

GENERIC**S** *bulletin*

THE BUSINESS NEWSLETTER FOR THE GENERIC MEDICINES INDUSTRY

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Par boosts its pipeline by purchasing Kali Labs

Par Pharmaceuticals will bolster its pipeline of abbreviated new drug applications when its parent company Pharmaceutical Resources acquires fellow US generics firm Kali Laboratories for US\$135 million in cash and warrants. The deal should also reduce Par's reliance on low-margin products sold through agreements with third parties.

Shareholder approval is not required, which will shorten the completion period to the end of June. Meanwhile, however, the firm will report lower than expected profits for the first quarter of 2004.

"We view this acquisition as the first step toward significantly expanding the scope of our research and development capabilities," commented Pharmaceutical Resources' president and CEO Scott Tarriff, "and substantially increasing the size of our product portfolio." Kali currently has 14 ANDAs pending approval by the US Food and Drug Administration (FDA).

"We picked up Kali just as it is coming to the apex of its hard work with drugs coming to market," Tarriff maintained. He noted that the deal – which will include Kali's leased manufacturing facility in Somerset, New Jersey, provided an agreement can be reached with Perrigo – would diversify Par's pipeline and add greater stability to its earnings.

The transaction would more than double Par's internal research and development capacity, Tarriff said, adding that another 10 employees would soon be added to Kali's 55-member research and development team.

Pharmaceutical Resources will pay US\$130 million in cash and US\$5 million as a share warrant. Tarriff said the price represented a five-times multiple on Kali's forecasted 2005 earnings. Furthermore, he added, the price was broadly similar to Par's cumulative profits on its deal to sell a version of Paxil (paroxetine) under an agreement with the originator, GlaxoSmithKline.

"We are swapping cash from a short-term asset in paroxetine for a long-term research and development pipeline," Tarriff stressed. As Par's dependence on products sold under licensing agreements shifted towards generics developed in-house, he said, the firm's gross margins would rise from around 38% towards the industry average of over 50%.

Kali's pipeline, Tarriff pointed out, provided Par with additional sustained-release and orally-disintegrating technology. It also offered new dosage forms, such as gels and

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Ivax challenges Recordati for Polfa Kutno

Ivax has entered the race for a stake in Poland's Polfa Kutno, raising Recordati's offer and making a bid worth up to US\$160 million in shares for the entire company. The Florida firm wants not less than 75% of Poland's 14th largest player, which last year had revenues of PIZ245 million (US\$64 million) and made an operating profit of PIZ48 million.

Ivax' offer is worth PIZ310 per share for between 75-92% of Polfa Kutno's 1.877 million shares, rising to PIZ325 for every share tendered when the offer is more than 92% subscribed. This contrasts with PIZ287 in cash offered by Italy's Recordati (**Generics bulletin**, 9 April 2004, page 5), which wants no more than a 49.99% holding in the Polish firm, which makes a wide variety of prescription and OTC medicines.

Ivax promised it would support Polfa Kutno's efforts to acquire shares from the state treasury in fellow Polish firm Jelfa. Meanwhile, Recordati pointed out that its offer had already begun and would end on 27 April, but gave no indication of the uptake.

Where China and India fit in global API supply chain

As more Indian firms become global players, Chinese firms are investing heavily in taking their place, Newport Strategies' Kate Kuhrt explains to Editor Mike Rice.

Chinese ingredient makers have not yet been seen as active participants in a US filing for a generic which challenges a listed patent. However, it will only be a matter of time.

The country is already an important supplier of active pharmaceutical ingredients (APIs) to purchasers of older, off-patent molecules. And increasingly it is moving towards newer ingredients.

India, meanwhile, has become adept at developing non-infringing processes in support of patent challenges. Some Indian companies are developing their own branded generics, pursuing alliances with US generics firms, and buying US and European generics operations.

And both countries have now had over 50 of their pharmaceutical plants inspected by the US Food and Drug Administration (FDA).

But it would be as wrong to lump together Dr Reddy's Laboratories with hundreds of local suppliers and call them "India" – or Hisun with ancient traditional producers under the name of "China" – as it would to say Pfizer and Ranbaxy USA represented "America", according to Newport Strategies' research manager Kate Kuhrt.

