sent Ipca’s shares up nearly 1.5% to INR979 on 25 April. Ipca’s shares have more than doubled in value since June 2018 as analysts have turned bullish on the company and earnings have accelerated.

Analysts say they expect the FDA to re-inspect Ipca’s three plants in fiscal year 2020 and are hopeful the import alerts will be lifted. They also forecast a pick-up in Ipca’s institutional business as supplies resume for global tenders in fiscal 2020. The Global Fund has again chosen Ipca to supply anti-malaria medicines and analysts project Ipca will post around 15% annual revenue growth for the 2019-to-2021 fiscal years.

Underscoring Ipca’s turnaround, in the third financial quarter ended 31 December 2018, the company’s year-on-year net profit surged 51.71% to INR1bn on a 10.24% leap in net sales to INR9.48bn, driven by domestic and branded formulation sales and API exports. For the fourth quarter, Mumbai brokerage Prabhudas Lilladher forecasts Ipca will post a 106% jump in net profit to INR1.05bn from a year earlier on sales up 24.2% to INR9.7bn.

CONTINUED FROM PAGE 7

Earnings fell and its shares tanked when the FDA slapped import alerts on three of its Indian factories – Pithampur, Madhya Pradesh and Silvassa – over quality lapses. The alerts meant Ipca could not export from those facilities to the US. These alerts also hit the company’s institutional orders, including from the Global Fund to Fight AIDS, Tuberculosis and Malaria. The public-private partnership scrapped its contract with Ipca to supply anti-malarial treatments to Africa.

The company, which has some 16 plants in total in India, has sought to remedy its FDA problems by remodeling its facilities. While waiting for the regulatory all-clear, Ipca has moved to build a strong domestic presence – Indian revenues have grown 10% over five years driven by new launches – and a diversified international business model.

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Pfizer Plans For Three Biosimilar Launches In Japan and US This Year

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Pfizer is preparing for three biosimilar launches this year as it looks to capitalize on its existing presence in the supportive cancer-care setting.

“Trastuzumab was already launched in the EU in the first quarter, and we look forward to the launch of trastuzumab in Japan in the third quarter,” Pfizer’s group president of Biopharmaceuticals, Angela Hwang, told investors. “Rituximab will also be launched in Japan, and that will be in the fourth quarter.”

“Bevacizumab will be launched in both the US and Japan in the fourth quarter,” she revealed.

“We’ve seen some nice uptake in the supportive oncology portfolio that we launched late last year and we look forward to the oncology biosimilar portfolio contributing to our growth,” Hwang stated.

Since the start of this year, Pfizer has already boosted its oncology biosimilars portfolio by obtaining an authorization in the EU for Zirabev, a biosimilar to Avastin (bevacizumab) for treating multiple forms of advanced or metastatic cancer previously known as PF-06439535.

And in the US, the FDA approved in March Pfizer’s Trazimera (trastuzumab-qyyp) biosimilar to Herceptin as a treatment for certain forms of breast and gastric cancer. Trazimera, which had already received EU authorization in July 2018, marked the firm’s first oncology monoclonal antibody biosimilar, and fifth biosimilar overall, approved by the FDA.

POTENTIAL US NODS FOR RITUXIMAB, BEVACIZUMAB AND ADALIMUMAB

“Over the rest of 2019,” remarked CEO Albert Bourla, “we are looking forward to potential US regulatory approvals for tafamidis in transthyretin cardiomyopathy, our Bavencio-Inlyta combination for the treatment of first-line renal cell carcinoma as well as for our biosimilar rituximab, bevacizumab and adalimumab molecules.”

“Revenues from our biosimilars portfolio grew 7% operationally in the quarter,” he said. “We received regulatory approvals during the quarter for two oncology biosimilars, and we see the potential for additional approvals in key markets later this year.”

Following its restructuring into a Biopharmaceuticals business unit – which
encompasses biosimilars and other hospital injectables such as anti-infectives, as well as novel brands – the Upjohn legacy business comprising 20 legacy oral-dose brands such as Lipitor (atorvastatin), Norvasc (amlodipine) and Celebrex (celecoxib) plus certain generics, and the Consumer Healthcare OTC operation, Pfizer no longer reports a consolidated biosimilars sales figure.

INFLIXIMAB SALES SLIPPED BY 4%

Pfizer’s Inflectra/Remsima (infliximab) biosimilar marketed through a co-operation with Korea’s Celltrion makes up part of the Inflammation and Immunology (I&I) sub-division within Biopharmaceuticals. In the first quarter of this year, Pfizer reported global Inflectra/Remsima sales down by 4% to $138m, although the performance was static in constant-currency ‘operational’ terms.

In the US, where Pfizer is suing Johnson & Johnson over alleged anti-competitive tactics to protect its Remicade reference brand, Inflectra/Remsima sales edged ahead by 5% to $57 million. But a reported drop of a tenth to $81m in the US group’s international region was due largely to a 6% slip to $71m in Pfizer’s Developed Europe region. Growth in other developed markets failed to offset sales of the biosimilar in emerging markets halving to $5m.

Inflectra/Remsima accounted for a little over 13% of Pfizer’s total Inflammation & Immunology turnover that grew by 2% as reported, and by 8% on an ‘operational’ constant-currency basis, to $1.037bn. Inflammation & Immunology made up a little over a tenth of BioPharmaceuticals business unit, with Oncology products – such as ibrance (palbociclib) – together contributing just over a fifth. Another fifth came from Pfizer’s Hospital portfolio that encompasses the legacy Hospira injectables portfolio. Hospital sales fell by 7% as reported, and by 3% on an operational basis, to $1.887bn.

Pfizer said its US Hospital sales fell by 8%, “primarily due to the continued, expected negative impact from generic competition for products that have previously lost marketing exclusivity”.

“In sterile injectables, manufacturing supply constraints continue to impact our top line in the US,” Bourla acknowledged. We have made some progress towards fixing these issues, particularly since [chief financial officer and EVP of global supply and business operations] Frank D’Amelio assumed responsibility for our global supplier organization on 1 November 2018. We expect these issues to be significantly improved by the end of 2019 and continue to expect this business to be a solid growth contributor in the future.”

