

**EMERGENCE OF THE BIOSIMILAR SECTOR AND OPPORTUNITIES FOR DEVELOPING
COUNTRY SUPPLIERS**

FARAH HUZAIR AND DINAR KALE

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1. Introduction

In last two decades firms from emerging countries such as India and China have dominated the production of active ingredients in pharmaceutical industries all over the world. Until recently firms from these countries were struggling to reverse engineer complex and expensive biologic products which are increasingly used to treat cancer, diabetes and other diseases. Biologics are a therapeutic drug category comprising large complex molecules such as growth factors, cytokines, hormones, monoclonal antibodies and vaccines. However, some pharmaceutical firms have developed capabilities to reverse engineer these biological products which have been termed 'Biosimilars'. Thus Biosimilars (also known as biogenerics or follow-on biologics) are biotech drugs that have been shown to have comparable quality, efficacy and safety to an original biologic product (Krull, and Rathore, 2010). This rise of biosimilars and capabilities for cheap production in developing country firms has potential to disrupt current market structure and transform patient care in developing countries as well as advanced countries. As biologic products begin to come off-patent, a market is emerging for biosimilars – copycat products produced at lower prices. It has been estimated that sales worldwide of biologics in 2009 reached \$130 billion (Manufacturing Chemist, 2010) and that biosimilars might offer reductions of up to 30% compared to an original biologic (Krull and Rathore, 2010; Iskowitz, 2010). This emergence of a new market dynamic is disruptive to current key players as it has potential challenge their current dominant hold over the market, while for firms from developing countries it creates a sea of opportunities. The potential to generate considerable cost savings for governments and health care systems has been widely commented on. Potential for saving of course depends on the willingness of existing and emerging suppliers to compete in the market to innovate and develop biosimilars and a well-established regulatory framework. Thus emergence of biosimilars has become a contentious issue and has led to debate among key industry players, non-governmental organisations and leaders of developed and developing countries (Harris, 2011).

Biosimilars are distinct from generics and as such, the sector deserves separate analysis. As large complex molecules, derived from specific cell lines, biologics are difficult to produce with consistency (Agres, 2011). Even if the formulation and production process is known, biosimilars as generic versions of a biological, cannot be identical to a reference biologic. Any small difference in the manufacturing process, input or purification procedure can result in a molecule significantly different in terms of efficacy and immunogenicity. This paper reviews study data collected at Innogen and the most recent literature to understand how the sector for biosimilars is evolving and the opportunities and challenges faced by emerging suppliers. The aim of the paper is to identify the gaps in the current literature and opportunities for further study in this area. Our analysis suggest that much of literature on biosimilars is focused on issues related to the development of governance mechanisms and potential market opportunities. Absent from the literature is any analysis of the evolution of firm level capabilities and policy frameworks that balance the needs of innovator and imitator firms without comprising affordable healthcare for poor people.

Section two of this paper describes the background of the biosimilar segment in biotechnology broadly covering size and growth of the market sector and the opportunities for emerging suppliers. Section 3 explains the methods used to identify the most recent literature and the study of Indian pharmaceutical companies conducted in

2010. In section 4 we examine the challenges and drivers of biosimilar development, including new directions in innovation and the limitations posed by patents and data exclusivity. Section 5 re-examines data collected for an Innogen study on Indian pharmaceutical companies and suggests what capacity exists for biosimilar development. In section 6 we conclude by highlighting the gaps in the current literature and the opportunities for further study.

2. Background

The potential for biologics in the treatment of existing and neglected disease is increasing as the blockbuster model in pharmaceuticals is gradually eroded and the role of biotechnology in drug development becomes more important (Chataway et al, 2007; Mitra, 2008; Tait and Mitra 2004). The growth of biologics is in fact, outstripping that of conventional pharmaceuticals (Mahler and Gray, 2011). Therapeutic biologics such as genetically engineered recombinant proteins and monoclonal antibodies now represent a large portion of newly approved therapies for conditions such as chronic inflammatory diseases and cancer (Kozlowski et al, 2011). A large number of biologics are approaching patent expiry, creating room for biosimilars (Wechsler, 2011; Mahler and Gray, 2011; Lee et al, 2011).

The cost of drugs in all countries represents a large fraction of the total health care bill. Sponsors claim that they will be able to market biosimilars at discounts of 25 to 30 percent off branded products. This may not be as much as the fall seen in the small molecules generic market (Krull and Rathore, 2010; Iskowitz, 2010), but payers say that prices that are just 10 percent lower will be able to gain market share and will represent a significant cost saving for patients in both regulated, and less regulated markets (Wechsler, 2011; Selz, 2010). For example, in a study in 2008, the German R&D institute for healthcare, IGES, identified potential savings of more than Euro 8bn by 2020 in Germany if biosimilars were to be prescribed. Another study has suggested that as much as \$2 billion can be saved by the European healthcare providers by just the first wave of biosimilar products (O'Donnell, 2006 cited by Krull and Rathore, 2010). In the US, savings in the high double-digit billions range are expected over a 10-year period (Ellis, 2010). According to the Congressional Budget Office, biosimilars may save consumers and health systems in the US as much as \$25 billion over 10 years as newly approved biosimilars drive the prices of biological drugs downward. There is particular need to reduce the cost of drugs in cancer care which is a growing burden in many countries, and biologics show promise in this field (Cornes, 2011). One example here would be the HPV vaccine, used to prevent cervical cancer.

