

Indian Pharma Sector

Bronco ride likely as FDA on the vigil

Reason for report: Sector update

Reportedly, the US FDA has become more stringent after ~250 deaths from blood thinner Heparin, largely imported from China. This combined with the US FDA planning to set up its first office in New Delhi later this month (subject to the Government approval) implies stricter monitoring of the Indian pharma manufacturing plants. In this light, the US FDA's actions have affected Ranbaxy the most with ~US\$30mn dent in CY09E PAT (~20% of normalised PAT or EPS of Rs3) followed by Caraco. Clearly, this is a concern for the Indian Pharma sector, for which the US generics market is critical. We believe Indian pharma companies would take appropriate and timely measures to resolve current issues and avoid future lapses. Given the current global economic slowdown, we maintain that quality Indian pharma players such as Glenmark and Sun Pharma (SPIL) will outshine peers and deliver absolute Rol of ~35-45% in the next 12-18 months.

- ▶ **Imported Heparin, the cause of rising death toll in the US.** Heparin Sodium is derived from pig intestines and is being sold in the US since 1930s. The drug is used before surgery (mostly cardiac) and dialysis to prevent blood clots. While imported Heparin has led to deaths in the past (55 in '06), the number has substantially increased to ~250 during January '07-May '08 due to contaminated batches of multi-dose Heparin from China. Heparin is made of complex and long chain of sugar molecules and contaminants (from animal cartilage) have a similar chemical structure as per the current testing by the US FDA. This has made the US FDA more vigilant, especially in case of imported drugs. The US FDA is planning to set up offices in China and India later this month.
- ▶ **Stricter US FDA finds faults with Ranbaxy & Caraco.** Earlier, when the US FDA inspected manufacturing plants in India, the pharma companies were notified 45 days in advance. This used to give Indian companies some time to comply with the norms with minor modifications, if required. With the US FDA planning to set up office in New Delhi with American staff (10-member team by end CY09) later this month, subject to Indian Government's approval, inspections can be more frequent and at a much shorter notice. The dispute between Ranbaxy and the US FDA, which stretched for more than two years, culminated in 30-drug ban by the latter in September '08. Caraco's (a SPIL subsidiary) Detroit facility received a Warning Letter from the US FDA in October '08.
- ▶ **Pharma offers better risk-return profile.** Despite rising concerns on stricter US FDA, we are selectively upbeat on the Indian pharma sector given its defensive nature. We reiterate Glenmark and SPIL as our top BUYs with potential upside of ~35-45% in the next 12-18 months at lower attendant risks. Dishman Pharma, a world-class player in API/intermediate contract manufacturing, is our top mid-cap BUY with potential upside of ~65% in the next 18-months.

Top picks

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Sun Pharma

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US FDA more vigilant

Harmful Heparin triggers stricter regime

What is Heparin?

Heparin Sodium is an anticoagulant (blood thinner) derived from pig intestines and is used to prevent blood clots during medical procedures. Commonly, the drug is used before heart surgery and for dialysis patients. Heparin is made of complex and long chain of sugar molecules.

Risks from imported medicines exposed in the US

Heparin is being marketed in the US since 1930s. The US uses 2 tonnes of Heparin per month, with 70% originating from China owing to large number of pigs killed in the country. The complexity of Heparin, which contains thousands of molecules, makes it difficult to identify impurities. The use of Heparin, in many cases, has caused severe side effects (such as allergic/hypotensive symptoms) – the US FDA received 350 negative reports on the drug, of which 40% were serious. Since January '07, 246 deaths have been reported to the US FDA. On investigating, it was traced to the presence of a contaminant, Over Sulfated Chondroitin Sulfate (OSCS). The contaminant's structure is very similar to Heparin's and therefore, it cannot be identified by the tests.

According to the US FDA, contaminated Heparin came from the factories of Scientific Protein Labs (a supplier to Baxter Healthcare Corporation of US) in China. Baxter and the US FDA are yet to determine how and when the contaminant entered the Heparin supply chain in China, which is now the largest supplier of raw ingredients for Heparin globally. Baxter supplies ~50% of the multiple dose vials of Heparin to the US. After adverse reports, Baxter was forced to suspend manufacturing and marketing of multiple-dose Heparin vials in the US in February '08. This has exposed the risks of imported medicines.