STERILE INJECTABLES IMPROVEMENTS TO SUPPLY ONGOING

Questioned by an analyst on whether resolution of the sterile injectables production problems remained on track for the end of 2019, D’Amelio stated: “Yes, we do plan on having significant improvements implemented by the end of 2019. But please also know along the way we’ve already implemented numerous preventive and corrective actions and we’ve seen a nice improvement in our overall supply to-date.”

“With its streamlined operating structure, relative autonomy and its leadership located in China, we believe Upjohn will help us seize the tremendous opportunity we see in emerging markets”

SPINNING UPJOHN OFF-PATENT BRANDS BUSINESS NOT A PRIORITY

Responding to an analyst’s question, Bourla acknowledged that he was often asked about spinning off the Upjohn business. “I understand the reasons,” he conceded. “Right now, nothing has changed other than Upjohn performed very well in the first quarter. I always said that our focus is to make sure that we stand up this business in a way that will operate effectively.”

Upjohn’s management was located in China “where most of the opportunities are, as evident from the first quarter, but also where most of the challenges will come,” Bourla said, noting the ongoing discussions around healthcare reforms in China. Separating Upjohn from Pfizer’s large Biopharmaceuticals unit was “a possibility down the road”, he conceded, “but that is not what is on my mind right now”. Rather, Pfizer’s focus was on running the Upjohn off-patent unit as a strong, standalone subsidiary within the group.

“Revenues for our Upjohn business in the first quarter increased 1% operationally, primarily due to 25% operational growth in emerging markets, driven by strong volume-driven operational growth in China, primarily from Lipitor, Norvasc, and Celebrex,” D’Amelio commented.

The emerging markets gains were partially offset by a 9% operational decline in developed markets, primarily driven by lower sales of Viagra (sildenafil) and Upjohn’s authorized generic of the erectile-dysfunction drug in the US “due to increased generic competition.” Lyrica (pregabalin) volumes were also down ahead amid wholesaler destocking ahead of loss of exclusivity and anticipated generic entry from 30 June this year which will add to ongoing generic competition in developed Europe. In general, D’Amelio said, Upjohn’s Greenstone authorized generic subsidiary was suffering from “industry-wide pricing challenges in the US.”

“With its streamlined operating structure, relative autonomy and its leadership located in China, we believe Upjohn will help us seize the tremendous opportunity we see in emerging markets,” Bourla commented. “As the global middle-class continues to rapidly expand, and as awareness of diagnosis and treatment options continue to improve, we believe the pharmaceuticals segment will continue to enjoy significant expansion in greater China and other emerging markets.”

While the US loss of exclusivity for Lyrica midway through this year would hamper Upjohn’s financial performance in 2019 and 2020, Bourla predicted that thereafter Upjohn would produce “very stable low single-digit growth” in top-line sales and “much higher on the bottom line.”
Australia Rolls Out Resources In ‘Biosimilar Week’

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Discussion videos, literature reviews, downloadable resources and interactive content are among the educational assets that have been made available to healthcare professionals by Australia’s Generic and Biosimilar Medicines Association as part of its ‘Biosimilar Week’ campaign.

Running from 29 April to 3 May, Biosimilar Week – announced earlier this year – is “an integral component of a comprehensive three-year education program on appropriate use of biosimilars, developed collaboratively by experts across medical specialities, pharmacy and the healthcare industry,” the GBMA explained.

Managed by the association’s education arm, GBMA Education, the initiative is funded by a ‘biosimilar education grant’ of A$5 million (US$3.5 million) that was awarded by Australia’s government to the GBMA last April to “complement and extend” activities being undertaken as part of the country’s biosimilar awareness initiative. The grant will be paid in four instalments and runs until December 2020.

The GBMA began to roll out activities under the grant midway through last year under Renée Richardson, GBMA Education’s project manager.

A ‘CRITICAL PART’ OF AUSTRALIAN HEALTH PROVISION
Kicking off the week-long education campaign, Australian health minister Greg Hunt said biosimilars were “a critical, fundamental part of our medicines provision in Australia”, representing “an important part of the Pharmaceutical Benefits Scheme (PBS), and a growing part.”

With biological drugs representing seven of the 10 highest-cost subsidised medicines under Australia’s PBS, Hunt said biosimilars played a “critical role in helping with the sustainability of the PBS” and could “play a very important role in conditions such as Crohn’s disease, arthritis, psoriasis, and certain types of cancer treatment.”

Biosimilars were “always taken through and assessed by the Pharmaceutical Benefits Advisory Committee (PBAC) before listing on the PBS,” Hunt emphasized.

Ultimately, he summarized, biosimilars were “about making medicines more accessible, and ensuring that we can get the best possible outcome for the whole of the Australian public.”

“Choice, understanding, safety and quality – those are the critical things, and that’s what biosimilar medicines do.”

BIOSIMILAR HUB OFFERS VIDEO SERIES
A biosimilar hub’s website, biosimilarhub.com.au – “an online platform designed to facilitate peer-to-peer information exchange between healthcare professionals,” according to the GBMA – collates the various resources provided by the association, with a separate section coming soon for patients and carers.

A series of video talks underpins Biosimilars Week, providing “insights into a range of topics across various areas including oncology, rheumatology, gastroenterology, hematology, dermatology and hospital pharmacy.”

This includes addressing points around safety and efficacy, clinical experience with biosimilars, approval and regulation, and the benefits of biosimilar medicines.

Speakers include the Australian government’s chief medical officer, Brendan Murphy, as well as medical specialists in individual treatment areas, along with pharmacist representatives.

’BALANCED, EVIDENCE-BASED AND RELEVANT’
The GBMA said its chief executive Marnie Peterson was “very appreciative of the extensive consultation and support offered by a wide range of healthcare and industry professionals in developing the educational materials to date and welcomes ongoing collaboration.”

“Our aim is to ensure that the healthcare professional education and future consumer communications are balanced, evidence-based and relevant to each audience’s needs,” Peterson explained. “We are looking forward to seeing the discussion that the Biosimilar Week activities spark, and we warmly invite feedback that will help develop the ongoing program.”