Unlike the development of an originator biologic, the development of certain biosimilars is attached to a smaller risk in terms of demonstrating safety and efficacy. If a biosimilar has a reference product with many years of data, production and market experience, and proven feasibility, the risks of developing a biosimilar are much more calculable. It should be an attractive opportunity for investment but the industry must have access to adequate capitalisation, which may prove to be an issue in low and middle income countries (Selz, 2010). It is important however, to consider that the cost of development and manufacturing for many biosimilars would still be quite high.

Finally, we look at cost. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimate it costs in the region of \$1.2 billion to develop a new biologic

compared with approximately \$375 million for a biosimilar (this depends on the type of biosimilar as costs vary significantly. These figures are more likely to apply to conventional biosimilar therapies and will exclude for example, cell therapies). Time lines for development, compared to a novel biologic are also considerably shorter, as there is no need for a Phase II programme and Phase I and Phase III can often be truncated (Watson et al 2010).

2.1 Size and growth of the market

There have been numerous and wide ranging estimates for the size and growth of the market in biosimilars. While some suggest growth reaching multi-billion dollar levels within five years, others argue that biosimilars will never be a threat to branded biologics (Biomedical Market Newsletter, 2011) due to the complex nature of production and limited scope for proving similarity to a reference product (see below).

In 2009, sales of biologics reached \$130 billion (Manufacturing Chemist, 2010). While this represents a fraction of total drug sales, the market for biologics is growing and recent industry predictions are that biopharmaceuticals will soon make up 50% of new drug approvals (Fernandez, 2010). In the four and a half years prior to late 2010, there were 58 approvals within the European Union and/or the United States, of which about 40% (25) were new biologics; and around 50% of the remaining approvals (28) were biosimilars and reformulated existing products. Monoclonal antibodies are the most rapidly growing class of biologic medicine, with over 40 per year entering clinical trials since 2007 (Mahler and Gray, 2011). A 2010 report by URCH publishing suggests that biosimilars could account for 2.6% of the biologics market by 2016 (Manufacturing Chemist, 2010).

A 2010 report by BioPortfolio estimated that the global biosimilars market would be worth \$19.4 billion by 2014, growing at an expected compound annual growth rate of 89.1% from 2009 to 2014 (Ariyanchira, 2010). This report was superseded by a more conservative estimate in 2011 of a worldwide market valued at \$3.7 billion by 2015, up from about \$250 million last year (Datamonitor, 2011 cited by Wechsler, 2011; Sutton, 2011).

The main companies with existing capabilities in biosimilars include: Merck, Sandoz (Germany, the generics arm of Novartis), Teva (Israel), Hospira (US), Dr. Reddy's Biocon Ltd. (India), Biopartners GMBH (Switzerland), Cipla Ltd. (India), Intas Biopharmaceuticals Ltd. (India), Shantha Biotechnics Ltd. (India) and Wockhardt Ltd. (India) (Biomedical Market Newsletter, 2011, 2011b). A number of companies are entering into strategic partnerships with biotechnology companies in order to acquire capabilities in biosimilar production. In October 2010, Pfizer announced a deal to work with Biocon (India's biggest biotech company) to bring a biosimilar insulin treatment to market (Economist, 2010). In January 2011 Parexel and Merck announced their alliance; Parexel will bring regulatory and clinical development planning to Merck BioVentures, which has a goal of five potential biosimilar products in late-stage clinical trials by 2012. There are further reports of planned activity. Amgen for example is reportedly considering biosimilars particularly in emerging markets like Asia and South America and the CEO of Biogen has suggested the company is in a prime position to develop biosimilars because of its manufacturing and expertise in biologics (Henderson, 2011).

The global distribution of key and niche players has been sketched as shown in table 1. At this early stage the prominence and potential of producers in the Asia Pacific is clear.

Table 1. Distribution of key and niche players in 2011

Region/Country	No. of key & niche players
The United States	11
Canada	2
Europe	16
France	1
Germany	10
The United Kingdom	2
Rest of Europe	3
Asia-Pacific (Excl. Japan)	28
Latin America	1
Africa	1
Middle East	2

(adapted from Biomedical Market Newsletter, 2011b)

2.2 Opportunities for emerging suppliers

There is considerable biologics R&D and commercial activity in the emerging markets of the BRIC countries (Brazil, Russia, India and China) and the Asian Pacific Rim region. The most obvious reason is cost arbitrage. In India for example, the cost of developing a biosimilar molecule requires an investment of about \$10 to \$20 million, as compared to \$50 to \$100 million in developed countries (Frost and Sullivan, 2011) (or even \$375 million as quoted by other authors).

Existing biosimilar producers are well-positioned to take advantage of predicted market growth because they already have an industry reputation and relationships with key stakeholders. However, branded pharma companies may also be looking to enter the biosimilars arena as a way of increasing sales. As described above, partnerships and mergers and acquisition are potential ways of achieving this (Sutton, 2011), possibly providing opportunities for emerging suppliers. Samsung along with other South Korean based electronics firms has announced its intention to enter the biologics market with a \$389 million investment in 2009. In 2011 Samsung entered into a partnership with Quintiles (a \$266 million venture) to start producing biosimilars in 2013 (Hoffman, 2011). Nair (2011) reports the partnering of Indian pharmaceutical firms with global manufacturers for the marketing of biosimilars. For example, India based Biocon India Ltd has partnered with Pfizer for the commercialisation of several insulin products.

