The World Generic Market Report 2012

Volume I: Global Overview and Company Profiles

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World Leaders in Health Industry Analysis

GDUFA

The issue of introducing generic drug user fees has been on the horizon for several years. With the current economic climate, and a rising need for the federal government and others to cut costs, it is no surprise that the issue has never gone away. After a great deal of discussions, on 6th December 2011, the FDA released its draft document, Proposed Human Generic Drug Performance Goals and Procedures Fiscal Years 2013 through 2017, which the GPhA expressed its strong support for a day later. The proposed programme will see the FDA receive nearly US$1.5 billion over five years in supplemental funding through the Generic Drug User Fee Act (GDUFA). The FDA's draft paper notes that the overall purpose of the programme is to ensure that participants in the US generic drug system comply with US quality standards, and to increase the likelihood that US consumers gain access to generics in a timely manner. The programme has three key aims:

- Safety; ensuring that industry participants are held to consistent quality standards;
- Access; expedite the availability of generic drugs through improved review times;
- Transparency; enhance the FDA's ability to protect Americans in the global supply environment by requiring the identification of facilities involved in the manufacture of generics.

Proposals to introduce a generic drug user fee programme have been tied to efforts to stem the growing backlog of pending ANDA applications. Quite simply, the FDA's funding has not allowed it to hire enough qualified staff to deal with the increasing number of generic drug applications entering the system. It is a proposal that has received a guarded response, however. Members of Congress in early 2006 questioned the wisdom of gathering fees from an industry that the FDA is charged with overseeing, and have questioned whether this would lead to increased industry influence at the agency. The GPhA at the time was also guarded. Whilst it encouraged efforts to clear the backlog, the organisation was not entirely convinced that user fees would lead to faster approval times, noting that the generic system, unlike the branded industry, had additional roadblocks in the form of legal challenges through patent infringement action and even citizen petitions lodged with the FDA. The GPhA's view on the issue has always been that a programme to introduce user fees must be balanced with measurable results.

The FDA held a public meeting on the subject in September 2010 in order to gather stakeholder input on the development of a user fee programme, and has held further meetings in the intervening period up until this latest announcement. The arguments regarding a user fee programme were essentially split between two camps: greater speed in reviewing ANDAs and greater safety, with proponents of the latter argument concerned that increased speed would not address issues such as inspections of overseas manufacturing plants.

The draft proposals now tabled by the FDA do appear to address both the speed and safety concerns, leading to the GPhA endorsing them. With regard to speeding up approvals, the draft proposes that the FDA will review and act on 90% of complete electronic ANDAs within 10 months after the date of submission, and will review and act on 90% of all ANDAs and ANDA prior approval supplements regardless of current review status pending on 1st October 2012 by the end of FY2017. This will eliminate the current backlog. The draft also proposes measures to increase inspections of both finished dosage form manufacturing facilities and active pharmaceutical ingredient facilities, in the US and abroad. The draft proposes employing a risk-adjusted biennial cGMP surveillance inspection model with a goal of achieving parity of inspection frequency between foreign and domestic establishments in FY2017.

On 8th February 2012, Representative Tim Murphy (R-PA), House Energy and Commerce Health Subcommittee Chairman Joe Pitts (R-PA), Ranking Member Henry Waxman (D-CA) and Subcommittee Ranking Member Frank Pallone (D-PA) introduced the Generic Drug and Biosimilar User Fee Act of 2012 (H.R. 3988), which authorises the generic drug user fee proposal.

FDA Inspections and Warning Letters

As noted above, an issue surrounding the generic drug user fees proposals has been that of inspections of foreign and domestic manufacturers of finished form pharmaceuticals and active pharmaceutical ingredients, with parties such as the GPhA arguing that FDA oversight of foreign firms has been lacking, to the detriment of the domestic industry. However, the FDA does carry out inspections of manufacturing facilities, and issues Warning Letters when deficiencies, often known as 483s in reference to the FDA's relevant form, are highlighted. The FDA can take enforcement action when issues are not rectified.

