3 December 2010

GENERICS bulletin

THE BUSINESS NEWSLETTER FOR THE GENERIC MEDICINES INDUSTRY

EU monoclonals guideline is released for comment

Interested parties have until 31 May 2011 to comment on a draft guideline on 'similar biological products containing monoclonal antibodies' that has just been released by the European Medicines Agency (EMA). The same deadline applies to a draft guideline on 'immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use' that was published on the agency's website at the same time.

In its 13-page main guideline that builds on the basis of an earlier concept paper (**Generics *bulletin***, 27 November 2009, page 19), the agency lays down both non-clinical and clinical requirements for prospective biosimilar monoclonal antibodies (mAbs). For non-clinical development, it proposes "a risk-based approach to evaluate mAbs on a case-by-case basis", thereby determining the extent of *in vitro* and *in vivo* studies required. Conducting "large comparative toxicological studies in non-human primates" is not recommended, the guideline states.

The clinical section is subdivided into discussions on pharmacokinetics, pharmacodynamics, clinical efficacy and clinical safety. Due to mAbs' long half-life, a parallel-group design for pharmacokinetics studies is acceptable, the guideline says, adding that single-dose studies in healthy volunteers might be justifiable. "For mAbs licensed in several clinical indications, it is not generally required to investigate the pharmacokinetic profile in all of them," it adds.

"Pharmacokinetic data can be helpful to extrapolate data on efficacy and safety between different clinical indications of the reference mAb," the guideline notes. A section on extrapolating indications adds that "applicants should support extrapolations with a comprehensive discussion of available literature on the involved antigen receptor(s), and mechanism(s) of action".

The European Generic medicines Association (EGA) said the guideline "appears to strike the right balance" between data requirements and market access.

In its immunogenicity guideline, the EMA notes that several strategies for reducing mAb immunogenicity are currently being considered, including protocols for inducing tolerance or 'de-immunizing' the mAb by deleting relevant T-cell epitopes. "Deletion of T-helper epitopes may result in reduced immunogenicity, whereas the reverse would be the case for deletion of T-regulatory epitopes," it notes.

Actavis strikes global insulin deal

Actavis has signed a letter of intent with Bioton for a deal that would give the generics firm global sales and marketing rights to Bioton's insulin products, including insulin analogues. Under the proposed terms of the deal – which the two firms expect to sign by the end of this year, subject to Actavis' due diligence – Poland's Bioton will be responsible for developing, registering and producing the insulin drugs. The two firms will share equally the resulting costs and profits from Actavis' sales of the products.

The agreement – which will cost Actavis a maximum of PlZ500 million (US$173 million) – is a key step towards the generics specialist becoming a major player in the biosimilars and biotech arena under its recently-appointed chief executive officer, Dr Claudio Albrecht (**Generics *bulletin***, 15 October 2010, page 20).

Actavis told **Generics *bulletin*** it was conducting a more thorough analysis of Bioton's sustained-release human growth hormone and had not yet reached a decision on whether to pursue the project. Discussing Actavis' interest in taking a 51% stake in Bioton's Biopartners affiliate earlier this year (**Generics *bulletin***, 17 September 2010, page 1), Albrecht said the once-weekly, sustained-release formulation – which Biopartners is poised to submit to the European Medicines Agency – had huge potential to improve compliance and treatment experience.

Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION

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FROM THE INDUSTRY

Balwant Heer, VP, Global Head - Product Safety & Risk Management, EU QPPV, Mylan, UK | Inge Bøgh Jansen, Director Pharmacovigilance Drug Safety, Actavis and Vice-Chair of the EGA Safety & Pharmacovigilance Working Group, DK | Augusto Filipe, Director Medical Department, Farmoz, PT and EudraVigilance Expert Working Group Member | Wendy Huisman, EU Pharmacovigilance QP, Teva Europe, NL, Chair of EGA Safety & Pharmacovigilance Working Group and EudraVigilance Expert Working Group Member

FROM THE EGA

Suzette Kox, Senior Director Scientific Affairs, EGA

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MANUFACTURING

FDA bars Claris from importing into US

Claris Lifesciences has received a warning letter from the US Food and Drug Administration (FDA) after failing to investigate thoroughly the contamination of intravenous products made by the company at its plant in Ahmedabad, India. Until the company's manufacturing practices were verified to comply with current good manufacturing practice (cGMP), the FDA said, the facility would be subject to an import alert preventing products made at the plant from entering into the US.

Earlier this year, the FDA told healthcare professionals not to use certain intravenous bags of the antibiotics ciprofloxacin and metronidazole – as well as the antiemetic ondansetron – made by Claris after the agency received reports that certain bags were contaminated with floating matter that "should not be present in a sterile injectable product" (**Generics *bulletin***, 18 June 2010, page 17).

Claris' complaint investigation report had failed to indicate what steps the company had taken to ascertain whether other customers had been affected by similar contamination problems, the FDA said. The report had also failed to identify when the contamination had started, had not identified the origin of the contamination, and had not explained why other products filled in the same packaging line had not been affected by similar problems. The agency also said it was "concerned" by Claris' failure to explain how it could be sure that only the bags identified by the complainants were contaminated, and not any of the other bags in related batches. Furthermore, the agency added, Claris had been marketing injectable sodium bicarbonate without a valid approval.

Sagent Pharmaceuticals, Claris' US distributor, had complained to Claris that bags of metronidazole were contaminated with cladosporium mould. However, the FDA said the manufacturer had not shown that it had initiated an investigation to identify the root cause of the contamination. Furthermore, Claris had disregarded Sagent's findings that the bags did not contain any leaks – claiming that its own methods of detecting leaks superseded Sagent's methods – but had not addressed the presence of fungi.

Pfizer – which last year struck a global deal to source sterile generics from Claris (**Generics *bulletin***, 1 June 2009, page 3) – had returned 33 unopened metronidazole bags to Claris after reporting contamination with fungi and bacteria. However, Claris had failed to identify the contaminants that Pfizer had visually observed in at least 31 of the bags, the FDA said.

DIVESTMENTS

Medley sells brands in Brazil

Sanofi-Aventis' Brazilian generics business, Medley, has agreed to sell three branded generics to Hypermarcas for R$84.0 million (US$48.8 million) in cash. The three products – Digedrat (trimebutine), Lopigrel (clopidogrel) and Pridal (domperidone) – generated sales of R$28.2 million and earnings before interest, tax, depreciation and amortisation (EBITDA) of R$16.0 million in the year ended September 2010.

Hypermarcas said the deal would bolster the Neo Química generics business that the consumer products group acquired at the end of last year (**Generics *bulletin***, 15 January 2010, page 5). In the first nine months of this year, Neo Química – which has more than 70 products awaiting approval by Brazil's medicines agency, Anvisa – generated sales of R$289 million, or 12.8% of Hypermarcas' turnover.

MERGERS AND ACQUISITIONS

Sigma takes Aspen's Pharmaceuticals bid

Aspen Pharmacare has confirmed it will buy Sigma's Pharmaceuticals division for A$900 million (US$885 million) after the South African company reached a formal agreement with the Australian firm on the terms of the sale and the ongoing relationship between the two companies. The transaction is due to be completed on 31 January 2011, five months after Aspen announced its bid (**Generics *bulletin***, 3 September 2010, page 3). Along with Sigma's generics business, the firm's Pharmaceuticals division includes its consumer healthcare brands such as Herron, as well as prescription brands, orphan drugs, medical products and a contract-manufacturing business.

The two companies have entered into a "long-term supply agreement" under which Sigma will act as Aspen's preferred distribution partner and Aspen will make products for Sigma "on an ongoing basis".

Sigma – which will retain its Healthcare wholesale and pharmacy retailing division – said selling its Pharmaceuticals division would significantly reduce its debt. In the year ended 31 January 2010, Sigma's Pharmaceuticals division incurred an operating loss of A$125 million after the firm wrote off A$375 million of goodwill attached to its Arrow generics operation (**Generics *bulletin***, 9 April 2010, page 3). Aspen and Sigma said the A$900 million purchase price represented a multiple of 12-times the Pharmaceuticals division's underlying earnings before interest and tax (EBIT) of A$75 million.

MERGERS AND ACQUISITIONS

Reddy's buys GSK's penicillins

Dr Reddy's Laboratories has struck a deal to acquire GlaxoSmithKline's (GSK's) US penicillins business. The two companies did not disclose the financial terms of the agreement, which is expected to close in the first half of 2011 and will give Dr Reddy's US rights to GSK's amoxicillin-based Augmentin and Amoxil brands, as well as ownership of an oral penicillins facility in Bristol, Tennessee. GSK will retain rights to the brands outside the US.

Abhijit Mukherjee, president of Dr Reddy's Global Generics business, said the deal allowed the Indian firm to enter the US pencillin-based antibiotics market and provided the firm with "manufacturing capabilities that did not previously exist within Dr Reddy's". The transaction was in line with Dr Reddy's strategy to "significantly scale up" its North American generics business, Mukherjee added.

GSK said selling the Bristol facility and divesting the brands in the US would allow it to "focus resources on our newer portfolio of differentiated products".

IN BRIEF

WOCKHARDT increased its turnover by 1.9% to Rs9.40 billion (US$205 million) in the **three months** ended 30 September 2010. The Indian firm said its domestic sales of branded generics grew by 19%, while turnover by Wockhardt USA shot up by 74% on recent launches as the business received approvals for three abbreviated new drug applications (ANDAs) during the quarter. In Europe, UK sales rose by 11% and Pinewood "stabilised its position in the Irish market". Excluding a debt-related exceptional item of Rs2.02 billion, Wockhardt's operating profit improved by 23.6% to Rs1.93 billion.

BUSINESS STRATEGY

Alvogen gets funds to push into top 10

Alvogen has successfully closed a private placement of securities that it believes, along with around US$200 million in funding that has already been committed, will give it the resources to become a top 10 global player by 2015. The US-based firm has a pipeline of 60 abbreviated new drug applications (ANDAs) in its home market and plans to submit more than 200 marketing authorisation applications in central and eastern Europe this year.

Speaking last month at the World Generic Medicines Congress Americas in Washington DC, US, Alvogen's executive chairman Robert Wessman said the generics industry environment had changed markedly since he had built up Actavis into a top five global player, largely through acquisitions. Whereas Actavis had capitalised on fragmented competition, many untapped markets and readily-available funding, industry consolidation meant the top 10 companies now controlled more than half the market, mature markets were seeing "drastic price erosion" and funding was hard to find.

"Collaboration is the key," Wessman insisted, arguing that among the industry's leading lights, only Teva and Sandoz would have the capabilities and resources to develop complex products such as biosimilars in-house. By building a network of strategic partners and focusing on relatively untapped markets in Asia and central and eastern Europe, Alvogen would more than double its turnover to US$85 million in 2010 and reach US$250 million next year, Wessman forecasted.

SECOND-QUARTER RESULTS

Cipla grows at home but margins decline

Growth of nearly a fifth in its domestic business helped India's Cipla to report a 12.0% rise to Rs16.2 billion (US$353 million) in group net turnover in the firm's financial second quarter ended 30 September 2010. Turnover from exports was ahead by just over a tenth to Rs8.32 billion (see Figure 1), as formulations exports increased by 14.1% to Rs6.64 billion despite adverse currency shifts.

However, Cipla's operating margin declined by 3.6 percentage points to 22.6%, which the firm attributed to increased overheads and staff costs at its new facility in Indore, Madhya Pradesh.

	Second-quarter sales (Rs millions)	Change (%)	Proportion of total (%)
Formulations	*6,639*	*+14.1*	*41*
APIs/others	*1,683*	*-1.3*	*10*
Exports	8,322	+10.6	52
India	7,564	+19.8	47
Technology fees/duties	268	-54.6	2
Cipla	**16,154**	**+12.0**	**100**

Figure 1: Breakdown by business and region of Cipla's net turnover in the three months ended 30 September 2010 (Source – Cipla)

BUSINESS STRATEGY/NINE-MONTH RESULTS

Stada makes a move into the Middle East

Stada Arzneimittel has started to build a presence in the Middle East by paying €1.0 million (US$1.4 million) for Egyptian Germa Pharm. The acquired firm – which is based in Cairo, Egypt – achieved a turnover last year of €0.8 million. The German group – in part through its Serbian subsidiary, Hemofarm – intends to "expand business activities in the Middle East" (**Generics *bulletin***, 9 April 2010, page 5).

In the first nine months of this year, Stada's sales outside of Europe – mainly in Asian markets – accounted for less than 5% of group turnover ahead by 3% to €1.18 billion. The German group's Generics sales stalled at €816 million, while its Branded Products division grew by 12% to €311 million following acquisitions.

Domestic Generics sales declined by 6% to €299 million, largely as a result of turnover under the German group's Aliud label falling by a tenth to €163 million. Stressing that it was focusing on maintaining operating profits as it bid for tender contracts, Stada said its market share through German pharmacies had slid from 13.4% to 12.6%.

However, the German slide was offset by double-digit Generics turnover advances in Belgium, Italy, Russia and Spain.

In Belgium, Generics sales rose by a tenth to €94.0 million, while controls on trade discounts in Italy spurred local turnover growth of 43% to €68.0 million (see Figure 1). Stada's Russian Generics sales increased by 15% to €77.9 million despite price controls for essential drugs – which account for two-fifths of the firm's turnover in the country – having come into effect on 1 April 2010.

A 12% Generics advance to €56.9 million in Spain more than compensated for a 3% drop to €53.6 million in France. But in Serbia, Stada shed two-fifths of its Generics turnover, which fell to €36.9 million as the firm deliberately rejected more than €10 million of orders to reduce exposure to bad debts. A new management team at local unit Hemofarm is revising Stada's Serbian business model (**Generics *bulletin***, 1 October 2010, page 22).

A one-time charge of €29.5 million to write-off bad debts in Serbia – along with €33.6 million in other charges such as for selling a Dutch packaging business and restructuring internal reporting lines (**Generics *bulletin***, 3 September 2010, page 1) – reduced Stada's group operating profit by 19% to €105 million. The Generics division's operating margin fell by 2.3 percentage points to 10.6%.

Country/ segment	Nine-month sales (€ millions)	Change (%)	Proportion of total (%)
Germany	*299*	*-6*	*25*
Belgium	*94*	*+10*	*8*
Russia	*78*	*+15*	*7*
Italy	*68*	*+43*	*6*
Spain	*57*	*+12*	*5*
France	*54*	*-3*	*5*
Serbia	*37*	*-40*	*3*
Others	*130*	*–*	*11*
Generics	816	±0	69
Branded Products	311	+12	26
Commercial/corporate	51	+18	4
Stada	**1,178**	**+3**	**100**

Figure 1: Breakdown by country and business segment of Stada Arzneimittel's sales in the first nine months of 2010 (Source – Stada)

MERGERS & ACQUISITIONS/ANNUAL RESULTS

Adcock aims to add presence in Nigeria

South Africa's Adcock Ingram intends to use its majority holding in Ghana's Ayrton Drug as a platform from which to build a major sales and marketing operation in western Africa. "We are currently considering the merits of a transaction in Nigeria," the firm's chief executive officer, Dr Jonathan Louw, told investors.

"We hope to put the war chest we are building to good use," Louw stated, noting that as of 30 September 2010 Adcock held cash and cash equivalents of R1.43 billion (US$203 million). The company was continuing to seek acquisitions and partnerships throughout sub-Saharan Africa, Louw stated, revealing that a couple of OTC and personal-care players in South Africa were "of particular interest" as Adcock looked to build critical mass in fast-moving consumer goods channels.

Once Adcock had by 2012 completed a programme of facility expansion and upgrades – culminating in international accreditations – the South African firm would explore acquisition and partnership opportunities in other emerging markets, Louw said. However, he stressed, the company would be "patient and selective". "We are not going to get into a bidding war and overpay," he promised.