As discussed above, biosimilar manufacture requires substantial investment in equipment, technology, materials and personnel. Manufacturers with biosimilar drug candidates are increasingly turning to contract manufacturing organizations (CMOs) and clinical research organizations (CROs) worldwide that offer the proficiency, staffing, and state-of-the-art technology for developing and validating analytical methods, preclinical

and clinical development strategies, and bio-manufacturing processes (Freitag and Egan, 2011; Henderson, 2011; Fernandez 2010). Again, India has upcoming CRO's which would add to Indian capabilities in biosimilars (Frost and Sullivan 2011).

Government policies to facilitate the growth and survival of emerging suppliers can be influential. Samsung's investments for example, dovetail with South Korean government initiatives that aim to develop the country's biosimilar industry (Hoffman, 2011).

Internationally also there is a growing imperative for organisations such as the World Health Organisation and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), to foster a more consistent global regulatory landscape for biosimilars (Mahler and Gray, 2011).

Emerging markets present not only an environment for the growth of industry, but also a consumer market. The middle classes in the less regulated developing countries, with increasing purchasing power and preference for state of the art goods and services, in the near future may provide a larger consumer market than developed countries (Selz, 2010).

Future regulatory change may open up opportunities for firms with competence and capability in the manufacture and regulatory approval procedures for biologics. For example, as of 2020, in the US, proteins will no longer be regulated as drugs, but as biologics. The expertise held by emerging suppliers or CRO's may be gainfully employed by firms with biosimilar or biologic candidates in their pipelines.

3. Research Methods

3.1 Literature review

Articles for this review were found using the EBSCO database. EBSCO includes Academic Search Complete, Business Source Complete, CINAHL, EconLit, EDS Foundation Index, Medline, Regional Business News and eBook Collection. The database was searched using "biosimilar" [or] "Follow on Biologic" in the title fields. The search yielded 981 articles. After removal of duplicates and articles relating to technical medical information on biologics, 397 articles remained.

Of the 397 articles on biosimilars and follow on biologics, overwhelmingly, the large number focused on regulatory development, mostly in the US. To understand the contribution thus far to the research questions posed, articles were removed on the following subjects: clinical development of biosimilars; applicability of biosimilars to particular medical fields (e.g. oncology, dermatology); regulation and regulatory harmonisation (where the article exclusively reported on the progress made by the FDA); safety of biosimilars and standards; legal considerations; uptake of biosimilars by pharmacies/practitioners; news on specific manufacturers and product approvals. This left 93 articles on the subjects of the biosimilars market; economic impacts; industry perspectives; global development; data exclusivity and patent rights.

Of the 93 articles of interest, most were short articles and news items published in periodicals, 22 were longer articles consisting of more than 5 pages and 2 were grey literature sources. A small number of articles (<5) were not available in full text. Table 2

shows the distribution of articles by year of publication, illustrating the growing interest in biosimilars. There were no articles in this search published before 2006. A summary of the most recent information on biosimilars is presented below. The summary is constructed primarily using articles from 2011 and 2010, utilising the most recently published articles first, and discarding earlier articles where information has been repeated or superseded by newer data.

Table 2 Articles published each year on the biosimilars market and economic aspects of biosimilars

Year	2011 ¹	2010	2009	2008	2007	2006
No of articles	20	21	22	17	7	6

3.2 Data collection on Indian pharmaceutical companies

In the case of the Indian pharmaceutical industry, secondary data was collected from annual reports, business magazines and consultancy reports. Annual Report present detailed information regarding a firm's activities and collaborations which was cross checked with information with business magazines and consultancy reports. Primary data was collected from interviews with biotech R&D heads in the Indian pharmaceutical firms such as Wockhardt and Dr.Reddy's Laboratories.

4. Challenges in biosimilar capability development

4.1 Firm level challenges in managing R&D and Manufacturing complexities

The cost of a biosimilar compared to an originator biologic may be smaller, but the cost of manufacturing a biotech product is approximately 5-10 times more than that for a small molecule product (Krull and Rathore, 2010). A small molecule generic costs between \$1.5 million and \$4 million to develop (Watson et al., 2010), whereas developing a biosimilar can cost between \$75 million and \$375 million and typically takes seven to eight years (Wechsler, 2011). High operating costs as well as larger capital investments associated with manufacturing of biosimilars (compared to development and production of small molecule products) are attributed to a number of factors. Krull and Rathore report high costs because of i) Complex manufacturing processes and inputs where a small change in process can lead to significant change in the efficacy of a biologic or immunogenicity; ii) The complexity of the biologic product which means that analytic tools alone cannot completely predict the behaviour of large complex molecules in the clinic; iii) Complex feed materials which can be uncharacterised and will impact on process consistency and quality; iv) Lack of understanding of the relationship between product and process demonstrated by unknown correlations between the clinical safety and efficacy of a biotech product and its product quality attributes generally. The complexities and unknowns have led some authors to suggest that greater consideration will need to be given to clinical trial design,

¹ Data collected up to August 2011. It is expected that by the end of 2011, this number will have exceeded the number of articles published in 2010.

target population and endpoint criteria for establishing equivalence. The trial must also be sensitive enough to detect any clinically meaningful differences. Therefore, the size of the trial may need to be even larger than that for the reference product in order to prove therapeutic equivalence with confidence (Watson et al, 2010), thus contributing to higher costs. In addition, in some markets such as Europe there is greater cost imposed by the regulatory authority (in this case, the EMA) for the requirement for long term post market safety monitoring (Schellekens, 2010).