ACTAVIS

Introduction

Actavis, originally named Pharmaco, was created in 1956; in May 2004 it changed its name to Actavis. The company was founded in Iceland, but has its headquarters in Zug, Switzerland. Actavis has over 10,000 employees operating in over 40 countries around the world. The firm has 14 manufacturing sites in 12 countries: the United States, Bulgaria, Iceland, China, Italy, India, Indonesia, Malta, Romania, Russia, Serbia and the United Kingdom. The plants produce a variety of medicines in different formulations, including tablets, capsules, injectables, suppositories, sprays, steriles, powders, oral liquids and semi-solids.

Company Details

Until May 2004, Actavis was known as Pharmaco, which was created in Iceland in 1956, formed by seven apothecaries. The company was originally set up as a purchasing alliance, but began producing its own pharmaceuticals in the 1960s. During the 1970s, Pharmaco also became the authorised agent in Iceland for a number of overseas pharmaceutical firms. The company operated only in the domestic Icelandic market until 1999, when Pharmaco invested in the Bulgarian firm, Balkanpharma; the two firms merged in 2000, initiating Pharmaco's entrance into foreign markets. In 2002, Pharmaco merged with Delta, another Icelandic firm that had originally been part of Pharmaco, and the merger established the company as one of the largest firms in Iceland.

In May 2004, Pharmaco changed its name to Actavis, taken from the Latin words 'acta', meaning action and 'vis', meaning strength. The name change was part of a series of changes made to create an international generic pharmaceuticals company; the various companies in the Pharmaco Group had been operating under different names for over 20 years, and the name change united them under a single brand identity.

In August 2007, Actavis was taken over by Novator, an investment group which included members of Actavis' Board. With the takeover complete, Actavis became a private company, with its shares delisted from the Icelandic stock exchange.

Actavis had a difficult year in the US in 2008, with product recalls being initiated from its Actavis South Atlantic and Actavis Totowa units. These led to congressional attention.

Actavis entered a restructuring phase in 2010. In February 2010, the firm announced plans to expand its manufacturing site in Iceland, creating 50 new jobs, and plans to divest its Norwegian plasters, athletic tape and adhesive coatings business. This was followed in March with news that the firm was divesting its Bulgarian distribution business, and in April Actavis announced plans to consolidate its New Jersey manufacturing operations, with the loss of some jobs. In May, the firm announced it had established a regional office for China in Beijing.

In July 2010, Actavis reported that it had successfully agreed a debt refinancing arrangement in collaboration with its lenders. The move should end the uncertainty that Actavis has faced since the global economic crisis began, and speculation that the firm may have had to be sold. On 22nd September 2010, the EC reported it had approved the proposed acquisition by Deutsche Bank of control over Actavis.

Organisational Structure

Although an Icelandic company, Actavis' headquarters is in Zug, Switzerland. The firm maintains development and manufacturing facilities in Europe, the US and Asia. In Europe, the firm has sales offices in Austria, France, Germany, the Netherlands, the Nordic region, Portugal, Switzerland, the UK, the Balkan region, Belarus, Bulgaria, the CIS, the Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Turkey and Ukraine. The firm has third-party sales in Germany, Iceland and the UK. European manufacturing facilities are located in Bulgaria, Iceland, Italy, Malta, Norway, Romania, Russia, Serbia, Turkey and the UK. R&D sites are located in Iceland, Malta and Romania.

