**From small molecule generics to biosimilars: Technological upgrading and patterns of distinctive learning processes in the Indian pharmaceutical industry.**


## Abstract

Technology upgrading is a key element of industrialisation and catch-up in developing countries. It is understood that a successful technology upgrading is linked to a coupling of global knowledge flows with local technology effort. However, the changing nature of technology and industries are challenging existing processes involved in the technology upgrading and creating new patterns of capability development. This raises the questions about factors and processes involved in technology upgrading in firms from developing countries. In this context, this paper explores the movement of Indian pharmaceutical firms from 'small molecule generics' towards targeting a new set of opportunities presented by the emergent biosimilar segment in the global generics market. Some leading Indian firms have adopted this technological upgrading route by making a gradual transition towards the development of biosimilar capabilities and using four case studies; this paper reveals internationalisations in the form of overseas acquisitions and collaborations with MNCs formed the key basis of technology upgrading strategy for the Indian firms. This paper further shows the hiring of biotech scientists working in advanced countries increasing R&D investment and reorganisation of R&D contributed to managerial upgrading and played a significant role in creating firms' ability to absorb external knowledge.



## Keywords

India, technological capabilities, internationalisation, the pharmaceutical industry, biosimilars

## Introduction

Technological upgrading is identified as one of the key element of industrialisation in the developing countries, and significant attention is paid to the role of 'technology transfer through trade' and 'Foreign Direct Investment (FDI)' as major drivers of technological upgrading (Ernst, 2008; Fu et al., 2011; Giroud et al., 2012). In recent years, there has been increasing focus on indigenous learning processes and internationalisation in acquisition and mastering of technologies that are new to those countries, if not to the world (Amann and Cantwell, 2012). The changing nature of technology and industries are affecting the factors and processes that are involved in the building of firm-level technological capabilities in the developing countries. This raises questions whether firms from developing countries can rely on indigenous learning processes to catch up with industrialised countries and whether external sources of knowledge such as internationalisation are major drivers of technological upgrading for developing country firms. Indian pharmaceutical industry is a good example for investigating this question.

Over the last three decades, the Indian pharmaceutical industry has emerged as the 'pharmacy of the world' and that growth story has been well documented (Lanjouw and Cockburn, 2001; Horner; 2014). The Indian industry employed 'reverse engineering' to copy or manufacture drugs using known processes at a cheaper cost. This 'imitation strategy' contributed to the development of basic technological capabilities in the Indian pharmaceutical firms. The signing of the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement in 1995 restricted the use of reverse engineering and changed the rules of the game for Indian pharmaceutical firms. This forced Indian firms to search for a new technology strategy and much of the scholarship in the most recent decade has focused on analysing technology strategies of Indian firms to this disruptive regulatory change (Athreye et al., 2009). As an initial response to the TRIPS-compliant patent regime, leading Indian firms adopted a strategy of exploiting process R&D capabilities by targeting small molecule (chemical-based drugs) generics markets in advanced countries. This imitation strategy built on existing capabilities and involved activities such as identifying needs in the market, locate knowledge that would meet the market needs, developing new and original production processes to manufacture drugs, and accessing markets in advanced countries. This exploitative process R&D strategy emerged as an initial response and became a dominant, widely duplicated strategy amongst leading firms in the post-1995 era (Kale and Wield, 2008). This contributed to the development of advanced technological capabilities for manufacturing of small molecules in the Indian pharmaceutical industry.

However, two decades after the signing of the TRIPS agreement evidence suggests that Indian firms are facing significant regulatory and market challenges to technology strategies and capabilities focused on small molecule generic markets, thereby threatening their long-term survival and growth. In this context, some Indian firms have adopted technological upgrading route by targeting biosimilar market segment as a new source of growth. Biosimilars represent a change in the landscape and a significant market opportunity for the Indian pharmaceutical sector. Biosimilars are what might be called generic versions of biologics - a therapeutic drug category comprising large complex molecules. Unlike small molecule drugs, the challenge of producing similar biological medicine stems not only from R&D but also from manufacturing and regulatory requirements. The biological medicines are produced in the living systems, and the unique manufacturing process brings in microheterogeneity and complexity. Due to these challenges, it is highly difficult to produce an identical copy of the nature and production of biological medicines. Thus, these biosimilars are not generics but 'similar' to original or reference product regarding safety, efficacy and quality. Manufacturing of biosimilars requires different production platforms and expertise in clinical trials management. Thus, technology strategies of Indian firms in biosimilar segment require significant adaptations and upgrades in such a way that they involve not only activities like benchmarking but also notable learning through substantial investment in R&D, production

and regulatory capabilities. Further, the complexity of biological drugs and evolving regulatory requirements have created a need for new sets of resources, knowledge and capabilities. This transition towards biosimilar development provides informative case studies to investigate factors and learning processes associated with the technological upgrading and examine their link with the development of world-frontier innovative capabilities.