The challenges are different, depending on whether a firm is an innovating biologics firm, switching to biosimilars, or a traditional generics manufacturer, entering into biologics production for the first time. For innovating manufacturing firms, a shift of focus from innovation to replication is required. This means companies must develop strategies to transform expensive development and manufacturing processes into lean analogs. They would have to reduce the cost per unit dose and make the same amount of drug with fewer batches through higher fermentation titers, higher purification recoveries, and longer shelf-life formulations. A different set of challenges is faced by generic manufacturers. They will need the expertise to reverse-engineer the biologic and to develop a stable, therapeutically active cell line. They also will need to develop manufacturing processes to meet specifications, predictably and consistently while applying specialized analytical tools. They will also need to invest in new infrastructures for controlling living cells, purification, and producing biologic products at commercial scale, consistently. New infrastructures and capital investment include bioreactors, purification suites, fill/finish operations, sterile environmental controls, and systems that are more liquids than solids-based. To ensure stability during production, storage, and shipping, generic-drug companies must be able to characterize and mitigate the risk of degradation mechanisms of complex biologics. They also must avoid long development times to maintain the revenue and market share advantages that first-to-file status provides. Equivalency standards will have to be closely adhered to, as even small differences between the biosimilar and the reference product (e.g. binding, activity, posttranslational modification, impurity profiles, and stability) can affect bioequivalence and put regulatory approval at risk (Lee et al, 2011).

The high cost of entry means that only those companies that are willing to absorb the costs and risks of development, registration and commercialisation will emerge as competitors (Greenland, 2010). The implications are that adequate capitalisation is essential for emerging suppliers and the role of partnerships, mergers and acquisitions will become more important. In the latter case particularly, the sector will continue to be dominated by a few large firms, mirroring perhaps the evolution of the vaccine industry.

Because biosimilars will have to demonstrate equivalence in its safety and efficacy profile with an originator drug, the main positive differentiator will be price. Competition on price alone may then erode margins for all supply side participants (Szymkowski, 2010; Selz, 2010). Industry commentators such as Selz (2010) argue this might not be sustainable. However, this might be a driver of innovation, if biosimilar companies innovate to create differentiation for their products based on optimised formulation, delivery modes, packaging variants or service aspects for example (Selz, 2010).

Selz (2010) suggests that uptake in the health care community may be limited by the scepticism displayed in reaction to the relatively fewer number of years of clinical

experience for each biosimilar, compared to the originator drug. This may outweigh the price advantage offered by a new biosimilar.

Lastly, originator drugs, although they eventually will come off-patent, are protected by a number of “IP walls”. IP is used not only to protect the formulation, but also the upstream and downstream processing elements and the analytical methods. The prospect of long, risky and costly patent litigation might be too heavy a burden for small biosimilar producers to consider (Frost and Sullivan 2011; Selz, 2010).

4.2 Directions in innovation

Regulatory requirements to demonstrate comparability with the innovator biologic has placed a new emphasis on analytical techniques and methodologies, and has revealed the limitations of analytical methodologies as well as the need for new, more sophisticated techniques (Mahler and Gray, 2011). To address these requirements, new process analytical technologies (PAT) can be used to enhance predictability and understanding, thus minimizing batch rejections and increasing manufacturing run rates to produce batches more efficiently. Other innovative technologies, such as disposable single-use systems (e.g., bioreactors, media and buffer tanks, and drug-substance container/closure systems) might improve scalability and effectiveness. These technologies have the potential to lower production costs by reducing the number of product-to-product and batch-to-batch changeovers and capital investments (Lee et al, 2011). Generally the consensus in the industry is that lowering cost of goods for biologics will be driven principally through innovation in downstream processing (Mahler and Gray, 2011).

Currently 60–70% of biologics are now produced in mammalian cells. There is a need for high yielding, transient expression systems. Progress in host cell engineering means that more stable cell lines can be generated compared to traditional amplified cell lines, and with more of a focus on product quality. Efforts are also being made to engineer cell lines with superior productivity characteristics (e.g., improved robustness, enhanced protein processing, and metabolic efficiency) (Mahler and Gray, 2011).

Novel drug-delivery technologies could be another area of focus for innovator biopharmaceutical companies. These technologies could help to increase market share and provide a source of sustainable competitive differentiation (Lee et al, 2011).

Biosimilar pipelines are rapidly shifting away from the initial focus on older, less complex biologics, towards the higher earning monoclonal antibodies as well as developing, “biobetters”. These are biologics, similar to an original product, but which offer improvements over the originator (Biomedical Market Newsletter, 2011).

4.3 Regulatory quagmire

The creation of a pathway for the approval of biosimilars has taken a long time (Agres, 2011). The EU is considered to be ahead of the US in the development of its regulatory pathway. The European Medicines Agency (EMA), published general guidelines on biosimilars in 2005 and approved its first biosimilar in 2006. Fourteen additional biosimilars have since been approved by the EMA (Tzeng, 2010). Australia adopted the EU guidance in 2008, and the World Health Organisation finalisation of its own

guidelines is expected imminently. Numerous other countries have produced draft or final guidelines on biosimilars, including Canada, Malaysia, Turkey, Taiwan, Korea, Singapore, Argentina and Saudi Arabia (Ellis, 2010). In the US however, the FDA is experiencing difficulty as it grapples with the problems of meaningful difference and degree of comparability between a biosimilar and its reference biologic (Simoens et al 2011). While guidelines for the US might be published this year, formal regulations might be some years away (DeArment, 2011).