"There is a tremendous diversity among Chinese and Indian companies producing APIs and finished-dosage forms," says Kuhrt. "There is a continuum from companies able to satisfy local demands to those meeting global demands for new molecules; from plants supplying local markets to those supplying global generics players and innovators by complying with the ever-changing good manufacturing practice (GMP) guidelines and FDA regulations."

However, a major difference between the API industries of the two countries is the numbers of firms that have for some years been able to supply to regulated markets, or what Newport, a provider of competitive intelligence for the pharmaceutical industry, calls "established" companies. According to Newport's databases, India currently has more than twice China's number of established API suppliers, and operates over three times the number of established sites.

Nevertheless, the differences between China's eight established manufacturers and India's 18 are small compared with the 500 or so firms operating in both countries. And as Kuhrt points out, as more Chinese API suppliers establish track records in regulated markets, they will continue to move up the rating scale.

Kuhrt describes India's Cipla as a typical established API supplier, whereas its compatriot Lupin would come into the "less established" category, although still quite capable of supplying regulated markets. Less established players have a weaker track record in supplying regulated markets, Kuhrt explains, either in terms of the

length of their history, or in the number of contemporary products that they supply.

Most of the API suppliers in both China and India are either "potential future" or "local" firms, according to Newport's ranking scale. As Figure 1 shows, more than 80% of firms in both countries are local in that they supply only to their local and other less regulated markets, and would not currently pass tough regulatory inspections. "Potential future" firms have limited experience in regulated markets, perhaps through supplying intermediates to more established API manufacturers, or through supplying older molecules.

Kuhrt cautions, however, that the numbers of companies in each category are changing rapidly. "Many companies in both China and India are investing heavily in the pharmaceutical industry," she says, "and are moving up the supply chain both in terms of value and capabilities."

Only about 1% of local manufacturers in both China and India are owned by "big pharma", Kuhrt adds, with just nine sites coming under their direct control in either country.

Developing new products very early

Looking in more detail at each of the countries, Kuhrt says companies like Cipla, Dr Reddy's and Ranbaxy are notable in India for the number of new molecules they develop very early. These progressive Indian firms have no counterparts at present to the east, as most Chinese suppliers concentrate on older molecules for which they are often the cheapest source.

Rosuvastatin – AstraZeneca's Crestor – is a good example, Kuhrt says, of how early Indian companies have their products ready. "A day after AstraZeneca announced the availability of Crestor in the US, Ranbaxy launched its own version in India," she observes.

"Generics firms that are challenging patents need either internal capabilities to develop non-infringing APIs, or deals with companies like Cipla, Dr Reddy's or Ranbaxy," comments Kuhrt. "European supplementary protection certificates (SPCs) are contributing to patent-challenge material being manufactured in India."

Newport believes latanoprost – Pfizer's glaucoma-treatment Xalatan – is a good example of a difficult API. Synthesising it takes over 20 steps, but worldwide demand is expected to be about 5kg. "It is an attractive product that is expected to be profitable," comments Kuhrt.

"We believe Par's abbreviated new drug application (ANDA) in the US references a drug master file (DMF) of Resolution – Arrow – in the UK. The DMF includes a manufacturing site in India, which we believe is Neuland. The Resolution DMF is currently the only file posted by the FDA,

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although we have heard about other exclusivelatanoprost deals.”

Olanzapine – Eli Lilly’s US\$4 billion serotonin antagonist Zyprexa – shows how Indian companies get involved with molecules at an early stage, as well as how they use patents on polymorphic forms as an offensive strategy, Kuhrt continues.

Newport first learned Cipla had an olanzapine API in September 2000, she explains, and polymorphic forms in December 2000. The Indian firm is behind Ivax’ first filing of an ANDA with a Paragraph IV patent challenge, Newport believes.

Similarly, Dr Reddy’s has challenged Pfizer’s olanzapine patents. It has had an alternative molecular form at least since November 1999, and filed a DMF in February 2001.

“Teva has also filed an ANDA for this product, but it has agreed to be bound by the outcome of the Dr Reddy’s/Ivax court case,” Kuhrt explains. “The question that Newport has not been able to answer so far is: ‘Where is Teva getting its API from? Is it from India?’”