This paper builds on over the last two decades of research on the evolution of technological capabilities in the Indian pharmaceutical industry. Using the case study research methodology, we selected four Indian pharmaceutical firms to focus our investigation. Primary data was collected through interviews with R&D scientists and key managers from the four Indian firms by using a semi-structured questionnaire. Data was triangulated with the help of secondary data sources and interviews with industry experts and analysed using a theoretical framework based on metrics derived from technological upgrading literature (Radošević and Yoruk, 2015). The research demonstrates that Indian firms experimented with technology strategy and invested in the development of organisational capabilities to make a gradual transition towards acquiring biosimilar capabilities. It does highlights internationalisations in the form of overseas acquisitions and collaborations with MNCs formed the key basis of technology up-gradation strategy for the Indian firms. This paper further shows the distinctive patterns of learning processes and key features of technological, regulatory and market strategies involved in technological upgrading by the Indian firms.

This paper is structured as follows: Section 2 briefly reviews the literature focused on the technology upgrading of capabilities in developing countries. Section 3 explains the salient features of the Indian pharmaceutical industry and highlights challenges to small molecule generics market strategy. Section 4 tracks the technological challenges associated with opportunities of the biosimilar sector. Section 5 details the data collection methods and the four Indian pharmaceutical firm case studies that are used to investigate learning processes associated with technology upgrading from small molecule generics to biosimilars. Section 6 discusses the findings of the research and section 7 concludes with an examination of the implications and lessons for policy.

## 2.0 Theoretical framework: Technological upgrading in developing countries

Technological upgrading in developing countries is an issue that has been widely discussed in the last 20 years by different theoretical research traditions and often discussed in the international context. Reviewing this literature, Amann and Cantwell (2012:357) suggest that the technological upgrading and economic catch-up literature have 'tended to disregard the firm level and focus on certain macro or industry level environment of economies that are beneficial to closing the gap with mature industrialised economies'. Building on that the focus of this research is the processes and strategies involved in the technological upgrading in the Indian pharmaceutical firms.

### Technology transfer, FDI and technology upgrading

The role of foreign direct investment and technology transfer in technology upgrading has been a critical area of research. Fu at al., (2011) suggests that technology transfer through the movement of goods, capital, people and international research collaboration may spur a learning process and technological upgrading at the local level. In this research, the role of multinational enterprises and FDI has received significant attention as key routes for technology upgrading in the developing countries (Pietrobelli and Saliola, 2008). FDI as a source of technological and managerial knowledge and financial resources has been viewed as a conduit for the transfer of advanced technology to developing countries (Lall, 2003). However, it is also argued that despite the possible benefits of technology transfer and FDI spillover, there may also be significant adverse effects on technological upgrading in domestic firms for a variety of reasons (Fu et al., 2011). For example, FDI may negatively affect the competitiveness of domestic firms and potentially crowd them out of the market (Hu and Jefferson, 2002), and foreign subsidiaries may remain as enclaves in a developing country

with a lack of effective linkages to the local economy. Significantly the private interests of the MNCs may not coincide with the social interests of developing countries (Lall and Urata, 2003).

Technological upgrading taking place in the Global Value Chains (GVC) has emerged as a key area of focus in studies of technology capability development (Hobday, 1995; Gereffi, 1998). This literature suggests that international knowledge and innovation exchange and collaboration has a significant impact on the innovation and technology upgrading of those firms that successfully integrate into the GVC. Ernst (2008) points out that in developing countries exploiting this potential source of knowledge and learning is especially important given that new frontier innovation is rarely created in developing countries and the bulk of knowledge and technology needs to be imported. For firms in developing countries, integration into GVCs does not only represent a new market for their products, but it also plays a growing and crucial role in accessing knowledge and enhancing learning and innovation. However, Fu et al., (2011:13) argue that the literature has not yet clearly settled how innovation systems and GVCs interact, and how this interaction is likely to affect enterprise learning.

Thus, the central role of technology transfer, FDI and GVCs in technological upgrading and driving industrial and economic growth is well established in development and catch-up studies, however, Amann and Cantwell (2012) suggests that firm-level technological capability building should be the key focus of technological upgrading as it reflects a continual change and transformation both the actors and their environment.

