Bridges to the Bloom:

The Future of Indian Biosimilars

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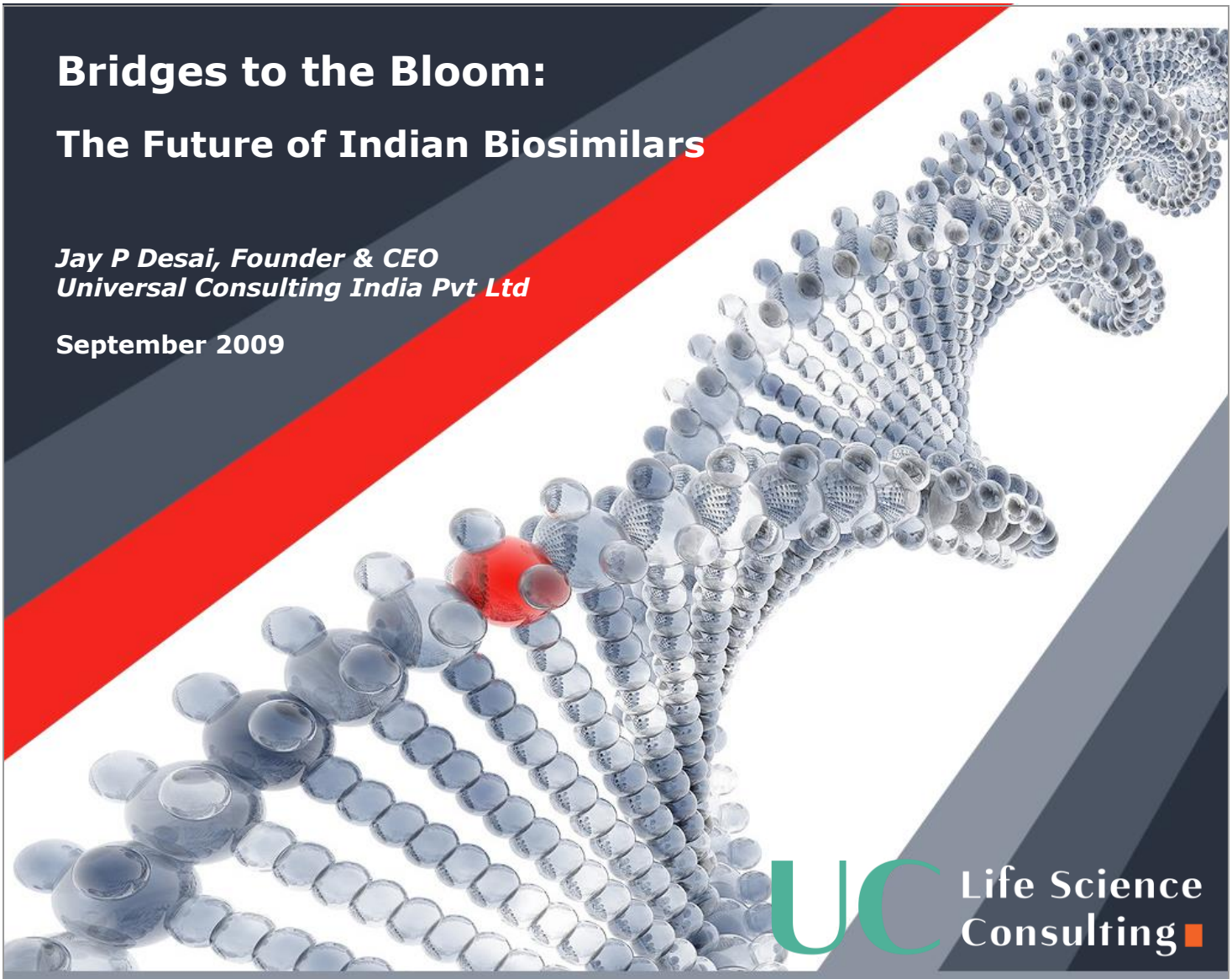


UC Life Science Consulting

The evolutionary pressure to merge the boundaries between pharmaceutical and biotechnology companies in order to survive and compete is increasing. At the same time, the focus on affordable medicines is gaining ground, for both chemistry-based as well as biotechnology-based drugs.