Business segment	Annual sales (Rs millions)	Change (%)	Operating margin (%)
Prescription	*1,666*	*+13.6*	*32.4*
OTC	*1,427*	*+10.7*	*28.5*
Pharmaceuticals	3,094	+12.3	30.6
Hospital Products	1,347	+7.8	18.8
Adcock Ingram	**4,441**	**+10.9**	**27.0**

Figure 1: Breakdown by business segment of Adcock Ingram's sales and operating margin in the year ended 30 September 2010 (Source – Adcock Ingram)

Ghana's Ayrton contributed sales of R43.5 million in the period between Adcock incorporating its 66% stake on 1 April (**Generics *bulletin***, 11 December 2009, page 3) and the end of the firm's financial year in September. Adcock's Prescription drug sales rose by 13.6% to R1.67 billion in the year to September 2010. The total comprised R1.06 billion from generics and R607 million from branded products. Price erosion on efavirenz and simvastatin was offset by strong sales of Gen-Payne (paracetamol/ibuprofen/codeine) and Adco-Zolpidem.

The Prescription business' gross margin improved by more than four percentage points to 58.2%, while its operating margin strengthened by 3.6 points to 32.4% (see Figure 1). Adcock attributed the OTC unit's operating margin falling by 2.7 points to 28.5% to consumers trading down to economy brands and costs associated with assimilating the Unique Formulations vitamins business acquired in November 2009. OTC turnover was up by just over a tenth to R1.43 billion, aided by strong sales of the Dawanol combination analgesic in Kenya and other eastern African markets such as Uganda.

"Double-digit growth in small-volume injectable drugs" contributed to the Hospital Products division's turnover rising by 7.8% to R1.35 billion as its operating margin improved by just over a percentage point to 18.8%. Adcock said it had 22 generic injectables pending approval, while a deal with South Korea's Celltrion would take the firm into the biotech oncology arena.

Baxter has elected not to exercise a call option to take majority control of Adcock Ingram Critical Care, which achieved annual sales of R1.04 billion. Separately, Adcock may sell its hospital supplies unit.

ANNUAL RESULTS

Russia leads increase in Egis' turnover

Double-digit sales growth in Russia and the Commonwealth of Independent States (CIS) enabled Egis to hit its target with a 2.4% turnover rise to HUF119 billion (US$592 million) in the year ended 30 September 2010. The Hungarian firm's sales of pharmaceutical products edged up by 0.8% to HUF90.1 billion, while its turnover from wholesaling and retailing activities rose by 7.7% to HUF28.9 billion.

Egis' export sales advanced by 2% to HUF86.2 billion, which equated to a 3% rise in US dollars to US$423 million (see Figure 1). The Hungarian firm said turnover in its "strategic markets" had strengthened by 12%, led by a 16% gain in Russia and the CIS.

Russian sales 12% higher at US$132 million included turnover of US$6.5 million through the country's DLO healthcare insurance scheme. Egis' sales in Ukraine climbed by 30% to US$19.8 million, while the firm's turnover in Kazakhstan shot up by 36% to US$10.1 million. Sales in Belarus rose by 8% to US$8.89 million, and turnover in other CIS countries was up by 23% to US$15.0 million.

Egis' sales in central and eastern Europe advanced by 9% to US$176 million. Introducing olanzapine helped to lift Polish sales by 5% to US$86.8 million, but launching metoprolol succinate could not prevent a 2% slide to US$22.1 million in the Czech Republic. Entering the oxaliplatin market contributed to sales rising by 16% to US$20.9 million in Romania and by 5% to US$20.7 million in Slovakia.

In Turkey, Egis' sales surged by 70% to US$8.63 million, while the firm's turnover in Bulgaria strengthened by almost a quarter to US$8.26 million. Combined sales in the Baltic States of Latvia and Lithuania edged up by 2% to US$3.53 million, and turnover in Vietnam – which Egis classifies as part of the region due to its similarity to central and eastern European branded generics markets – advanced by 29% to US$5.12 million.

The Hungarian company's domestic sales increased in line with the local market, growing by 4% to HUF32.7 billion. A third of that total came from products licensed from the firm's majority shareholder, Servier, such as the recently-introduced Coverex AS Komb Forte (perindopril/indapamide) antihypertensive. Other branded generics that Egis has launched in Hungary over the past few months include Emperin (betahistine), Granegis (granisetron), Grimodin (gabapentin), Topepsil (topiramate) and Yarocen OD (mirtazapine).

The Hungarian market had stabilised as no major changes to regulations were implemented, Egis commented. Average price cuts were running at less than 1%, the firm noted. Following a HUF489 million payment to the national health insurance fund, OEP, in the financial first quarter through a mandatory 12% reimbursement clawback and fees for registering sales representatives, Egis broke even in calendar 2010 after the government allowed firms to reclaim payments made in previous years provided they made certain research and development investments.

	Annual sales (US$ millions)	Change (%)	Proportion of total (%)
Russia	*132.0*	*+12*	*31*
Ukraine	*19.8*	*+30*	*5*
Other CIS	*34.0*	*+22*	*8*
Russia/CIS	185.8	+16	44
Poland	*86.8*	*+5*	*21*
Czech Republic	*22.1*	*-2*	*5*
Romania	*20.9*	*+16*	*5*
Slovakia	*20.7*	*+5*	*5*
Others	*25.5*	*+33*	*6*
Central and eastern Europe	176.0	+9	42
Other finished dose	23.3	-35	6
APIs/others	38.3	-25	9
Exports	**423.4**	**+3**	**100**

Figure 1: Breakdown by market of Egis' export sales in the year ended 30 September 2010 (Source – Egis)

Egis said a 35% decline to US$23.3 million in sales of finished-dose pharmaceuticals in the rest of the world was in line with forecasts. Turnover from active pharmaceutical ingredients (APIs) and related products down by a quarter to US$38.3 million was also as the firm had expected.

The company's gross margin improved by 0.7 percentage points to 56.1%, while both its sales and marketing and its research and development expenses rose by 8% to HUF28.1 billion and HUF10.9 billion respectively. However, Egis pointed out that its total operating costs had increased by just 3% as tight controls had reduced its administrative expenses by 13% to HUF10.0 billion.

Strong sales in its strategic export markets and lower production costs – offset in part by weaker utilisation of its API facilities – lifted Egis' operating profit by a tenth to HUF15.5 billion. The firm's operating margin improved by nearly a percentage point to 13.0%.

3 December 2010 **Issue 143**

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Printed by Warwick Printing Company Limited, Leamington Spa CV31 1QD, UK.

ISSN 1742-0784
Company registered in England No 2765878.

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ANNUAL RESULTS

Covidien's turnover slides down by 13%

Competition to its generic hydrocodone and immediate-release oxycodone reduced Covidien's Specialty Pharmaceuticals sales by 13% to US$473 million in the US group's financial year ended 24 September 2010. That decline excluded the one-off turnover of US$354 million that Covidien generated in the previous year from extended-release oxycodone before it was forced to withdraw from the US market.

Covidien's sales of active pharmaceutical ingredients (APIs) dipped by 2% to US$395 million (see Figure 1).

	Annual sales (US$ millions)	Reported change (%)	Change at CER* (%)
Contrast Products	604	+2	±0
Radiopharmaceuticals	519	-7	-7
Specialty Pharmaceuticals	473	-13	-13
Active Ingredients	395	-2	-3
Pharmaceuticals	**1,991**	**-5**	**-6**

* constant exchange rates

Figure 1: Breakdown by business and region of Covidien's Pharmaceuticals sales in the year ended 24 September 2010. The figures exclude one-time US sales of US$354 million from extended-release oxycodone in the year ended September 2009 (Source – Covidien)

FIRST-QUARTER RESULTS

Aldara deal delivers steep rise for Perrigo

Securing rights to market an authorised generic of Graceway's Aldara (imiquimod) 5% cream in the US helped Perrigo to increase its Prescription Pharma sales by 47% to US$69.3 million in the OTC store-brand specialist's financial first quarter ended 25 September 2010.

In April this year, Perrigo secured rights to distribute an Aldara authorised generic until a key patent expires on 24 February 2011 (**Generics *bulletin***, 23 April 2010, page 17). This deal followed Nycomed's launch with 180-day exclusivity at the end of February, a move that recently survived Graceway's bid for a preliminary injunction (**Generics *bulletin***, 30 June 2010, page 13). Perrigo in September obtained its own approval for a version of the keratosis and carcinoma treatment after Nycomed's 180-day exclusivity expired.

Affected by the terms of the deal with Graceway, the Prescription Pharma division's gross margin slid down by 7.4 percentage points to 40.1%. Adjusted for acquisition-related amortisation and research and development write-offs in the comparable 2009 quarter, the generics division's operating margin fell by 6.6 percentage points to 29.2%.

Supplying bulk temozolomide in Europe lifted Perrigo's active pharmaceutical ingredients (API) sales by 13% to US$37.4 million. A 12-point gross margin gain was reflected in the division's operating profit more than doubling to US$10.3 million. The US firm's total operating profit – including its OTC and nutritional businesses – climbed by 55% to US$112 million on turnover 21% higher at US$641 million.

THIRD-QUARTER RESULTS

Valaciclovir doubles Ranbaxy's US sales

Strong sales of valaciclovir tablets increased Ranbaxy Laboratories' US sales by 94% to US$86 million in the third quarter of this year. Ranbaxy said it had retained more than a third of the market for the antiviral drug after its 180-day exclusivity ended on 23 May this year, while its US OTC business also expanded. Including Canadian sales around a tenth higher, the firm's sales in North America rose by 70% at constant exchange rates (CER) to US$105 million.

Arun Sawhney – who in late August replaced Atul Sobti as managing director (**Generics *bulletin***, 3 September 2010, page 27) – said the firm was working hard to resolve its good manufacturing practice (GMP) issues in the US, such as by co-operating fully with the US Food and Drug Administration and Department of Justice.

Other areas of focus included improving the firm's "operational performance" and maximising synergies with parent group Daiichi Sankyo, such as launching levofloxacin in Romania and South Africa.

Region/ business	Third-quarter sales (US$ millions)	Change at CER* (%)	Proportion of total (%)
India	106	+18	26
North America	105	+70	26
Europe**	41	-13	10
Romania	19	+20	5
Africa	35	-6	9
Asia-Pacific	27	-24	7
CIS	26	+11	6
Latin America	24	+6	6
APIs/others	23	-12	6
Ranbaxy	**406**	**+13**	**100**

* constant exchange rates ** excluding Romania

Figure 1: Breakdown by region and business of Ranbaxy Laboratories' sales in the third quarter of 2010 (Source – Ranbaxy)

Domestic turnover improved by 18% to US$106 million (see Figure 1) as Ranbaxy increased its market share for all of its key consumer healthcare brands. But sales in Europe – excluding sales up by a fifth to US$19 million in Romania – tumbled by 13% at CER to US$41 million, which Ranbaxy attributed to "channel issues".

The CER decline in Africa – where Ranbaxy recently opened a production plant in South Africa (**Generics *bulletin***, 17 September 2010, page 2) – was 6% to US$35 million. "Our antiretroviral performance and the new facility will help the region," the company insisted.

Turnover slumped by 24% to US$27 million in Ranbaxy's Asia-Pacific region, but the company said sales were up slightly when the effects of divesting certain operations in China and Japan were excluded.

The Indian firm raised its sales in the Commonwealth of Independent States (CIS) by 11% at CER to US$26 million "amid volatile currency movement". Turnover in Latin America was up by 6% to US$24 million, excluding exchange-rate shifts, as Ranbaxy's Brazilian business performed better. Sales of active pharmaceutical ingredients (APIs) and other products fell by 12% to US$23 million as group turnover improved by 13% to US$406 million.

Staff costs a quarter higher at US$79 million cut Ranbaxy's earnings before interest, tax, depreciation and amortisation (EBITDA) by a third to US$29 million. But financial gains, largely from exchange-rate shifts, more than doubled the firm's pre-tax profit to US$76 million.

SECOND-QUARTER RESULTS

Indoco expands its supply agreements

Indoco has struck a supply agreement with South Africa's Aspen for a number of oral liquids and tablets as well as creams in Latin America and sub-Saharan Africa. The Indian company said the products would be manufactured at its Goa oral solids, liquids and semi-solids facility, for which good manufacturing practice (GMP) approval had been recently renewed by Australia's Therapeutic Goods Administration (TGA). The agreement follows an earlier deal with Aspen for ophthalmic products (**Generics *bulletin***, 7 May 2010, page 7).

At the same time, Indoco has also extended the deal it struck with Watson earlier this year to develop and manufacture sterile products for the US company (**Generics *bulletin***, 12 February 2010, page 17). It has agreed to supply four further products in addition to the original six covered by the agreement. These four products had a combined US market size of US$765 million, Indoco claimed.

Sales rising by 38.7% for the three months ended 30 September 2010 pushed the Indian company's turnover up to Rs1.32 billion (US$29.8 million) as both domestic sales and exports increased by just under two-fifths to Rs920 million and Rs403 million respectively (see Figure 1). Whilst total formulations sales had grown by 36.7% to Rs1.24 billion, sales of active pharmaceutical ingredients (APIs) had seen "remarkable growth" of 75.8% to Rs86.3 million, Indoco said.

Turnover more than doubled in emerging markets

In emerging markets, turnover had more than doubled to Rs81.5 million, Indoco noted. Over the three months, the company registered five products in the Philippines, with a further six entering the final stages of registration. Nine products were close to being licensed in Cameroon, Indoco said. During the quarter, the firm also entered the Namibian and Botswanan markets for the first time.

In Hungary, Indoco's levocetirizine tablets received regulatory approval, which the firm said would open up opportunities across the European Union (EU) through the mutual-recognition procedure. Indoco also filed new product applications in Australia and the UK, and registered its paracetamol tablets in Denmark with supply due to start by the end of 2010.

Whilst the company's ratio of material consumption to sales had risen by more than three percentage points to 45.8%, related staff costs and research expenses had fallen, Indoco said. This helped raise Indoco's earnings before interest, taxes, depreciation and amortisation (EBITDA) by just over 50% to Rs230 million, giving the firm an EBITDA margin that was 1.3 percentage points higher at 17.4%. The Indian firm's pre-tax profit climbed by 77% to Rs170 million.

	Second-quarter sales (Rs millions)	Change (%)	Proportion of total (%)
Formulations	*884*	*+37.2*	*67*
APIs	*36*	*+85.4*	*3*
India	920	+38.6	70
Formulations	*353*	*+35.4*	*27*
APIs	*51*	*+69.6*	*4*
Exports	403	+39.0	30
Indoco	**1,323**	**+38.7**	**100**

Figure 1: Breakdown by region and product segment of Indoco's sales for the three months ended 30 September 2010 (Source – Indoco)

NINE-MONTH RESULTS

Russia and Romania drive Richter's rise

Double-digit growth in Russia and Romania, as well as in its home market of Hungary, increased Gedeon Richter's Pharmaceutical sales by 16.8% to €674 million (US$918 million) in the first nine months of this year. Including its Romania-based wholesaling and retailing operations, the company raised its turnover by 12.9% to €782 million.

The firm's 40.6% Pharmaceutical rise to €222 million in Russia included around two months' worth of inventory stocking ahead of a new medicines law that set maximum wholesale and retail margins for essential drugs and came into effect from 1 September. The Russian rise was almost matched by a 40.2% advance to €34.5 million in Ukraine as the local political and economic climate stabilised. The rest of the Commonwealth of Independent States (CIS) contributed a 37.2% advance to €48.7 million.