**Firm-level technological upgrading in the developing countries**

Technological upgrading at the firm level has been the critical area of focus for innovation study scholars focused on the development of technological capabilities in the developing countries (Bell and Pavitt, 1993, Lall, 1992; Dutrenit, 2000; Figueiredo, 2006; Amann and Cantwell, 2013). Bell and Pavitt, (1993) define technological capabilities as "the stock of resources needed to generate and manage technical change, including skills, knowledge and experience and institutional structures and linkages". This definition suggests that technological capabilities refer to both; a technical knowledge component which enables firms to generate innovations, and an organisation component which enables firms to manage the implementation of their in-house innovations and their linkages with external sources of knowledge. Different technologies differ greatly in their learning requirements, entailing different costs, risks, duration and linkages. This definition further suggests a different set of capabilities that need to be acquired, those that are concerned with the organisation, coordination and managerial aspects of technological capabilities. These latter capabilities often are much more difficult to develop than engineering know-how and include capabilities to access complementary assets, absorptive capabilities, and innovation capabilities. All these capabilities are required to adopt, adapt, and modify technologies developed elsewhere, to introduce modifications and incremental innovations, and eventually to generate new products and processes (Malerba and Nelson, 2012). This insight infers that interactions between technical capabilities and organisations capabilities are a key issue in the technological upgrading in developing country firms. This literature further suggests that technology upgrading is not an automatic process; some latecomer firms succeed, and others fail in catching up with the technological frontier (Dosi, 1988; Lall, 1992; Hobday, 1995; Bell and Pavitt, 1993). However, Figueiredo (2006:6) argues that "more effort is needed to expand the focus of analysis to not only within boundaries of the latecomer firm but also the links between capability building within the firm and other external factors such as innovation systems and macroeconomic policies".

Over the years few studies have tried to explain the building of firm-level innovative technological capabilities in the late industrialising countries by focusing on intra-firm strategies (Dutrenit 2006; Athreye et al., 2009) and taking external factors into account (Kim and Nelson, 2000). These firm-level studies in the catch-up literature tend to focus on the significance of imitation in the development of innovative capabilities (Kim and Nelson, 2000).

Mainly focussing on creative imitation, Kim and Nelson (2000:5) argue that "most innovations do not involve breakthrough inventions but are deeply rooted in existing ideas". Elaborating on this further, Malerba and Nelson (2012) point out that "catching up does not mean cloning". They suggest that the outcome of an imitation effort reflects modifications required to fit practice to local contexts. Due to this, the development process involves innovation in the Schumpeterian sense: 'as a break from traditional ways of doing things'. Using the conceptual framework focused on the paths and width of technology upgrading (fig 1), Radosevic and Yoruk (2015) suggest that these firm-level studies have shown paths of upgrading of firms in developing countries through a variety of interrelated, sometimes similar and sometimes unique taxonomies. They conceptualise technology upgrading as a three-dimensional process and argue that technology upgrading is multidimensional processes and consists of three major dimensions: technology, structural change and interaction with the global economy.

Further, sectors change over time following life cycles in a coevolutionary process along with various actors, knowledge and institutions. In some cases, evolution is triggered by changes in demand, users and applications, and that can alter the context in which firms operate (Christensen and Rosenbloom, 1996). This results in changes in technological and learning regimes and patterns of innovation (Malerba and Nelson, 2012) and can lead to a change in the knowledge base of innovative activities, requiring new types of competencies. This dynamic and evolutionary view implies that the boundaries of sectoral systems regarding knowledge, actors, and institutions may evolve, with new types of actors entering and new vertical and horizontal linkages and interdependencies formed among industries and technologies (Malerba and Nelson, 2012). Amann and Cantwell (2012) argue that this trend towards a greater interdependence and international integration in the processes of firm-level capability building has an impact on the national specific ecosystem, giving rise to the importance of internationalisation and global knowledge flows in studies of firm-level technology upgrading. They point towards the 'rising globalisation of the technological knowledge bases, the internationalisation of epistemic and professional communities of practice and related science as well as the increased international interconnectedness of business relationships as a major influence on the firm level technological upgrading' (Amann and Cantwell, 2012:355). Building on that Radosevic and Yoruk (2015:11) argues that a successful technology upgrading is never entirely autonomous process, but it is always linked to the inflow of foreign knowledge skills, which are coupled with domestic technology effort. Reviewing this technology upgrading literature, Fu et al., (2011) raises key unanswered questions about nature of interactions and relationship between indigenous innovation and acquisition of foreign technology in an increasingly globalised world This suggests a need for unpacking the nature of interactions, processes and strategies involved in leveraging domestic innovation effort with global knowledge flows. Further, Bell and Figueiredo (2013) argue that the study of the technological capability development in latecomer firms operating in the intensive technological sector has been limited and under-researched. This paper builds on and adds to the research focused on firm-level factors and processes involved in technology upgrading by exploring internationalisation strategies and learning processes involved in the development of biosimilar capability by the Indian pharmaceutical firms.