Table 1: Deaths from Heparin though January 1, '07- May 31,'08

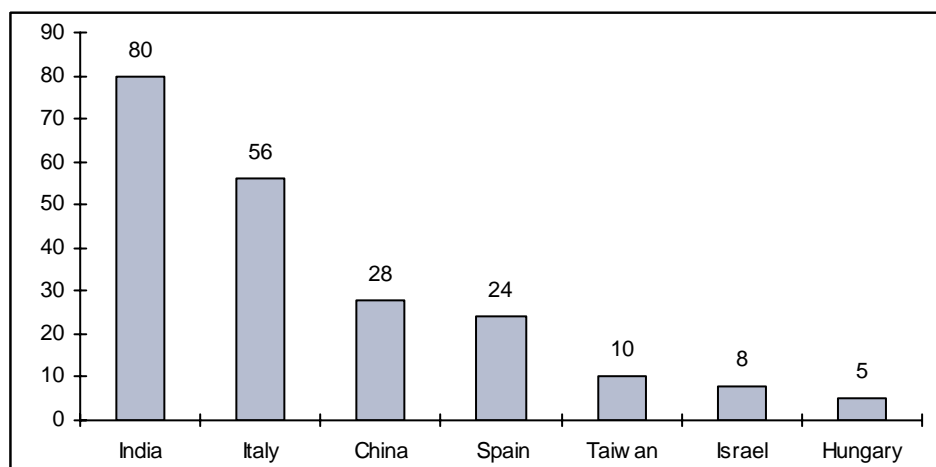
Timeframe	Number of reported deaths*	Reported deaths with one or more allergic/hypotensive symptom(s)
Jan-07	6	3
Feb-07	2	1
Mar-07	5	2
Apr-07	7	4
May-07	3	1
Jun-07	5	2
Jul-07	6	3
Aug-07	4	4
Sep-07	3	2
Oct-07	10	5
Nov-07	12	11
Dec-07	34	23
Jan-08	50	32
Feb-08	49	29
Mar-08	14	10
Apr-08	7	4
May-08	5	3
Unknown date	24	10
Total	246	149

*The reports in this table concern Heparin produced by any manufacturer
Source: US FDA

US FDA to open offices in China & India in December '08

The Heparin case has made the US FDA more stringent and vigilant, especially in case of imported drugs. The FDA is planning to set up offices in China and India later this month with American staff to ensure the safety of imported food and medicinal products. The first overseas office will be in China, for which the US Government has recently secured the approval. A US FDA official will arrive in Beijing in end-December '08, with additional staff coming in '09. The FDA will deploy eight US nationals in China. The US FDA plans to establish its first office in India (in New Delhi) later this month subject to the approval of the Indian Government. This office will employ 10 US nationals by end-CY09. The higher staff strength in India is justified given that: i) India has the highest number of US FDA approved manufacturing plants outside the US (Chart 1), and ii) drugs worth US\$2-3bn are exported to the US annually. Such offices will provide technical advice, conduct additional inspections and work with Government agencies and private sector entities to develop certification programmes.

Chart 1: US FDA approved plants outside USA



Source: Industry

US FDA increases vigil on India

Ranbaxy & Caraco face the brunt

Within just three months, three Indian companies, Ranbaxy, Caraco & Lupin have faced the US FDA's ire (Table 2).

Table 2: Recent adverse findings by the US FDA

Date	Company	US FDA action
16-Sep-08	Ranbaxy	Bans 30 drugs manufactured at Dewas and Paonta Sahib in India
31-Oct-08	Caraco	Issued warning letters for deficiencies in quality control at Detroit plant in the US
14-Nov-08	Lupin	FDA Form 483 issued with 15 inspectional observations for Mandideep, India facility

Source: Company data, US FDA

Ranbaxy, hit the worst

US FDA banned 30 drugs of Ranbaxy

Since early '06, manufacturing deficiencies in Ranbaxy's Paonta Sahib facility in Himachal Pradesh was initially the bone of contention between the company and the FDA. The dispute finally culminated in the US FDA banning 30 drugs manufactured at Ranbaxy's two plants, Paonta Sahib and Dewas (Madhya Pradesh) in India. Of the 30 banned drugs, three drugs (Simvastatin, Acyclovir and Loratadine OTC) are also manufactured at the company's other plants. Besides, the US FDA has permitted Ranbaxy to sell Ganciclovir (Ranbaxy enjoys exclusivity for this in the US) to avoid shortage of a cheaper generic version. Thus, overall, Ranbaxy's exports (of the remaining 26 drugs manufactured at Indian plants) would be affected, the more important drugs being Isotretinoin (sold as *Sotret* with estimated annual sales of ~US\$50mn) and Valacyclovir HCl (for which Ranbaxy has 180-exclusivity from December '09). Ranbaxy is exploring alternatives such as filing from its other plants or outsourcing to mitigate the affect of the ban. The ban has led to a sharp 50% drop in Ranbaxy' stock price YTD.