Polish sales fell by 2.9%, or by 11.1% in local-currency terms, to €50.3 million as sales of non-promoted generics tumbled. But growth in Romania of 15.5% to €22.3 million – as higher sales of Aflamil (aceclofenac), Moduxin (trimetazidine) and Vidotin (perindopril) offset the negative effect of delayed payment terms and a 5% to 12% clawback by the country's statutory health insurance fund – led a turnover rise of 3.8% to €169 million in the European Union, excluding Hungary.

A strong performance by Larus (atorvastatin) and the firm's range of oral contraceptives generated sales growth of 11.5% to €17.1 million in the Czech Republic and of 7.0% to €15.1 million in Slovakia. Launching Zaranta (rosuvastatin) helped to lift turnover in Bulgaria by 6.7% to €8.4 million. Sales in the Baltic States were 9.1% stronger.

A 1.1% turnover rise to €44.7 million in western Europe included sales of €19.1 million in Germany and €8.3 million in France.

The Hungarian firm's domestic sales were just over a tenth higher at €89.3 million (see Figure 1), aided by only "insignificant" price cuts to date this year and launching Nebibeta (nebivolol).

Exports to the US declined by a tenth to €76.7 million as generic competition increased to drospirenone-based contraceptives.

A 6.2% decline to US$107 million in wholesaling and retailing turnover – along with the inventory stocking in Russia – helped to lift Richter's gross margin by 4.6 percentage points to 61.3%. The group's operating margin improved by just over five percentage points to 23.7%.

After the quarter closed, Richter announced deals to acquire Swiss gynaecology specialist PregLem and Grünenthal's oral contraceptive portfolio (**Generics *bulletin***, 12 November 2010, page 15).

	Nine-month sales (€ millions)	Change (%)	Proportion of total (%)
Russia/CIS	304.8	+40.0	39
European Union*	168.8	+3.8	22
Hungary	89.3	+10.5	11
US	76.7	-10.1	10
Rest of World	34.3	+12.1	4
Pharmaceutical	**673.9**	**+16.8**	**86**
Wholesale/retail	**106.6**	**-6.2**	**14**
Other/corporate	**1.6**	**-21.2**	**–**
Gedeon Richter	**782.0**	**+12.9**	**100**

* excluding Hungary

Figure 1: Breakdown by country and business of Gedeon Richter's sales in the first nine months of 2010 (Source – Gedeon Richter)

IN BRIEF

ACETO is looking for **acquisitions** "within areas with which we are comfortable", the active pharmaceutical ingredients (APIs) supplier has told investors. Stressing that its balance sheet was strong enough to capitalise on opportunities, the US-based firm said any deal should be accretive to earnings. In Aceto's financial first quarter ended 30 September 2010, group turnover advanced by 24.1% to US$87.7 million. Health Sciences sales rose by 12.6% as the company continued to roll out finished-dose generics in the US, where sales of intermediates also improved. The firm's push into Japan's intermediates market was progressing "very cautiously", Aceto added.

CEPHALON said its sales of generic pain products totalled US$61.4 million in the **third quarter** of this year following the US firm's acquisition of Swiss generics market leader Mepha. Just over half of that total – US$34.0 million – came from the firm's own off-patent Actiq (fentanyl) lozenges. Generic central nervous system drugs and oncology treatments in Europe contributed US$8.61 million and US$5.55 million respectively to group turnover up by nearly a third to US$707 million. Other generics, mainly in Europe, added US$83.4 million, of which US$54.1 million came from Mepha. Cephalon expects to report group sales of about US$2.7 billion this year, rising to around US$3.0 billion in 2011.

GENERICSWEB – the patent intelligence specialist – has won an **export award** in its home state of New South Wales, Australia. The Sydney-based company generates just 3% of its turnover from its domestic market.

PODRAVKA'S Pharmaceuticals sales dropped by 2% to CrK514 million (US$97.2 million) in the **first nine months** of this year as an 8% decline in Croatia to just over Crk300 million outweighed 10% growth in other markets. Pharmaceuticals accounted for 19% of the Croatian food and drinks group's turnover, which declined by 3% to CrK2.71 billion. However, a better gross margin contributed to the division's operating margin rising by 2.6 percentage points to 11.2%. Podravka said its board had declined an offer from Hungary's OTP Bank to buy 10.65% of the firm's shares.

CARDINAL HEALTH is to spend US$1.3 billion on strengthening its presence in the New York area by buying local pharmaceuticals distributor **Kinray**, which has an annual turnover of US$3.5 billion.

AKORN said strong sales of antidotes and erythromycin 1g ointment more than doubled its core turnover to US$21.7 million in the **third quarter** of this year. Including the US firm's discontinued vaccines business, the reported sales growth was 12%. Replacing expired batches of antidotes and launching hydromorphone 10mg/ml in three pack sizes almost trebled sales of hospital and injectable drugs to US$8.2 million. Turnover from ophthalmic drugs nearly doubled to US$7.8 million after the firm introduced erythromycin, while contract-service revenues almost trebled to US$5.6 million, largely due to making more vancomycin 5g through a joint venture with India's Strides Arcolab. Better facility utilisation rates raised Akorn's gross margin by 39 percentage points to 52.7%, enabling the US firm to report an operating profit of US$3.99 million, compared to a loss of US$3.84 million in the 2009 third quarter.

LANNETT said losing sales of US$2.8 million after the US Food and Drug Administration (FDA) forced it to stop selling unapproved morphine sulfate solution was partly responsible for its turnover falling by 19% to US$25.4 million in the US firm's financial **first quarter** ended 30 September 2010. Suing the FDA over the morphine decision partly caused Lannett's US$0.73 million operating loss.

BUSINESS STRATEGY

Aurobindo launches into Maltese market

Aurobindo has launched its first products directly into the Maltese market under its own label. The move follows about 18 months after the Indian firm officially opened its first European facility on Malta, enabling batch-release of its products into the European Union (**Generics *bulletin***, 1 June 2009, page 3).

Eight anti-diabetic, anti-infective and central nervous system products have been launched in the initial phase, represented by 15 stock-keeping units. The firm intends to have commercialised a further 14 molecules in the local market by the end of next year, and to have achieved a local turnover of about €5 million (US$7 million) by its 2013/14 financial year.

Malta's attraction for Aurobindo and other non-European firms is that products that were never patented in the country can be stockpiled there in readiness for a Day 1 launch elsewhere in the European Union (EU). Aurobindo is releasing batches from Malta for its own use as well as for third-party firms, which have audited and approved the Maltese facility. Its products are present in about 15 EU countries, and it supplies Pfizer, for example, with many products for European markets, especially France (**Generics *bulletin***, 12 February 2010, page 15).

Batch-testing of sterile products should soon be possible at the Maltese facility, but the company is still mulling over whether to extend the laboratories and warehouse unit into a fully-fledged manufacturing plant. Aurobindo already has facilities in Brazil, China and the US.

PRICING AND REIMBURSEMENT

Australian industry slams reform to PBS

Reforms to Australia's Pharmaceutical Benefits Scheme (PBS) are "inappropriate, ill-considered and rushed", according to the country's Generic Medicines Industry Association (GMiA). The association said that the Australian government's plans to slash funding of the PBS by A$1.9 billion (US$1.9 billion) over five years through price cuts were "a cynical cash-grab" that played "Russian roulette with a national treasure".

Measures set out in the National Health Amendment (PBS) Bill 2010 – which was passed by Australia's parliament on 23 November – were "flawed" and "altogether unnecessary", said the GMiA, pointing out that a ten-year process to reform the PBS that had begun in 2007 was already exceeding the government's savings target (**Generics *bulletin***, 5 March 2010, page 14).

Average 23% price cut in 2012

The 2010 bill builds on the 2007 reforms, such as by introducing mandatory price disclosure for multisource products from 1 December 2010. All drugs that are not exempt from this price disclosure – which is intended to "achieve a PBS price that more closely matches the price at which multiple brand medicines are actually being sold as a result of competition in the market place" (**Generics *bulletin***, 28 May 2010, page 12) – will be subject to average 23% price cuts on 1 April 2012.

On 1 February 2011, multisource medicines will be subject to one-off price cuts of either 2% or 5%, depending on whether they are on the F2A formulary as less competitive drugs or the F2T formulary for products that were subject to greater pharmacy discounts as of 1 October 2006. Also from 1 February next year, the mandatory price cut applied to off-patent brands when the first bioequivalent alternative is listed on the PBS will increase from 12.5% to 16%.

These measures result from a memorandum of understanding that Australia's government agreed with brand industry body Medicines Australia. The GMiA described the "protectionist deal negotiated in secret" as a "highly irregular and inappropriate government process", arguing that the government's failure to consult with generics firms could lead to drug shortages and supply-chain disruptions. Medicines Australia insisted the reforms would give Australian taxpayers a "fairer deal" as the PBS had for years been "paying overblown prices for older, off-patent medicines".

REGULATORY AFFAIRS

EGA stresses duplicates issue

Europe's generics industry "needs to find a solution urgently" to the European Commission's recently-adopted prohibition on the same group of companies submitting duplicate dossiers through the centralised procedure, the European Generic medicines Association (EGA) has highlighted to Europe's regulators.

Representing the EGA at the association's third Info Day with the European Medicines Agency (EMA), Teva's Michael Banks said the Commission's approach to duplicate submissions "constitutes a barrier to trade and access to the single market".

Banks – who chairs both the EMA-EGA working group and the EGA's regulatory and scientific affairs committee – insisted that banning duplicates "creates a distortion between the centralised and decentralised procedures and will slow down the dynamic of market penetration of generic and biosimilar medicines".

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PATENT LITIGATION

FTC regards rule as settlement 'plan C'

Issuing an agency rule that would "shift the burden of proof" onto companies to show 'pay for delay' patent-litigation settlements promoted competition would be a viable "plan C" if legislation and pending court appeals fail, the US Federal Trade Commission's (FTC's) Thomas Rosch believes.

"I believe a legislative fix is likely the only way to eliminate these anti-competitive settlements," Commissioner Rosch told delegates to the World Generic Medicines Congress Americas held in Washington DC, US, last month. However, he added, previous unsuccessful attempts to tack provisions onto a war-funding bill had been a "terrible idea".

Rosch insisted the FTC's 11th Circuit appeal in a case regarding Androgel (testosterone) "should be winnable". In granting a motion to dismiss the case earlier this year (**Generics *bulletin***, 5 March 2010, page 1), an Atlanta district court had, according to Rosch, erred by permitting settlements within the "scope of the exclusionary potential of the patent". Rather, he argued, a patent's exclusionary potential was a function of whether the patent owner enforced it in line with antitrust laws.

Speaking at the same conference, Congressman Henry Waxman highlighted a recent Congressional Budget Office (CBO) report that found banning pay-for-delay settlements would save US$2.7 billion over 10 years (**Generics *bulletin***, 3 September 2010, page 16). "Hopefully we will get another opportunity to enact this legislation," he said.

PRICING AND REIMBURSEMENT

Quebec revises its pricing plan

Cuts to generics prices in Quebec will be phased in over the next two years, according to advice published by the Canadian province's Medicines Council. Prices will be reduced in Quebec in three stages, eventually matching those of Ontario by April 2012, the council said.

Earlier this year, Quebec's health minister Yves Bolduc said the province would cut its generics prices at around the same time as Ontario reduced its prices (**Generics *bulletin***, 16 July 2010, page 6). Ontario recently began to implement the plans announced earlier this year to cut its generics prices to 25% of those of the equivalent brands (**Generics *bulletin***, 23 April 2010, page 9).

Until April 2011, the price of a generic in Quebec must be no more than 37.5% of that of the province's brand price. However, if the lowest generic price in the rest of Canada – according to October's price list – is higher than the 37.5% figure, generics in Quebec will be able to match the higher price. Between April 2011 and April 2012, similar rules will apply, but with a 30% threshold and using a price list from February 2011. And after April 2012, all generics prices in Quebec will have to be lower than or equal to the lowest price in Canada.

If the brand equivalent to a generic is not listed in Quebec – or if the brand price in the province has already been lowered to match generics – an average of prices in Quebec and Ontario will be used.

The new rules will come into effect as soon as possible.

IN BRIEF

THE UK GOVERNMENT has launched a six-month review of the country's **intellectual-property system**. It will be led by Professor Ian Hargreaves, a digital economy expert from Cardiff University.

PRICING & REIMBURSEMENT

Gemme tells France to look beyond cuts

Increasing prescription within France's *répertoire* of generic equivalents, expanding the *répertoire* to cover a wider range of treatments, and more closely controlling doctors' ability to mark prescriptions as non-substitutable are three ways in which the country's generics industry association Gemme says greater savings could be made within France's healthcare budget. The association has also urged the country's government to promote more widely an existing scheme that allows prescription costs for generics to be paid directly by health insurers, rather than paid by the patient and later reclaimed.

France's government recently announced plans to cut prices and reduce the reimbursement rates of certain medicines as part of its attempt to save €2.4 billion (US$3.3 billion) from the country's healthcare budget in 2011 (**Generics *bulletin***, 15 October 2010, page 1). However, Gemme pointed out that generics manufacturers had already agreed to considerable price cuts over the past three years, leading to ex-factory prices of omeprazole and simvastatin falling by around 75% over a five- to six-year period. Rather than lowering prices, the association suggested, it was important for France to consider the savings that could be achieved through greater generic penetration.

Gemme urged the government to limit its use of reference prices – or *tarifs forfaitaires de responsabilité* (TFRs) – that aligned reimbursement prices for brands and generics listed in the same group in the *répertoire* (see page 20). TFRs should be just one part of a wider generics policy, Gemme said. The association also voiced its support for the government's plans to encourage higher rates of generic prescribing. If the current rate of generic prescribing within the *répertoire* was increased by just one percentage point, Gemme said, €105 million more could be saved from France's healthcare budget.

EUROPEAN LEGISLATION

EGA welcomes balanced line

The European Parliament has "ensured a proper balance" between improving patient access to objective information on prescription drugs and avoiding commercial advertising, the European Generic medicines Association (EGA) insists. On 24 November, the parliament adopted two legislative reports that outlined rules at European Union and member state levels. Firms will be able to provide non-promotional information such as package inserts, but – as is currently the case – will not be able to advertise brands through broadcast or print media.

Greg Perry, director-general of the EGA, said it was particularly important that the parliament had limited pharmaceutical companies to providing information on just their own products, as this would help to avoid the misinformation campaigns that were highlighted in the European Commission's pharmaceutical sector inquiry. "It is very significant that the members of parliament have responded to these findings of the sector inquiry, and we hope that the member states will do so too in the next legislative round," Perry maintained.

IN BRIEF

ACTA – the **Anti-Counterfeiting Trade Agreement** – has been released in final draft form. A footnote says parties may exclude patents and data protection from civil-enforcement measures.

MARKET FORECAST

Industry has reached 'mid-life crisis' point

The global generics industry has reached an "inflection point" in its evolution, according to Buddy Gumina, a partner at private-equity firm Apax Partners. "The generics industry is going to change dramatically and, in some respects, will be unrecognisable in three to four years time," he told delegates to the World Generic Medicines Congress Americas held in Washington DC, US, last month.

"Industry is in a mid-life crisis," Gumina argued, highlighting declining growth forecasts after a wave of patent expiries in 2012 and 2013. "What will happen after this bolus, and will you have to be in biosimilars?" he wondered, adding: "Investors do not like uncertainty."

Noting that Apax had recently agreed to sell for US$1.2 billion the Qualitest generics business for which it had paid around US$900 million in 2007 (**Generics *bulletin***, 1 October 2010, page 1), Gumina believed forecasts of sales stagnation would increasingly push originators into the generics sector. "Big pharma is coming in a big way," he warned, predicting that major generics players would be viewed as takeover targets over the next three to four years. "The players on the generics field will be very different," Gumina believed, predicting a new wave of nimble, entrepreneurial generics start-ups.

Apax viewed several small to medium-sized generics players as attractive acquisition targets or opportunities for investment in return for a minority stake, he added.