## 3.0 The Indian pharmaceutical industry

The Indian pharmaceutical industry ranks 3rd regarding volume and 14th in terms of value. It was valued at $12 billion in 2013 (Panchal et al. 2014). It comprises 250 large units (which includes the public sector, domestic firms and foreign subsidiaries), and 8000 small-scale units. The large units contribute almost 70% to total national pharmaceutical activity and therefore dominate the Indian pharmaceutical sector. The Indian pharmaceutical industry has come a long way. From importing bulk drugs, it has moved into exporting formulations to the highly-regulated markets of the developed world. It represents one of the most successful cases of self–reliant development in post-independence India.

### The dominance of small molecule generics business model

The growth of the Indian pharmaceutical industry was slow until the patent act of 1970 and government investment which closely followed. The 1970 Patent Act allowed patents only for production processes and not products, triggering an era of reverse engineering. The Indian pharmaceutical firms focused on adapting technology to firm and country specificity, and efforts in these directions fostered the development of a knowledge base. These firms used reverse engineering or duplicative imitation as the primary mechanism for knowledge acquisition and built basic process R&D capabilities in the manufacturing of small molecule generics. After the liberalisation of the pharmaceutical market in the mid-1990s, some Indian pharmaceutical firms moved toward the highly regulated generic markets in advanced countries. Indian pharmaceutical firms initially exported formulation products to least developed and developing countries, but after 1990 they started exporting formulation products to generics markets in advanced countries. The technology strategy of 'incremental imitation' involving the manufacture of products by developing non-infringement processes which could be converted into a patent creating value for firms emerged as a principle response of the Indian firms. Indian firms started developing processes which contained some patentable novel elements. This allowed Indian pharmaceutical firms to develop the regulatory capability required to access global markets, build organisational structures to manage original research, and gain entry to the generic markets of advanced countries. However, emerging R&D, market and regulatory challenges in the small molecule generics strategy and opportunities in biosimilar market has spurred Indian firms to invest in technological upgrading strategy focused on biosimilar as a distinctive alternative source of long-term growth

### 3.1 Challenges to the small molecule generics business model and need for technological upgrading

The shrinking market share in generic markets due to increased competition and regulatory hurdles in advanced country markets created uncertainty about potential sources of long-term growth for the leading Indian firms.

#### Market challenges: Saturation of the market for 'small' molecule generics in advanced countries

Indian firms' business models generally rely strongly on small molecule generics markets in advanced countries for revenue and growth. However, the saturation of these markets, in part linked to changes in regulation, has significantly reduced the value of these markets for Indian firms. Until 2003, many innovative Indian firms generated profit by aiming for first to file status in the US generics market, which provided 180 days market exclusivity to generics manufacturers. In 2003 however, this provision was diluted allowing for more than one generics manufacturer to enjoy the 180-day exclusivity, provided they file their Abbreviated New Drug Application (ANDA) on the same day. This dented profit margins significantly. In addition, the entry of large pharmaceutical firms into international generics markets has led to increased competition, further eroding the profit margins of Indian manufacturers.

#### Regulatory challenges: Problems with US FDA

The Indian pharmaceutical industry has the largest number of USFDA (Food and Drug Administration) approved manufacturing plants outside the US, and in 2013 accounted for 39% of all approvals for generic drugs (Balakrishnan, 2014). The strong presence of Indian firms in the US market brought about intense scrutiny which resulted in more than 30 import alerts received by Indian firms since 2009. The FDA has identified some Indian pharmaceutical manufacturers who have had problems with data integrity and Good Manufacturing Practices (GMP) at their respective facilities. This data is intended to ensure that products meet pre-established specifications for purity, potency, stability and sterility (Gaffney, 2015). Since 2013, the FDA has banned around 30 Indian plants for various violations (Gaffney, 2015; FDA website, 2015). In 2014, the FDA issued import alerts against ten plants, including units of two leading Indian firms; Sun Pharmaceuticals and Cadila Pharmaceuticals.