CY09E PAT to be likely dented ~US\$30mn

We believe that it may take about a year for Ranbaxy to fully comply with the US FDA recommendations so as to rescind the ban on the 30 drugs. The estimated annual sales and PAT from the banned drugs are US\$150mn & US\$30mn (or ~20% of the normalised PAT with year ending June '08). Ranbaxy has already provided for Rs3.5bn inventory write-offs in Q3CY08 for the banned drugs to bridge the potential inventory-related losses and sales returns. Besides, lower profitability in the branded generics market and higher costs have led to a loss of Rs49mn in Q3CY08 compared with Street and I-Sec PAT estimates of Rs1.5-1.7bn! Consequently, we cut our CY08E, CY09E & CY10E EPS estimate 50%, 33% and 32% respectively.

Table 3: Ranbaxy – Earnings revision

(Rs mn, year ending December 31)

	CY08E			CY09E			CY10E		
	Old	New	% chg	Old	New	% chg	Old	New	% chg
Operating Income	81,065	76,235	(6.0)	91,091	78,062	(14.3)	102,975	90,547	(12.1)
EBITDA	13,804	9,127	(33.9)	15,736	10,838	(31.1)	18,270	13,450	(26.4)
PAT	7,481	3,510	(53.1)	8,625	5,359	(37.9)	10,320	6,535	(36.7)
EPS (Rs)	15.4	7.8	(49.5)	17.7	11.9	(32.9)	21.2	14.5	(31.7)

Source: I-Sec Research

Our earlier fair value of Rs682/share (refer to our report '*Momentous deal*' dated June 16, '08) included the upside from tendering shares in the open offer at Rs737/share. This upside was Rs339/share (given 46% acceptance ratio), which Ranbaxy's shareholders realised on tendering shares in the open offer. Reducing this upside from Rs682/share leaves us with an adjusted earlier fair value of Rs343/share, which we have lowered to Rs262/share (at 14x normalised EPS of Rs13.2 plus Rs79/share NPV from FTFs), implying a potential upside of 25% in the next 12-18 months.

Caraco

On October 31, '08, the US FDA issued a warning to Caraco for poor quality control at its Detroit plant in the US. Notably, in June '08, the US FDA issued FDA Form 483 to Caraco, in response to which the latter undertook corrective action, which was largely completed. Despite that, the US FDA indicated non compliance. Note that Caraco had last received a warning from the US FDA in FY01. Since then, every year, improving compliance with the FDA has been the company's top priority, and Caraco has taken necessary measures to achieve it. We believe non compliance is not of a serious nature and will be sorted in the next 2-3 quarters given that it is faster for the US FDA to reinspect (if required) the Detroit facility than a facility in India. In the short term, this may affect the approval of Caraco's 19 pending ANDAs. Notably, 80% of the total 96 ANDAs (including Caraco's) pending approval from the US FDA are from SPIL's Indian plants and, hence, will not be affected. Also, all key first-to-files are filed from the Indian plants and will be unaffected. However, owing to the above factors, Caraco's stock price has crashed ~70% since October 31, '08.

More Indian companies could face the heat

On November 14, '08, the US FDA inspected **Lupin's** manufacturing facility in Mandideep, India. The inspection was a routine Good Manufacturing Practices (GMP) audit. An FDA Form 483 (inspection report) was issued listing 15 inspectional observations. Lupin addressed eight of the observations immediately and added that a complete response will be submitted to the FDA soon. The outcome of this inspection does not affect the supply of the products manufactured at this facility or pending ANDAs. Lupin manufactures cephalosporins & non cephalosporins APIs at this facility, which likely accounted for ~25% of US sales at US\$175mn in FY08. However, if the company is unable to resolve the issues raised by the FDA, it could lead to a warning letter by the FDA. With the problem being not so severe, the stock dipped ~8% after the announcement on November 14, '08, but fully recovered afterwards.