MARKET RESEARCH

Portugal recovers after cuts

Portugal's generics market showed improvement in September, recovering sharply after an August slump according to figures from the country's medicines agency, Infarmed. Sales had fallen steadily in value since June, after pricing regulations cut generics prices for reference products with a wholesale price of over €10 (US$13.60) to under 35% of the originator price (**Generics *bulletin***, 18 June 2010, page 13). However, Portugal's September sales figures – in both volume and value terms – were the highest of the year so far.

Volume sales for the month reached 4.74 million units, a higher figure than in any other month since Infarmed's records began in 2005. And by value, monthly sales exceeded €60 million for only the third time since 2005 at €62.0 million. Market penetration was at its highest rate for 12 months, with a volume rate of 19.8% and value penetration that was just over a fifth of the total medicines market.

Over the first nine months of 2010, volume penetration averaged 17.9% of the total medicines market, which was more than two percentage points higher than the average for the whole of 2009. This rise was due to penetration of the market available to generics growing by more than three percentage points to 33.6% and the size of this off-patent sector creeping up by 0.7 percentage points to 53.5% of the total pharmaceuticals market. Volume sales for the nine months were 32.8 million units, which generated turnover of €469 million at retail prices.

IN BRIEF

COUGH MEDICINES containing **antihistamines** are to be contra-indicated for children younger than two years old in France, following a risk-benefit analysis.

REGULATORY AFFAIRS

EGA offers solution to EU cost of ageing

Rising healthcare costs due to the European Union's (EU's) ageing population will be unsustainable without greater use of generics, according to the European Generic medicines Association (EGA). Addressing members of the European Parliament (MEPs) and other stakeholders at an event held in the European Parliament, the association's director-general Greg Perry urged policymakers to "exploit the advantages" offered by generics and biosimilars.

Professor Steven Simoens of Katholieke Universiteit Leuven, Belgium, said IMS Health figures indicated that a 20% increase in the market share of generics in key areas among the elderly could save an additional €16 billion (US$22 billion) from EU healthcare budgets. However, Simoens said to overcome older people's reservations about generics, more information should be provided to both patients and prescribers. Financial incentives such as lower patient co-payments for generics could increase penetration, he suggested.

IMS' Alan Sheppard insisted authorities' focus on generics prices did not always deliver maximum savings. Instead, he argued, they should implement 'generics first' policies for treating certain diseases. Sheppard said there was "no reason why hypertension in 90% of patients should not be treated with generics of 'gold standard' treatments".

Belgian MEP Anne Delvaux, who hosted the EGA event, called on policymakers and healthcare professionals to use generics wherever available. However, she warned that the benefits of generics were being undermined by brand firms' anticompetitive behaviour, as identified by the European Commission's pharmaceutical sector inquiry (**Generics *bulletin***, 1 August 2009, page 11).

Bulgarian MEP Antonyia Parvanova agreed with Delvaux' comments, claiming the Commission had not yet taken steps to address these "vicious practices" that delayed generic market entry and had "a major negative impact on the sustainability of European healthcare". Parvanova also urged the European authorities to review the duration of originators' patents and employ cost-benefit assessments.

The EGA's director of pharmaceutical policy, Elke Grooten, pointed out that savings were being lost due to delays in generics receiving national pricing and reimbursement clearance. Christophe Roeland from the Commission's Directorate-general for Enterprise noted that the pharmaceutical sector inquiry had covered this topic, which the Commission would address next year as part of its review of the Transparency Directive 89/105/EC.

REGULATORY AFFAIRS

Languages block EU patent

Disagreement over the language regime of a single European patent system has prevented the 27 member states of the European Union (EU) from reaching unanimous agreement on how to proceed. Earlier this year, the European Commission proposed that EU patents should be examined and granted in either English, French or German (**Generics *bulletin***, 16 July 2010, page 10).

Despite the lack of unanimous agreement, European Commissioner Michel Barnier indicated that several EU member states supported moving towards "enhanced cooperation". Barnier said that the Commission would take action as soon as it received a formal request for enhanced cooperation, adding that December's meeting of the EU's competitiveness council would be a chance to move forward quickly.

ONCOLOGY DRUGS

Docetaxel arrives in EU before US entry

Companies including Actavis have seized on patent expiry for Sanofi-Aventis' Taxotere (docetaxel) in major European Union (EU) markets to introduce the oncology drug at the end of November. But as **Generics *bulletin*** went to press, Hospira was still awaiting final clearance from the US Food and Drug Administration (FDA) to launch the cancer drug on the other side of the Atlantic.

Describing docetaxel as "the largest oncology product ever to go off patent in Europe" – with annual sales of around €800 million (US$1.05 billion) in 29 European countries – Actavis said it had launched a unique 140mg single vial that was more convenient and would reduce wastage.

The firm – which is also offering 20mg and 80mg sizes – said it had introduced docetaxel concentrate under its own label in Germany, Sweden, the Netherlands and the UK. In Germany and the UK, it is also offering the chemotherapy agent through its Medis third-party business. National Health Service (NHS) list prices in the UK range from £160 (US$249) for the 20mg/1ml vial to £900 for the 140mg/7ml version.

In the US, Hospira said on 15 November that it expected final FDA approval for its docetaxel "no later than within 10 business days". Earlier this year, the injectables specialist convinced a Delaware district court that two patents protecting Taxotere until January 2013 were invalid due to obviousness and inequitable conduct (**Generics *bulletin***, 1 October 2010, page 11).

ANTIEMETICS

Dutch court decides listing is infringing

Publishing the forthcoming availability of a generic in a database for pharmacists constitutes an infringing offer for sale, even when the generics firm states that it will not launch until after patent expiry, the Court of Appeal in The Hague, the Netherlands, has decided.

Reversing a lower court ruling, the Court of Appeal said Pharmachemie had infringed the Dutch part of GlaxoSmithKline's (GSK's) European patent EP0,226,266 by including its generic ondansetron antiemetics in the G-Standaard drugs database for pharmacists, albeit without a selling price. A letter sent by the Teva subsidiary to G-Standaard users stressed that the firm would not sell ondansetron before 25 June 2006, the day after expiry of the '266 patent.

Pointing out that publishing in the G-Standaard was the means *par excellence* of informing trade channels that a cheaper generic was available, the Court of Appeal said Pharmachemie's actions were likely to affect the prescribing, dispensing and ordering behaviour of healthcare professionals.

Offer to sell is enough to infringe

It was irrelevant, the court maintained, that no actual sale would take place within the term of the '266 patent – an offer to sell through the G-Standaard published on 16 May was sufficient to infringe. It was similarly irrelevant, the court added, that it had been common practice to list generics in the G-Standaard ahead of patent expiry, as this did not excuse patent infringement.

"Exploiting and enforcing patent rights until their very last day of validity does not represent an abuse of those rights," the court insisted. "That is not changed by the fact that a semi-public body's system prevents competitors from entering the market immediately upon patent expiry," it added, dismissing Pharmachemie's argument that GSK had employed "artificial tricks" to extend its monopoly rights.

Having quickly rejected Pharmachemie's invalidity arguments, the court awarded costs of around €130,000 (US$178,000) against the generics firm, as well as damages to be determined.

ONCOLOGY DRUGS

APP and Teva lose on Alimta

Fresenius Kabi's APP Pharmaceuticals and Teva Parenteral Medicines have failed to prove that the US compound patent protecting Eli Lilly's Alimta (pemetrexed disodium) chemotherapy agent is invalid. Lilly's US patent 5,344,932 – which it licenses from Princeton University – expires on 24 July 2016. In the first nine months of this year, US Alimta sales totalled US$722 million.

In a bench ruling, Delaware district Judge Gregory Sleet found in favour of Lilly. APP had argued that each of the asserted claims in the '932 patent was invalid for double-patenting. Teva had insisted one or more claims failed to meet "the requirements for a proper dependent claim" and that "the differences between the subject matter of the claims of the '932 patent and the relevant prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art".

Lilly recently sued both APP and Teva in an Indiana district court over a recently-issued Alimta patent – US patent 7,772,209 which expires on 24 November 2021 and covers 'novel antifolate combination therapies'.

FEBRUARY 16-18, 2011

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GASTROINTESTINAL DRUGS

Krka's esomeprazole hit by Austrian block

Krka has been forced to stop marketing esomeprazole in Austria after AstraZeneca persuaded Vienna's commercial court to issue a temporary injunction. The Slovenian generics specialist – which had launched its rival to AstraZeneca's Nexium esomeprazole brand in April this year – said it would appeal.

The injunction issued by the commercial court prohibits Krka from marketing any form of product in Austria that contains esomeprazole with an optical purity of more than 99.8%. AstraZeneca's motion for an injunction was based on Krka's alleged infringement of the Austrian part of European patent EP1,020,461, which was granted last year and covers the esomeprazole magnesium salt. Earlier this year, AstraZeneca had obtained injunction against esomeprazole launched in Austria by Sandoz' 1A Pharma and Hexal units.

Austria was just one of the European Union markets that traditionally applied six-year data exclusivity in which Krka had launched esomeprazole, the others being Denmark, Ireland and Slovenia. In Denmark, several injunction hearings took place during November, while in Ireland, AstraZeneca sued Krka and Wockhardt's Pinewood in August this year. In October, a district court in Ljubljana, Slovenia, refused AstraZeneca's request for an injunction against Krka.

The '461 patent is the subject of legal disputes all across Europe. Ranbaxy has recently brought an invalidity challenge in the UK, while in Germany – where several firms, including Krka's Tad, introduced esomeprazole in September and October this year (**Generics *bulletin***, 17 September 2010, page 15) – the originator has requested injunctions.

A similar injunction request against Krka is pending in Sweden, while hearings on the '461 patent's validity are scheduled for late November in Italy and early next year in the Netherlands. In France, Ratiopharm and Ethypharm are leading the fight against the '461 patent, while Teva has triggered a revocation action in Belgium. Legal processes involving Krka and Sandoz are also underway in Finland, Poland, Norway and Spain, while Krka and Zentiva have challenged esomeprazole magnesium patents in Estonia, Latvia and Lithuania.

AstraZeneca said 13 notices of opposition against the '461 patent had been filed with the European Patent Office (EPO) before the opposition deadline of 22 April 2010.

IN BRIEF

COBALT PHARMACEUTICALS has been blocked by a US preliminary injunction from launching at risk a generic version of Roche's **Boniva** (**ibandronate**) osteoporosis brand. A 30-month stay on final approval for the Watson affiliate's abbreviated new drug application (ANDA) ended on 16 November 2010.

TEVA has secured a positive opinion from the committee for human medicinal products (CHMP) within the European Medicines Agency for **lamivudine/zidovudine** 150mg/300mg film-coated tablets, which are equivalent to GlaxoSmithKline's **Combivir** antiretroviral brand. In the UK, Teva has just launched **prednisolone** 2.5mg and 5mg enteric-coated tablets that are equivalent to Alliance's **Deltacortril** brand and has pushed into the UK's wound-care sector by introducing the PolyHeal dressing based on polystyrene microspheres.

HOSPIRA has launched in the US gemcitabine 2g vials with 180-day exclusivity. They are equivalent to Lilly's Gemzar oncology agent.

SCHIZOPHRENIA DRUGS

Abilify patent holds against attack in US

The only patent listed against Otsuka's Abilify (aripiprazole) in the Orange Book maintained by the US Food and Drug Administration (FDA) is valid and enforceable, New York district Judge Mary Cooper has decided. Cooper ordered that defendants Apotex, Sandoz, Sun, Synthon and Teva be refused final approval for their abbreviated new drug applications until paediatric exclusivity attached to Otsuka's US patent 5,006,528 expires on 20 April 2015. The Japanese firm's US marketing partner, Bristol-Myers Squibb, reported US sales of the schizophrenia brand that were down by 6% to US$1.42 billion in the first nine months of this year.

Having conceded infringement, the generics firms argued that the '528 patent was invalid due to obviousness and obviousness-type double patenting, and was also unenforceable due to inequitable conduct.

Addressing obviousness, Cooper rejected the generics firms' reliance on three compounds disclosed in a prior-art patent covering a wide genus of carbostyril derivatives. "The prior art does not teach either the unsubstituted butoxy [compound] or the 2,3 dichloro propoxy compound as a starting point, and mere structural similarity does not by itself render the claimed compound obvious," Cooper ruled, adding that Apotex' reliance on another compound was also flawed. Abilify's status as the US' sixth-largest drug also suggested it was not obvious.

The double-patenting attack centred on aripiprazole not being patentably distinct from the unsubstituted butoxy disclosed in the prior-art US patent 4,734,416. But Cooper said this argument failed on the same grounds as the obviousness approach. Regarding inequitable conduct, Cooper said the generics firms had failed to show that Otsuka had intentionally withheld information that was material.

ALZHEIMER'S DISEASE DRUGS

Mylan Canada wins battle

Mylan has fought off Janssen's attempt to get a Canadian court order barring approval for the generics firm's rival to Reminyl ER (galantamine) 8mg, 16mg and 24mg extended-release capsules for treating Alzheimer's disease. The relevant claims of Canadian patent 2,310,950 covered "a method of medical treatment that cannot be monopolised under a Canadian patent", Judge Robert Barnes decided.

Meanwhile, Canada's Federal Court of Appeal has upheld Barnes' decision to throw out a trademark covering the colour of GlaxoSmithKline's Advair Diskus (fluticasone/salmeterol) inhaler (**Generics *bulletin***, 9 April 2010, page 18).

ALLERGY DRUGS

Perrigo ships Synthon's tablets

Perrigo has started shipping levocetirizine tablets in the US with 180-day market exclusivity immediately after its Dutch partner received final approval for its alternative to the Xyzal allergy remedy that Sanofi-Aventis markets for UCB. First-filer Synthon licensed exclusive US sales and distribution rights to Perrigo just over two years ago (**Generics *bulletin***, 19 September 2008, page 14). Quoting Wolters Kluwer data, the two firms said US Xyzal sales rose by 12% to US$224 million in the year ended September 2010.

Zydus tries novel strategy on Strattera

For most of the time since the patent litigation over Eli Lilly's attention deficit hyperactivity disorder (ADHD) drug Strattera (atomoxetine hydrochloride) began in 2007, the case has followed a fairly typical path. The FDA says the first abbreviated new drug application (ANDA) – or applications – containing paragraph IV certifications to the key Strattera patent 5,658,590 were submitted on 29 May 2007 (see Figure 1), exactly one year before the end of atomoxetine's new chemical entity (NCE) exclusivity.

As Lilly started suing over the '590 patent – which expires on 26 May 2017 – it became clear that as many as 10 companies may have submitted their ANDAs on the first day possible and would likely share 180-day market exclusivity if their patent challenges succeeded. "Although Strattera is a successful product – Lilly reported US brand sales of more than US$445 million in 2009 – a generic market with so many players offers much lower rewards than some of the filers may have anticipated," commented Thomson Reuters, which compiles a database of paragraph IV patent certifications (see Figure 2).

But one ANDA filer, India's Zydus Cadila, took a different path in December 2007 by stipulating that the '590 patent – the only patent listed against Strattera in the Orange Book maintained by the US Food and Drug Administration (FDA) – was valid, enforceable and covered its proposed generic atomoxetine. "At that point, Zydus was no longer a party to the ongoing litigation," Thomson Reuters noted.

Having granted Lilly summary judgement of infringement and denied the ANDA filers' motions for summary judgement of invalidity, a New Jersey district court in August this year determined that the '590 patent was invalid for lack of enablement and utility. Because Lilly had not submitted test results showing that atomoxetine could be used to treat ADHD – and because a person of ordinary skill in the art would not have recognized the claimed method's utility in light of the specification – the patent was not properly enabled. The FDA promptly granted final approval to atomoxetine ANDAs filed by firms including Actavis, Aurobindo, Mylan, Sandoz, Sun, Teva, and Zydus.