### 3.2 Biosimilar: Opportunities and challenges

A biologic or biological drug is a large complex molecule that has been sourced from a living cell, for example, insulin. Traditionally biologicals have been developed to address the most challenging illnesses such as cancer, autoimmune diseases, diabetes, growth hormone deficiency and inflammation. Biosimilars are similar in terms of quality, safety and efficacy to an already licensed reference biological product – it is an interchangeable generic equivalent. Unlike small molecule generics, biosimilars are produced in living organisms, heterogeneity, with 'some allowable' structural variations are fully expected when compared to innovator product (Rader, 2014). The chemically synthesised small molecule is expected to be equivalent (not just similar) to the reference product.

**Opportunities**

The growth in the biosimilar market is driven by several factors such as original biologics coming off patent, pressure on governments all over the world to reduce healthcare costs, and the development of regulatory guidance in key markets around the world. With clinical testing not including large Phase III type efficacy and safety studies, biosimilar requires less investment and time for their development and thus, provides cheaper alternative and more competition for reference products previously lacking generics type competition (Rader, 2014).

The global market size of biologics was estimated at US$169 billion in 2012 (IMS, 2013). Various patents for top-selling biologics are due to expire between 2012 and 2019, creating a biosimilar market worth of $100 bn by 2020 (Wechsler, 2011). Biosimilars are poised to acquire a significant share of the generics pharmaceutical market. Singh (2015) suggests that globally, revenues from biosimilars have risen from $1.1 million in 2007 to $86.9 million in 2014. There are already 21 approved biosimilars in Europe, and many of the 150 biosimilars in development will also be introduced into the European market. It is expected that biosimilars will account for 4% to 10% of the global generic market total by 2020.

Governments in different countries and regions are establishing new regulatory guidelines to facilitate the entry of affordable biosimilars. Major developed regions such as the EU, US, Japan, and Canada and many of the largest emerging markets such as China, Brazil, South Africa, and India have established biosimilar pathways or produced regulatory guidelines specifically for complex biosimilars. Moreover, in 2010 the WHO offered guidance on biosimilar approval standards for regulatory agencies to use as a basis for local requirements. There is a certain convergence around regulatory requirements and the emergence of a significant new market opportunity. By establishing a common development platform for most markets, the Indian firms minimise the duplication of effort across pre-clinical and clinical development, accelerate development, and reduce investment costs.

#### 3.2.2 Challenges in the development of biosimilar capability

Switching to biosimilars is not an easy, minimum risk strategy. Biosimilars are too complex to manufacture in the same way as simple small molecule drugs (e.g. aspirin) and require considerable financial and organisational investment in developing regulatory, technical and scientific capabilities. Table 1 lists some key differences between small molecule generics and biosimilars.

**Table 1 Difference between small molecule and biosimilar product development (Jonker-Exler, 2015)**

| Key issues | Small molecule | Biosimilar |
|---|---|---|
| Example | Acetylsalicylic acid (Aspirin) (180 Da) | Monoclonal antibody (~150,000Da) |
| Entity | Chemical | Protein |

| | | |
|---|---|---|
| Structure | Small, simple, well characterised | Large, complex, heterogeneous |
| Stability | Stable | Unstable |
| Manufacturing process | Predictable and precise method, identical copies in batches | Living cell-based complex technology; batch to batch variation, sensitive to storage and handling |
| Knowledgebase | Chemistry based requiring strong process R&D skills | Biology-based process R&D and manufacturing capabilities |
| Mode of administration | Usually amenable to ingestion | Usually, requires injection or infusion |
| Regulatory | Uniform requirement of bioequivalence data for product approval in advance and developing country markets | Challenges of forming uniform regulation in advance markets but requires clinical trials data |
| Immunogenicity | Mostly non-immunogenic | immunogenic |

Elaborating on the distinction between the biosimilar and small molecule generic, McKinon and Lu (2009) point out 'complexity' as a critical difference. Conventional drugs can be characterised entirely based on their chemical structures, whereas biological drugs tend to be recombinant proteins with structural complexity and high molecular weight. The complexity of biological drugs emanates from the elaborate manufacturing and regulatory processes involved in their production. Due to the complexity of the manufacturing process, the possibility for variance is very high, and a slight variability in process or input can lead to slightly different large complex molecules, which in turn can have significant effects on safety, quality and efficacy. As a result, biosimilars are considerably more expensive to manufacture than small molecule generics. For example, the production cost of small molecule generics manufactured using classical chemical synthesis can be less than US$5 per gram, while biological produced in living cells incur costs of US$ 100-1000 per gram (Sommerfeld and Strube, 2005). It is imperative for manufacturers to find a production process that would keep the cost affordable to patients for doses at higher than 5 mg/kg body weight and week. Thus, technical competencies are required for upstream verification of similarity or comparability with an innovator product and downstream pharmacovigilance data generation.