The current view on the Indian biosimilars industry is that at some point in the not-to-distant future, it will replicate the relative success of the Indian pharma generics industry, in the global markets. The reality may well turn out to be quite different. A broad and deep chasm lies ahead for Indian biosimilar manufacturers. The task of bridging this crevice is no ordinary one.

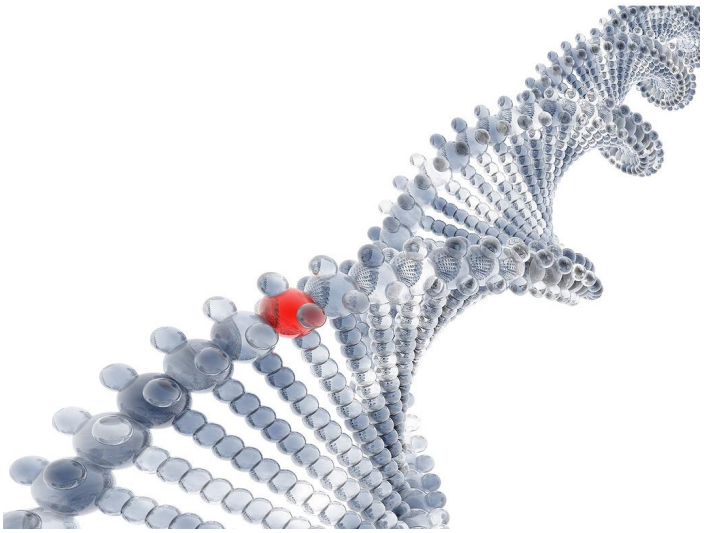
There are *five bridges* that an Indian bio-pharmaceutical company must traverse, all of them equally important to success. These bridges span the chasm of *affordability*, *assets*, *approvability*, *acceptability* and *availability*. The ability to safely cross over these spans, will determine the level of success we are likely to see in the Indian biosimilars industry.

The path Indian biosimilar manufacturers seek to travel over the next few years will slowly but surely, reveal the biggest hurdles they are ever likely to face. This journey, executed with strategic foresight, meticulous planning and patience, however, could lead to a bloom they can fully harvest.

Introduction

Biosimilars are large molecule, protein-based bio-pharmaceuticals, with complex three-dimensional conformational structures that modulate their biological activity. They are "similar", but not identical versions of the genetically engineered biological products manufactured by the innovator bio-pharmaceutical companies. These "biosimilar" products are also referred to as "follow-on biologics".

Recombinant DNA products like hormones, thrombolytic agents, growth factors, interferons, interleukins and therapeutic monoclonal antibodies are the broad categories of products that are classified under the umbrella term, biosimilars.



Key Drivers of Growth

There are a number of drivers for the growth of the biosimilars market worldwide. Key among them, are the following; a shift to chronic diseases like cancer and diabetes, the rising cost of treatment with innovator biologics, almost US$ 26 billion worth of innovator biologics going off-patent in the next ten years and the evolutionary pressure to merge the boundaries between pharmaceutical and biotechnology companies, in order to survive and compete.

In India, the interest in biosimilars is additionally spurred on by multiple factors. Firstly, under the TRIPS agreement, pre-1995 product patents were exempt thus granting some biologicals, the rights to continue manufacturing. Secondly, biotechnology drugs (besides insulin) are free from the government's price control act, allowing independence in price setting. Thirdly, an increase in the number of "biotechnology parks", some of them public-funded have acted as a catalyst for the industry. Lastly, there seem to be signs of acceptance of locally manufactured biosimilars among healthcare professionals within the country.

The "made-in-India" biosimilars market (domestic plus exports) in 2008 was around US$ 200 million, with an expectation to reach around US$ 580 million by 2012. The size of the "imported" innovator biologics market was just a little larger, at around US$ 220 million.