"It is at this point that things began to get unusual," remarked Thomson Reuters. While Lilly's appeal against the district court's ruling was hardly unexpected, the US Court of Appeals for the Federal Circuit barred generic launches pending resolution of the appeal (**Generics *bulletin***, 3 September 2010, page 23). Because Zydus was no longer a party to the district-court litigation, the Indian firm was not named in the appeal or injunction.

Realising its error, Lilly sought unsuccessfully to add Zydus as a named defendant-appellee. The Indian firm then in late October initiated a declaratory judgment action against Lilly in the New Jersey district court, arguing that it was restricted from launching by neither the Court of Appeals' injunction nor the 2007 consent judgement barring it from entering the market during the life of the '590 patent, a life it said ended with the district court's invalidity ruling. In mid-November, Zydus stipulated that it would not market atomoxetine commercially until either the district court delivered a declaratory-judgment ruling or ended the injunction, or the Court of Appeals confirmed the '590 patent was invalid. An appeals hearing is scheduled for 9 December.

"Zydus could find itself in the paradoxical position of being the only company to enjoy generic exclusivity, having failed to pursue its patent challenge where others succeeded," Thomson Reuters observed.

KEY DETAILS: STRATTERA

Brand:	Strattera
Active ingredient:	atomoxetine hydrochloride
Delivery form:	10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg capsules
Brand owner:	Eli Lilly
Annual US brand sales:	US$288 million*
First paragraph IV filing accepted by FDA:	29 May 2007
Known paragraph IV filers:	Actavis, Apotex, Aurobindo, Glenmark, Mylan, Sandoz, Sun, Synthon, Teva, Zydus Cadila
Patents at issue – expiry dates:	5,658,590 – 26 May 2017
District court location:	New Jersey Court of Appeals (Federal Circuit)
Litigation references:	Lilly vs Actavis *et al* 2010-1500 Zydus vs Lilly 2:10-cv-05584
Other FDA Orange Book patents with expiry dates:	None

* nine-month US brand sales reported by Lilly.

Figure 1: Key details of paragraph IV challenges to Eli Lilly's Straterra (atomoxetine) attention deficit hyperactivity disorder drug in the US (Source – Thomson Reuters)

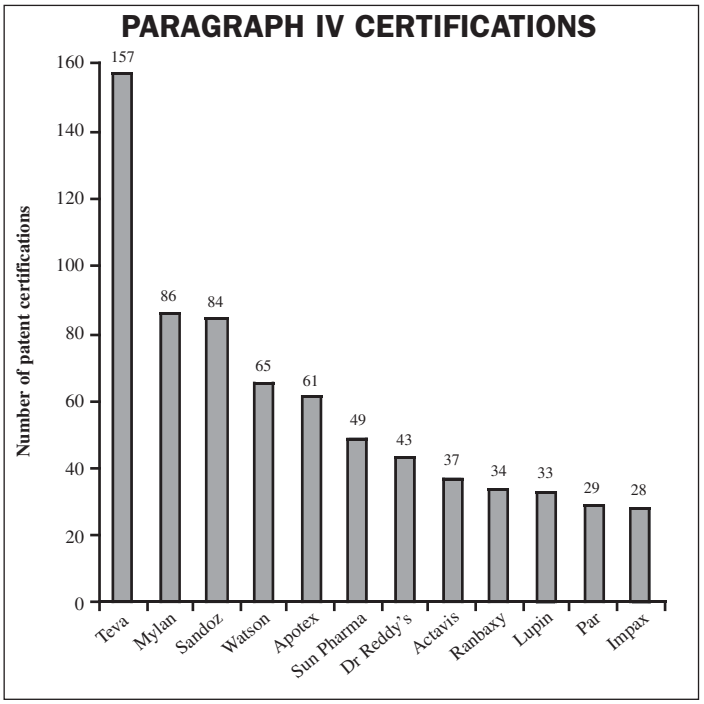

Figure 2: Numbers of paragraph IV patent certifications recorded by Thomson Reuters to September 2010 (Source – Thomson Reuters)

OPHTHALMIC DRUGS

Greece's Alapis wins EU latanoprost battle

Greek company Alapis intends to roll out latanoprost eye drops throughout the European Union (EU) after it was among five firms that successfully opposed Pfizer's European patent EP1,225,168 covering the Xalatan glaucoma treatment.

The opposition division of the European Patent Office (EPO) communicated on 12 November its decision to revoke in full Pfizer's '168 patent, which covers "prostaglandin derivatives for the treatment of glaucoma or ocular hypertension". If the decision becomes final, all the patent claims will be invalid throughout the EU. Watson's Breath, Lareq Pharma, Mylan and Ratiopharm had also opposed the '168 patent.

Holds authorisations in Italy, Spain and UK

Alapis has already obtained marketing authorisations for latanoprost in Italy, Spain and the UK through the EU's decentralised procedure, while in its home market and Bulgaria the Greek firm secured national approvals. Authorisations in Croatia, Serbia and Switzerland should be granted in the near future, Alapis added.

"The positive outcome of the patent-litigation case, the successful registration of the product in a number of countries, and the strategic co-operation with companies which have licensed our generic latanoprost are in line with Alapis' stated goal of dynamically entering the market for ophthalmic products," stated the Greek company's vice-president and chief executive officer Stelios Kymbaridis.

ONCOLOGY DRUGS

Teva's temozolamide must wait until 2013

Teva will have to wait until August 2013 to launch a rival to Merck & Co's Temodar (temozolamide) brand in the US after a US Court of Appeals overturned a Delaware district court ruling that a key patent was unenforceable. The ruling is also a blow to Perrigo, which is to supply Teva with the active pharmaceutical ingredient (API) for the brain-cancer drug.

At the start of this year, Delaware Judge Sue Robinson found that Merck's US genus patent 5,260,291 – for which paediatric exclusivity expires on 11 February 2014 – was unenforceable due to inequitable conduct and 'prosecution laches', or an unreasonable and unexplained delay in seeking a patent, such as repeatedly abandoning and refiling applications (**Generics *bulletin***, 12 February 2010, page 15).

Shortly after that decision, Teva agreed – subject to "limited exceptions" – not to market generic temozolamide while Merck appealed Robinson's verdict. In return, the Israeli firm won rights to start selling the oncology drug from August 2013, effectively ignoring Merck's six-month paediatric extension for the '291 patent (**Generics *bulletin***, 26 March 2010, page 17).

Overturning the district court ruling in a two-to-one decision, Court of Appeals Judges Alan Lourie and Pauline Newman said Robinson had erred on the issue of inequitable conduct. "A court cannot simply infer that an applicant 'should have known' the materiality of withheld information, and thus intended to deceive the US Patent and Trademark Office (USPTO), because the applicant knew of the information, and the information is material," they stated.

Addressing prosecution laches, Lourie and Newman noted that Teva's Barr had filed an abbreviated new drug application (ANDA) more than 13 years after the '291 patent had been issued and over seven years after Temodar had been approved in the US. "Barr has failed to establish that it or others developed or invested in temozolamide – or any other claimed tetrazine compound – between 1982 and 1991, the period of delay," they insisted.

But Judge Sharon Prost dissented, claiming that her colleagues had propounded "a new and unsupportable legal standard for prosecution laches". "By stalling prosecution for its own business purposes for a nearly a decade, [Merck's partner] Cancer Research obtained a patent which does not expire until 2014 – almost 32 years after the first application in this chain was filed," Prost pointed out. Barr had been "unable to enter the market without risking a patent-infringement suit until a date far later than the one it would have faced had Cancer Research not engaged in its excessive delays," she argued.

UROLOGY DRUGS

Synthon claims a world first

Synthon believes it has become the world's first company to obtain marketing authorisations for generic tamsulosin extended-release tablets. The Dutch company – which claims it is Europe's leading supplier of tamsulosin capsules – said it had secured clearance in all major European countries, having "successfully concluded multiple registration procedures". The tamsulosin hydrochloride 0.4mg extended-release tablets are equivalent to the Omnic Ocas brand that Synthon said Astellas had launched as part of its lifecycle-management strategy for the benign prostatic hyperplasia brand. Synthon said European sales of tamsulosin tablets reached €181 million (US$244 million) last year.

ANTIHYPERTENSIVES

France to introduce new reference prices

Several branded and generic antihypertensives will have reference prices imposed on them from 1 January 2011 in France, according to a decision by the country's economic committee for healthcare products (CEPS). Benazepril 5mg and 10mg tablets, fosinopril 10mg and 20mg tablets and fosinopril/hydrochlorothiazide 20mg/12.5 mg tablets will be subject to the reference prices, along with trandolapril capsules in 0.5mg, 2mg and 4mg strengths.

CEPS applies reference prices – or *tarifs forfaitaires de responsabilité* (TFRs) – to product groups listed in France's *répertoire* of generic equivalents in which generics are failing to achieve target penetration rates. By setting a common reimbursed retail price for both the branded reference product and its generic equivalents, the committee is attempting to remove the financial incentive for pharmacists to dispense a brand product when generic substitution is possible. Of all reimbursable generics sold in France, around 20% by volume and around 15% by value are subject to TFRs.

Other drugs receiving reference prices from the start of January include the anti-inflammatory betamethasone 2mg tablets and nimesulide 100mg tablets, brimonidine tartrate 2mg/ml eyewash, and ciclopirox 8% antifungal nail solution. Transdermal fentanyl pain-relief patches in 12µg, 25µg, 50µg, 75µg and 100µg strengths are also covered by the measures, as well as cholesterol-lowering fluvastatin 20mg and 40mg capsules and anti-epileptic oxcarbazepine tablets in several strengths.

RESPIRATORY DRUGS

Par is Reddy's rival for zafirlukast tablets

Par Pharmaceutical has reacted to Dr Reddy's Laboratories' US launch of a generic version of AstraZeneca's Accolate (zafirlukast) 10mg and 20mg tablets by introducing an authorised generic of the asthma drug through a deal with the brand firm. US Accolate sales were around US$50 million in the year to August 2010.

Reddy's had launched with 180-day market exclusivity after New Jersey district Judge Mary Cooper granted the Indian firm summary judgement of non-infringement regarding US patent 5,482,963, which expires on 9 January 2013. The '963 patent covers 'Form A' amorphous zafirlukast stabilised using polyvinylpyrrolidone (PVP). Reddy's used hydroxypropyl cellulose as its stabiliser.

Argument around doctrine of equivalents

The litigants agreed that while the Reddy's compound did not literally infringe the '963 patent, it fell under the doctrine of equivalents that prevents working around patents by using "unimportant and insubstantial substitutes for certain elements". But Reddy's argued AstraZeneca could not assert infringement because it had only obtained or 'prosecuted' the '963 patent by demonstrating surprising results from using PVP as a stabilising binder.

"A competitor looking at the prosecution history as a whole would reasonably believe that AstraZeneca clearly and unmistakably surrendered binders other than PVP," Cooper ruled.

ANTIDEPRESSANTS

Australian firms fail on venlafaxine XR

Australian generics players Sigma, Alphapharm and Generic Health have failed in their challenges to Wyeth's Australian method-of-use patent 2003,259,586, which was granted in May 2007 and protects the firm's Efexor-XR (venlafaxine) extended-release antidepressant. However, Sydney Federal Court Judge Jayne Jagot has recommended an expedited appeal process.

Jagot had last year issued interlocutory injunctions that barred marketing of Sigma's Evelexa XR, Alphapharm's Enlafax-XR and Generic Health's Generichealth XR rivals to Efexor-XR (**Generics *bulletin***, 25 September 2009, page 17). At the time, Jagot noted that Wyeth's Efexor-XR was Australia's leading antidepressant with annual sales of A$115 million (US$114 million).

Delivering her verdict of more than 200 pages, Jagot dismissed the generics firms' wide-ranging attacks based on lack of inventive step. "It would have been far from obvious to the skilled addressee that the solution to the 'problem' of the immediate-release formulation was a method of treatment involving the single daily-dosing formulation as claimed," she stated, noting Efexor-XR's commercial success.

Jagot was similarly unimpressed by the generics firms' attempts to have the '586 patent revoked on the basis of false suggestion or misrepresentation. "The applicants have not established any ground to justify revocation of the patent in whole or in part," she said. An attempt by Alphapharm and Generic Health to avoid infringement by construing "a single daily dosing formulation of venlafaxine hydrochloride" to exclude products that used hydrogel technology must fail, Jagot added.

Staying her orders to destroy the generic venlafaxine products pending appeals, Jagot granted in part Alphapharm's motion to redact certain information that was subject to confidentiality agreements with its supplier, Greece's Pharmathen. Wyeth undertook not to delist Efexor-XR from Australia's Pharmaceutical Benefits Scheme (PBS) – ensuring the generics could, upon a successful appeal, be listed on the PBS as bioequivalent – but refused to pledge that it would not launch an authorised generic.

ANTIDEPRESSANTS

Actavis attacks Oleptro in US

Actavis South Atlantic has filed an abbreviated new drug application (ANDA) including a paragraph IV challenge to a key US patent protecting Labopharm's Oleptro (trazodone) 150mg and 300mg extended-release tablets. Canada's Labopharm said it was reviewing Actavis' notice letter. The ANDA challenges US patent 6,607,748, which expires on 29 June 2020 and is the only patent listed against the once-daily antidepressant in the Orange Book maintained by the US Food and Drug Administration (FDA). Labopharm pointed out that Oleptro was also covered by new dosage-form (NDF) exclusivity that would prevent ANDA approval until 2 February 2013.

IN BRIEF

PHARMAC – New Zealand's pharmaceutical management agency – has started a sole-supply tender process for **tacrolimus** capsules. The deadline for bids is 17 December. Pharmac is also reimbursing Mylan's Loxalate (escitalopram) and Arrow-Sertraline from 1 December.

JANUARY

24 January

■ 4th EGA Pharmacovigilance Discussion Forum

25-26 January

■ 10th EGA Regulatory & Scientific Affairs Conference

London, UK

The European Generic medicines Association's Pharmacovigilance Forum will look at issues including the new European Union legislation and risk-management. Speakers include Peter Arlett, head of sector for pharmacovigilance and risk management at the European Medicines Agency and Linda McAvan, European Parliament rapporteur of the pharmacovigilance package. This meeting will precede the EGA's two-day conference on Regulatory and Scientific Affairs.

Contact: Cristina Romagnoli, GPA Conferences.
Tel: + 377 93 501 348.
E-mail: info@gpaconferences.com.
Register online at www.gpaconferences.com.

FEBRUARY

14-15 February

■ PharMeet

Lisbon, Portugal

This event will offer opportunities to network as well as to strike licensing deals for a wide range of products, including biosimilars.

Contact: PharMeet.
Tel: +34 91 637 0660.
E-mail: contactevents@pharmeet.com.
Website: www.pharmeet.com.

16-18 February

■ GPhA Annual Meeting

Orlando, USA

This is the three-day conference of the US generics body and will look at regulatory issues, as well as providing networking opportunities.

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

17-18 February

■ Pharmaceutical Regulatory Affairs in the Middle East

London, UK

Covering countries including Egypt, Israel, Jordan, Libya, Oman, Qatar, Saudi Arabia and United Arab Emirates, this two-day conference will provide an overview of the regulatory environment, and look at product registration and harmonisation and recent developments.

Contact: Management Forum.
Tel: +44 1483 730071.
E-mail: registrations@management-forum.co.uk.
Website: www.management-forum.co.uk.