**The challenge of different knowledge base: Process R&D and Manufacturing capabilities**

Accessing small molecule generics markets in advanced countries involved creating non-infringing processes or invalidating an existing patent. The knowledge base for this builds on organic and synthetic chemistry skills (accumulated through reverse engineering). Some Indian firms have used this base to add a patentable, innovative element that provides value through leveraging process R&D capabilities. In the case of biosimilars, these firms need expertise to reverse-engineer biologics and develop stable, therapeutically active cell lines. They also need to develop manufacturing processes to meet specifications and to invest in new infrastructures for controlling living cells, purification and producing biologic products consistently at commercial scale (Lee et al., 2011). In the manufacturing of biological drugs, product quality is defined by the process (e.g. equipment, the sequence of unit operations, operation parameters) because no complete analysis of these complex molecules is possible (Sommerfeld and Strube, 2005). As a result, the production process is fixed after the first clinical lot production in a pilot plant leaving no scope for modifications or optimisations parallel to production whereas, in small molecule productions, it is possible to perform process optimisation in parallel to production. This difference in the manufacturing process demands an advanced level of biological process R&D and production capabilities for the development

of biosimilar. Joe Thomas, CEO of Stellis Biopharma points out limitations of production technology currently used by Indian manufacturers,

> "The earlier model of Indian generic companies with strong domestic franchise investing in capacities to meet international requirements is not practical in a biopharma setting. Unlike generics, biosimilar uptake is relatively low in India because of their high cost, and biomanufacturing capacity creation is much more resource intensive than in small molecule."
>
> (Stanton, 2017)

In this regard, the main constraint for Indian firms is the lack of knowledge of biology pertinent to biosimilars and absence of expertise with regards to quality, safety and efficacy (Interview, senior scientist, Serum Institute of India, 2014).

**The challenge of different knowledge base: Regulatory capabilities**

In the case of small molecule generics markets, Indian firms have to conduct bioequivalence or bioavailability studies to establish similarity of the therapeutic product and novelty of production process to get approval from regulatory authorities to sell in the market. However, in the case of biosimilars, Indian firms are facing severe challenges in satisfying the regulatory requirements for biosimilars, which are not only different from that, which applies to generics and biologicals but also differ from country to country and involves the collection of extensive clinical data requiring clinical trials over a more extended period.

To enable cost-effective global development, Indian firms will need to consolidate their efforts to harmonize development requirements, particularly their choice of global reference products and how they define them. The complexity of the manufacturing process requires multiple points of comparison to reference product. Thus, the creation of the creation of structural analytic goalposts or reference points for developing highly similar products will call for trade-offs and design expertise combined with an understanding of the likely clinical implications (Daalgard et al., 2012). Further, as biosimilar progresses through comparability stage-gates, both pre-clinical and clinical studies are required to make a full assessment of the similarity of a candidate biosimilar to its reference product. For instance, difficulties arise in using in vivo pharmacokinetic/pharmacodynamic (PK/PD) and toxicological models because complex biosimilars demonstrate species-specific pharmacodynamics profiles that limit the extrapolation of data from one species to another. Indeed, there is no established in vivo pharmacology model other than non-human primates, and as a result, extensive in vitro assessments are needed (Radar, 2014; Daalgard et al., 2012). Thus, the understanding the possibility and consequences of even small variation requires knowledge in new fields of biology. The head of biosimilars at a leading Indian firm further illustrates this with the example of immunogenicity. In the case of small molecules, drugs rarely elicit immune responses, but large molecules such as biologicals can trigger immune responses of different consequences (Interview, 2014). In the case of biosimilar candidates, there must be equivalent immunogenicity compared to a reference biologic. Also, establishing systems for phase IV, post-market adverse event reporting and generation of pharmacovigilance data involves long-term financial investment and superior organisation capability.

- **Financial and infrastructural resources**

The regulatory frameworks, rigorous clinical trials and extensive clinical data required for biosimilars create financial and technological capability challenges for Indian firms. The average cost of clinical development for biosimilar ranges from $40 million to $300 million, and development takes up to 5 years; comparatively, development costs $2 to $5 million for a generic drug and takes 2 to 3 years (Grabowaski et al., 2014). G.V. Prasad, vice chairman and CEO of Dr Reddy Labs (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)

Referring to financial challenges, a senior pharmaceutical scientist based at Utrecht University in the Netherlands argues:

> "[US and European] markets will be dominated by 'Big Pharma'. It takes between 50 and 100 million euros to develop a biosimilar that meets the regulations in Europe, the US and Japan…. that is in addition to post-marketing costs and pharmacovigilance demands. I do not see how a small company, especially from India and China, even if they have the technical skills and money to develop a high-quality biosimilar could be able to compete with Teva, Sandoz or Hospira" (Interview, Jayaraman, 2010)

In this context, for Indian industry acquisition of biosimilar capability will require investments in technology upgrading by the reorganisation of R&D, building a new manufacturing and regulatory capabilities.