Other related initiatives in 2019 include a “national multi-disciplinary event” in August-September through which healthcare professionals will be able to “share the latest updates and insights on biosimilar medicines”, as well as ongoing hospital-based education sessions and GBMA promotional activities at conferences and education sessions from July through to November.
Teva has received a negative opinion on its hybrid application for cabazitaxel from the European Medicines Agency’s committee for human medicinal products, recommending that the European Commission refuse a marketing authorization for the prostate cancer treatment.

In its application, Teva made reference to Sanofi’s Jevtana (cabazitaxel) as well as the originator’s Taxotere (docetaxel). The Israeli firm’s generic was “expected to work in the same way as the reference medicine, Jevtana,” the CHMP pointed out, adding that the drug was to be available as a concentrate to be made into a solution for infusion.

“There was no need for bioequivalence studies to investigate whether Cabazitaxel Teva is absorbed similarly to Jevtana to produce the same level of the active substance in the blood,” the CHMP explained, “because Cabazitaxel Teva is given by infusion into a vein, so the active substance is delivered straight into the bloodstream.”

Teva had “presented data from the published literature” to demonstrate that its generic was similar to Jevtana, which Sanofi says is covered by EU regulatory exclusivity until March 2021.

In making reference to Taxotere, Teva’s application stated that cabazitaxel was a derivative of docetaxel, and “the active substances do not differ significantly in their safety and effectiveness”, referring to published data and an expert opinion to support this.

**DATA NOT SUFFICIENT TO CONSIDER BOTH SUBSTANCES THE SAME**

However, the CHMP said it “did not agree that the data presented by the company were sufficient to support the claim that cabazitaxel and docetaxel should be considered the same active substance.”

“Although cabazitaxel is a derivative of docetaxel, laboratory studies have shown that cabazitaxel and docetaxel have different properties,” the committee pointed out. “For example, cabazitaxel can cross the blood-brain barrier while docetaxel cannot.”

“Additionally, laboratory data suggest that cabazitaxel can be effective at treating cancer that is resistant to docetaxel,” the CHMP noted, adding that data from clinical studies “also showed differences in the safety profile of the two active substances.”

“Furthermore,” the committee observed, “patients receiving cabazitaxel are exposed to the unchanged substance plus two active breakdown products, which are not formed when docetaxel is given.”

“Based on these findings, the CHMP was of the opinion that it cannot be concluded that cabazitaxel and docetaxel do not differ significantly with regard to safety and effectiveness,” the committee concluded. “Thus, Taxotere cannot be used to support the application for Cabazitaxel Teva and the CHMP recommended that Cabazitaxel Teva be refused marketing authorization.”

Teva now has the option to request a re-examination of the CHMP’s opinion, but must do so within 15 days of receiving notification of the negative opinion.
Biogen claims lead among adalimumab biosimilars in Europe

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Biogen believes that its Imraldi adalimumab biosimilar is outperforming other rivals to AbbVie’s Humira reference biologic in Europe. “Our data indicate that Imraldi is the market-leading Humira biosimilar in Europe,” chief financial officer Jeff Capello told investors.

Having developed the biosimilar through its Samsung Bioepis joint venture with Samsung Biologics, Biogen launched Imraldi in Europe on 17 October last year, immediately upon expiry of Humira’s supplementary protection certificate. The biosimilar brand generated sales of $16.7m between mid-October and the end of December last year. (Also see “Benepali surge and Imraldi gains drive Biogen biosimilars past US$500m” - Generics Bulletin, 1 Feb, 2019.)

Pricing dynamics in line with expectations

“For its first full quarter in the market,” Capello revealed, “Imraldi exceeded 200,000 doses with sales in 18 different countries.” The rate of uptake for biosimilar adalimumab had, he said, been generally steeper than for the two previous anti-TNF biosimilars, etanercept and infliximab. Capello described pricing dynamics for adalimumab in Europe as “more or less in line with what we expected”, although he pointed out that different contracting and tendering practices meant that such dynamics varied “very dramatically country-by-country.”

The more rapid uptake of adalimumab over the 2015 entry of infliximab and the 2016 launch of biosimilar etanercept is borne out by the latest IQVIA volume data released by Germany’s Pro Biosimilars industry association. The data shows biosimilar adalimumabs capturing around a quarter of the local market by volume within just two months. Trastuzumab biosimilars that also entered the German market last year have shown a similar uptake trajectory, needing just six months to take half of the market.

In Germany, Imraldi entered the market with a list price that was just over 40% lower than the cost of the reference brand, AbbVie’s Humira, according to the association of statutory health insurance doctors for the North Rhine region, the KVNO. (Also see “Imraldi sets pace on German price cuts” - Generics Bulletin, 2 Nov, 2018.)

A few weeks later, the deep initial discount won Biogen a nationwide supply contract for the biosimilar with Germany’s GWQ group of health insurance funds. (Also see “German funds select Imraldi due to price” - Generics Bulletin, 16 Nov, 2018.)

Pointing out that Germany was Europe’s largest anti-TNF market, Capello told investors that Imraldi accounted for around two-fifths of total biosimilar adalimumab sales in Germany that had seen Humira already surrender just over a third of the local market. “We’re very encouraged by what’s happening in Germany where we really have started out strong,” he stated.

International Humira sales down 27.9%

The impact of competition in Europe from not only Imraldi, but also from Amgen’s Amgevita, Mylan’s Hulio and Sandoz’ Hyrimoz biosimilars, was reflected in AbbVie’s International Humira sales outside of the US falling by 27.9% to $1.23 billion in the first quarter of this year. But 7.1% US growth limited to 5.6% the global fall in Humira sales to $4.45bn.

And competition could soon intensify with the European Commission having recently granted a marketing authorization for Fresenius Kabi’s Ldacio biosimilar. This followed a positive European Medicines Agency opinion earlier this year.

Kabi has sued Biogen in several European countries, alleging that Imraldi infringes its European patent EP3,148,510, which was issued in June last year and expires in May 2035. A hearing before Denmark’s Maritime and Commercial High Court is scheduled for next month, while infringement and revocation trials have been set for July 2019 in the UK Patents Court and for October 2019 in a district court of the Hague, the Netherlands. Similar proceedings are also underway before courts in Paris, France; Düsseldorf, Germany; and Milan, Italy, but no hearings have been scheduled.