The recognised need to reduce the cost of drugs has led to The Affordable Care Act of 2010 in the US which included the Biologics Price Competition and Innovation Act (BPCIA). This act authorised government agencies to establish an abbreviated regulatory pathway for approving biosimilars with an aim to reduce spending on prescription drugs. Notwithstanding the complex situation in the US, regulatory authorities have begun to clarify their requirements for testing and approving biosimilars (Wechsler, 2011), better paving the way for their development.

4.4 Patents and data exclusivity

There is a significant difference between the position of the US and the position of regulatory agencies in the rest of the world (including the EU). EU guidelines acknowledge that biosimilars are different from their original reference product in terms of their raw materials and manufacturing processes, and that slight differences can significantly alter the safety and effectiveness of a biosimilar. Therefore, the EMA is using a case by-case approach, which requires comparability between the biosimilar and the innovator product to be justified by appropriate studies, such as clinical trials. Although European requirements for biosimilars are extensive when compared with small-molecule generics, they do not necessarily include full Phase III clinical trials in all cases and therefore can provide an abbreviated pathway for approval (Fernandez, 2010). In July 2009, two US healthcare bills, the *Biologics Price Competition and Innovation Act of 2007* and the *Pathway for Biosimilars Act* were proposed, containing adaptations of the Hatch-Waxman Act (which currently provides 5 years of data exclusivity for new chemical entities and new biological entities), to create an approval pathway for biosimilars (Grabowski, 2008; Tzeng, 2010). The two bills survived committee votes in US Congress and the Senate respectively before being reconciled and passed by the House of Representatives in March 2010 as part of the Healthcare Reform legislation. The legislation now stipulates that biosimilars must be subject to at least one clinical trial to demonstrate safety and efficacy. The new law guarantees manufacturers a period of 12 years exclusive market access for innovator biologics during which, the FDA cannot approve a product based on innovator studies².

² Further explained by Agres (2010) : "Part of problem is ambiguity in the law, which does not specify whether the 12 years of exclusivity refers to marketing or to protection of data. The U.S. Food and Drug Administration (FDA) is currently drafting a regulation that will answer that question as it outlines how the law will work in practice, including how much, if any, additional clinical testing will be required of generic applicants. Should the FDA decide that the law refers to data exclusivity, generic competitors will likely have to wait the full 12 years before gaining access to a reference drug's underlying composition. They would then have to spend time developing a bioequivalent version before submitting an abbreviated approval application, giving the pioneer drug company months, if not years, of additional unencumbered sales. On the other hand, should the FDA interpret the law as referring to 12 years of marketing exclusivity, competitors might gain access to a pioneer drug's underlying data in as few as four years after it had originally been approved. This would allow generic manufacturers time to develop a bioequivalent version and hit the ground running when the 12 years are up" (Agres, 2010).

Biosimilars sponsors also have to wait four years to even submit a 351(k) application to the agency following first licensure of a reference product (Wechsler, 2011). This 12-year protection for original biologics compares with only five years of protection for conventional drugs before generic versions appear. Currently, pioneer biological drugs in Europe are entitled to 10 years of data exclusivity before generic competition is allowed (Agres, 2011).

On considering similar biological legislation in 2008, the Congressional Budget Office estimated that over 10 years, as much as \$25 billion could be saved through its provisions for FDA approval of biosimilars by significantly driving reductions in the prices of biological drugs. However, when discussing the 12 year data exclusivity to innovator biologics manufacturers, the World Generic Medicines Congress (London, UK in February 2010), concluded that the extended exclusivity period has significant implications in delaying biosimilar development. Consequently, the provision is facing strong opposition from generics manufacturers and some politicians who argue that a shorter exclusivity period is necessary to make the development of biosimilars financially viable (Fernandez, 2010). The opposing side of the argument is of course, that sufficient time needs to be given for innovators to recoup the investments made to produce original biologics. Innovation in biologics has important benefits effecting overall social welfare as well as showing promise in specific areas such as cancer treatment (Grabowski, 2008). Grabowski (2008), in a portfolio study of new chemical entities between 1980 and 1984 demonstrates a mean break-even time of 16 years. Between 1990 and 1994, this had decreased to 15 years. For biological entities, mean break even times vary in his model, ranging from 12.9 to 16.2 years, depending on the parameters used for calculation. While arguments exist that oppose such analyses, or the basis for cost estimates, the FDA remains under pressure to strike the appropriate balance between competition and innovation (Grabowski, 2008; Tzeng, 2010).

5. The Indian pharmaceutical industry and capabilities for biosimilars

In the last two decades the Indian pharmaceutical industry has emerged as a cheap supplier of drugs to the rest of the world. Taking advantage of weak patent law introduced in 1970s by the Indian government, local firms used reverse engineering to develop cheap drugs, and as a consequence, extensive process R&D capabilities. Post TRIPS agreement these firms entered generic markets in advanced countries and made a mark using their superior process R&D skills, cheap production processes and deep distribution and marketing capabilities (Kale, 2007). Some Indian firms such as Cipla played a significant role in reducing prices of HIV cocktail drugs to poor populations of developing countries. For example, in beginning of 2000 Cipla offered to sell HIV cocktail at less than 4 % of prices charged by MNC firms and forced these companies to reduce their prices for African country populations. Now Cipla is one of the world's largest producers of antiretroviral (ARV) drugs to fight HIV/AIDS. Estimate from few years ago indicated that 40 per cent of HIV/AIDS patients undergoing ARV therapy were using Cipla drugs (Sharma, 2011).

