FORMULA OF SUCCESS
Emerging trends in Biosimilars in India
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1. GLOBAL BIOSIMILARS INDUSTRY

1.1 Market Overview

Biosimilars products/‘follow-on’ biologics are medicines similar to already patented/registered biotech products, but are manufactured by new companies after the patent expiry of the originator product. The global Biosimilars market is expected to grow to US$ 10 billion by 2015, with growth largely driven by US$79 billion worth of biologics going off-patent by 2015 and more broadly, growing demand for biologic medicines as opposed to conventional pharmaceuticals. The number of companies producing Biosimilars is likely to remain limited, because unlike the small molecule generic industry which is highly fragmented, the Biosimilars industry is defined by long product development lead-times (8-10 years) and high fixed costs.

The global Biosimilars market is expected to grow to US$ 10 billion by 2015, with growth largely driven by US$ 79 billion worth of biologics going off-patent by 2015.
Despite costly development and manufacturing, Biosimilars are typically marketed at prices 25 to 40 percent below original branded products, which is their primary appeal to customers. From a product perspective, sales remain highly concentrated, with the top 25 Biosimilars products currently driving 83 percent of global Biosimilars sales. Geographically, sales of biotech products are concentrated in the United States (US) and Europe, which not only provide the greatest market opportunities, but also the highest regulatory hurdles for Biosimilars.

![Biotech Patent Expiries in US and Europe](image)

Source: Credit Suisse Report on Biosimilars

2. **GLOBAL BIOSIMILARS INDUSTRY: COMPETITIVE ANALYSIS AND SOLUTIONS**

2.1 **SWOT Analysis**

The Biosimilars industry is fast-growing and has a strong economic value proposition. However, there are a number of competitive threats that make a well-developed strategy critical to any country wishing to develop this sector.
Strengths

- Lower price point and similar effectiveness to originator products
- Shorter time to market than originator products
- Higher probability of Return on Investment (ROI) than with new product R&D
- Due to rapidly increasing healthcare costs, there is high consumer demand for discounted high quality treatments

Weaknesses

- Cost of Biosimilars products to consumers in emerging markets is still relatively high unlike small molecule generics that are at heavy discounts to originators
- Extensive funding is required due to emerging rigorous regulatory requirements
- Lack of widespread awareness and credibility of industry

Opportunities

- Large and growing market for biopharmaceutical products
- Emerging regulatory frameworks provide structured approval guidelines
- High-revenue bio-pharmaceutical projects that have less equivalent Biosimilars approved / available in their portfolio

Threats

- Future regulations for Biosimilars is still being defined
- Particularly in the US, few Biosimilars have been formally approved, resulting in little precedence for future rulings
- The industry will require greater focus on new investments for future growth
2.2 Market Attractiveness Scoring and Solutions

Biosimilars fill a unique niche depending on whether the market is regulated, semi-regulated, or unregulated. In each of these markets, there are a number of parameters that companies should consider before attempting to set up production or market a product.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regulated Markets</th>
<th>Semi-Regulated Markets</th>
<th>Un-regulated Markets</th>
<th>Market Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of R&amp;D/Production</td>
<td></td>
<td></td>
<td></td>
<td>As market matures, international companies should shift R&amp;D/Production to semi-regulated markets</td>
</tr>
<tr>
<td>Manufacturing and Clinical Trial Capabilities</td>
<td></td>
<td></td>
<td></td>
<td>MNCs are pursuing partnerships with firms in low cost locations, for access to low cost manufacturing capabilities</td>
</tr>
<tr>
<td>Government Support of Industry</td>
<td></td>
<td></td>
<td></td>
<td>Numerous Biosimilars companies are coming up in countries with supportive governments for the sector such as India</td>
</tr>
<tr>
<td>Regulatory Rigidity</td>
<td></td>
<td></td>
<td></td>
<td>Pharmaceutical giants are navigating difficult regulatory paths in developed markets, while smaller companies are targeting developing countries</td>
</tr>
<tr>
<td>Attractiveness of Biosimilars to Physicians/Consumers</td>
<td></td>
<td></td>
<td></td>
<td>Due to the size and market potential of US and Europe, companies are patiently waiting for higher product adoption, while also aggressively marketing to developing countries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Favourable Market Dynamic</th>
<th>Neutral Market Dynamic</th>
<th>Unfavourable Market Dynamic</th>
</tr>
</thead>
</table>
2.3 A Complex Global Industry