The S10 patent is entitled ‘Liquid pharmaceutical composition’ and covers aqueous formulations of adalimumab that include a histidine buffering agent, a sugar stabilizer and a polysorbate surfactant.

Patent litigation against Richter as well as Kabi

Furthermore, Biogen and Samsung Bioepis are disputing Gedec- on Richter’s assertion that Imraldi infringes European patent EP3,212,667 that was issued in September 2018 and expires in October 2035. Richter’s ‘667 patent, entitled ‘Pharmaceutical anti-TNF-alpha antibody formulation’ presents a list of aqueous adalimumab formulations that are “free of a phosphate buffer”.

Biogen reported first-quarter Imraldi sales of $35.7m, just over
doubling from $16.7m in the fourth quarter of 2018.

The firm’s sales of its Flixabi (infliximab) biosimilar more than doubled over the prior-year quarter to $14.7m. “In the first quarter,” Capello revealed, “Flixabi exceeded 100,000 doses for the first time in a quarter.”

“Benepali has been strengthening its leadership position in countries, such as Germany, the UK, Denmark and Norway, shipping again more than 1m doses in the quarter,” he added. Sales of the etanercept biosimilar edged up by 2.6% over the prior-year period to $124.0m, although the total was down slightly versus the fourth quarter.

“We expect uptake of Biogen biosimilars to contribute estimated healthcare savings of up to €1.8bn ($2.0bn) in 2019 across Europe”

“In Europe, around 145,000 patients are currently on Biogen biosimilars,” the company stated. “We expect uptake of Biogen biosimilars to contribute estimated healthcare savings of up to €1.8bn ($2.0bn) in 2019 across Europe.”

Biogen – which holds a 49.9% stake in the Samsung Bioepis venture that is also working on biosimilars of trastuzumab and bevacizumab – reported total biosimilars turnover ahead by 36.8% to $174.4m, “primarily due to the launch of Imraldi in the fourth quarter of 2018.” This growth was achieved despite a negative $9.6m exchange-rate impact.

Biosimilars accounted for 6.5% of the group turnover that increased by 11.5% to $3.49bn. Three-quarters of sales came from multiple sclerosis brands such as Tecfidera (dimethyl fumarate) and nearly a fifth from the Spinraza (nusinersen) treatment for spinal muscular atrophy.

BIODENT BELIEVES IN US BIOSIMILARS OPPORTUNITY

“We do believe in the value-creation opportunity offered by the biosimilars, also in the US,” CEO Michel Vounatsos insisted. “The savings opportunity is up to $250bn in the next 10 years if we have an effective biosimilars market in the US. And we don’t speak about that enough. But I believe what is being discussed in terms of rebates and new rebates policy will address this potential gap.”

“We are very pleased with our portfolio. We are very pleased with our performance. We do not intend to stop here,” Vounatsos pledged.

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CENTRIENT ACCUSES INDIA’S DALAS OF AMOXICILLIN PATENT INFRINGEMENT

PENELOPE MACRAE

Centrient Pharmaceuticals, which seeks to use “green technology” to make generic antibiotics and other drugs, has slapped Dalas Biotech with a lawsuit accusing the Indian company of patent infringement involving its amoxicillin trihydrate API.

In its lawsuit filed in the Delhi High Court, Centrient’s Indian subsidiary, Centrient Pharmaceuticals Private Ltd., asked for a permanent injunction to ban the manufacture, use and sale in India and export of an active pharmaceutical ingredient (API) produced by Dalas containing amoxicillin trihydrate. Centrient says Dalas is using a manufacturing process which infringes on its patent. Centrient also is seeking an unspecified sum in damages from Dalas.

It is the second time Centrient has taken court action in India over what it says is infringement of its amoxicillin trihydrate production process. In 2017, after Centrient filed a court case, the Delhi High Court issued an injunction banning China’s Sinopharm Weiqida Pharmaceutical from manufacturing, importing and exporting, or selling amoxicillin trihydrate API in India. The court ruled that Sinopharm Weiqida was infringing the process patent held by Centrient, then known as DSM Sinochem Pharmaceuticals (DSP).

“After having previously filed patent litigation against Sinopharm Weiqida Pharmaceuticals for patent infringement in India and the court granting an injunction since April 2017, Centrient shows it will continue to rigorously enforce its IP assets worldwide against any additional potential infringers in India or abroad,” said Centrient’s chief executive, Karl Rotthier. Rotthier said Centrient “holds a world-class intellectual property portfolio.” This means the company aims to strongly use the law to protect its “innovative sustainable and environmentally friendly technology” worldwide, he said.

Centrient said patent 247,301, which the company alleges Dalas violated, involves an enzyme process for preparing amoxicillin trihydrate with a low free-water content. Dalas, which is headquartered in the northern Indian state of Rajasthan, is a manufacturer of fermentation enzymes, pharmaceutical intermediates and pharmaceutical drugs. Dalas could not be immediately reached for comment on the lawsuit.

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INTELLECTUAL PROPERTY

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SINOPHARM WEIQIDA LAWSUIT INVOLVES SAME PATENT
The lawsuit Centrient filed against Sinopharm Weiqida Pharmaceuticals also involved patent number 247,301. Three months ago, the Delhi High Court issued a second injunction against Sinopharm Weiqida barring the firm from exporting, importing and selling its amoxicillin trihydrate in India. The court also found Sinopharm Weiqida guilty of contempt of court for failing to abide the 2017 preliminary injunction and ruled the company was infringing Centrient’s patent.

Centrient Pharmaceuticals, wholly owned by global investment firm Bain Capital Private Equity, is the leading supplier and producer of beta-lactam antibiotics worldwide as well as a provider of next-generation statins and antifungals. The company, based in Rotterdam, develops, produces and sells intermediates, APIs and drug products, employing what it says are more environmentally friendly methods.

Centrient says its patented processes use “sustainable, green enzymatic methods” to make amoxicillin and other antibiotics. During the 1990s, the company developed the enzymatic processes used in its production of antibiotics which it says led to major improvements in the drugs’ environmental performance. Centrient’s enzymatic method replaces the traditional 13-step antibiotic production process with natural processes that eliminate use of solvents and other chemicals.