Aurobindo: regulatory approvals

		As of 31st March 2011	Approved
Generics	US FDA	197	133
	Europe	103	73
	South Africa	279	83
	Total	**579**	**289**
Active ingredients DMFs	US FDA	154	-
	Europe – new registrations	84	-
	Europe – multiple registrations	1,187	-
	Other regions	426	-
	CoS	86	-
	Total	**1,937**	**-**
Patents and designs	Filed	464	-
	Registered	57	-

Aurobindo ANDA Approvals, January 2002 – December 2011

Name/dose	Date Approved	ANDA #
Mirtazapine tablets 7.5 mg, 15 mg, 30 mg, and 45 mg	Oct-04	76-921
Citalopram hydrobromide tablets 10 mg (base), 20 mg (base), and 40 mg (base)	**Oct-04**	**77-031**
Metformin hydrochloride tablets 500 mg, 850 mg, and 1 g	Jan-05	77-095
Zidovudine tablets USP, 300 mg	**Sep-05**	**77-267**
Zidovudine oral solution USP, 50 mg / 5 ml	**Sep-05**	**77-268**
Amoxicillin tablets USP, 500 mg and 875 mg	Nov-05	65-256
Amoxicillin capsules USP, 250 mg and 500 mg	Nov-05	65-271
Cephalexin capsules USP, 250 mg and 500 mg	Nov-05	65-253
Mirtazapine orally disintegrating tablets, 15 mg and 30 mg	Dec-05	77-376
Lisinopril tablets USP, 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg	Feb-06	77-622
Cefuroxime axetil tablets USP, 125 mg (base), 250 mg (base) and 500 mg (base)	Mar-06	65-308
Lisinopril and hydrochlorothiazide tablets 10 mg / 12.5 mg, 20 mg / 12.5 mg and 20 mg / 25 mg	Mar-06	77-606
Zidovudine capsules USP, 100 mg	**Mar-06**	**78-128**
Citalopram hydrobromide oral solution 10 mg (base) / 5 ml	Aug-06	77-812
Meloxicam tablets, 7.5 mg and 15 mg	Oct-06	78-008
Simvastatin tablets USP, 5 mg, 10 mg, 20 mg, 40 mg and 80 mg	Dec-06	77-691
Bisoprolol fumarate tablets USP, 5 mg and 10 mg	Dec-06	77-910
Amoxicillin for oral suspension USP, 200 mg / 5 ml and 400 mg / 5 ml	Dec-06	65-334
Amoxicillin tablets 200 mg and 400 mg	Jan-07	65-324
Cefadroxil capsules 500 mg	Jan-07	65-352
Cefprozil for suspension 125 mg / 5 ml and 250 mg / 5 ml	Jan-07	65-381
Sertraline hydrochloride, EQ 25 mg (base), 50 mg (base) and 100 mg (base) tablets	Feb-07	77-206
Didanosine, 10 mg / ml oral solution	**Mar-07**	**78-112**
Ciprofloxacin hydrochloride, 250 mg (base), 500 mg (base) and 750 mg (base) tablets	Apr-07	77-859
Zolpidem tartrate, 5 mg and 10 mg tablets	May-07	78-413
Cefprozil, 250 mg and 500 mg tablets	May-07	65-340
Cefpodoxime proxetil, 50 mg (base) / 5 ml and 100 mg (base) / 5 ml oral suspension	Jun-07	65-409
Cefpodoxime proxetil, 100 mg (base) and 200 mg (base) tablets	Jun-07	65-370
Trandolapril, 1 mg, 2 mg and 4 mg tablets	Jun-07	78-438
Terbinafine hydrochloride, 250 mg (base) tablets	Jul-07	78-297
Amlodipine besylate, 2.5 mg (base), 5 mg (base) and 10 mg (base) tablets	Jul-07	78-021
Hydrochlorothiazide, 25 mg and 50 mg tablets	Jul-07	40-780