Low-cost volunteers and strong clinical trial capabilities in the country have been the major cost-eroding factors for India. Building on this experience in the pharmaceutical generic industry in advanced countries, Indian firms are now targeting biological markets in developing as well as developed countries. Some of these firms have evolved capabilities for development and manufacturing of biosimilar products at much cheaper

rates and now trying to enter world market. India has in fact already introduced insulin and erythropoietin biosimilars, proving an ability to contribute to the market (Frost and Sullivan, 2011).

The Indian Government is playing an important role in encouraging the biosimilar industry. Biotechnology parks are under construction in Hyderabad, Pune, and Bangalore which provide special tax incentives to participants to support cost containment (Frost & Sullivan 2011). The department of biotechnology in India is inviting proposals from Indian companies, working on biosimilars, under its biotechnology industry partnership program. According to the proposal, the Indian Government will provide support to biotech companies on a cost-sharing basis for development of novel and high-risk technologies and to enhance existing R&D capacities, specifically for biosimilars. Analysts recognise that the rate of growth in India and other countries, will be largely dependent on the transparency of approval processes and government support. To sell in Europe and the United States, emerging suppliers must have certified facilities with the FDA and the EMA. While the cost of compliance may be higher, this may enhance credibility in the biosimilar market (Frost and Sullivan 2011).

The Indian pharmaceutical industry ranks 12th in the world in terms of value and is the second largest market in the world. Indian firms have traditionally focused on small molecules and chemistry dominated process R&D. However, in the post 1990 era some Indian firms entered the vaccine market and began investing in the development of biotechnology capabilities. Some of the early starters such as Wockhardt and Shanta Biotech developed collaborations with international research institutes and companies in order to develop vaccines for the domestic market.

Ariyanchitra (2010) suggests that the Indian biosimilar market is worth around \$200 million and there are 7-10 companies that have developed capabilities in the manufacture of recombinant products. She further suggests that Indian firms have expertise in gene manipulation and fermentation but have recently invested in other key areas such as bioprocess development and cell-line development. One or two companies have generated their own clones and cell lines.

Another significant challenge for Indian firms is accessing biosimilar markets in advanced countries as regulatory frameworks in the two most important markets of the world, the US and Europe, are still at nascent stages of development. G.V.Prasad, vice chairman and CEO of DRL explains;

"It is a big game. It will cost at least \$20 million to take a biosimilar drug to the European market. It takes only a small fraction of that amount for a conventional generics pharma product," (Suresh, 2008).

However some Indian firms have made the move towards introducing biosimilar products in the Indian domestic market. Desai (2009) point out that more than 40 biologics are marketed in India, of which 25 are biosimilars and are manufactured locally while another 25 biosimilars are in the final stages of development. Some of the products Indian firms are manufacturing include for example insulin, filgrastim, streptokinase, hepatitis B vaccine and rituximab. Table 3 provides details of leading Indian firms involved in the development of biosimilar products.

Table 3 Data of key Indian biosimilar players (Annual Reports, 2010)

Firms	Turnover Rs million	Overseas Revenue Rs Million	R&D intensity	Target + current biosimilar portfolio
DRL	74693	53340 (71%)	7%	Filgrastim, Rituximab, pegfilgrastim
Cipla	64830	35409 (55%)	4%	Avastin (Bevacizumab, Herceptin (trastuzumab), Enbrel (etanercept)
Biocon	28137	~ 14068 (50%)	10%	Human insulin, Insulin Glargine, Erythropoietin (EPO), Filgrastim (GCSF), Streptokinase, Monoclonal Antibodies
Intas	15474.50	5321.02 (34%)		Pegfilgrastim, Filgrastim, Erythropoietin, Recombinant Interferon Alfa-2b
Wockhardt	37500.00	27000 (72%)	1.87%	Human insulin, Monoclonal Antibodies, Erythroprotein, insulin glaritus

Many of the companies license recombinant clones from CIGB in Cuba or other countries. Insulin, the Hep B vaccine, GM-CSF, and several other FDA-approved therapeutic products are manufactured using *S.Cerevisiae*. Since the introduction of these products from Indian companies, the cost of insulin and Hep B vaccine has dramatically declined in the Indian market, and now these products are widely available in India.

5.1 Dr. Reddy's laboratories (DRL)

The most ambitious firm is possibly Dr. Reddy's Laboratories Ltd. (DRL) this pharmaceutical company is focusing on emerging markets such as India and Latin America. Their aim is to be one of the largest pharmaceutical firms in the world, competing with those like Roche, announcing plans to expand into biosimilars with an investment of 30 million dollars to improve research facilities (Dankekar, 2010). DRL launched its first biosimilar product, filgrastim in 2001 and following on that in 2007 the company launched its second product Reditux in the Indian domestic market.

In the last decade Dr. Reddy's Laboratory (DRL) has consistently ranked amongst the top ten pharmaceutical firms in India. Now the company has 15 manufacturing plants in India, 2 plants in UK and 1 in China. It has set up 23 subsidiaries for distributing and marketing pharmaceutical products in the domestic and international markets. DRL which started as a bulk drug manufacturer in the 1980s, moved to a formulation-focussed company in the early 1990s, upgraded itself as a US focussed pharmaceutical company in the mid 1990s, and finally it is transitioning into 'a research based international company'. Since the start of its operation DRL has continuously sought to move up value chain in terms of pharmaceutical products, markets and capabilities. Dr. Reddy's laboratories (DRL), founded by Dr. Anji Reddy in 1984, has grown into a fully integrated pharmaceutical company with an annual turnover of Rs. 75,000 million in 2010.