In addition, Centrient says the key enzymatic step in its statin production process also reduces its dependency on solvents and chemicals. The company markets its APIs and finished dosage forms using this “green technology” under the brand name PureActives. The company says that besides consuming fewer natural resources and using less energy, its environmentally sustainable manufacturing processes deliver better yields and efficiencies in raw material use.

Centrient says its strategy for the future is aimed at providing a greater range of high-quality, sustainable finished dosage forms, and building a “strong and differentiated brand in the generic pharmaceutical industry” as it grows globally.

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BIOESIMILAR

Samsung Bioepis’ Etanercept Nod Prompts US Lawsuit

PENELOPE MACRAE
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Samsung Bioepis, the joint venture between Samsung Biologics and Biogen, has won US Food and Drug Administration approval for Eticovo (etanercept-ykro), the second approved US biosimilar rival to Amgen’s Enbrel. The originator immediately sued for patent infringement in a bid to protect its best-selling brand, which generated $4.81bn of its $5.01bn total turnover last year in the US. Samsung Bioepis has not announced a US launch date for the tumor necrosis factor (TNF) inhibitor.

In the suit brought in a New Jersey district court by Amgen and its partner Roche on 29 April, the plaintiffs allege infringement of five patents: US patents 8,063,182 and 8,163,522, collectively the ‘Roche’ patents; and US patents 7,915,225 and 8,119,605, as well as 8,722,631, collectively the ‘Immunex’ patents.

Noting the approval of the Eticovo abbreviated biologic license application (aBLA) on 25 April as biosimilar to Enbrel, the suit alleges that “Bioepis was either aware of each of these patents or was willfully blind to their existence.”

“Bioepis’s etanercept biosimilar product, like [Amgen subsidiary] Immunex’s Enbrel, has been approved for five indications: treating rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and plaque forms using this “green technology” under the brand name PureActives. The company says that besides consuming fewer natural resources and using less energy, its environmentally sustainable manufacturing processes deliver better yields and efficiencies in raw material use.

Centrient says its strategy for the future is aimed at providing a greater range of high-quality, sustainable finished dosage forms, and building a “strong and differentiated brand in the generic pharmaceutical industry” as it grows globally.

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If Amgen wins in court, Enbrel could enjoy US market exclusivity through to April 2029
psoriasis,” the court filing observes. “In addition, the route of administration of Bioepis’ etanercept biosimilar is the same as that of Immunex’ Enbrel, and the approved dosage form and strength of Bioepis’ etanercept biosimilar represent a subset of the approved forms and strengths of Immunex’s Enbrel.”

In particular, the plaintiffs complain that Samsung Bioepis has failed to provide them with a copy of its sBLA or details of its manufacturing process, as detailed in the Biologics Price Competition and Innovation Act (BPCIA). Furthermore, they say that the biosimilar developer has failed to provide the required 180-day notice of commercial marketing.

According to the suit, the ‘182 and ‘522 Roche patents are directed respectively to “a fusion protein incorporating a TNF-binding portion of the p75 TNF receptor” that covers etanercept and “nucleic acids, host cells and methods of using such nucleic acids and host cells to make the p75 TNF receptor fusion protein”. The three Immunex patents “disclose and claim methods of using etanercept to treat psoriasis and/or psoriatic arthritis”.

SECOND BIOSIMILAR ETANERCEPT IN US

FDA clearance for Eticovo single-dose pre-filled syringes with all five eligible indications marks the agency’s second approval for a biosimilar of Enbrel.

In August 2016, the FDA gave its nod to Sandoz’ Erelzi (etanercept-szsz) for the same indications as Enbrel. But Sandoz has been unable to market Erelzi in the US as Amgen won an injunction blocking sales and the two companies have been embroiled in litigation ever since.

Sandoz has stipulated to infringement, but is asserting that the three Immunex psoriasis patent are invalid for obviousness-type double patenting. The psoriasis patents also render obvious asserted claims in the ‘182 Roche patent, as do other prior-art patents. Furthermore, Sandoz is alleging a lack of written description and enablement, including against the ‘522 Roche patent.

If Amgen wins in court, Enbrel could enjoy US market exclusivity through to April 2029 and while a verdict is expected soon, either side could appeal.

Presenting its first-quarter financial results to investors, Amgen – which derived more than a fifth of its group sales from Enbrel – said it was simply waiting to learn the court’s decision. “We are waiting for the judge to rule and there is nothing new to report,” CEO Bob Bradway told analysts.

The approval of Eticovo “adds to our growing portfolio of anti-TNF medicines in the US, where we believe biosimilars can bring meaningful value to the country’s healthcare system,” said Christopher Hansung Ko, chief executive of Samsung Bioepis.

Both Samsung Bioepis and Sandoz have launched their Enbrel biosimilars in Europe.

European regulators approved Samsung Bioepis’ etanercept biosimilar three years ago and it is sold in the EU by Biogen under the brand name Benepali. Samsung Bioepis’ etanercept biosimilar is sold in 38 countries including the 28 EU nations as well as in Canada and Australia. Health research firm IQVIA attributes to Benepali a 40% share of the etanercept biosimilar market in Europe, outpacing its Sandoz’s rival, Erelzi.

SAMSUNG BIOEPIS’ FIRST-QUARTER SALES JUMP 35% YEAR-ON-YEAR: BIOGEN

Samsung BioLogics joined forces with Biogen in 2012 to establish Samsung Bioepis. The partnership has been a good contributor to Biogen’s earnings and last June the company announced it would exercise a call option to buy shares worth $677m and hike its stake in Samsung Bioepis to 49.9% from 5.4%.

The partnership has three biosimilars on the market: Benepali; Imraldi (adalimumab), a biosimilar of AbbVie’s best-selling rheumatoid arthritis drug Humira; and inflammatory drug infliximab, a version of J&J/Merck’s autoimmune drug Remicade that is sold as Flixabi in the EU and as Renflexis in the US.

During the first quarter of 2019, Samsung Bioepis’ biosimilars revenue jumped 35% year-on-year to $175m, according to Biogen’s first-quarter results.

