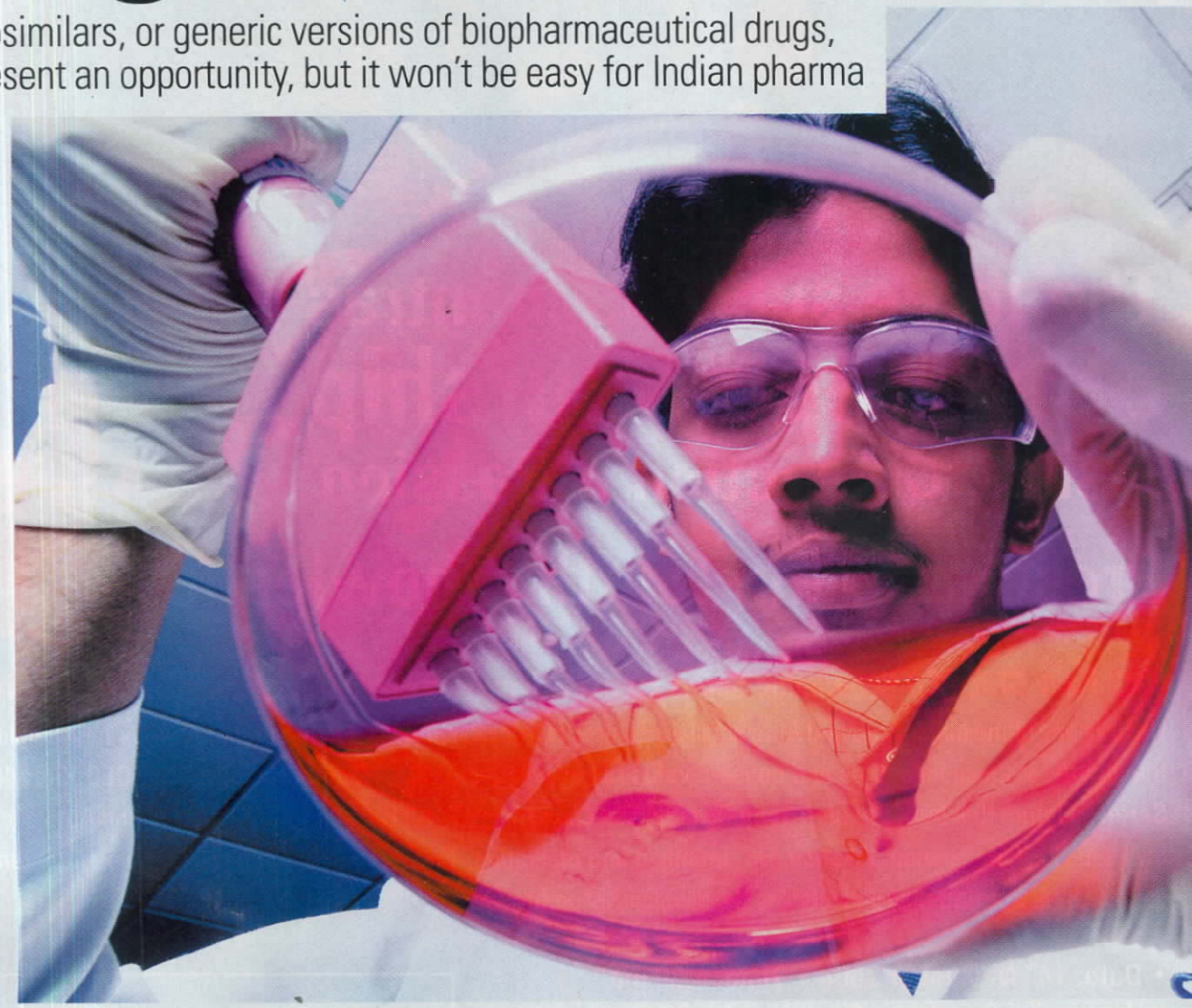
High-Protein Ambi

Biosimilars, or generic versions of biopharmaceutical drugs, present an opportunity, but it won't be easy for Indian pharma