8-10 December

■ 13th IGPA Annual Conference

Mumbai, India

This three-day conference is being organised by the Indian Pharmaceutical Alliance and is the global event of the worldwide generics industry. It is the annual joint meeting of the Canadian, European, Indian, Japanese and US generics industry associations, the CGPA, EGA, IPA, JGA and GPhA. Speakers will include Didier Barret, chairman of the EGA and chief executive officer of Mylan Europe, and Paul Bisaro, chairman of the GPhA and Watson's chief executive officer.

Contact: IPA. Tel: +91 22 2600 0632. E-mail: info@ipa-india.org.
Register online at www.igpamumbai2010.com.

22-25 February

■ World Generic Medicines Congress Europe

London, UK

This four-day event will provide interactive networking opportunities and includes pre- and post-conference workshops. Topics to be covered will include sustainability, global intellectual property developments, and biosimilars. Speakers will include Robert Wessman, executive chairman of Alvogen, Gerard van Odijk, president and chief executive officer of Teva Pharmaceuticals Europe and Henry Waxman, member of the US Congress.

Contact: Sabrina Khamissa, HNC.
Tel: +44 207 608 7055.
E-mail: skhamissa@healthnetwork communications.com.
Website: www.healthnetworkcommunications.com/2011/genericsuk.

28 February – 1 March

■ EuroPLX 45

Lisbon, Portugal

This two-day meeting provides a forum for companies to discuss licensing, marketing and distribution opportunities for patented drugs, generics, OTC medicines and nutraceuticals.

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

2 & 3-4 March

■ Generics and Biosimilars Asia

Singapore

This is a two-day event which will be preceded by two workshops. The conference will look at topics including the outlook for the off-patent drugs industry, regulatory issues, market access and pricing strategies, collaborations and strategic alliances and biosimilars.

Contact: IQPC.
Tel: +65 6722 9388.
E-mail: enquiry@iqpc.com.sg.
Website: www.genericsbiosimilarsasia.com.

MARCH

18 March

■ 7th EGA Legal Affairs Forum

Brussels, Belgium

This one-day event organised by the EGA will cover patent issues and will also provide networking opportunities.

Contact: Cristina Romagnoli, GPA Conferences.
Tel: + 377 93 501 348.
E-mail: info@gpaconferences.com.
Register online at www.gpaconferences.com.

28-30 March

■ DIA 23rd Annual EuroMeeting

Geneva, Switzerland

Keynote speaker at this event covering patient safety, counterfeiting, global drug development and biologicals will be European health commissioner John Dalli. Other speakers will include the EGA's Suzette Kox on biosimilars.

Contact: Drug Information Association (DIA).
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Prices rise as citalopram stocks shrink

Four products were granted the concession of 'no cheaper stock obtainable' (NCSO) status in November by the UK Department of Health as a result of shortages in the market. These were gabapentin 100mg and 400mg capsules, citalopram 20mg tablets and tamoxifen 20mg tablets. The concession allows pharmacists to dispense a more expensive alternative product and to be reimbursed accordingly.

A glance at Figure 1 illustrates the problem. All three strengths of citalopram were affected, but the prices of the 20mg strength in particular rocketed upwards. At £4.63 (US$7.24), the average trade price of a 28-tablet pack of citalopram 20mg in November was more than three-times higher than it had been a month earlier.

Without the concession, pharmacists would have been badly out of pocket because the Drug Tariff reimbursement price of the product was only £1.30. Historically, citalopram prices have been low, and the antidepressant's reimbursement price had recently been reduced still further. As a member of category M of the Drug Tariff, citalopram's price had been reduced from £1.46, which was based on historical quarterly market data provided by generics firms. Actual market prices had then been uplifted to provide a pharmacy profit margin.

Taking the market as a whole, price falls were few and quite modest in November. Glimepiride was a notable exception, with all four strengths appearing in Figures 1 and 2. Metformin was another product to appear in two tables – Figures 1 and 3 – but for reason of its double-digit average price increases. Prices for tamoxifen 20mg that was granted an NCSO concession rose sharply, while gabapentin 100mg was just outside Figure 3 with an 18% average price rise to £6.54.

BIGGEST FALLERS

Product/Strength/Pack size	Lowest price	Change (%)	Average price	Change (%)
Bendroflumethiazide tabs 2.5mg 28	£0.18	-22	£0.32	-16
Glimepiride tabs 2mg 30	£0.32	+10	£0.54	-15
Glimepiride tabs 3mg 30	£0.37	-12	£1.06	-15
Zolpidem tabs 5mg 28	£0.49	±0	£0.56	-15
Glimepiride tabs 1mg 30	£0.24	±0	£0.52	-14
Loperamide caps 2mg 30	£0.25	±0	£0.43	-13

BIGGEST RISERS

Product/Strength/Pack size	Lowest price	Change (%)	Average price	Change (%)
Ciprofloxacin tabs 750mg 10	£0.61	±0	£1.44	+63
Amiloride tabs 5mg 28	£0.26	+63	£0.51	+33
Metformin tabs 500mg 28	£0.22	±0	£0.41	+30
Tamoxifen tabs 20mg 30	£1.99	+34	£3.75	+26
Isosorbide tabs 10mg 56	£0.26	+4	£0.50	+25
Propranolol tabs 40mg 28	£0.17	-6	£0.36	+25

Figure 1 (below): Comparison between the periods 1-31 October 2010 and 1-24 November 2010 of the lowest and average UK trade prices of fast-moving generics. Each average price was calculated from at least 11 data points. Figure 2 (above) and Figure 3 (above right): Biggest changes recorded between the periods 1-31 October 2010 and 1-24 November 2010 in lowest and average UK trade prices of about 120 commonly-dispensed generics. The basket specifically excludes the 'fast movers' shown below, but includes other presentations of the same products. Each average price was calculated from at least 21 data points (Source – WaveData).

FAST MOVERS

Product/Strength/Pack size	Lowest price	Change (%)	Average price	Change (%)
Alendronate tabs 70mg 4	£0.30	+30	£0.56	+36
Amlodipine tabs 5mg 28	£0.20	±0	£0.30	±0
Amlodipine tabs 10mg 28	£0.25	-11	£0.38	-3
Carvedilol tabs 6.25mg 28	£0.40	+5	£0.49	±0
Carvedilol tabs 12.5mg 28	£0.46	±0	£0.62	-3
Ciprofloxacin tabs 500mg 10	£0.25	-7	£0.39	-13
Citalopram tabs 10mg 28	£0.44	+52	£0.99	+54
Citalopram tabs 20mg 28	£1.10	+108	£4.63	+259
Citalopram tabs 40mg 28	£0.69	+17	£1.33	+53
Clarithromycin tabs 250mg 14	£1.02	-5	£1.45	-2
Enalapril tabs 20mg 28	£0.26	-10	£0.42	-3
Fosinopril tabs 20mg 28	£1.45	±0	£1.93	±0
Glimepiride tabs 4mg 30	£0.61	±0	£0.89	-8
Lamotrigine tabs 50mg 56	£1.52	+1	£2.21	+3
Lamotrigine tabs 100mg 56	£1.59	+2	£3.66	+1
Lansoprazole caps 15mg 28	£0.44	±0	£0.59	+5
Lansoprazole caps 30mg 28	£0.99	-4	£1.26	+5
Lisinopril tabs 5mg 28	£0.18	±0	£0.29	+11
Lisinopril tabs 10mg 28	£0.19	±0	£0.34	+12
Lisinopril tabs 20mg 28	£0.34	±0	£0.51	+9
Metformin tabs 500mg 84	£0.52	+2	£0.83	+16
Mirtazapine tabs 30mg 28	£0.79	-8	£1.26	+1
Omeprazole caps 10mg 28	£0.60	-19	£0.94	+1
Omeprazole caps 20mg 28	£0.75	±0	£1.04	+9
Ondansetron tabs 4mg 30	£2.95	-1	£4.62	-6

FAST MOVERS

Product/Strength/Pack size	Lowest price	Change (%)	Average price	Change (%)
Paroxetine tabs 20mg 30	£0.95	+1	£1.41	+7
Pravastatin tabs 20mg 28	£0.85	-9	£1.27	-2
Pravastatin tabs 40mg 28	£1.29	-7	£1.84	+2
Ramipril caps 2.5mg 28	£0.35	+6	£0.57	+11
Ramipril caps 5mg 28	£0.48	+4	£0.63	+3
Ramipril caps 10mg 28	£0.56	-2	£0.71	±0
Risperidone tabs 2mg 60	£0.78	-9	£1.53	±0
Sertraline tabs 50mg 28	£0.44	±0	£0.91	-4
Sertraline tabs 100mg 28	£0.70	±0	£1.16	+4
Simvastatin tabs 10mg 28	£0.17	+13	£0.21	+3
Simvastatin tabs 20mg 28	£0.22	±0	£0.28	+2
Simvastatin tabs 40mg 28	£0.40	+3	£0.50	+4
Sumatriptan tabs 50mg 6	£0.72	+1	£0.92	-1
Tamsulosin caps 400µg 30	£0.77	-3	£1.13	+7
Terbinafine tabs 250mg 14	£1.09	-3	£1.42	+4

Teva reveals aspirations for its respiratory brands

More than doubling sales of branded respiratory products over the next five years is a key component of Teva's plan to become a US$31 billion business by 2015. David Wallace reports.

Teva says it is still on track to meet its ambitious target of more than doubling its turnover before the end of 2015. Having expanded in the European Union (EU) through buying Ratiopharm earlier this year, the company is also increasing sales in "key emerging markets", with forecasted annual growth of 10% in Eastern Europe, 12% in Latin America and 14% in Russia supporting its goal of increasing turnover from US$13.9 billion in 2009 to US$31 billion by 2015 (**Generics *bulletin***, 15 January 2010, page 20).

One of the key pillars of Teva's long-term growth strategy is expanding the branded side of its business, which covers both branded generics and original treatments developed by the company. For many years, Teva admits, its branded business was seen as being limited to its multiple-sclerosis therapy Copaxone (glatiramer acetate). However, the firm has recently made an effort to reduce its dependency on this single product and to diversify its branded business into several areas, one of which is respiratory products.

Since acquiring Ivax in 2006, the Israeli firm's global turnover from respiratory products has nearly trebled, with annual sales projected to reach US$1 billion for the first time by the end of this year. And between 2010 and 2015, Teva expects its respiratory business to more than double in size. Sales of around US$2.4 billion in 2015 will contribute 26% of its expected total branded sales of US$9.2 billion (see Figure 1).

The Israeli company is confident that its ambitious respiratory plans will succeed. It is already marketing respiratory products in six of the seven leading countries globally. Together, these seven markets account for more than 80% of the current global respiratory market value of US$34 billion (see Figure 2). Teva only lacks a presence in Japan, but it plans to concentrate its immediate respiratory efforts on the EU and US.

Teva needs to achieve a compound annual growth rate (CAGR) of 14% over the next five years to reach its overall US$31 billion target by 2015, a rate that is almost matched by the five-year CAGR of the top seven respiratory markets. However, the company intends to increase its respiratory sales more rapidly, aiming for a CAGR of 20.5% for the business unit's turnover that will increase respiratory sales from US$1 billion to US$2.4 billion by 2015 (see Figure 3).

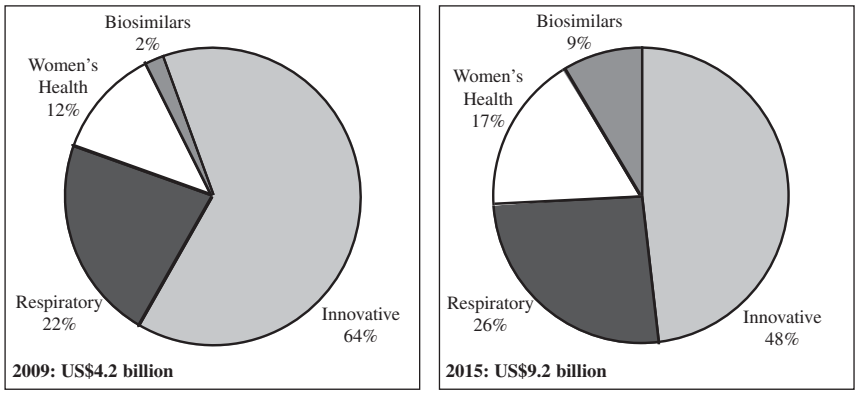

Figure 1: Breakdown of Teva's growth targets for branded sales between 2009 and 2015

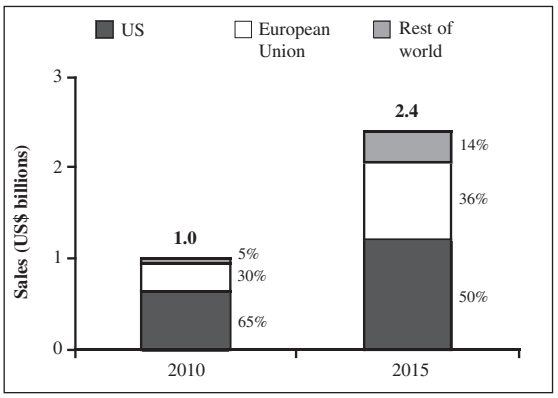

Figure 3: Teva intends to more than double its branded respiratory sales between 2010 and 2015 (Source – Teva)

This growth will be achieved through increasing sales of Teva's QVAR (beclomethasone dipropionate) and ProAir (albuterol sulfate) brands, as well as by launching new products. These include a nasal version of QVAR, as well as a series of combination products that will be delivered through Teva's proprietary inhaler device, Spiromax.

Teva says it is currently ranked fifth among the world's respiratory players (see Figure 4), and the company is aiming to at least maintain this position over the next five years. The stringent regulatory requirements and lengthy development pathways of the respiratory market, Teva says, mean that high levels of technological expertise and financial resources are needed to take advantage of the opportunity offered by respiratory products. Or, as the company's president and chief executive officer Shlomo Yanai claims, "only a few players can play this game".

Although the company says it does not yet have plans to target all respiratory product categories, it claims that the products in its pipeline cover around three-quarters of the current US$34 billion global opportunity. The company estimates the peak sales potential of its pipeline to be around US$5 billion.

Teva acknowledges that any company developing respiratory products faces demanding hurdles due to the complex and lengthy development pathways of the leading markets. This is particularly true in the US, which accounts for around half of all worldwide respiratory turnover and – along with the EU – is the market where Teva expects to achieve the majority of its respiratory growth.

Rather than taking the traditional generic route of an abbreviated new drug application (ANDA) in the US, Teva's pipeline of in-development products will be subjected to full clinical trials for new drug applications (NDAs). This is due to the stringent requirements of the US Food and Drug Administration (FDA), which requires generic orally-inhaled products (OIPs) to

demonstrate that they are essentially a "direct copy" of the reference product in terms of their ingredients, performance, and method of delivery. These requirements make the development of true generic OIPs unlikely at this time, Teva believes.

The company intends to drive growth during the early years of its five-year plan by increasing sales of its existing QVAR brand through "aggressive market penetration" in the US. Currently, Teva says, QVAR boasts a growth rate of around 30% and accounts for about 20% of the inhaled corticosteroids (ICSs) market in the US, although the product is being used for a slightly higher proportion of new prescriptions. The company says the product's small particle size of one micron provides a unique benefit to asthma sufferers, as it allows particles to pass through both large and small airways.

In the short-acting beta agonist (SABA) market of rapid-relief products, Teva intends to maintain its leadership in the US with its ProAir product, which has a share of around half of the market, the firm claims. Lifecycle improvements – including adding a dose-counter and introducing a version of the product that uses the Spiromax inhaler – will help ProAir maintain this position, Teva says.