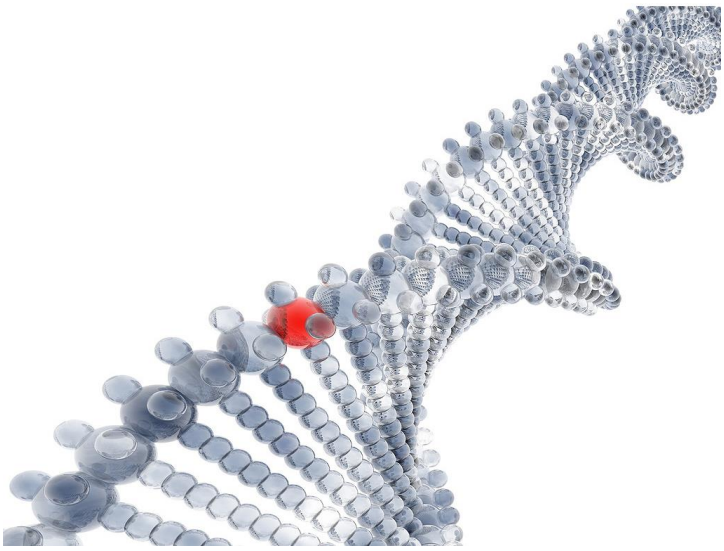
Replicating the Pharma -Generics Model

India, due to its inherent advantages in low cost manufacturing and highly skilled, reasonably priced workforce, accompanied by combination of accident and design, has had some success in the global generics marketplace.

On a relative basis, compared to other industries in the country, the pharma generics business is a storied business model, which other industries seek to emulate. The ability to manufacture generics at a substantially lower cost than the small molecule innovators, the 2nd largest number of US FDA approved manufacturing plants, the strong reverse chemical engineering skills acquired under the radar screen of a favourable regulatory framework, plentiful talent and a domestic market that is hungry for affordable medicines, have together conspired to create a generics powerhouse, albeit not without its attendant quality control problems in recent

times.

The current "theory-in-use" is that India will at some point in the not-to-distant future, replicate the relative success of its pharma generics industry (though small in absolute dollar terms), in the biosimilars market worldwide. The "theory-in-practice" may well turn out to be quite different, with a broad and deep chasm that lies ahead. The task of bridging this crevice is no ordinary one.



The Five Bridges

To understand if Indian bio-pharma companies will succeed globally in the biosimilars space, we need to clearly understand how wide the chasm is and the bridges that the Indian biosimilars industry must cross.

There are five bridges that an Indian bio-pharma company must traverse, all of them equally important to success. These bridges are those of affordability, assets, approvability, acceptability and availability. The ability to safely cross over these spans, will determine the level of success we are likely to see in the Indian biosimilars industry.

It is important to inspect each of these bridges with a critical eye to assess the level of effort and time required to cross the chasm.

Bridge 1: The Bridge of Affordability

The ability of the population to pay for biosimilars has to be seen from both a *domestic Indian* and a *global overseas* markets perspective.

Consider the domestic Indian market with almost 75% (approx 848 million) of its population living in the rural areas. Here, affordability and awareness of even the basic medical care is suspect. Countrywide, only 1 % of the population has an income greater than US$ 20,000 pa. To make matters worse, 971 million people (86% of the population) have no health insurance.

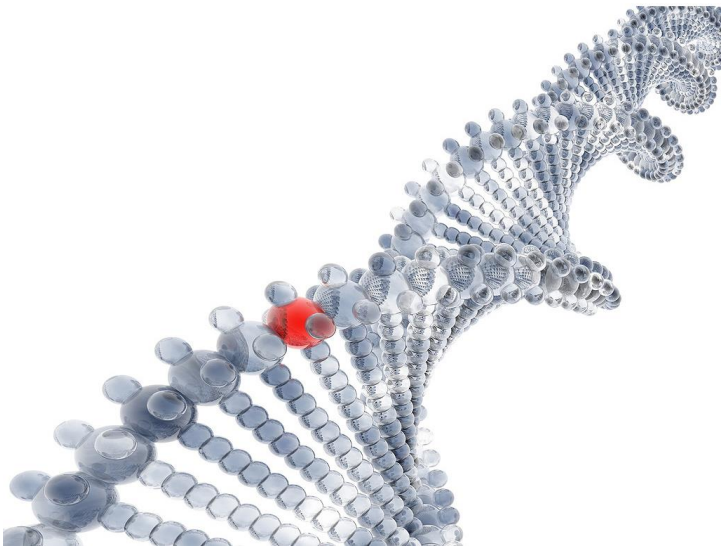
Biosimilars like Erythropoietin, G-CSF and Streptokinase, currently manufactured and sold in India can be anywhere between 25%-50% cheaper than the imported innovator products. While not having the larger price differential that is seen between small molecule innovator drugs and their generics, this is still a reasonable saving.