Nandita Datta

THESE DAYS, IN THE STERILE BIOTECHnology labs of many Indian pharmaceutical majors, there is a sense of purpose—to become the first company to launch biosimilars, generic versions of biopharmaceutical drugs, which, themselves, are innovative medicines produced using biotechnology methods. Companies like Biocon, Reliance Life Sciences and Dr Reddy's believe this can generate $21 billion in sales from Europe and the US in the next six to seven years. They are scrambling to put out an India-made biosimilar product, at least by 2011.

There is a lot at stake. For the Indian pharmaceutical industry, which has so far relied on low-risk process chemistry skills to earn a place for itself in the global generics marketplace, developing bio-similar drugs is seen as being worth the risk. Why? Simply, because of the huge commercial rewards it will ensure once the US opens up its market to biosimilars the same way Europe did three years ago.

However, because the dynamics of this market are unlike anything that the Indian

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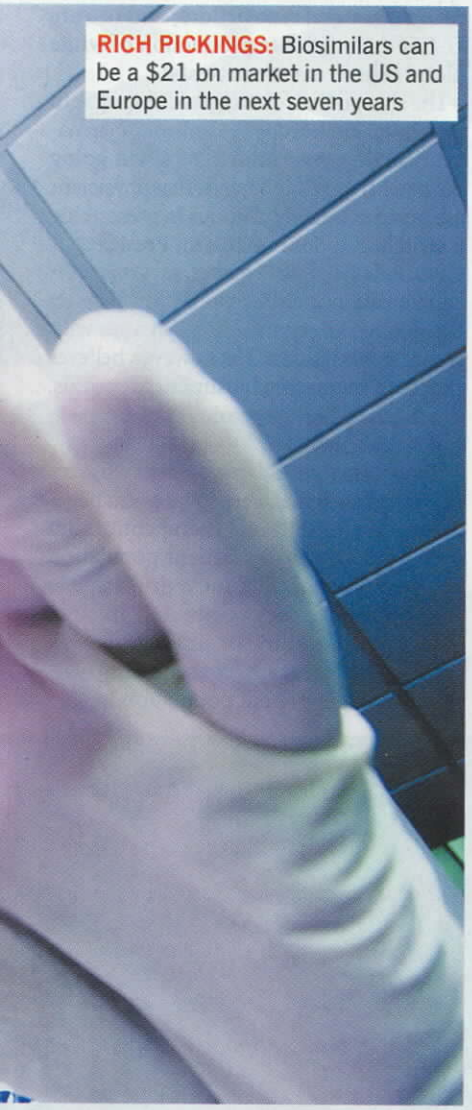


RICH PICKINGS: Biosimilars can be a $21 bn market in the US and Europe in the next seven years

PHOTOGRAPHS BY SHRIKANT KOLARI

pharmaceutical industry has experienced so far, the road ahead is expected to be slow and fraught with challenges. But, what is clear is that the biosimilars market is a blockbuster in the making.