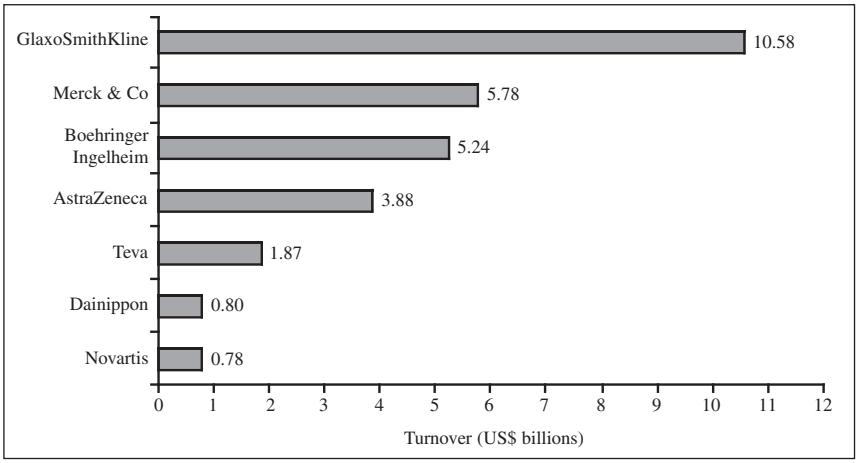

Figure 4: Top seven respiratory players ranked by annual sales to June 2010 (Source – Teva/IMS Health)

Aiming for 10 filings by 2015

In addition to strengthening its existing brands, new product launches are also a key part of Teva's strategy. The company's pipeline comprises nine products that Teva intends to be the subject of marketing-authorisation submissions worldwide by 2015. The firm said it had received promising results from Phase III trials for its QNAZE (beclomethasone dipropionate) product – a nasal version of QVAR in dry aerosol form – which it intends to have ready for submission by 2011.

Although Teva's pipeline is based around existing molecules and combinations – the patents for many of which have either expired or are due to expire within the next few years in leading markets – the firm is aiming to differentiate its products from those of its competitors through delivery devices such as its EasiBreathe and Spiromax inhalers.

Teva says the Spiromax device is the foundation of its respiratory portfolio, with a proprietary technology that is easy to use and allows accurate and consistent dosing at low flow-rates. This addresses an "unmet need", the company insists, from patients that struggle to use complex metered-dose inhalers (MDIs), such as AstraZeneca's Symbicort (budesonide/ formeterol).

Budenoside/formoterol is expected to be the first Spiromax combination launch, with Phase III trials due to be completed by 2012. However, Spiromax fluticasone/salmeterol – a rival to GlaxoSmithKline's Advair combination brand in the US – is "the real jewel of the portfolio", Teva says. This, along with Spiromax fluticasone propionate, is due to be ready for regulatory submission in 2014.

In the EU, where less stringent regulatory requirements make the development of generic OIPs more feasible, Teva intends to submit marketing-authorisation applications for Spiromax budenoside/ formoterol and a fluticasone propionate MDI in 2011. Fluticasone/salmeterol is due to follow in 2012, both with the Spiromax inhaler and with a MDI.

Clearly differentiating the individual Spiromax products, Teva acknowledges, will be important. This could be achieved by a different physical appearance such as through colour, the company suggests. However, having only one device means that patients only need to learn one method, the firm points out.

Nearly 12 months after announcing its five-year growth strategy, Teva remains firmly convinced of the opportunities offered by the respiratory market. Providing the company can stay on track to meet its goals, it should be halfway towards realising the US$5 billion peak sales potential for its current pipeline of respiratory products by 2015. G

	Sales in 2005 (US$ billions)	Proportion of total (%)	Sales in 2010 (US$ billions)	Proportion of total (%)	Compound annual growth rate (%)
US	*9.8*	*49*	*18.3*	*54*	*+17*
Japan	*1.7*	*9*	*2.4*	*7*	*+9*
Germany	*1.1*	*6*	*1.7*	*5*	*+10*
UK	*1.5*	*8*	*1.7*	*5*	*+2*
France	*1.2*	*6*	*1.6*	*5*	*+7*
Spain	*0.7*	*4*	*1.1*	*3*	*+10*
Italy	*0.7*	*4*	*0.9*	*3*	*+8*
Top seven	17	85	28	82	+13
Other	3	15	6	18	–
Global	**20**	**100**	**34**	**100**	**+12**

Figure 2: Breakdown of global respiratory sales in 2005 and 2010 for the top seven markets, with 2010 sales calculated on the basis of first-half figures (Source – Teva/IMS Health)

Leading players dominate Germany's tender process

As Germany prepares to introduce another raft of reforms, the country's top generics players are leading contract awards. Aidan Fry reports.

Over recent years, almost the only constant in Germany's pharmaceuticals policy has been a constant flood of new regulations. Faced by a drugs bill that last year increased by more than 5% to over €32 billion (US$42 billion), the country's coalition government reacted in time-honoured fashion – by introducing measures that promise long-term structural reforms, but slash prices and margins in the short term.

For Germany's generics players – but not for their originator rivals – the latest reforms package is a story of evolution, rather than revolution. The tender processes and resulting rebate contracts that were brought in through reforms that came into effect on 1 April 2007 will be tweaked rather than revised by the so-called 'AMNOG' package. This was passed in second and third readings by Germany's lower house of parliament, the *Bundestag*, on 11 November. As the package does not require ratification by the upper house of parliament, the reforms will come into effect on 1 January 2011.

Short-term savings of €2.4 billion per year – half of which will come from raising the clawback on medicines outside Germany's reference-price system from 6% to 16% – are to be complemented by removing unnecessary bureaucracy and making structural changes.

The structural changes are directed at originators, recognising that more than a quarter of the money that Germany's statutory health insurance funds spend on medicines is devoted to just 2.5% of all medicines dispensed. For the first time, brand firms will be required to negotiate prices for their drugs directly with the insurance funds. Within a year of market entry, original drugs will undergo a cost-benefit assessment, and any drugs considered to offer no clinical benefit over medicines already on the market will be brought into the country's reference-price system.

Perhaps because the cost of drugs within the reference-price system fell by 2% in 2009 – compared to a 9% rise for medicines outside the system – generics are not specifically targeted in the short-term savings measures. Instead, the government has chosen to squeeze margins for both wholesalers and pharmacists.

Measures affecting Germany's generics industry are instead included in a raft of loosely-defined medium-term measures. "Rebate contracts for off-patent and multisource medicines will be made more competitive and more patient-friendly," the government promises in a background paper annotating the legislation.

"Flanking regulations" to ensure competition are promised without further definition. "This will ensure that enough operators remain in the market and that price competition does not in the medium term become an oligopoly," the background paper insists. The consumer-friendly promise is to be delivered by allowing patients to choose to pay extra to receive a particular company's product that is not covered by a rebate contract negotiated by their insurance fund.

The paper also addresses industry concerns over a continuous downward price spiral brought about by making medicines priced at least 30% below the relevant reference price exempt from patient co-payments. "During the annual reference-price revision for groups containing medicines that are exempt from co-payments, prices should not be systematically reduced down to the 30% exemption limit," it states.

Furthermore, the paper clarifies, rebate contracts are to be regulated under cartel law, with disputes to be handled by Germany's civil, rather than the social, courts.

Applying cartel law to rebate contracts is "a heavy-handed bar on funds' freedom to operate", according to Germany's vociferous AOK fund, which insures around 25 million Germans, or almost a third of the country's population. The AOK has argued that statutory health insurance funds are subject to various requirements to deliver care and services, and thus should not be treated as if they are commercial entities. The umbrella association of statutory funds, the *GKV-Spitzenverband*, agreed, warning that transferring jurisdiction to civil courts would lead to "conflicting judgements".

Funds oppose use of cartel law

"Statutory funds don't need cartel law – all the measures needed to avoid misuse of market power are already anchored in social law," maintained the AOK's legal expert Professor Thorsten Kingreen. Noting that the fund had already fought more than 100 cases against 40 pharmaceutical firms, Kingreen argued that the government's move would create both legal uncertainty and huge bureaucracy that would endanger savings. This year, the fund would save €520 million through contracts reached through tender processes, he pointed out.

While most of Germany's generics players remain opposed to the entire concept of tenders and rebate contracts, the industry's objections to the latest reforms have centred on a series of minor alterations to regulations that are intended to clear up certain legal vagaries.

Industry association Pro Generika, which represents the country's leading generics players, is particularly concerned about changes making medicines substitutable provided they share at least one common indication. The onus would be on health insurance funds, the association stressed, to ensure that patients did not receive products that were not indicated for their particular ailment (**Generics *bulletin***, 1 October 2010, page 6).

Furthermore, Pro Generika urged the funds to ensure that healthy competition remained in Germany's generics market, given that firms that did not receive contracts would effectively be excluded from doing business with the awarding fund. "Active ingredients should not be included in tenders until at least two years after they lose

	First-half sales (million packs)	Change (%)	Proportion of total (%)
Patented brands	74	+2.3	22
Generics	*212*	*+1.1*	*63*
Off-patent brands	*50*	*-9.3*	*15*
Off-patent market	262	-1.1	78
German market	**335**	**-0.4**	**100**

Figure 1: Breakdown by product type of Germany's statutory health insurance market in terms of pharmaceutical volume through pharmacies in the first half of 2010 (Source – Pro Generika/IMS Health)

patent protection," the industry association argued.

Legislators, Pro Generika complained, had also failed to provide any clarity on planned changes to Germany's pack-size ordinance, which classifies reimbursed drugs into three pack sizes termed N1, N2 and N3. The changes are intended to lay down parameters within which pack sizes can be considered substitutable. "It is unclear whether many safe medicines will no longer be reimbursed by statutory insurance funds from July 2011 due to a sudden and arbitrary change in the ordinance," the association maintained.

In general, the reform package was "a missed chance" to strengthen patient safety and create a reliable framework within which generics firms could operate, Pro Generika contended.

Quoting IMS Health data, Pro Generika said generics saved Germany's statutory health insurance funds €4.33 billion in the first six months of 2010, suggesting annual savings will exceed €8.6 billion. This total, the industry association pointed out, was based on list prices and did not include the additional savings that the funds realised through the confidential rebates offered via tender processes.

Germany's generics market was just over twice the size of the off-patent brands sector, accounting for 28% by value of all medicines sold through pharmacies under the umbrella of the country's statutory healthcare system. At list prices, generics sales edged up by 0.9% to €4.15 billion in the first half of 2010. The value gain was slightly slower than the 1.1% volume growth to 212 million packs, which represented 63% of the total market (see Figure 1). Thus, even without taking rebates into account, generics accounted for almost two-thirds of medicines provided by funds, but caused barely a quarter of the funds' drugs bills.

Meanwhile, the funds continue to chase ever-greater savings through rebate contracts. The AOK's fifth tender round – covering 12 molecules, including the blockbuster antiplatelet agent clopidogrel – came into effect on 1 October this year. The deadline for submitting bids in the fund's sixth tender process that covers 87 molecules with a combined annual turnover of around €2.2 billion passed on 22 November. "With the sixth round in place [from 1 June 2011], we will save our 25 million AOK members about €700 million next year," the AOK stated.

Including the 12 molecules with a combined annual turnover of €143 million for which rebate contracts began on 1 October 2010, the AOK currently has deals in place covering 155 active ingredients. As the fund awarded contracts for each of those ingredients in five regions, the AOK has to date concluded a total of 775 individual rebate contracts, each spanning two years.

Seemingly mindful of the German government's desire to promote competition and offer opportunities for smaller, domestic generics players, the AOK stressed that it had given contracts to 41 different companies. However, several of these firms belonged to the same parent group. And as can be seen from Figure 2, the local market leaders continue to dominate the fund's tenders.

Global market leader Teva – largely through its recent takeover of Ratiopharm – captured just over 200 of the 775 regional contracts, while German market leader Sandoz and its 1A Pharma affiliate secured 145 deals. The country's third-placed player, Stada, gained 55 contracts, while Sanofi-Aventis and its Winthrop generics unit obtained a total of 72 deals.

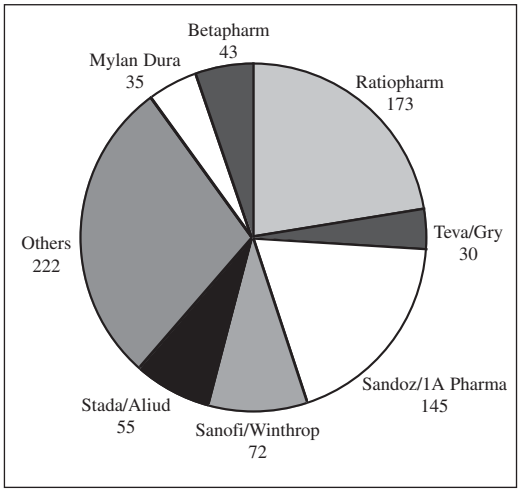

Figure 2: Breakdown by company of the 775 rebate contracts that Germany's AOK statutory health insurance fund currently has active (Source – AOK/Generics bulletin)

The Dr Reddy's subsidiary Betapharm was the next most successful with 43 contracts, just ahead of Mylan Dura on 35. Firms including Torrent's Heumann, Neuraxpharm and Actavis each got into double figures.

By dividing its awards for each active ingredient into five regions, the AOK said it had given smaller operators a greater opportunity to participate. However, in practice, deals for all but 26 of the 155 active ingredients went to the same company in all five regions. On that basis, the AOK's decision to extend its sixth tender to seven regions appears unlikely to make much difference (**Generics *bulletin***, 1 November 2010, page 10).

Tenders run by other funds have shown a similar trend in being led by Germany's market leaders. For example, the GWQ ServicePlus group of 36 funds – which together insure around six million members (**Generics *bulletin***, 17 September 2010, page 18) – said last month it had given more than half of its 156 contracts to Germany's "big three", led by Sandoz' 1A Pharma with 45 deals. Stada followed with 26 contracts, and Teva captured 16, including three each under the AbZ and Ratiopharm labels. Mylan Dura got eight contracts, Actavis seven and Biocon's Axcount six, while Dexcel and Winthrop each gained five and Aurobindo got four. The contracts start on 1 February 2011.

Rebate contracts have drastically diminished the value of Germany's generics market. And the focus they have placed on firms' access to a low-cost global supply chain and their ability to manage administrative complexity appears to be playing into the hands of the industry's leading players.

Finished forms advanced on many fronts by Indian firms

With the global IGPA conference taking place in India for the first time, Mike Rice takes a closer look at the local firms' progress.

Leading Indian generics firms are at something of a crossroads. In a matter of a few decades, or much less in many cases, they have expanded from local operators or active pharmaceutical ingredient (API) suppliers to leading finished-dose producers for the regulated markets of Europe and the US, either directly or through local partners. They are also making concerted efforts to be part of Japan's growing generics industry, as well as major players both in emerging markets like Russia and less developed parts of the world.

The vast majority of the 121 tentative and final approvals, for example, granted by the US Food and Drug Administration (FDA) under the President's emergency plan for AIDS relief (PEPFAR), have gone to Indian firms, as Figure 1 shows. The only exceptions are South Africa's Pharmacare, China's Zhejiang Huahai and Barr of the US before it merged with Teva, although India's Matrix is also now part of US-based Mylan.

But there have been stumbles along the way, as you might expect for firms moving so quickly along the bumpy road of global expansion. Many or even most acquisitions in Europe and the US have proved less than successful – mentioning no names – and these coupled with rapid expansion have also brought financial difficulties. Regulatory concerns have also arisen as first Ranbaxy and more recently Sun and its Caraco subsidiary have fallen foul of the FDA's inspectors. Claris is the latest example (see page 3).

As a result, changes in direction have been made and businesses divested or new partnerships sought. Notable examples are Orchid's recent sale of its injectables interests to Hospira (**Generics *bulletin***, 9 April 2010, page 4) and Wockhardt's disposal last year of Germany's Esparma (**Generics *bulletin***, 8 July 2009, page 5) as well as seeking buyers for its nutrition and animal health businesses.