The sales leap was propelled by launching Imraldi in Europe last October. Imraldi posted 114% revenue growth quarter-on-quarter to hit $36m. Sales of Humira in the US where AbbVie faces no biosimilarity competition climbed 7.1% to $2.3bn in the first quarter, but globally net revenues for Humira fell by 5.6%, highlighting the problems ahead for AbbVie as patent expiration brings more biosimilarity competition. Meanwhile, sales of Benepali, which is market leader in countries like Germany, were up 3% year-over-year in the first quarter for a total of $124m in revenue. First-quarter revenue from Samsung Bioepis’ infliximab more than doubled from a year earlier to hit $15m.

Benepali has been strengthening its pole position in countries like Germany and the UK, shipping over 1m doses in the first quarter. Flixabi, meanwhile, in the first quarter exceeded 100,000 doses for the first time in a quarter. Towards its first full quarter in the market, Imraldi had exceeded 200,000 doses with sales in 18 different countries. Biogen said the rate of Humira biosimilar adoption has been “steeper” than for its previous two anti-TNFs and that its data suggests Imraldi is the market-leading biosimilar in Europe. In Germany, the largest anti-TNF market in Europe, Humira biosimilars have already grabbed a 35% market share with Imraldi capturing 40% of that number.

Samsung Bioepis says it is developing a pipeline of biosimilar candidates that includes six late-stage candidates for indications that include immunology, oncology, and diabetes. The company is also hoping to go beyond biosimilars and develop its own novel biologics. It has one novel drug SB26, also known as TAK671, intended to treat severe acute pancreatitis that is undergoing Phase I clinical trials. SB26 is the first therapeutic candidate in a risk-sharing strategic collaboration agreement between Samsung Bioepis and Takeda aimed at co-developing multiple novel biologic therapies. Among other pipeline drugs are a bevacizumab biosimilar undergoing a Phase-3 clinical study. Bevacizumab, sold under the trade name Avastin, is a medication used to treat a number of types of cancers and a specific eye disease. Another is a biosimilar for ranibizumab, trade name Lucentis, undergoing a Phase III study for treating macular degeneration. A third is a biosimilar for eculizumab, trade name Soliris, for treating atypical hemolytic-uremic syndrome which is in Phase I trials.

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India Slams USTR Report As An Attack On Low-Cost Generics

PENELOPE MACRAE

India's government and the leading domestic drug manufacturers' association have deplored the US Trade Representative office's decision to place the country yet again on its "priority watch list" of nations that fail in Washington's view to adequately protect intellectual-property rights, calling the move an attack on affordable generic medicines.

The government and the Indian Pharmaceutical Alliance or IPA, which represents 22 of India's biggest domestic pharmaceutical firms, defended India's Patent Act as compliant with the international Trade-Related Aspects of Intellectual Property Rights (TRIPs) Agreement. They said the law strikes an important balance between rewarding innovation, protecting IP and safeguarding public health.

"We strongly disagree with the observations made by the USTR," India's health ministry secretary Preeti Sudan told local media. "We view this as opposition to low-cost generics and the thriving Indian drug manufacturing industry which is (known as) the 'Pharmacy of the World'," she said.

The USTR said in its annual Special 301 Report that it kept India – the world's biggest generics exporter – on the watch list for allegedly failing to make "sufficient measurable improvements to its IP framework." Over the past year, "India took steps to address IP challenges... (but) long-standing deficiencies persist. India remains one of the world's most challenging major economies with respect to IP protection," the USTR declared.

Humanitarian group Médecins Sans Frontières joined India in rejecting the USTR's conclusions. "At a time when medicine prices are soaring – including in the US – the USTR's report undermines the efforts of US lawmakers and patient advocates seeking to make medicines more affordable domestically," MSF said.

USTR REPORTS NO BREAKTHROUGHS ON IP

The USTR said it engaged with India to secure "meaningful" IP reforms on long-standing issues like patentability criteria, the potential threat of compulsory licensing and "unauthorised disclosure" of test data to obtain marketing approval for pharmaceutical products but made no breakthroughs. The USTR added the government of India, banded with 10 other countries on the watch list including China, Indonesia and Russia, has made it difficult for "innovators to receive and maintain patents in the country."

India's has languished on the USTR's priority watch list since the start of the Special 301 process in 1989, barring several years in the early 1990s. A country's inclusion on the list falls just short of imposing trade sanctions. The IPA's secretary general Sudarshan Jain said the association was disappointed by the USTR's decision. "If you see, we have made significant progress on the IP front, we have been TRIPs-compliant," said Jain, whose association accounts for more than 80% of India's pharmaceutical exports and over 50% of the domestic market.

For instance, the IPA said steps to augment manpower and streamline procedures have resulted in a "transformation" of the Patent Office. Patents pending examinations slid to 127,881 as of 31 December 2018, from 204,177 as of 31 March 2017. India now examines trademark applications in one month and registrations are completed in a year or less. India, the IPA said, now has one of the lowest examination times for trademark registration globally and it is believed the patent examination backlog will be eliminated in about two years.

"We strongly disagree with the observations made by the USTR. We view this as opposition to low-cost generics and the thriving Indian drug manufacturing industry."

In addition, India has not issued a compulsory license – long a bugbear of global companies – "in years," Jain noted. The only compulsory license India has granted was in 2012 for Bayer's Nexavar (sorafenib) to a local firm to sell a cheaper copy of the cancer medicine deemed unaffordable for most Indians. Under TRIPs, countries can grant compulsory licenses and at least eight western European countries have provisions to bestow compulsory licenses on public interest grounds "even broader" than India's, the IPA said. "Also, the (Indian) courts have been responsive (to IP concerns)" in patent rulings, Jain added.

Multinational companies have long been up in arms over India's strict patent laws. Unlike many Western nations, India does not award patents for 'evergreening' or tweaking existing drug formulas to
Kabi, Mylan and Neptune Thwarted In US Pemetrexed Proceedings

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Fresenius Kabi, Mylan and Neptune Generics have failed to convince the US Court of Appeals for the Federal Circuit that a method-of-treatment patent protecting Eli Lilly’s Alimta (pemetrexed disodium) cancer drug until May 2022 is unpatentable as obvious.