Market and competitive pressures for Biosimilars vary from country to country, but may be broadly segmented according to countries that are:

- Regulated markets
- Semi-regulated markets

Along with being a potential niche low-cost power in unregulated and semi-regulated markets, Indian players are gearing to adopt guidelines more in line with the US or European Union (EU). As more and more Indian companies pass the rigid approval processes including extensive clinical trials, India will soon emerge in a strong position as a relatively low cost supplier of Biosimilars products.
3. GOVERNMENT REGULATION AND POLICIES

The dynamic and complex nature of the global Biosimilars industry has made it difficult for regulatory organizations to formulate and implement a uniform set of standards for approval of new products.

**Divergent Interests**
Producers of originator drugs have a lot to lose from the widespread adoption of Biosimilars and have questioned the safety of Biosimilars products.

**Uncertain Long-Term Impact**
Even in countries with regulatory bodies that have approved Biosimilars, the credibility of such products within the medical community as equivalent long-term substitutes for originator products is often debated.

**Complex Molecules**
The molecular complexity of biotechnology products has traditionally driven regulators to treat Biosimilars cautiously, often requiring expensive clinical trials and preventing smaller players from entering the space.

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**An Evolving Global Regulatory Environment**

<table>
<thead>
<tr>
<th>Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union (EU)</td>
<td>While the European Medicines Agency (EMA) has been a global leader in providing a formal path for approval of Biosimilars products, adoption of Biosimilars products varies on a country to country basis within the EU’s member nations. Regulation drafted by developed countries outside US are often based on EMA approval standards.</td>
</tr>
<tr>
<td>United States (FDA)</td>
<td>The Food and Drug Administration (FDA) has lagged the EU in providing a clear path for Biosimilars approval in the United States. However, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 provides a framework for Biosimilars approval and the FDA is preparing to provide further guidance to companies seeking approval for Biosimilars products.</td>
</tr>
<tr>
<td>World Health Organization (WHO)</td>
<td>In 2009, The World Health Organization (WHO) published Guidelines for Evaluation of Similar Bio-therapeutic Products, outlining high-level guidance for national regulatory agencies to determine similarity and comparability of Biosimilars with originator products. While the WHO guidelines provide a framework for regulatory agencies in developing markets, regulators' ability to evaluate and formally approve products often remains minimal.</td>
</tr>
<tr>
<td>India</td>
<td>A National Biotechnology Regulatory Authority (NBRA) Bill is soon expected to be passed, which is likely to significantly streamline the approval process. Currently, companies seeking to market Biosimilars in India must receive approval from multiple government agencies, significantly increasing the time it takes to bring products to market. A clearer pathway will reduce complexity and cost currently associated with the approval process.</td>
</tr>
<tr>
<td>China</td>
<td>Despite a long history of domestically produced and consumed Biosimilars products, there remains no specific process for approval of Biosimilars products, separate from the process for simple molecule products. Generally, the bar for product approval set by the Chinese State Food and Drug Administration remains lower than in Europe or the United States.</td>
</tr>
</tbody>
</table>
4. BIOSIMILARS INDUSTRY IN INDIA

4.1 Market Overview

The Indian Biosimilars industry is estimated to be a US$ 338 million industry that has been growing at a Compounded Annual Growth Rate (CAGR) of 30 per cent since 2008. This growth rate is expected to continue till 2012. There are around 25 Indian companies operating in the Biosimilars space, marketing close to 50 products in the Indian market and few of these products in some of the unregulated markets.

Industry Growth Drivers

US$ 79 billion worth of biologics is expected to go off-patent globally by 2015, providing a lucrative global opportunity for Biosimilars companies. At the same time, rising cost of treatment with original branded products is resulting in Biosimilars being used globally as substitutes since they are 25 to 40 percent less expensive as compared to branded originators.