In 2008 DRL made a mark in the biosimilars market by launching Rituximab used in the treatment of certain lymphomas, leukaemia's and rheumatoid arthritis. In 2010-11, it grew by 75% over the previous year and emerged as the fifth largest brand in DRL's product portfolio. In 2010 Dr. Reddy's launched the first generic Darbepoetin Alfa in the world for treating nephrology and oncology indications. In same year DRL also launched an affordable form of Pegfilgrastim, which is used to stimulate the bone marrow to fight infection in patients undergoing chemotherapy.

According to its 2010 Annual Report, DRL has sold some 1.4 million units of its biosimilars, which have treated almost 97,000 patients across 12 countries.

5.2 Intas

Intas Biopharmaceuticals Limited (IBPL) was founded in 2000 as an independent biotechnology division of Intas Pharmaceuticals Ltd. Intas launched its first biosimilar product filgrastim (granulocyte colony-stimulating factor, G-CSF) in July 2004, followed by an erythropoietin injection in Aug 2005 and Interferon α 2b in April 2007. Intas is focusing on developing biosimilars and second-generation products (superior generics) for the regulated markets of Europe and US after having established its presence in India and other semi-regulated markets.

Intas Biopharmaceuticals Ltd signed an agreement with Canadian drug major Apotex Inc in May 2008, to co-develop and market the low-cost version of a biotech cancer medicine filgrastim (G-CSF) in North America and Europe and in January 2009 extended their agreement to develop a biosimilar version of pegfilgrastim. This collaboration gives Apotex the rights to market the product manufactured by Intas Biopharmaceuticals in North America, Europe and selected other countries.

According to its 2010 annual report Intas is already present in around 70 semi-regulated markets and has plans to launch its entire range of biotech products in regions like South-East Asia, Latin America, CIS & Russia and Africa in the near future. Rustom Mody, chief scientific officer and director (Quality), IBPL explains Intas's strategy for advanced markets such as Europe and USA;

"Our strategy would be a step-wise approach from active pharmaceutical ingredients (API) to biosimilars to contract research to collaborative research & bio-betters to novel

biologics. The company is aiming to replicate its biosimilar success of India and semi-regulated markets in Europe & the UK".

Intas Biopharma plans to invest about US\$ 30 million to set up a new drug manufacturing facility dedicated to large-scale manufacturing of monoclonal antibody based products. Commercial production at the proposed facility is likely to commence by 2011.

5.3 Wockhardt

Wockhardt Ltd was started by the Khorakiwala family in 1959 as a small pharmaceutical distribution and selling entity. The company set up its first formulation plant in 1977 and soon established a bulk drug plant in 1983. Now Wockhardt has 8 manufacturing plants in Aurngabad – 6 in the new biopharmaceuticals complex in addition to one each in Chikalthana and Waluj. In 1998 Wockhardt acquired Merind Pharma and became one of the largest producers of Vitamin B12 in Asia. In 2004 Wockhardt commissioned a state of the art production facility dedicated to manufacturing only biotech products. The company went public in 1992 and in the same year started building biotechnology capability by hiring scientists from local R&D institutes and forming collaborations with overseas biotech firms. Dr. M.K.Sahib, head of biotech operations in 2004 explains the seeds of biotechnology capability development in Wockhardt;

"I joined here in 1991-92 and came from CDRI. I had vast experience in the regulation of gene expression in mammalian systems as well as microbes and that helped me here.... we started here the recombinant area in collaboration with Rhein-biotech and we have today all the expression system that are approved for the manufacture of recombinant products, E-Coli, yeast and mammalian cells. We are the only Indian company who is manufacturing in India while others are importing. [For other] products like Hepatitis vaccine we have the largest brand and third is recombinant insulin. We will also have a very strong pipeline for different recombinant products. Bio-generics will be the first and then there will be second generations and also monoclonal antibodies".

Biotechnology is Wockhardt's R&D thrust area and with three exclusive products in the market, the company has been the front runner in biotechnology research. From the early 1990s the company has spent 20 -30% of its total research budget on biotech R&D. In 1995 Wockhardt formed a joint venture with the German firm Rhein Biotech to manufacture hepatitis B vaccine and in 2000 the company launched its first biotech product, a hepatitis B vaccine called Biovac-B. This joint venture helped the company to develop manpower trained in biotechnology R&D and provided access to crucial know-how. In 2002 Wockhardt acquired Rhein Biopharm and got hold of co-exclusive licence on Rhein Biotech's Hansenula polymorpha technology for the production of Hepatitis-B vaccine in India.

In 2001 Wockhardt indigenously produced a drug called erythropoietin (EPO) for severe anaemia. In India, erythropoietin was produced for the first time using genetic engineering methods. However for Wockhardt an important milestone in biotech R&D came with development of human insulin. In 2003, Wockhardt launched a human insulin named Wosulin. Wosulin become the first Human insulin to be made indigenously by an Indian company. At that time Wockhardt was only the fourth company in the world and

the first outside US and Europe to develop, manufacture and market this life saving drug used in diabetes.

In 2010 Wockhardt entered into a strategic alliance with Sheffield Bio-Science of the US, which will exclusively distribute Wockhardt's recombinant insulin in cell culture markets globally.

5.4 Biocon

Biocon, established in 1978 by Kiran Muuzumdar Shah, is a fully integrated biopharmaceutical company focused on biopharmaceuticals, custom research and clinical research. Located in Bangalore, India, Biocon has two subsidiaries, Syngene, a custom research organization, and Clinigene, a clinical research organization. Biocon's presence straddles four main therapeutic areas: Diabetology, Cardiology, Nephrology and Oncology.