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Volume II: National Markets

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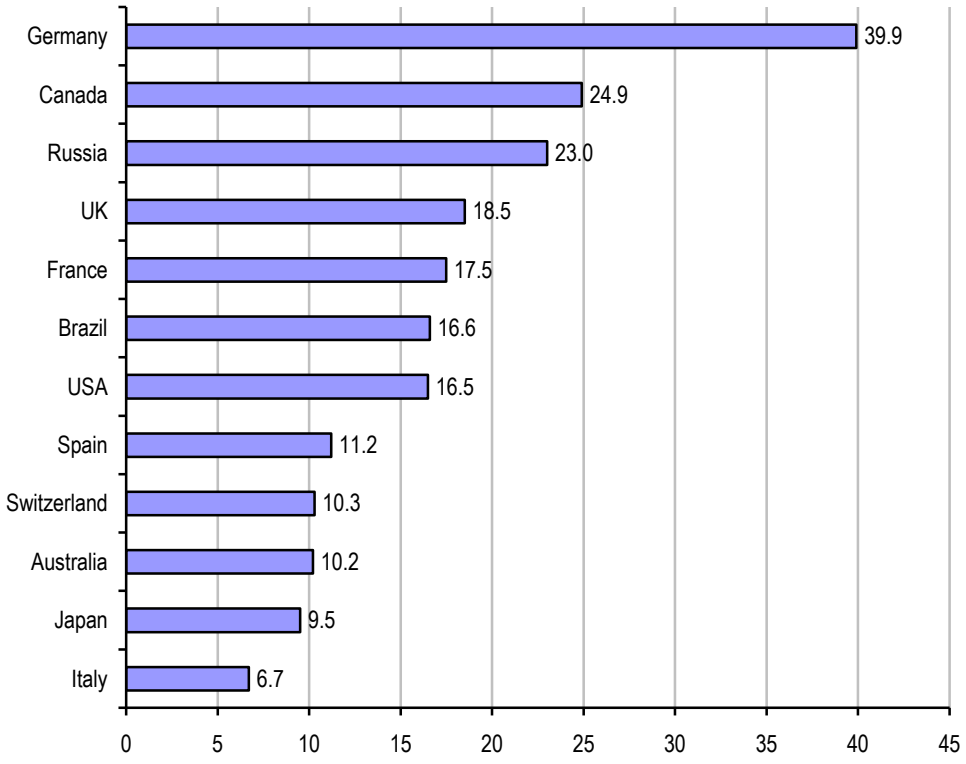
Germany has the highest level of generic penetration, at 39.9% in 2010. This is partly due to high usage, but also to relatively high prices for older branded generic products. In Russia the figure is around 23%, but this will include a large proportion of products which would not be considered legitimate generics in western Europe. Elsewhere, the highest levels of generic penetration are to be found in Canada and the UK, with 20-25%. Penetration has always been relatively low in the USA due to high branded prices, although patent expiry and generic incentives are causing this to rise.

Generic Pharmaceutical Expenditure as % of Total Market, 2011

	Generic Market Value as % of Total Market
Australia	10.2
Brazil	16.6
Canada	24.9
France	17.5
Germany	39.9
Italy	6.7
Japan	9.5
Russia	23.0
Spain	11.2
Switzerland	10.3
UK	18.5
USA	16.5

Generic Pharmaceutical Expenditure as % of Total, 2011



BRAZIL

Introduction

Brazil is the largest and richest country in Latin America, with a population of 193 million and a GDP of US$2,506 billion in 2011. The population aged 65 years & over only represents 6.7% of the total in 2011, but this translates into 12.9 million people. Additionally, social inequalities mean that an estimated 40% of the population does not have access to pharmaceuticals, which brings further generous market opportunities for producers of cost-effective bioequivalent generic medicines.

Brazil's pharmaceutical market is the second largest in Latin America, after Mexico. Increasing demand and strong local currency values have inflated its pharmacy sector in dollar values, which ranked first in Latin America in 2006, after overtaking Mexico. Most importantly, Brazil has the largest market for bioequivalent generic pharmaceuticals, which now ranks among the top ten worldwide. The hospital sector is also keen to encourage further use of bioquivalent generics, particularly for chronic diseases.