Compared to traditional generics, however, biosimilars are more expensive on a relative basis, due to the high cost of developing cell-lines, higher cost of technical manpower and the cost of importing manufacturing equipment like fermenters. The population that can currently afford Indian-made biosimilars is a thin sliver, but clearly, this works more against the pricey innovator biologics who may plan to sell their products in the country.

The key question to ask about the Indian markets is not whether a biosimilar will be a preferred substitute to an innovator biologic, but whether a chemical generic will be the preferred substitute to a biosimilar.

In the global overseas markets, the potential

does exist to sell Indian biosimilars in un-regulated and semi-regulated markets, but the costs and process of approval in regulated markets may prove to be larger barriers than anticipated. Undoubtedly, the higher cost of clinical trials and other requirements to meet all the regulatory approvals will erode the price arbitrage that Indian biosimilars currently possess, compared to the innovator biologics.



Bridge 2: The Bridge of Assets

There are two key assets that must be in place for success in the biosimilars industry- *research* manpower and manufacturing infrastructure.

Research Manpower – India is reputed to produce a large number of PhDs, almost 7,700 in 2007, the same number as the US and slightly shy of the China figures. Of these, about 1,500 were bioscience and biochemical engineering PhDs, a surprisingly small number, compared to the almost 650,000 Masters students graduating in the same field. Relatively few universities offer graduate programs in molecular biology and human genetics. Around 35% of graduate students go overseas for their PhDs, due to inadequate academic infrastructure, lower quality of faculty and poor academic resources in the country.

A trickle of a reverse migration from the hallowed halls of western universities and research labs of bio-pharma corporations has, however, resulted in a slow and steady build-up of overseas-trained talent in the country. The net impact for the biosimilars business is that while Indian expertise for gene manipulation and fermentation exists domestically, capabilities in cell-line development and process development are still nascent. There is a reasonable amount of R&D activity, however, around cancer therapeutics and diabetes.

Manufacturing Infrastructure – There are five bio-pharmaceutical manufacturing clusters that seem to be emerging around the country, in New Delhi, Ahmedabad, Mumbai-Pune corridor, Bangalore and Hyderabad.

The Indian government too is attempting to create an environment conducive for the growth of the industry. The Biotechnology Industry Partnership Program (BIPP), the Biotechnology Industry Research Assistance Council (BIRAC), exclusive Biotech Parks and some tax incentives, are all designed to encourage investments and progress in this sector. With a 30% expected CAGR, especially from exports into semi-regulated and un-regulated markets, investments specifically into biosimilar manufacturing capabilities are increasing. But significantly more financial investments will be needed to build the scale, research capabilities and the manufacturing ecosystem needed to create a global powerhouse in biosimilars.

While there are almost 300 biotech and bio-pharma based companies in the country, only 40-45 companies focus on biologics, of which around 16-20 companies market biologicals (many imported), but only 7-10 of these companies actually manufacture biosimilars in India. Contract manufacturing so far appears to be limited to Insulin.

There are roughly 40 biologicals that are marketed in India, of which around 25 are

biosimilars manufactured in the country. Another 20-25 products are in the pipeline. Local manufacturing primarily revolves around Insulin, Erythropoietin and Granulocyte-Colony Stimulating Factor.

Bridge 3: The Bridge of Approvability

A clear regulatory pathway for biosimilars in India is likely to be introduced in 2010. Currently, Indian regulators consider biologics on a case-by-case basis and recommend extensive clinical trials only if deemed essential. Phase I and Phase II trials are typically not required since the DCGI provides approval based on global clinical trials data.

A large number of regulatory bodies are involved in the approvals of biosimilars in India. These include the Institutional Bio Safety Committee (IBC), the Review Committee on Genetic Manipulation (RCGM), the Recombinant DNA Appraisal Committee (RDAC), the Drug Controller General of India (DCGI), the Central Drug Standards Control Organisation (CDSCO) and the Genetic Engineering Approval Committee (GEAC.) A single umbrella organisation, the National Biotechnology Regulatory Authority (NBRA) is now also being set up.