Given the increased vigilance by the US FDA, we can safely assume that more Indian pharma companies may face the heat. Hence, it is important that such companies should strictly adhere to all requirements of the US FDA.

Valuations attractive

The ongoing financial slowdown has led to an unprecedented decline in global equities, including India. Since Pharma is defensive in nature, historically, the sector has mostly outperformed other economy-sensitive sectors and indices during weak growth environment. As a result, we expect the Indian pharma sector to selectively perform well in the next 12-18 months. Besides, based on our **pick-and-choose investment strategy** (that has worked in the bear and the bull market in the past decade), we prefer stocks with robust business model, high growth at lower attendant risks and competent management. Generally, such companies have higher earnings predictability and better visibility as regards positive newsflow. Based on this strategy, we continue to reiterate Glenmark and SPIL as our top two BUYs in the sector. In the past five years Glenmark and SPIL's market cap rose 11x and 4x respectively compared with the Sensex's 2x.

We expect **our top large-cap BUYs in the sector, Glenmark and SPIL**, to outshine peers and the Sensex, and deliver potential upsides of 37% and 44% respectively in the next 12-18 months. Continued under-ownership of the sector by institutional investors and receding risk appetite will aid sector performance. In outsourcing, we have recently initiated coverage on two world-class API/Intermediate Contract Manufacturing companies, **Dishman (our top mid-cap BUY)** & Divi's Labs with 18-month fair value estimate at Rs214 and Rs1,527 respectively.

Table 4: Comparative valuations

Company	Rating	Price (Rs)	P/E (x)		EBITDA margin (%)	EV/E (x)	RoCE (%)	Mktcap/ Sales (x)	Mkt. cap (US\$ mn)
			FY09E	FY10E					
Glenmark	Buy	321	9.9	7.8	32.3	21.6	35.6	3.0	1,612
Sun Pharma	Buy	1,029	11.9	13.3	46.2	19.4	31.5	5.2	4,284
Dishman Pharma	Buy	128	7.0	5.2	19.0	11.7	10.7	1.0	206
Divi's Labs	Buy	1,185	15.7	12.5	40.8	17.1	43.4	5.8	1,537
Cadila	Buy	250	11.5	9.1	16.6	10.3	16.7	1.2	631
Ranbaxy	Buy	211	13.1	9.3	15.1	19.9	10.8	1.0	1,580
Dr. Reddy's Labs	Buy	479	14.1	13.3	15.5	14.2	7.3	1.4	1,613
Alembic	Buy	31	5.2	3.7	14.2	6.8	16.3	0.4	86
GSK Pharma	Buy	1,185	22.4	19.6	32.2	15.1	31.5	6.0	2,016
Aventis	Buy	867	12.0	10.5	20.5	8.0	23.8	2.0	401
Cipla	Hold	184	19.7	15.3	20.1	22.2	17.8	2.9	2,872
Wockhardt	Hold	99	2.9	2.4	24.1	5.8	12.7	0.3	218
Average/Total			11.8	10.5	23.1	19.6	21.5	2.2	17,056