Biocon was the first Indian company to manufacture and export enzymes to the US and Europe in 1979. It was primarily focussed on enzyme manufacturing from 1978 to 1997. In 1989, Biocon was acquired by Unilever. In the mid-1990s, Kiran Mazumdar-Shaw decided to focus on biopharmaceuticals rather than enzymes and in 2001 it started manufacturing insulin. After the 2001 patent expiration on Lovastatin, one of the earliest cholesterol blockers, Biocon got permission from Indian regulators to sell the generic in India. In 2001 Biocon became the first Indian company to get U.S. Food & Drug Administration permission to sell Lovastatin in the U.S (Egan, 2004).

In 2010 Biocon and Pfizer entered into a global agreement for the worldwide commercialization of Biocon's biosimilar insulin and insulin analog products. Biocon set out to establish a state-of-the-art biopharmaceutical manufacturing facility at BioXcell, a custom built biotechnology park and ecosystem in Malaysia. The worldwide requirements for Biocon's biosimilar versions of insulin and insulin analog products would be catered for by Biocon's existing facility in India and from the Malaysian facility when the facility becomes operational.

5.5 Cipla

Cipla or 'Chemical, Industrial and Pharmaceutical Laboratories Ltd' was started by Dr. Hamied in 1935. Over the last five decades Cipla has developed extensive capabilities in reverse engineering small molecules and has emerged as a cheap supplier of generic products to Indian domestic as well as advanced markets. From early 1990s, Cipla was among the top five companies in the Indian pharmaceutical sector. Post 2000 Cipla overtook other Indian and MNC firms to become the largest pharmaceutical company in the domestic market.

Cipla gained prominence globally with its offer to sell HIV drugs to African countries at much lower prices than MNC firms. This created significant controversy and forced MNC firms to lower their prices for African markets. Post 2000 Cipla is targeting its attention at the global biosimilar markets and started entering into collaborations for biotechnology capability development. With no expertise in reverse engineering of large molecules or proteins, Cipla hit a roadblock and entered into strategic alliances in order to build its biologic capabilities. In 2004 Cipla had formed a 50:50 joint venture with Avesta

Biotherapeutics and Research (ABRPL) —between its group company Meditab Specialties and Bangalore-based Avestha Gengraine Technologies (Avesthagen) to develop about a dozen biosimilar drugs, mainly to treat cancer and heart conditions. .However, the joint venture failed to meet its research targets and Cipla is now forced to look at alternate options (Business Standard, 2010). According to Economic Times (2010) Cipla aims to buy a 40 percent stake in Goa-based Mab Pharm and a 25 percent stake in Bio Mabs, Shanghai to gain the rights to sell biosimilars in India.

Cipla is targeting three of Roche's top biologics: Avastin, Herceptin and Enbrel. These account for \$19 billion in annual revenue. Cipla is establishing a manufacturing plant to produce biosimilars in Goa, and the company expects to launch its first biosimilar products in early 2012.

6. Conclusions and areas for further study

Increasing demand for biologics for new and improved disease treatments alongside the demand for more cost effective treatment has created a growing market for biosimilars in both developed and developing countries. This review highlights the favourable position for suppliers that aim to provide biosimilars for markets regulated by authorities other than the FDA. Most suppliers for biosimilars are based in the Asia-Pacific region and in Europe. A number of strategies are being developed by innovating companies and emerging suppliers to develop capabilities in order to compete in the biosimilars market, including investment, partnerships, mergers and acquisitions. At the same time there are challenges in addressing the high costs of regulatory compliance, capital investment for new biological production methods and innovating to improve analytical methods and product differentiation. Risks still remain with costs of litigation stemming from regulation (particularly in the area of data exclusivity) that is still evolving.

Section 5 has illustrated the promise of the Indian pharmaceutical sector in particular, where capabilities are developing in gene manipulation and fermentation. Other key areas however, such as bioprocess development and cell-line development, are absent. The Indian pharmaceutical sector, in the attempt to pursue biosimilars is likely to face the challenges of developing process R&D expertise in biotechnological, availability of skilled human resource in biochemistry and medicinal biology and developing financially robust strategies to operate in uncertain regulatory environments in advanced countries.

Much of the work on the biosimilar market and sector has been written by those who are closely linked to industry and the literature therefore is widely reflective of industry perspectives. Articles are short and offer opinions and news, without offering in-depth critical analysis (with the exception of law-based articles that have examined the precarious situation of the FDA and US regulation). It appears that in the last two years there has been very little published in social science journals which is not of the opinion or news kind. In particular we find that the questions about the wider innovation system, impact on society or the effect of national and regional government incentives on the structure and capabilities of the industrial sector, are not asked, nor answered.

Capabilities of innovation systems to deliver biosimilars as a solution to the health system problems that contribute to worsening social welfare, poverty and injustice, are vital to examine at this time. Capabilities are impacted by external factors such as economic stability, political harmony, government economic and industrial policy, and specific regulatory frameworks. Capabilities are also created by factors internal to the firm environment, for example; the development of personnel, the ability to learn and rearrange competences in order to respond to the market and external stimuli and the ability to innovate. For a national innovation system to respond to this new biosimilar market, the system as a whole needs to have adequate links between actors and a strong institutional framework for knowledge flow and learning. These are the gaps in the current literature which require further study.

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