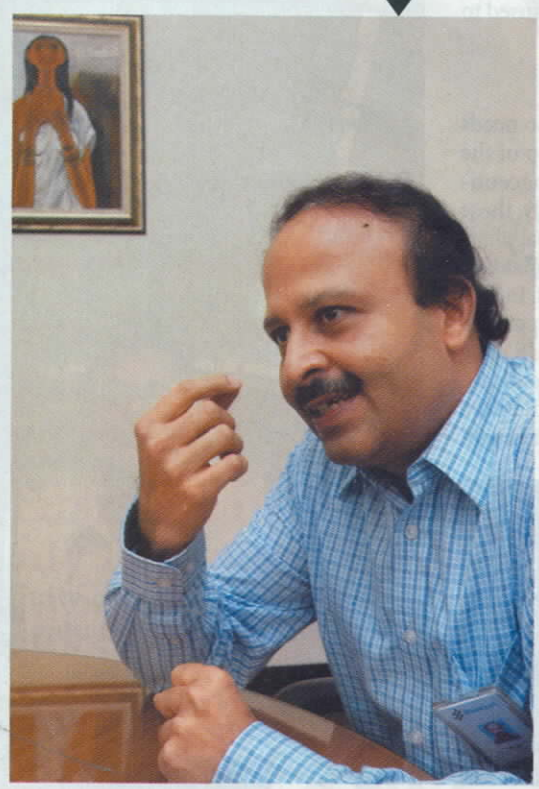
Booster Dose

The biggest growth driver for biosimilars will be the US market, once it opens up. A Bill that permits biosimilars is pending before the US Congress. While the Democrats favour its entry, the Republicans have opposed it. However, the recent huge electoral gains for the Democrats may herald an early decision on biosimilars. Because the US accounts for 55% of the global biopharmaceuticals market and has a very strong generics culture, the potential opportunity is immense.

Europe, on the other hand, accounts for 25% of the global biopharmaceuticals market, with the most attractive biosimilar destination in the region being Germany, thanks to its well-developed generics market and high biopharmaceutical usage.

Realising this opportunity, Indian pharmaceutical firms have been quick to step in. Biocon recently acquired a majority stake in German drug marketing firm AxiCorp, Dr Reddy's purchased Germany's fourth-largest generics firm Betapharm in 2006 and Wockhardt bought Esparma in 2004. Mergers and acquisitions apart, the Indian pharmaceutical industry's biosimilars strategy also involves research collaborations and marketing tie-ups. This is unsurprising given the high cost of development, manufacture and marketing of biosimilars.

> "Biosimilars is only a stepping stone, not the end. Our focus is biopharmaceuticals, and biosimilars is how we will get there"
>
> **Arun Chandavarkar**
> **Chief Operating Officer, Biocon**



Developing a biosimilar can cost $10-40 million, as compared to $1-2 million required for a conventional generic drug. And, the time-to-market can range from 36-48 months in the case of biosimilars, compared to just 12-18 months for a conventional generic drug. "The higher cost of development and lower probability of successful launch puts R&D investment at risk. This is new territory for conventional generics firms," cautions Sujay Shetty, Associate Director (Pharma), PricewaterhouseCoopers.

Boutique biotech firms like Avesthagen and Zenotech, for example, are planning to piggyback on the marketing prowess of big Indian firms such as Cipla and Ranbaxy, respectively. Dr Reddy's is believed to be in talks with a global biotech firm for technological expertise and global reach. Similarly, Biocon has inked a series of collaborations with academia and research institutions to explore new R&D opportunities.

Such tie-ups stem from the understanding that the traditional generics model—launching new products regularly to maintain growth—won't work for biosimilars. For one, the cost involved in such an approach will be prohibitive. Second, there aren't that many biopharmaceutical candidates for a company to rely on these alone to launch a product every year.

To succeed in this market, companies will need to have adequate financial resources to develop these products and to accept upfornt risks in development, commercialisation and capital investment.

"The initial success will depend on effective marketing and promotional strategies. Only later, as biosimilars become more widely accepted, will the low-cost advantages play out," Shetty says. The steep price discounts that are normal in conventional generics are also unlikely in biosimilars because of the higher costs involved in development and manufacturing.

In addition, the skill-sets required for biosimilars—biology R&D and conducting clinical trials—necessitates a mindset change in traditional Indian pharmaceutical firms. Hence, companies with a history of innovative research may be better poised than pure generic players to succeed since the skill-sets required are similar.

"Biosimilars are only a step-

The Opportunity In Europe

Biopharma drugs worth $13.2 billion have gone off-patent in Europe, which is an opportunity for Indian companies.