Currently, there is a market shift towards diseases such as cardiac, diabetes and cancer which have treatment options with complex biotech drugs. A rise in the number and quality of tertiary care centers is resulting in greater usage of biotech products. Following figure shows the key industry growth drivers for Biosimilars in India.

US$ 79 billion worth of biologics is expected to go off-patent globally by 2015, providing a lucrative global opportunity for Biosimilars companies.
• Patented drugs going off patent
• Shift in disease patterns and product demand
• Better tertiary care products
• Rising healthcare costs

4.2 Indian Players in Biosimilars Industry

Indian companies enjoy lower facility and development costs than peers in developed countries and seem poised to repeat successes achieved in small molecule generics by partnering with larger multinational corporations (MNCs) for clinical trials, regulatory approval process in the EU / US and marketing to physicians / consumers.

Following table provides an analysis of the capabilities of Indian players and their partnerships with foreign companies. Many Indian players have developed and matured their product development and manufacturing capabilities and are progressing towards achieving better clinical trial capabilities.
<table>
<thead>
<tr>
<th>Company</th>
<th>Product Development</th>
<th>Manufacturing</th>
<th>Clinical Trials</th>
<th>Partnerships</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocon</td>
<td></td>
<td></td>
<td></td>
<td>Mylan, Pfizer</td>
<td>Capabilities driven by strategic alliances with global leaders</td>
</tr>
<tr>
<td>INTAS</td>
<td></td>
<td></td>
<td></td>
<td>Apotex</td>
<td>First Indian company to receive EU-Good Manufacturing Practice (EU-GMP) certification</td>
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<tr>
<td>Dr. Reddy’s</td>
<td></td>
<td></td>
<td></td>
<td>GSK</td>
<td>Partnership with GSK for assistance in manufacturing and marketing; have a WHO certified cGMP manufacturing facility</td>
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<tr>
<td>Reliance Life Sciences</td>
<td></td>
<td></td>
<td></td>
<td>Reliance Genmeds</td>
<td>Have multiple cGMP facilities in India in addition to main plant in Ireland</td>
</tr>
<tr>
<td>Lupin Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td>Lilly</td>
<td>Five manufacturing facilities across India; emerging capabilities in Biosimilar space</td>
</tr>
<tr>
<td>Cipla</td>
<td></td>
<td></td>
<td></td>
<td>BioMAb EGR²</td>
<td>Bought 40 per cent stake in Goa-based Mab Pharm; and a 26 per cent stake in Bio Mabs in China to grow MAB capabilities</td>
</tr>
<tr>
<td>Shantha Biotech</td>
<td></td>
<td></td>
<td></td>
<td>International Vaccine Institute</td>
<td>Subsidiary Shantha West in San Diego has developed 4 MABs; R&amp;D partnership with International Vaccine Institute</td>
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<tr>
<td>Zenotech</td>
<td></td>
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<td></td>
<td>Ranbaxy</td>
<td>Ranbaxy holds 45 per cent stake in Zenotech Labs for marketing Biosimilar products</td>
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<tr>
<td>Wockhardt</td>
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<td></td>
<td>N/A</td>
<td>Recently opened a large Biotech Park in Aurangabad, designed according to US and EMEA standards</td>
</tr>
</tbody>
</table>

**Supplier Capability Scale**

- Very Low
- Low
- Average
- High
- Very High
4.3 Current and Future Products of Indian Players

Indian companies have launched Biosimilars across product areas, but certain product types remain more attractive entry opportunities. A number of companies are focusing on monoclonal antibodies (MAB) for their role in cancer therapy. A large share of the market is expected from MABs in the future Biosimilars marketplace. Likewise, Enbrel [for treating inflammatory disease] and Insulin [diabetes] may be favourable product areas to enter due to the high anticipated market potential and relatively low market penetration by Indian suppliers.