Other collaborations she mentions are Mallinckrodt, which in addition to using internal sources, collaborates with India’s Cadila Pharma for fluoxetine; and Apotex, which has publicly announced supply agreements with Glenmark for the vasodilator amiodarone and with Lupin for the antibiotic cefuroxime.

Newport has heard that Ranbaxy also sources APIs from compatriot Matrix and China’s Hisun. The latter route east is also taken by Dr Reddy’s, she observes, which at times gets low-cost APIs for its Indian final dosage-form business from China, leaving its own more-expensive GMP capacity free for making non-infringing APIs for regulated markets.

Kuhrt draws attention to Indian firms’ responses to the imminent prospect of product patents, which will be introduced locally for the first time next year.

They will still have the option to make off-patent molecules and intermediates, she says, although many are “rushing out lots of new molecules” to get them commercialised before the deadline.

Some Indian API manufacturers are trying to move up the value chain and replicate the success of Dr Reddy’s and Ranbaxy with finished-dosage forms. Others, meanwhile, are carrying out custom manufacturing for clinical studies in the expectation that they will be in a unique position to take on commercial-scale manufacturing once the product is nearing approval.

All of this is happening against a backdrop of increasing investment in research and development by Indian API firms to come up with new molecular entities and new polymorphic forms which they can patent for themselves.

Kuhrt points out that investing in new molecular entities is unlikely to pay off in the near term, although putting money into polymorphic forms may pay off sooner. She adds that top flight firms like Ranbaxy are also securing their future by entering into drug-discovery and clinical development collaborations, covering a wide range of therapeutic areas, with originators like GlaxoSmithKline (**Generics bulletin**, 7 November 2003, page 6).

Buying European and US players

Furthermore, Indian API manufacturers are going beyond their earlier aspirations to market finished-dosage forms outside their home market and are buying European and US players. Kuhrt mentions Ranbaxy’s entry into the French market by acquiring RPG from Aventis (**Generics bulletin**, 16 January 2004, page 3), Wockhardt’s burgeoning UK presence through its CP Pharmaceuticals purchase (**Generics bulletin**, 5 March 2004, page 8), and Unichem’s Niche Generics joint venture with ex-Bioglan directors.

Sun Pharmaceuticals has been investing in the US through local player Caraco (**Generics bulletin**, 5 March 2004, page 5), but the preferred route into the US market for Indian API producers up to now has been through alliances, observes Kuhrt. A few more examples of alliances she mentions are:

- Watson and Cipla, which was widened last December, 12 months after the alliance was struck (**Generics bulletin**, 9 December 2003, page 3)
- KV and Glenmark for eight unspecified products (**Generics bulletin**, 2 February 2004, page 3)
- Baxter and Lupin for the antibiotic ceftriaxone
- Par and Dr Reddy’s

Indian companies are also pursuing branded generics, Kuhrt points out. This is both in terms of new salts, like Dr Reddy’s unsuccessful US launch of AmVaz, its antihypertensive amlodipine maleate (**Generics bulletin**, 5 March 2004, page 13); and through drug-delivery technologies, such as Ranbaxy’s new drug application (NDA) in the US for its Riomet diabetes brand, comprising metformin oral solution (**Generics bulletin**, 16 February 2004, page 10).

Turning to Chinese API producers, Kuhrt

Indian API manufacturers are going beyond their earlier aspirations to market finished-dosage forms outside their home market and are buying European and US players

	India		China	
	Manufacturers	Sites	Manufacturers	Sites
Established	18	43	8	13
Less established	17	36	11	12
Potential future	56	89	44	76
Local	454	494	395	430
Unrated	11	13	2	2
Big Pharma	7	9	5	9
Total	563	684	465	542
<i>FDA inspected</i>	–	54	–	54

Figure 1: Manufacturers of active pharmaceutical ingredients (APIs) in China and India, ranked according to regulatory, quality and product criteria (Source – Newport Strategies)

maintains that they are some way behind their Indian counterparts. "We believe China does not have a fully-integrated, world-class global company like some of those found now in India; currently it lacks entrepreneurs of the calibre of the people that established those firms in India."

"No Chinese API manufacturer has attained the global reach, or has the development, launch, regulatory or intellectual-property capabilities of the integrated Indian companies. China is still lacking the broad-based experience and high-quality managers of the leading Indian companies."