Generic pharmaceuticals are eroding branded medicines and competing with similar products. In the long-term, continuing patent enforcement and generics penetration are expected to constrict the market for similar medicines. Nevertheless, producers of similar medicines are shifting production from similar to bioequivalent medicines, in an effort to stay afloat in the market and maximise their opportunities in this fast-growing sector. Strong competition, however, has made generic prices unsustainable for small producers.

Key Facts, 2011

• Population (millions)	192.8
• GDP per capita (US$)	12,998
• Total Health Expenditure (US$ billions)	220.2
• Health Expenditure per capita (US$)	1,142
• Health Expenditure as % of GDP	8.8
• Total Pharmaceutical Market (US$ billions)	34.8
• Pharmaceutical Expenditure per capita (US$)	181
• Generic Pharmaceutical Market (US$ billions)	5.8
• Generic Expenditure per capita (US$)	30
• Generic Market Value as % of Total Market	16.6

Major Generic Product Approvals, 2002-2010

	Original brand	Patent holder	Year
Loratidine	Claritin	Schering Plough	2002
Isotretinoin	Accutane	Roche	2002
Metformin	Glucophage	Bristol-Myers Squibb	2002
Cefuroxime axetil	Ceftin	GlaxoSmithKline	2002
Paroxetine	Paxil	GlaxoSmithKline	2003
Gabapentin	Neurontin	Pfizer	2003
Mirtazapine	Remeron	Organon	2003
Quinapril	Accupril	Pfizer	2003
Fluconazole	Diflucan	Pfizer	2004
Benazepril hcl	Lotensin	Novartis	2004
Ciprofloxacin	Cipro	Bayer	2004
Ribavirin	Rebetol	Schering Plough	2004
Metformin hcl ER	Glucophage XR	Bristol-Myers Squibb	2004
Azithromycin	Zithromax	Pfizer	2005
Fentanyl	Duragesic	Ortho-McNeill	2005
Fexofenadine	Allegra	sanofi-aventis	2005
Levofloxacin	Levaquin	Ortho-McNeill	2005
Ramipril	Altace	King Pharmaceuticals	2005
Zidovudine	Retrovir	GSK	2005
Gabapentin	Neurontin	Pfizer	2006
Meloxicam	Mobic	Boerhinger-Ingelheim	2006
Ondansetron	Zofran	GSK	2006
Pravastatin	Pravachol	Bristol-Myers Squibb	2006
Simvastatin	Zocor	Merck & Co	2006
Zonisamide	Zonegran	Dainippon	2006
Amlodipine	Norvasc	Pfizer	2007
Carvedilol	Coreg	GSK	2007
Granisetron	Kytril	Roche	2007
Setraline	Zoloft	Pfizer	2007
Terbinafine	Lamisil	Novartis	2007
Zolpidem	Ambien	sanofi-aventis	2007
Divalproex sodium	Depakote	Abbott Laboratories	2008
Stavudine	Zerit	Bristol-Myers Squibb	2008
Zaleplon	Sonata	King Pharmaceuticals	2008
Sumatriptan succinate	Imitrex	GSK	2009
Topiramate	Topamax	Ortho-McNeil	2009
Bicalutamide	Casodex	AstraZeneca	2009
Nateglinide	Starlix	Novartis	2009
Amlodipine & benazepril	Lotrel	Novartis	2010
Anastrozole	Arimidex	AstraZeneca	2010
Atomoxetine	Strattera	Eli Lilly	2010
Enoxaparin sodium	Lovenox	sanofi-aventis	2010
Losartan potassium hcl	Cozaar/Hyzaar	Merck & Co	2010
Naratriptan hcl	Amerge	GSK	2010
Tamsulosin hcl	Flomax	Boehringer Ingelheim	2010
Venlafaxine	Effexor XR	Pfizer	2010

Source: CDER, Report to the Nation to 2005, Espicom

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