<table>
<thead>
<tr>
<th>Company/Product</th>
<th>EPO(^1)</th>
<th>Insulin</th>
<th>HGH(^2)</th>
<th>Interferon</th>
<th>GCSF(^3)</th>
<th>MAB</th>
<th>Enbrel</th>
<th>Streptokinase</th>
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<td>Biocen</td>
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<td>Intas Biopharmaceuticals</td>
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<td>Dr Reddy’s Labs</td>
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<td>Reliance Life Sciences</td>
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<td>Bharat Biotech</td>
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<td>Lupin</td>
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<td>Wockhardt</td>
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<tr>
<td>Ranbaxy &amp; Zenotech Labs</td>
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<tr>
<td>ShanthaBiotechnics (Sanofi Aventis)</td>
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<tr>
<td><strong>Expected Global Biosimilars Market Share (2015)</strong></td>
<td>11%</td>
<td>10%</td>
<td>6%</td>
<td>9%</td>
<td>10%</td>
<td>36%</td>
<td>12%</td>
<td>&lt; 8%</td>
</tr>
</tbody>
</table>

\(^1\) Erythropoietin  \(^2\) Human Growth Hormone  \(^3\) Granulocyte Colony-Stimulating Factor

Source: Credit Suisse Report on Biosimilars; company web sites; BioPharm International
5. INDUSTRY CHALLENGES AND POSSIBLE SOLUTIONS

5.1 Regulated Markets

Due to the inherently complex nature of Biosimilars, companies face several challenges for regulatory approval and market place acceptance in regulated markets.

Regulatory and Legislative Considerations

Unlike traditional pharmaceuticals that may be replicated to exact chemical specifications in a laboratory, Biosimilars are complex structures of molecules, making it more difficult to prove equivalence to branded predecessors. Strict regulations and expensive clinical trials, as well as relatively new approval processes in some countries (e.g. US) make regulatory approval difficult.

Quality and Safety Considerations

Due to the complex nature of biopharmaceutical products and differences in the source living cells used by producers, it is difficult to exactly replicate an originator’s product, raising questions about quality and efficacy of Biosimilars products. Many physicians are opting to wait before they recommend Biosimilars products to patients, encouraged by campaigns from originator companies.

Cost Considerations

Barriers to entry into the Biosimilars market are high, without guaranteed return on investment. Developing a Biosimilars product is still a relatively expensive and time consuming process (it can take 8-10 years to introduce a Biosimilars drug in the market). The expensive research and development lifecycle more closely resembles next-generation drugs rather than inexpensive generics.

Often compared to the market for generic drugs in which India has experienced success as a manufacturer and exporter, the evolving Biosimilars industry has unique economics and challenges.
5.2 Unregulated/Semi-Regulated Markets

The focus of Indian companies thus far has been primarily on semi-regulated and unregulated markets, which present a unique set of accompanying challenges.

**Regulatory and Legislative Considerations**

Without formal regulatory framework for Biosimilars in India (and other emerging markets such as Brazil and China), the path to approval is unpredictable, sometimes increasing costs and process complexities. Recent indications are that India will move to a more structured approval process, which is good news for Indian companies and consumers, assuming that the final process is not as costly as in regulated countries.

**Quality and Safety Considerations**

While the less burdensome clinical trial and approval process reduces the cost associated with delivering products to consumers, Indian produced Biosimilars do not have the same credibility as international competitors. A formal and replicable approval path would increase transparency and help Indian companies gain credibility in international circles.

**Cost Considerations**

Indian patients and those in similar emerging markets are price sensitive, with products that are 25-40 per cent lower prices compared to originator products not being affordable to majority of the population. The new middle class in India and other developing markets present an attractive emerging demographic sector to which Indian Biosimilars companies may market cost effective products.

6. NEW TRENDS, PRACTICES AND THEMES

Partnerships will continue to transform the Biosimilars Industry. With limited growth potential in generic drugs, global pharmaceutical companies are increasing their focus on Biosimilars drugs. In order to gain access to developed markets in the long-term, Indian companies are increasingly partnering with international pharmaceutical giants to develop and market Biosimilars products. Indian companies gain marketing capabilities, technological know-how, and regulatory process expertise from MNCs, while international companies seek to build their product pipelines and low cost manufacturing capabilities.
### Cipla pays US$ 65 million for stake in two Asian Bio-techs

Cipla purchased a 25 percent share in Shanghai based Bio Mabs and a 40 percent stake in Goa based Mab Farm in 2010.