**5.0 Research Methodology**

This paper investigates the firm level learning processes and interactions with the external environment involved in the technology upgrading in the Indian pharmaceutical industry by focusing on the case studies of four Indian pharmaceutical firms (Table 2).

The principal reasons for focussing on these firms are twofold. One, the four firms selected for the study are among the top 20 Indian pharmaceutical firms. Further, there is a robust correlation between size and R&D intensity in the Indian pharmaceutical sector (Pradhan, 2007). Therefore, any investment in the biosimilar market is likely to emerge only from the top firms. Second, the firms selected for study operate in both; small molecule generic markets as well as biosimilar markets. Further, these firms are at different stages of developing biosimilar product portfolios and thus provide ideal cases to track challenges involved in technological upgrading. Firms such as Biocon and DRL are early entrants in biosimilar and small molecule generic market while Lupin/Cipla is a late entrant.

**Table 2 Firms under study (Annual Reports, 2016)**

| **Firms** | **Nature of firm** | **Turnover 2016-17** Rs ₹ million (approx. US $ million) | **Biosimilar Products** | **Supply of Biosimilar in the overseas market** |
|---|---|---|---|---|
| Biocon | Biotech | 40787 (636.89) | Human insulin, Insulin Glargine, Erythropoietin, Filgrastim, Streptokinase, Itolizumab, Trastuzumab | 27 countries |
| Cipla | Pharma | 146300 (2284.47) | Etanercept | India |
| DRL | Pharma-biotech | 148000 (2311.00) | Filgrastim, Rituximab, pegfilgrastim, darbepoetin alpha | 12 countries |

| | | | | |
|---|---|---|---|---|
| Lupin | Pharma | 174943 (2731.73) | Filgrastim, Peg-Filgrastim, | India |

This study builds on the over last two decades of the research on the evolution of technological capabilities in the Indian pharmaceutical industry. In 2016-17 intense data collection was carried out to gather primary data on biosimilar capability development in the Indian pharmaceutical industry. The data collection primarily focused on the external linkages and distinctive learning processes involved in the development of biosimilar capabilities. Primary data for the case studies was collected through interviews with R&D presidents, senior scientists and heads of biotech R&D in the four firms. In parallel, interviews with a key member of the Indian pharmaceuticals industry association and with a senior sector specialist journalist were conducted. In total 20 interviews lasting 45-60 mins were conducted. Interviews were recorded and transcribed. This data was triangulated by using information from various secondary sources such as annual reports, analysts' presentations and articles in the business press.

The literature review on technological upgrading at the firm level in emerging countries provides major categories for investigation. It highlights the need to expand focus on factors within boundaries of the firm and also explore links between capability building within the firm and other external factors such as innovation systems and macro-economic policies (Figueiredo, 2006). Based on the that a semi-structured questionnaire was used with questions focused on the response of Indian firms to the factors and processes involved in technological upgrading from small molecule to biosimilars. Interviews focused on firm strategy, challenges and organisational learning activities involved in the acquisition of new knowledge required for biosimilar capability development. It also covered questions regarding the relevance of existing pharmaceutical R&D and manufacturing in the development of biosimilar capabilities and differences with small molecule generic markets.

We employed an analytical framework based on the 'dimensions and paths' framework proposed by Radosevic and Yoruk (2015) (Fig 1). Dimension 1 consists of the intensity of technology upgrading as depicted by different types of innovation activities and dimension two is about the spread or width of technology such as diversity of technological knowledge, the firm's structure. Dimension 3 depict knowledge flows into the economy through different forms. This framework is modified and employed to analyse data presented in this paper.

The analysis of the empirical evidence was carried out by using various analytical techniques such as pattern matching (Yin, 1994) and by the building of analytical tables (Miles and Huberman, 1984). Building on the analytical framework a strategy of pattern coding is used to identify the processes and strategies involved in technological upgrading within and across firms (Eisenhardt, 1989). The theoretical framework provided broad categories for the classification of the data, and various pattern codes are classified under those broad categories. The key categories included internal organisational changes, motives of internationalisation and collaborations and the role of path dependency in shaping new capabilities. These patterns were supplemented by secondary data which were collected from industry journals, industry association publications and annual reports of firms.