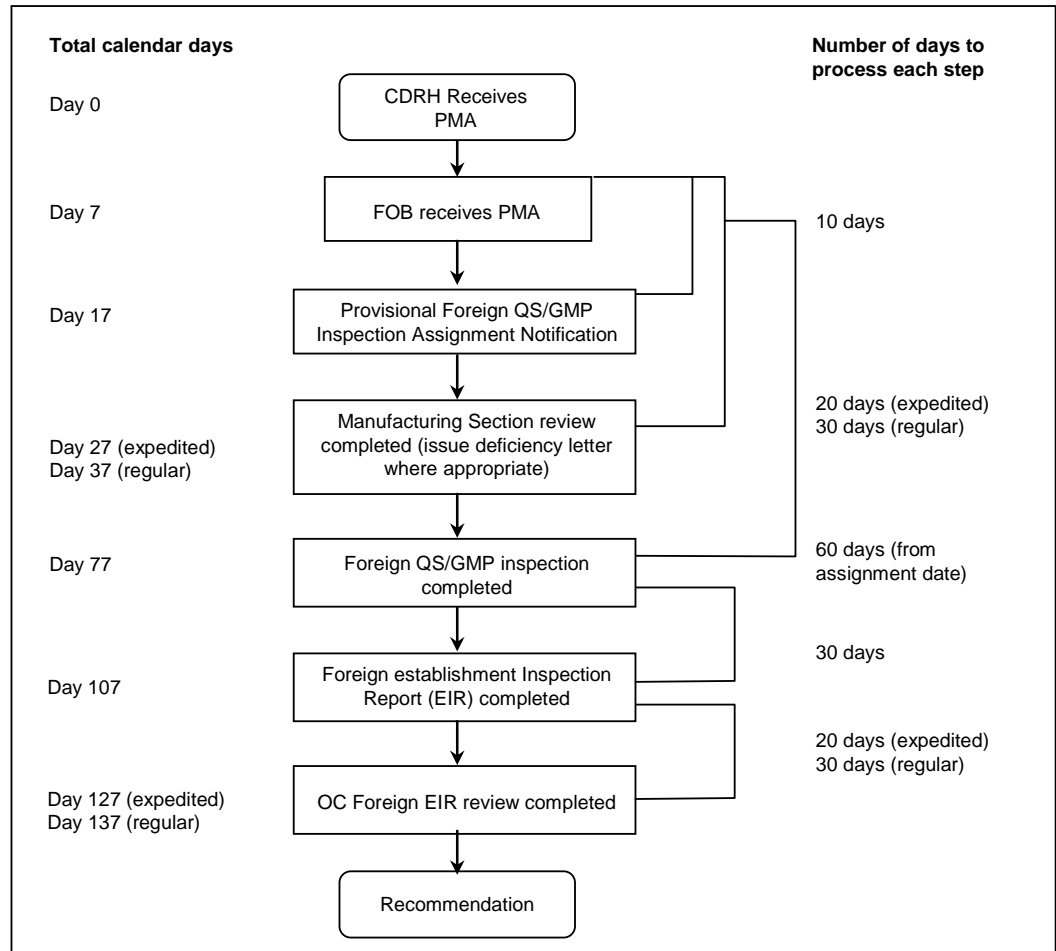
Source: Company data, I-Sec Research

Appendix I: US FDA inspection/approval process

Foreign inspections by US FDA

Typically, the US FDA conducts over 200 foreign drug manufacturing inspections every year. The US FDA field staff is expected to complete the inspection within 60 days after they are instructed to do so. It takes ~130 days for expedited pre-marketing approval application (PMA) review and ~10 days more for non-expedited PMA review (Chart 2).

Chart 2: US FDA approval process



CDRH – Centre for Devices and Radiological Health; FOB – Field Operations Branch; QS/GMP – Quality Systems/ Good Manufacturing Practices; OC – Office of Compliance;
Source: US FDA

FDA Form 483 & Warning Letters

After the completion of inspection by the US FDA field staff, the observations are given in a pre-designed form called FDA Form 483.

FDA Form 483

This form is a 'Notice of Inspectional Observations'. After completing an inspection of the manufacturing facility, the FDA investigator issues an FDA Form 483, listing the deficiencies in the quality system. The observations are based on the inspector's interpretations of the regulations as regards operational GMP quality system.

Untitled Letter

An Untitled Letter is an initial correspondence with the regulated industry that cites violations which do not meet the threshold of a Warning Letter. Untitled Letters are intended to cover those circumstances wherein the agency needs to communicate with the regulated industry about violations that do not meet the threshold of regulatory significance as described above. The three types of letters related to licenced products issued by FDA, pursuant to section 6.3 of these procedures, do not necessarily fall within the definition of an Untitled Letter; however, they are Untitled Letters covered by the scope of these procedures.

Warning Letter

A Warning Letter is a correspondence that notifies the regulated industry about the violations documented by FDA during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the FDA considers one or more products, practices, processes or other activities to be in violation of the Federal Food, Drug and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance i.e. those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act. The pharma company is expected to respond to a Warning Letter within 15 days.

Response to FDA Form 483/Warning Letter

The company must promptly respond to FDA Form 483 and Warning Letter and identify the course of action to correct the findings with a timeframe. A detailed response to each item addressed will be required. The quality and promptness of the response to this letter is extremely important. A typical course of action for a pharma company receiving these would be the following:

- Analyse the key issues/observations of the FDA Form 483 and/or Warning Letter
- Chalk out a detailed plan of action
- Propose corrective actions for the quality system
- Suggest an appropriate timeline to satisfy the US FDA
- Assist in implementing corrective actions in response to FDA Form 483
- Readiness to clarify any query by the US FDA

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