Brand name	Active ingredient	Therapy area	Patent-holder	Patent expiry	Global sales ($ mn)	Biosimilars approved *
Cerezyme	Imiglucerase	Gaucher's disease	Genzyme	2001	993	Nil
Humulin	Human Insulin	Diabetes	Eli Lilly	2001	1,005	Nil
Novolin	Human Insulin	Diabetes	Novo Nordisk	2001	1,618	Nil
Intron-A	Interferon Alpha	Oncology	Schering-Plough	2002	287	Nil
Avonex	Interferon Beta	Oncology	Biogen	2003	1,543	Nil
Humatrope	Somatropin	Growth hormone	Eli Lilly	2003	414	2
Nutropin	Somatropin	Growth hormone	Genentech	2003	370	Nil
Procrit	Erythropoietin Alpha	Anemia	J&J	2004	3,324	3
Epogen	Erythropoietin Alpha	Anemia	Amgen	2004	2,455	3
Neupogen	Figrastim	Oncology	Amgen	2006	1,216	2

* By EMEA (European Medicines Agency, the EU regulatory agency that evaluates medicinal products)

Source: PWC, Industry sources

ping stone for us, not the end. Our aim is to focus on biopharmaceutical research —and biosimilars is the way we are going to get there," says Arun Chandavarkar, Chief Operating Officer, Biocon.

And, for Indian pharmaceutical firms waiting for the biosimilar story to unfold in Europe and the US, near-term opportunities lie in the domestic market (at Rs 600 crore and growing at 20% per annum), as well as in exports to the unregulated markets of Latin America, the Commonwealth of Independent States and the Middle-East. Most of these companies have commercialised at least three to four products each in India. Already, if unconfirmed reports are to be believed, Dr Reddy's and Biocon are poised to file their first biosimilar products for European regulatory approval next year. Both companies, however, refused to comment on this development.

Slow Response

The importance of biosimilars also needs to be viewed against the backdrop of the growing popularity of biopharmaceutical drugs the world over. Currently, these drugs account for 15% of the global pharmaceutical market, but they are estimated to touch 25% over the next 5-10 years. In fact, most of the new drug applications approved in recent times by European or US drug regulators have been biopharmaceuticals. As their numbers swell from less than 200 currently, the canvas for biosimilar manufacturers will widen proportionately. That is when Indian pharmaceutical firms hope to make their killing with quality drugs at affordable prices.

Having said that, these are early days still and the response to biosimilars in Europe, the only regulated market where the pathway has been finalised, hasn't justified all the initial enthusiasm.

Sandoz's Omnitrope, the first biosimilar human growth hormone product to be launched in Europe, has so far managed to corner less than 2% of the market since its launch in 2006. The product was priced 20% cheaper than Eli Lilly's patented biopharmaceutical drug Somatropin. Although the entry of a second biosimilar product, Valtropin by Biopartners, saw the discount widen further, it did not do much to shore up market share. Till date, the European regulatory authority EMEA has approved only 10 biosimilar medicines: two are growth hormones (to treat growth deficiencies), six are erythropoietin (to treat anemia associated with malignancy and renal failure) and two are G-CSF (to stimulate production of white blood cells in cancer patients).

The slower-than-anticipated response to biosimilars in Europe (despite biopharmaceutical drugs worth $13.6 billion going off-patent) seems to suggest that physicians are being extremely cautious in prescribing a switch. KV Subramaniam, President & CEO, Reliance Life Sciences, says it is critical to create awareness among physicians on the quality, safety and efficacy issues with regard to biosimilars. He, however, believes that with increasing biosimilar approvals, physicians will start gaining confidence in inter-changeability.

"Biopharmaceuticals have addressed areas of clinical need that were so far unmanageable with conventional therapeutics. But only a fraction of the patient population has been able to afford these drugs due to the steep prices they command," he says. "The entry of biosimilars will pave the way for affordable therapy, consequently benefiting a larger patient population."