It is for these reasons, Kuhrt continues, that China has so far not been an active participant in patent challenges in the US. "Chinese companies have not been able to develop non-infringing processes and comprehensive technical packages 10 years before patent expiry," she notes. "We also believe a shortcoming of Chinese API manufacturers has been their focus on short-term targets rather than on long-term opportunities and sustainable profits."

But this is changing, she adds, with assistance from overseas. "China is no longer merely a low-cost threat; Chinese firms are important suppliers of intermediates to key API manufacturers. They are also significant suppliers of APIs to purchasers of older, off-patent molecules, and increasingly will be moving towards making newer molecules," asserts Kuhrt. "It is no longer simply about low-cost supply, as China is investing heavily in people, plant and quality."

Kuhrt underlines the fact that Chinese companies are preparing for inspections by hiring consultants. Western-educated Chinese are returning to the country and being joined by westerners looking to take advantage of the opportunities.

Overseas customers are providing expertise, she says, and bad plants are being closed. Furthermore, factory managers are becoming younger, applying their western training in more entrepreneurial ways; while research and development centres are "springing up all over", underscored by collaborations with universities and foreign firms.

Taking advantage of China's prices

Right now, however, companies are taking advantage of China's cheaper prices. Kuhrt mentions Perrigo, the leading US supplier of store-branded OTC products, and originator firms which are outsourcing APIs and intermediates for older products to reduce costs and free-up capacity. "Innovator outsourcing has slowed with the dearth of new molecules, but is expected to pick up in 2005-2006 and onwards," she says.

Generics companies, Kuhrt maintains, can also find that pricing is problematic with some Chinese firms, which she says can be "wild cards". "Low pricing out of China can be helpful when negotiating with more-established API suppliers. But in actually dealing with the Chinese, the lack of a clear cost structure or market basis can be difficult, and can mean some oddly inconsistent pricing between different suppliers of the same product."

Intermediates often come from China, she notes, and leading Indian API suppliers like Dr Reddy's make use of them, as do western API producers like

Portugal's Hovione, which gets supplies from a small number of high-quality plants.

China also continues to be a strong player in fermentation products, she notes, and is a source of supply in this area to Indian firms. "We have heard that at times this Chinese material also ends up in regulated markets under Indian companies' labels," reports Kuhrt.

She questions whether generic acarbose API, a small-volume, high-cost fermentation product in Bayer's Glucobay/Precose diabetic brand, is finding its way into the west via India. Similarly, she adds, Chinese simvastatin may be arriving in regulated markets by the same route.

China's development as a source of APIs will depend, Kuhrt believes, on companies' willingness to spend money. "To date, no Chinese company has been willing to invest on the scale necessary," she insists, pointing out that Dr Reddy's required many years and millions of dollars before it was profitable in the US. "The competition is tougher than ever before, and the investment needs are extremely high."

Kuhrt spells out the facts of life for aspiring API suppliers: "Deals between generics and API manufacturers are being done earlier and earlier, increasing risk."

"There is increased pressure to challenge or circumvent patents. This means firms must be ready very early with product and technical package. But developing early is more risky; yet so too is developing later, as the product may have to be too competitively-priced for the API supplier to make money."

She reckons that API development must start 8-10 years before brand patent expiry to allow five years of work before a successful patent challenge. "Today, strategic generics firms are planning for 2013 and beyond. Increasingly, targets are evaluated before a branded product is even launched in major markets."

Relationships are also important. Kuhrt says patent challenges are based on a good understanding between API manufacturer and generics firm which takes years to develop. But because of consolidation in the industry, there are fewer and fewer, increasingly powerful global generics players with worldwide sourcing.

Meanwhile, backward integration is seeing API manufacturers being bought by generics firms, reducing the number of independent operators. There is also increasing consolidation among API manufacturers in both China and India.

"China and India have taken their places in the global supply chain, serving both generics and innovator companies. They will play an essential role in future, with Chinese firms moving towards newer molecules, and Indian companies playing a major role in supplying new molecules, supporting patent challenges, and becoming increasingly important players in the finished-dose market," says Kuhrt.

Generic profitability is increasingly dependent on high-calibre API sources, she adds, which means opportunities for established, independent API suppliers in both China and India. **G**

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