Meanwhile, Aurobindo has become Pfizer's supplier for many generic products in Europe and the US, a trend that has since been copied by Strides and Claris; while AstraZeneca is also looking to Torrent as well as Aurobindo (**Generics *bulletin***, 17 September 2010, page 3). Dr Reddy's is now GlaxoSmithKline's partner for the emerging markets from which the Indian firm pulled out last year when it slimmed its direct presence from over 50 markets to the 10-15 countries where its finished-dosage sales were growing well (**Generics *bulletin***, 3 April 2009 and 19 June 2009, both page 3).

Matrix and Ranbaxy, however, are to date the only major Indian players to be acquired by larger pharma concerns, namely Mylan of the US and Japan's Daiichi Sankyo (**Generics *bulletin***, 19 June 2008, page 1). It seems highly likely though that they will be joined by others. India's new patent law, coupled with a massive home market with growing wealth, make the country an attractive prospect that an Indian firm's domestic infrastructure would open up for a foreign firm. The Indian firm's infrastructure in other emerging markets would be a bonus.

Prices, however, will not be cheap. Assiduous talking up of their prospects by reference to their impressive number of abbreviated new drug applications (ANDAs) in the US – regardless of the utility of some

	Prescriptions (millions)	Share (%)	Change (%)
Teva	557	21.6	+0.9
Mylan	340	13.2	+12.6
Watson	199	7.7	-2.7
Sandoz	179	6.9	-3.0
Greenstone (Pfizer)	111	4.3	+25.2
Qualitest	97	3.8	+11.3
Apotex	94	3.6	+2.2
Lupin	**92**	**3.5**	**+49.6**
Mallinckrodt	88	3.4	-5.0
Dr Reddy's	**71**	**2.7**	**+39.6**
Top 10	**1,828**	**70.8**	**+6.5**
Amneal	67	2.6	+97.7
Actavis	67	2.6	-7.9
Par	46	1.8	-8.6
Aurobindo	**39**	**1.5**	**+41.4**
Lannett	35	1.4	+2.3
Zydus	**34**	**1.3**	**+34.5**
Hikma	34	1.3	+37.7
Taro	31	1.2	+16.4
Bedford/Roxane (Boehringer)	29	1.1	+7.6
Ranbaxy	**29**	**1.1**	**-41.0**
Top 20	**2,238**	**86.6**	**+7.3**
Total US market	**2,584**	**65.9***	**+7.0**

* percentage of total prescription market

Figure 2: Top 20 generics companies in the 12 months to December 2009 by the number of prescriptions dispensed in the US with unbranded generics (Source – IMS Health)

	Prescriptions (millions)
Mylan	+35.3
Amneal	+33.1
Lupin	**+30.4**
Dr Reddy's	**+20.2**
Teva	+17.1
Cadista	**+12.5**
Aurobindo	**+11.3**
Hikma	+9.5
Qualitest	+9.0
Zydus	**+8.7**

Figure 3: Top 10 firms by absolute increases in US prescriptions dispensed with their products in the 12 months to December 2009 (Source – IMS Health)

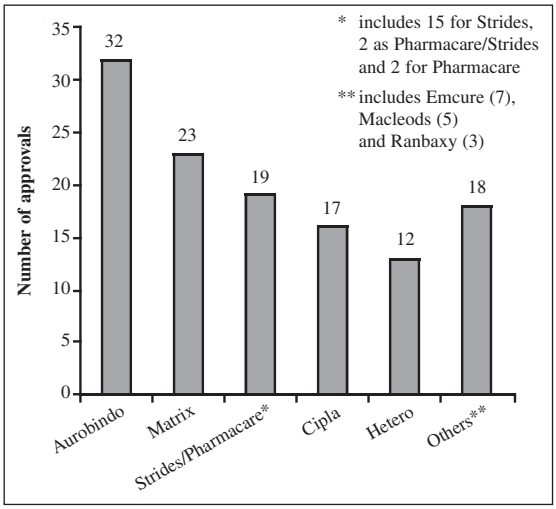

Figure 1: Tentative and final approvals – 121 in total – granted by the US Food and Drug Administration (FDA) under the PEPFAR scheme (Source – FDA)

of these ANDAs in already overcrowded categories – have ensured that Indian firms' capitalisations are high relative to their sales and operating profits. Some Indian generics firms have higher market worths for their operational sizes than larger and more successful generics firms with their share listings elsewhere.

Nevertheless, five of the leading 20 generics firms in the US last year – measured by prescriptions dispensed with their unbranded products – were Indian. They were headed by Lupin in eighth place, ahead of Dr Reddy's in 10th. With the exception of Ranbaxy, whose good manufacturing practice (GMP) troubles had started with the FDA (**Generics *bulletin***, 6 March 2009, page 1), the firms all performed about 40% better than they had a year earlier (see Figure 2).

Claiming 12 of the 25 products it marketed in the US were market leaders and 22 were in the top three, Lupin pointed out that US$127 million – or 37% – of its "stellar" US sales in the year to 31 March 2010 had come from branded products including the acquired AllerNaze (triamcinolone) and Antara (fenofibrate) brands (**Generics *bulletin***, 16 October 2009, page 15).

Lupin moved over 30 million more of its US products in 2009, as Figure 3 shows, while Dr Reddy's achieved a 20 million increase. According to IMS Health, Torrent was the fastest-growing Indian firm by total prescriptions dispensed in the US market last year, recording an increase of 159%. Jubilant's US generics subsidiary Cadista was just behind with a 137% rise.

The additional number of prescriptions dispensed with Lupin's simvastatin was greater than for any other US product last year, as it racked up 12.2 million extra.

According to its reported sales for 2009, Ranbaxy is still India's largest seller of finished-dosage forms outside of its domestic market, although its US problems dented the overall total (see Figure 4).

Dr Reddy's and its German Betapharm subsidiary also suffered from the market changes in Germany in its most recent financial year to 31 March 2010. European generics sales fell by 19% to US$215 million and North American turnover of US$374 million suffered from lower turnover of sumatriptan authorised generics.

Sun – like Ranbaxy – suffered a sales setback after the FDA sent a warning letter to its US subsidiary Caraco (**Generics *bulletin***, 14 November 2008, page 3). Such was the impact of its US reverse on Sun's overall results that its turnover dipped by 7% to just over US$900 million in the year to 31 March 2010.

Finally being allowed to swallow up Israel's Taro in September should help Sun's progress. However, receiving its own GMP warning letter from the FDA at about the same time will surely hamper the Indian firm further (**Generics *bulletin***, 17 September 2010, page 3).

Four of the top seven Indian generics players reported lacklustre annual results in their most recent financial years (see Figure 5). Ranbaxy's North American sales were down by 9% to US$397 million as it reported that the FDA had told it to conduct a global review of all of its sites that make products for the US market. But such are the vicissitudes of the US market that launching valaciclovir with 180-day generics market exclusivity at the end of 2009 boosted Ranbaxy's first-quarter US sales in 2010 by 222% to US$263 million (**Generics *bulletin***, 28 May 2010, page 10).

Biocon with 44% reported the most impressive sales improvement, which the biotech specialist hopes to continue as a result of its recent insulin deal with Pfizer (**Generics *bulletin***, 1 November 2010, page 13).

	Formulations exports (US$ millions)	Change (%)
Ranbaxy [1]	1,048	-6
Dr Reddy's	855	-7
Lupin [2]	601	+28
Cipla [2]	515	+7
Aurobindo [2,3]	412	+33
Sun [2]	375	-12
Glenmark [2]	321	+13

1 = Year to 31 December 2009
2 = Reported in rupees; converted at US$1=Rs45
3 = Total formulation sales

Figure 4: Total formulations sales by leading Indian firms outside of their domestic market in the year to 31 March 2010 (Source – Company reports)

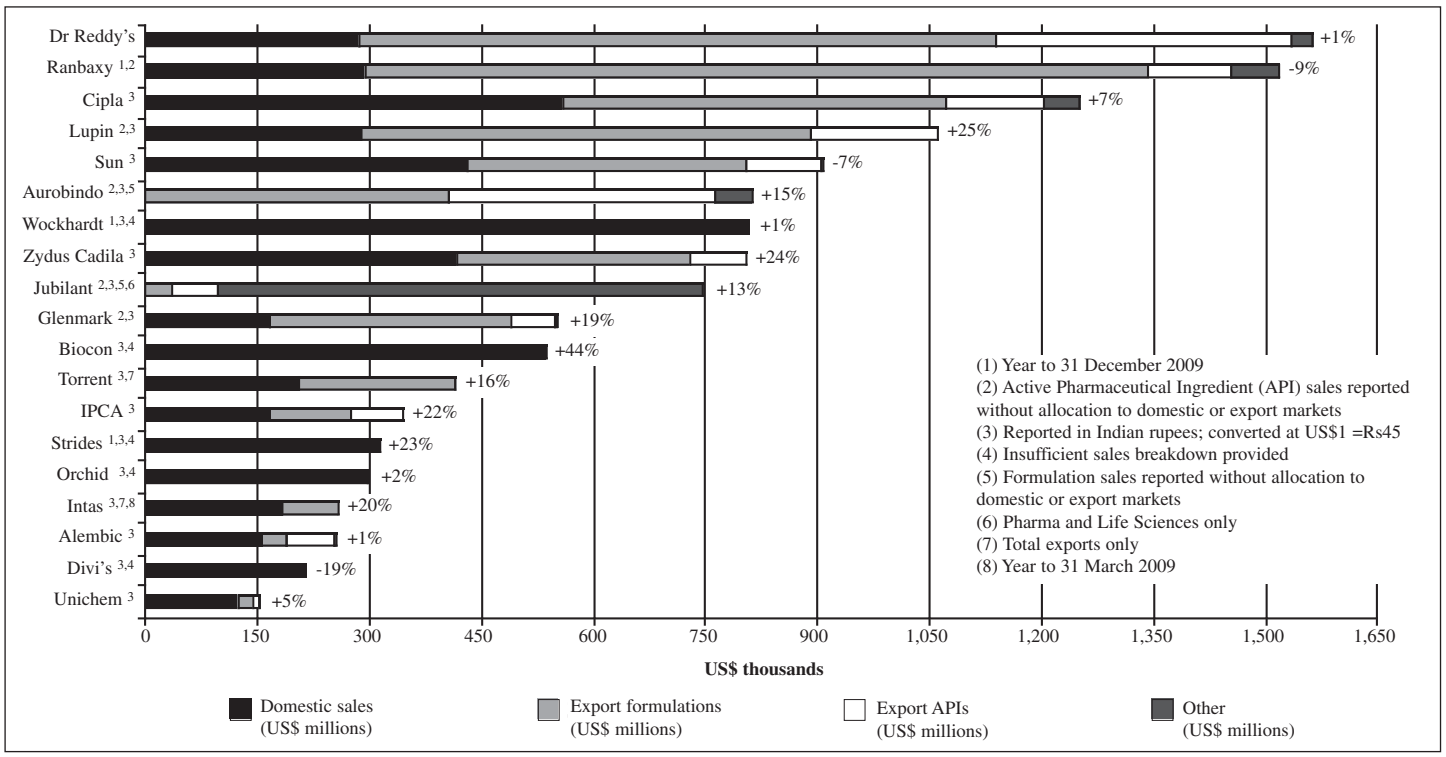

Figure 5: Reported turnover in US dollars of leading Indian generics companies for the year to March 2010 unless otherwise stated. Results not reported in US dollars have been converted at the rate shown, but growth figures are as reported. Business breakdowns have been quoted for domestic sales and export sales of formulations and active pharmaceutical ingredients (APIs) wherever possible and unless otherwise stated (Source – Company reports)

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INDUSTRY ASSOCIATIONS

Teva's Dethlefs has role at German body

The head of Teva's operations in Germany, **Sven Dethlefs**, has been elected deputy chairman of German generics industry association Pro Generika. He takes over from Ratiopharm's managing director **Oliver Windholz**, who will also hand over his corporate responsibilities to Dethlefs at the end of this year (**Generics *bulletin***, 17 September 2010, page 27).

Anne Demberg, director of strategic management and political affairs at Stada, has replaced her colleague **Peter Kraus** on Pro Generika's board. Demberg – who also heads Stada's Cellpharm nephrology and oncology unit in Germany – has been acting as the association's interim managing director ahead of the imminent arrival of **Bork Bretthauer** at the start of next year (**Generics *bulletin***, 12 November 2010, page 23).

APPOINTMENTS

Sandoz recruits Teva regulator

Sandoz has recruited a former senior director of regulatory affairs at Teva USA to serve as vice-president of regulatory affairs for its own US operation. **Nicholas Tantillo** held a similar position at Barr before its takeover by Teva, and has also worked at Revlon and Wyeth. In addition, he has served on the steering committee of the US Generic Pharmaceutical Association (GPhA).

Teva recently appointed **Gary Buehler** – the former head of the Office of Generic Drugs (OGD) with the US Food and Drug Administration (FDA) – as vice-president of regulatory strategic operations (**Generics *bulletin***, 1 November 2010, page 22).

APPOINTMENTS

Ethypharm strengthens team

Drug-development specialist Ethypharm has strengthened its team by appointing a general manager in China and a communications head.

In China – where Ethypharm markets 16 products and has another nine awaiting approval – the firm has brought in **Zhong Chongyu**, who was previously head of sales and marketing at Invida China. Chongyu, 42, has also worked as head of business unit for Sandoz China. He will report to Ethypharm's executive vice-president of business development, Alexandre Williams. As vice-president of communications, **Frédéric Fougerat**, 44, reports to chairman and chief executive officer Hugues Lecat. He was previously with the Geoservices Group.

APPOINTMENTS

Hospira appoints quality chief

Hospira has appointed **Francois Dubois** to take up the company's newly-created position of senior vice-president for quality from 3 January 2011. The role will give him responsibility for Hospira's global quality systems, reporting directly to the company's chairman and chief executive officer Christopher Begley. Dubois, 57, previously served as vice-president of quality at biotech firm Tengion.

RESIGNATIONS

Hermelin leaves KV as Divis takes lead

KV Pharmaceutical's **Marc Hermelin** has resigned from the company's board of directors after being excluded from participating in federal or state healthcare programmes by the US department of health and human services (HHS). KV said Hermelin had voluntarily resigned "in an effort to avoid adverse consequences to the company", as the HHS could also have excluded the company from such programmes had he remained. Hermelin led KV as chief executive officer between 1975 and December 2008, when he was replaced on an interim basis by former Ethex generics division president David Van Vliet (**Generics *bulletin***, 16 January 2009, page 31).

The troubled company has also appointed **Greg Divis** as permanent chief executive officer. Divis was made interim president and interim chief executive officer of KV in June following Van Vliet's departure (**Generics *bulletin***, 18 June 2010, page 11). The lead director of KV's board, Joseph Lehrer, said Divis would use his "exceptional leadership skills and vast knowledge of the pharmaceutical industry" to guide KV through "an important time in its recovery".

KV revealed that it had entered into a loan agreement for up to US$120 million. The firm recently received approval from the US Food and Drug Administration (FDA) to return the first of its generic products to the market (**Generics *bulletin***, 17 September 2010, page 3).

APPOINTMENTS

Strides gets Specialties CEO

Strides Arcolab has appointed **Venkat Iyer** as chief executive officer of its Specialties sterile injectables division. Iyer, who has 28 years of experience in the healthcare industry, joined the Indian company in 1999 and was promoted to the company's board of directors earlier this year (**Generics *bulletin***, 1 February 2010, page 23).

At the same time, the company rebranded the division under the name Agila Specialties. Strides said the new identity reflected the division's "smart, agile, determined and pragmatic" ethos, as well as communicating the company's "seriousness and intent to be a steriles powerhouse". Agila – which accounts for around 28% of Strides' group turnover (**Generics *bulletin***, 30 June 2010, page 20) – operates seven production facilities around the world.

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