In several *inter partes* reviews before the Patent Trial and Appeal Board (PTAB) within the US Patent and Trademark Office (USPTO), generics players including Nep- tune and Sandoz had argued that the 22 claims of Lilly’s US vitamin-regimen patent 7,772,209 were obvious in light of prior-art articles and patent applications. But the PTAB in October 2017 upheld the claims of the ‘209 vitamin-regimen patent as valid.

The ‘209 patent relates to administering folic acid and a methylmalonic acid (MMA) lowering agent, such as vitamin B12, to reduce the toxic effects of the chemotherapy agent pemetrexed. A six-month pediatric extension expires on 24 May 2022 and the ‘209 patent is the only patent listed against Alimta powder for injection in the Orange Book maintained by the Food and Drug Administration, as the pemetrexed molecule patent expired in January 2017.

**APPEAL FOCUSED ON THREE PRIOR-ART REFERENCES**

On appeal, the three generics firms focused on three prior-art references: two abstracts by the ‘209 patent’s inventor, Niyikiza I and II; and European patent application EP0,595,005.

Highlighting the ‘005 application’s disclosure of administering folic acid and vitamin B12 to lower homocysteine levels, the generic petitioners argued that the PTAB had erred in finding a skilled person would not have been motivated to administer both an MMA-lowering agent like vitamin B12 along with folic acid. But the Court of Appeals disagreed.

“Each step of the board’s analysis is supported by substantial evidence,” the appeals panel maintained. While Niyikiza I disclosed that elevated levels of homocysteine were predictive of pemetrexed toxicity, the court credited expert testimony that a skilled person would have read Niyikiza II “to mean that elevated MMA levels were not a predictor of pemetrexed-induced toxicity.” The evidence, it said, pointed to pemetrexed-induced toxicity correlating with folate deficiencies, but not with vitamin B12 deficiencies.

Tackling the generics firms’ argument that the EP005 application taught administering both folic acid and vitamin B12 to lower homocysteine levels, the Federal Circuit said this amounted to a challenge to the PTAB’s factual findings that the application “does not discuss antifolates generally.”

“Because the board did not err in its obviousness analysis, substantial evidence supports its underlying fact findings, and subject-matter eligibility is not properly before the court in an appeal from an IPR decision, we affirm”

“Given the contrast between the specific, directly applicable teachings of Niyikiza II and the tangential, general statements of EP005, substantial evidence supports the board’s finding that EP005 did not provide information as to how pre-treatment with folic acid and vitamin B12 would impact toxicity effects,” the appeals panel stated.

The PTAB had correctly disregarded Lilly’s communications with the FDA and comments on the prior-art references after the patent’s critical date, as these had been “made through the lens” of the claimed invention, the Court of Appeals determined. And the board had been correct to take
Polish Plan For Specialist Courts Is Put To The Public

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The prospect of specialist courts in Poland hearing patent and other intellectual-property (IP) disputes has moved closer after the country’s ministry of justice launched a public consultation on a bill and other legislative measures. Local lawyers believe the move away from common-law courts dealing with specialist IP matters could both accelerate proceedings and improve the quality of verdicts.

At present, IP infringement allegations are dealt with through Poland’s common court system, with appeals going up to the country’s Supreme Court. Invalidation and revocation proceedings are heard by the country’s patent office, but can be revised by administrative courts.

Under the legislative proposals, local law firm ZM Legal noted, four dedicated departments dealing with IP matters will be created at district court level in the cities of Gdansk, Katowice, Poznan and Warsaw. There will also be two corresponding specialist units within the Courts of Appeal in Katowice and Warsaw.

Warsaw court to focus on technical issues

While all of these newly created departments will have competence to hear a wide range of IP disputes, covering not only patents but also trademarks, copyrights and other issues, it is foreseen that the IP department of the Warsaw court will deal with IP disputes of a technical nature. Professional representation of parties before the specialist courts will be mandatory, unless that case is straightforward, which ZM Legal said had the aim of “improving the speed of IP proceedings”.

Addressing delegates to Medicines for Europe’s legal affairs conference shortly before the Polish ministry launched the public consultation, Jacek Myszko, senior counsel at local law firm Soltysinski, Kawecki & Slezak, welcomed the move towards resolving IP issues more efficiently. Dedicated IP courts, he believed, would provide greater certainty around disputes over patents protecting medicines, including biological drugs.

However, Myszko was sceptical as to whether the planned legislation would tackle other weaknesses of the Polish legal system, such as difficulties in recouping legal costs and damages from losing parties, as well as a tendency for injunctions to halt generic launches. He also observed that reimbursement decisions on several biosimilars had been held up for some time without a clear indication of the reasons for the delays.
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New FDA Commissioner Promises More Of Same, But Better

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“Let me dispel any misconceptions that the change in leadership reflects some desire of the president and the secretary health and human services for the FDA to go in a different direction from the Gottlieb era”

Geneic and biosimilar medicines will continue to be at the forefront of activities at the US Food and Drug Administration (FDA) under the leadership of acting commissioner Ned Sharpless.

“We will continue our important and successful work to increase competition and rein in prescription drug costs through advances in our generic drug and biosimilars programs,” Sharpless told the agency’s staff in his first FDA ‘all hands’ meeting held a week after taking over from Scott Gottlieb.

“I am not planning any radical changes from what the FDA has been trying to accomplish,” reassured Sharpless, who was formerly director of the US National Cancer Institute.

“Let me dispel any misconceptions that the change in leadership reflects some desire of the president and the secretary health and human services [Alex Azar] for the FDA to go in a different direction from the Gottlieb era. That is not the case. Secretary Azar and the White House have been very clear with me that they have been impressed with the FDA’s efforts and would like to see this strong progress continue,” Sharpless stated. He also highlighted bipartisan support in Congress for the agency’s mission.

Promising to “get out in the field” to experience first-hand the agency’s work beyond its Maryland headquarters, oncologist Sharpless pledged that the FDA would be “guided by the science” as it tackled numerous challenges including: recruiting and retaining staff; improving aging infrastructure; using modern technology such as blockchain and artificial intelligence; addressing inspections, counterfeiting and dangerous marketing; and regulating new products including gene therapies and CBD oil.