- The acquisition will provide Cipla with the right to market Biosimilars drugs of the two companies in India and abroad.
- The main goal of these investments was to create Biosimilars of current expensive biologics such as Avastin, Herceptin and Enbrel for sale in India.

### Pfizer invests US$ 200 million in Biocon

Pfizer’s 2010 investment gives it the right to market Biosimilars insulin drugs across major global markets.

- Aside from the initial investment, Biocon is eligible to receive developmental and regulatory payments of US$150 million
- The deal gives Pfizer access to the lucrative US$ 14 billion insulin market

### Mylan partners with Biocon to enter the Biosimilars space

American pharmaceutical company, Mylan, entered into an agreement with Biocon in 2009 to collaborate in the development, manufacture, supply and commercialization of multiple Biosimilars drugs in the global marketplace.

- As part of the agreement both companies will share development, capital and other costs to take the products to market
- Mylan granted exclusive rights for commercialization in US, Europe and Japan, while rights will be shared in other markets

### Ranbaxy enters into a strategic alliance with Pfenex

In March 2010, Ranbaxy announced its decision to enter into an alliance with American Pharmaceutical company - Pfenex, for the development of an undisclosed therapeutic Biosimilars protein.

- Under this agreement, Pfenex would receive royalty payments and maintenance fees on product sales
- Scientists from both companies would collaborate in developing the strains and the process for development and commercial production of the Biosimilars product

### 7. CONCLUSION AND PATH FORWARD

Biosimilars in India has already attracted large investments in areas of research, clinical trials and manufacturing. In future, Indian market will also see lot of strategic partnerships emerging between global and Indian companies to leverage each other’s potential. The Indian Biosimilars market provides numerous growth and investment opportunities for Indian and Foreign players.
**Path Forward for Indian Biosimilars**

1. Establish Clear Pathway for Regulatory Approval of Products
2. Huge Opportunity for Investment in Indian Market
3. Establish Partnerships with International Industry Leaders
4. Export to Unregulated and Semi-Regulated Countries
5. Market to Physicians Serving the Emerging Middle Class

**Market to Physicians Serving the Emerging Middle Class**

As new middle class continues to emerge in India and other developing economies, demand for high quality, reasonably priced Biosimilars products is likely to increase.

**Huge Opportunity for Investment in Indian Market**

The requirement of intensive research and clinical trial demands large scale investment for Biosimilars Industry. Increased funding will allow Indian companies to build robust product pipelines and increase the number of products that come to market.

**Establish Partnerships with International Industry Leaders**

Access to state of the art labs, experience with rigorous clinical trials, and funding to support these activities mean that international pharmaceutical giants have much to offer India based market entrants. A lower R&D and manufacturing cost structure and a highly skilled workforce, make India an ideal location for international companies looking to reduce costs and increase margins.
Export to Unregulated and Semi-Regulated Countries

Due to fewer regulatory hurdles, developing countries are the most attractive export opportunities in the short-term. In the long-term, developed countries are the most significant opportunities for revenue generation and ROI due to a high demand for advanced treatments.

Establish Clear Pathway for Regulatory Approval of Products

A transparent approval process will increase product quality and decrease the time-to-market for affordable and potentially life-saving Biosimilars products. Reforming the regulatory environment will increase Indian Biosimilars companies’ credibility and provide a platform to enter other regulated global markets in the future.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAGR</td>
<td>Compounded Annual Growth Rate</td>
</tr>
<tr>
<td>MNC</td>
<td>Multi National Companies</td>
</tr>
<tr>
<td>MAB</td>
<td>Monoclonal Antibodies</td>
</tr>
<tr>
<td>SWOT</td>
<td>Strength Weakness Opportunity Threat</td>
</tr>
<tr>
<td>EU-GMP</td>
<td>European Union’s Good Manufacturing Practice</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>cGMP</td>
<td>Current Good Manufacturing Practices</td>
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</tbody>
</table>
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