The regulatory pathway for biosimilars is still unclear in the US. As the fog lifts from the horizon in 2010, it will be critical for Indian companies to adapt to this evolving landscape. The attendant risk of rejection as the molecule traverses the development phase is even more sharply exacerbated in the case of biosimilars.

The ability to understand, adjust and comply with the regulatory and administrative requirements in the US and the EU will be the acid test of the deftness of Indian biosimilar players. This will be the inflection point in the industry life cycle of companies manufacturing biosimilars from India.

Bridge 4: The Bridge of Acceptability

Will follow-on biologics that are "Made-in-India" ever be recognised and accepted in the advanced western markets that are highly regulated? Will these biosimilars meet the stringent quality, safety and efficacy norms that are the hallmarks of internationally reputed bio-pharmaceutical brands?

Indian companies have followed different strategies to cross this bridge, but all with the same outcome in mind.

In an effort to climb the quality ladder and imbibe significantly better research skills, Indian bio-pharma players have started collaborating with public scientific institutions at home, as well as with overseas universities. To get a grip around the complex regulatory processes, a number of Indian companies have set up strategic alliances and joint ventures with overseas bio-pharma companies to facilitate co-development and entry into the regulated markets, when the time is ripe. To ensure direct access to a marketing and distribution channel, some of them have acquired bio-pharma companies in regulated markets.

The key to acceptability, however, lies in the answer to the question- will physicians and patients accept a follow-on biological that is "Made-in-India"?

The growth of locally produced biosimilars in India as well as in some semi-regulated and un-regulated markets shows that acceptability of the Indian brand is reasonable, allowing fairly rapid penetration.

In India, the physician, partly in consultation with the patient, decides on the biosimilar to

be prescribed, based on affordability and perceived quality. Marketing incentives provided to the distribution channel also play a role in pushing sales of a particular brand.

In the EU, prescription and inter-changeability of biosimilars will be the physicians' responsibility. The regulatory body might even compel physicians to prescribe biosimilars by brand name only. This will mean that Indian biosimilar companies will have to invest substantially in building relationships with physicians to improve brand recognition and recall. Relationships will also have to be built with key constituents in the largely government-run healthcare systems in place.

In the US, similar constraints will be in existence with respect to working with physicians, but additionally, Indian companies will have to develop brand-recognition with the insurance firms, who play a key role in the penetration profile of a bio-pharma drug.

Clearly, in the regulated western markets, a lot of heavy-lifting will need to be done in the years ahead, for the "Made-in-India" biosimilar brand to achieve the respectability needed to reach critical mass.

Bridge 5: The Bridge of Availability

Biologicals, unlike most chemical generics, are highly temperature-sensitive and this poses tremendous challenges for the logistics and distribution end of the business.

In the regulated western markets, the presence of extensive end-to-end cold-chain distribution infrastructure ensures that fragile biological material is delivered in perfect administering conditions, to the point of use. The Indian biosimilar aspirant overseas will need to bear the attendant higher costs associated with this logistics channel.

Unfortunately, this cold chain logistics network is weak back home in India. While the urban distribution network is more reliable, but by no means perfect, the rural distribution network is broken and fragmented. The primary distribution from the manufacturer's warehouse to the regional distribution centre is by air, the secondary distribution to and from the local distribution centre, especially into semi-urban and rural areas, is by road and by definition, unreliable and irregular.

Indian companies at home will have to bridge the chasm of availability, while keeping one eye on the bridge of affordability, to reach deeper into the market, as income levels rise over the next decade.

Bridging the Chasm

As Indian biosimilar manufacturers prepare to cross these *five bridges*, it would be worthwhile for top management to ponder the challenges that lie ahead. Developing a bouquet of strategies that allows them to bridge the chasm of *affordability*, *assets*, *approvability*, *acceptability* and *availability* should clearly be on the top of their strategic agenda.

The path they seek to travel over the next few years could very well be the single biggest hurdle that Indian bio-pharma will ever face.

Executed with strategic foresight, meticulous planning and patience, however, could lead to a bloom they can fully harvest.

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