WEB SITE REVAMP INCLUDES IMPROVED GUIDANCE SEARCHES

He highlighted progress that had already been made under his watch by launching an improved, more user-friendly FDA website. This includes a new page detailing upcoming product-specific guidelines (PSGs) for complex generics. In listing which guidelines on drug development the industry should expect, the agency says it is responding to a recommendation in a report released in January 2018 by the US Government Accountability Office (GAO) entitled “Generic Drugs: FDA Should Make Public Its Plans to Issue and Revise Guidance on Nonbiological Complex Drugs.”

“This new web page provides information about FDA’s plans for issuing new or revised PSGs in the coming year for complex products as defined in the Generic Drug User Fee Amendments Reauthorization (GDUFA II) commitment letter,” explained the agency, which will update the list each quarter as it issues a new set of guidelines. “The information on this web page is anticipated to help generic drug companies better plan their development of complex generic drug products.”

In general, the PSG page has been enhanced to include “text searching for active ingredient or reference-listed drug (RLD) or reference standard, filtering search results, easy-to-follow navigation, and more.” Users can export search results in Excel, CSV or PDF format.

PRODUCT GUIDANCES SUPPORT FIRST-CYCLE APPROVALS

In one of her first actions since replacing Kathleen Uhl as director of the FDA’s Office of Generic Drugs (OGD), Sally Choe credited PSGs in part for reducing quality of abbreviated new drug application (ANDA) submissions, thereby ensuring that generic competition was approved more quickly.

“PSGs provide detailed advice on the evidence recommended to demonstrate bioequivalence for a particular RLD,” she maintained. “They support the high first-cycle adequate rate for the bioequivalence sections of ANDAs.”

“The PSGs web page contains almost 1,700 PSGs, and new guidelines are added every quarter,” Choe pointed out. In 2018 alone, the agency had issued 76 PSGs for complex generics.

Giving the keynote presentation at the FDA’s recent Generic Drug Forum, Choe said the agency had given a refuse-to-receive (RTR) status to a quarter of filings made in the fiscal 2016 cohort year. But that proportion had roughly halved to 13% in the fiscal 2017 cohort, and the figure for fiscal 2018 was significantly lower again at 8.3%.

The reduction in RTR filings in the first year of GDUFA II had coincided, she said, with a record number of ANDA approvals in the 12 months ended 30 September 2018 – 781 final and 190 tentative approvals.

Choe said the standard 10-month ANDA review timeline under GDUFA had brought “predictability,” with the FDA having made commitments on acting within goal dates on not only final and tentative approvals, but also complete response letters (CRLs).

PRE-ANDA MEETINGS AID BIOEQUIVALENCE APPROACHES

For content not covered by PSGs, Choe said the pre-ANDA meetings on complex generics for which GDUFA II laid down

REGULATION
The number of product-specific guidances posted by the FDA in each fiscal year (Source - FDA)

Number of Guidances Posted

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<th>Fiscal Year</th>
<th>New Draft</th>
<th>Revised Draft</th>
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The 136 new draft product-specific guidances issued in fiscal 2018 was the highest number since fiscal 2015.

More than 200 new and revised draft product-specific guidances were issued by FDA in fiscal 2018

The 136 new draft product-specific guidances issued in fiscal 2018 was the highest number since the 154 released in fiscal 2015.

Commitments and timelines were providing "opportunities to discuss new or alternative bioequivalence approaches for complex products". She stressed that the FDA was exceeding its targets, with almost all decisions on whether to grant or deny a meeting made within 30 days, and a perfect record on holding, responding to and recording minutes from meetings.

The figure of 83 pre-ANDA meeting requests received in fiscal 2018 was nearly three-times as high as in any preceding year.

The scientific foundation for meetings and recommendations on complex products was, Choe said, provided by GDUFA-funded science and research activities. "In 2018; she observed "GDUFA funded more than $14m in OGD regulatory science research programs. This involved 24 new contracts and grants, as well as 75 ongoing research collaborations.

Regulatory science priorities for the current 2019 fiscal year are: complex active ingredients, formulations or dosage forms; complex routes of delivery; complex drug-device combinations; and tools and methodologies for bioequivalence and substitutability evaluation.

The FDA on 1 May held a public workshop on generic drug regulatory science initiatives. This meeting at the agency's White Oak campus in Silver Spring, Maryland, is to gather input from stakeholders including industry, academia, patient advocates and professional societies on the agency's GDUFA II commitment to develop an annual list of regulatory science initiatives for generics. This input will inform the FDA's regulatory science plan for its 2020 fiscal year.

Addressing the Alliance for a Stronger FDA just days into Sharpless' tenure, deputy commissioner for policy legislation and international affairs, Anna Abram, stressed that increasing drug competition would remain central to the agency's policies and actions. "Although the FDA does not have a direct role in drug pricing, we do have a role to play in facilitating robust and timely market competition for lower-cost generic drug products, biosimilars and interchangeable biological products," Abram explained.

Looking at small-molecule generics that accounted for 90% of all prescriptions written and generated savings of $265 billion in 2017, Abram said the agency had "given considerable attention" to factors influencing generic competition, such as incentivizing competition on sole-source generics, providing guidance and assistance on developing complex generics, and tackling originators attempts to game the system to extend their monopolies beyond what Congress intended.

Complex generics accounted for about 14% of all generic approvals last year, she observed, while almost one in 10 approvals were for first generics.

"In 2018, we approved or tentatively approved more than 1,000 generic drugs with record-breaking highs in October and November," Abram observed.

Since the record-breaking start to the FDA's financial year starting 1 October 2018 – its second year under the second iteration of GDUFA – final ANDA approvals have stabilized in the first three months of 2019 at 80-90 per month.

Highlighting the agency's mission to facilitate generic competition, Abram observed that eight products had now been approved with 180-day competitive genetic therapy (CGT) exclusivity. The FDA's 2020 budget proposal sought to prevent ANDA applicants from parking indefinitely similar 180-day exclusivity as first filers against listed patents by triggering exclusivity once a subsequent applicant was ready for final approval, but for the exclusivity, she explained.

"We are also proposing to clarify the 180-day forfeiture provision under which first applicants with a deficient application may avoid forfeiting their exclusivity even when the application is deficient for reasons other than a change in, or review of, FDA requirements for approval," Abram explained.

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