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> **President & CEO, Reliance Life Sciences**

Innovator companies, too, have been playing up concerns on safety and efficacy issues just like Big Pharma did with conventional generics in the late-1980s.

Villoo Morawala-Patell, Chairperson & Managing Director, Avesthagen, says it is normal for the first round of biosimilars to face resistance. "Change is never easy, especially in a market that is dominated by Big Pharma. But we believe that the situation will change in the next few years and the commercial rewards will be well worth the investments we have made," she says.

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Another reason for the slow pick-up of biosimilar products is the confusion regarding different international non-proprietary names (or INNs) for biosimilars and the reference drug. Different INNs hinder generic prescribing and substitution. Interestingly, recent news reports indicate that this issue will be settled once and for all—in fact, similar INNs have been allowed in some recent biosimilar approvals in Europe. Once the guidelines are clear, biosimilar developers will have much more reason to cheer.

Different Strategy

Unlike conventional generics, a biosimilar strategy isn't about copying a drug using a chemical process and going to market on patent expiry. It is more about clinical outcomes as well as large upfront investments in R&D and marketing. The vastly different compositions of the reference products—biopharmaceuticals in the case of biosimilars or a new chemical entity (NCE) in the case of a conventional generics product—render their respective generic products as different as chalk from cheese.

Biopharmaceuticals (also called biologicals) are more complex and much larger than entities produced through a chemistry process. Biopharmaceuticals are proteins —a sequence of amino acids that are strung together in a chain. Amino acids by themselves are not active—it is the folding of the amino acid sequence that results in a three-dimensional structure, which gives the protein its unique ability to bind specifically to some target. In more complex proteins, some of the amino acids are modified by attaching certain sugar groups—this attachment alters the protein's specificity and pharmacokinetics (how the drug is absorbed in the human body).

On the other hand, NCEs are typically small molecules that have no complex three-dimensional structure—hence, there is no specificity of binding. They act not only where you want them to, but also in other areas. A chemically synthesised cancer drug, for example, will act on cancer cells as well as on normal cells. An oncology biopharmaceutical, on the other hand, will act only on cancer cells.

Because of the complexity involved, biopharmaceuticals are manufactured using living cells that are genetically modified to produce the protein. On the other hand, NCEs are manufactured using a chemistry process. The formulation, or dosage form, is also different for the two classes of drugs. Proteins have a large molecular weight (they are 100-1,000 times larger than NCEs) and, hence, can't be administered orally. They have to be injected into the body.

Biosimilars also require careful handling—the three-dimensional structure of a protein can be easily destroyed by changes in storage conditions. In addition, firms that develop biosimilar products do not use the same manufacturing process as the reference drug, and the slightest change in these processes can have dramatic consequences on the protein's characteristics.

Biosimilars are also expected to undergo immunogenicity studies to ensure the drug does not trigger an immune reaction in the body—this is not required in the case of conventional generics.

But, by far, the biggest difference between conventional generics and biosimilars is the nature of clinical data that companies have to submit to the regulatory authorities. Conventional generics require only a bio-equivalence study and bio-availability data—to ensure that the copy is equivalent to the reference drug in terms of dosage and absorption by the body. Pharmacodynamics data (or the response of the body to a drug to prove its efficacy) is not required.

So, a generic producer of cholesterol-lowering Simvastatin will only have to ensure that its drug and the reference product are absorbed by the body in a similar way and that they remain in the body for the same length of time. It doesn't have to prove that cholesterol is coming down the same way. The assumption is that if the two drugs are structurally similar, they should have the same efficacy. This is not the case with biosimilars, where companies are expected to undertake efficacy studies because the generic product is never structurally identical to the reference product.

Says Chadarvakar of Biocon: "If I am making generic insulin, I need to prove that my product lowers body glucose in a similar manner and that the HbA1c count (used to monitor diabetic patients) is within controlled limits, just like the reference product."

And therein lies one of the key challenges that will dog the manufacturers of biosimilar products. ■