## 5.0 Firms under study

This section presents the case studies of technological upgrading in the four Indian pharmaceutical firms based on the data collected from primary and secondary sources.

### 5.1 Dr Reddys Laboratories (DRL)

Dr Anji Reddy founded DRL in 1984 with the aim of creating an innovative Indian pharmaceutical company. DRL started as a bulk drug company and then gradually moved into

the formulations business. In 1986, it started operations on branded formulations and within a year launched Norilet, DRL's first recognised brand in India. In 1989, DRL's early successes were with R&D in non-biologics, notably Omeprazole in 1989 and Fluoxetine in 2001. This success was followed by the launch of Ibuprofen tablets in the United States under its brand name. In the following decade, DRL emerged as a global generics player with innovative process capabilities and stable marketing network in the USA and other advanced countries.

**Processes involved in technological upgrading: Biosimilar capability development**
DRL set up biotechnology R&D in 1999 as a separate business unit and within two years launched its first biosimilar product, Filgrastim. In 2003, this effort received a boost with the hiring of Dr Cartikeya Reddy from Genentech Corporation as head of the Biological division. With extensive experience and knowledge in biotechnology R&D, Dr Cartikeya Reddy helped DRL to accelerate the development of its biosimilar business and in 10 years succeeded in launching three more biosimilars; Darbepoetin, Alfa Pegfilgrastim and Rituximab. In 2007, DRL had a breakthrough in biosimilars when it became the first company in the world to launch Rituximab biosimilar, referencing Roche's original $6 billion cancer drug, Rituxan. By 2010, DRL was operating with three dedicated biological manufacturing facilities and a team of more than 300 scientists and engineers. At this stage, DRL adopted a strategy of commercialising its biosimilars in emerging markets as a step towards gaining approval in the US and Europe. This strategy allowed DRL two advantages. First, it helped the company to gather significant real-world experience and clinical data on the performance of its products and, second, it provided DRL with an opportunity to generate revenue that could be utilised for developing assets for approval in advanced country markets. Following on from that strategy, in 2010, DRL began selling its Rituximab in emerging markets at a 30-50% discount compared to the innovator brand.

In 2012, DRL started planning to enter the US and European markets. As part of that strategy, DRL entered an alliance with Merck Serono, a division of Merck KGaA, Darmstadt, Germany, in June 2012. Merck KGaA is a global pharmaceutical company with proven expertise in developing, manufacturing, and commercialising biopharmaceuticals. The partnership was to co-develop and globally commercialise a portfolio of biosimilar compounds in oncology, primarily focused on monoclonal antibodies (mAbs). The alliance allowed DRL to mitigate the risks involved in developing a biosimilar — the cost is pegged at $100-200 million, with 70% going towards clinical development. By 2013 DRL had started applying for approvals from regulators from advanced countries. In 2013, the company filed a US investigational new drug (IND) application for its proposed Rituximab biosimilar and Pegfilgrastim and received permission to proceed with the Phase-I trials in 2014. At present, DRL is involved in planning, designing and executing studies under these INDs. In 2016 DRL in-licensed three biological drugs from Amgen to sell in the Indian domestic market.

In 2017 DRL installed India's first single-use manufacturing platform to expand the biologics production capacity at its facility in Hyderabad. This platform allows multi-product manufacturing and improves productivity by increasing the number of batches that are manufactured. This marks a significant step for the DRL and Indian industry regarding upgrading of production capabilities for development of biosimilars.

### 5.2 Biocon
Biocon, established in 1978, is a fully integrated biotechnology company focused on biologics, custom and clinical research. In the mid-1990s, Biocon decided to focus on biopharmaceuticals rather than enzymes and set up an in-house biotech research programme. After the 2001 patent expiration on Lovastatin, one of the earliest cholesterol blockers, Biocon obtained permission from the US Food & Drug Administration (FDA) to sell the generic in the US. In 2001 Biocon became the first Indian company to sell Lovastatin in the US.

To generate an alternate source of revenue and develop regulatory capabilities, Biocon established Syngene in 1994, a contract research company, and Cyngene, a clinical research organisation, in 2000. These ventures helped Biocon to develop complementary capabilities in clinical R&D, generate a steady stream of revenue and establish collaborative linkages with overseas pharma companies.

**Processes involved in technological upgrading: Biosimilar capability development**

The big breakthrough for the company came with the development of a human insulin product in 2003. Biocon became the first company in the world to manufacture insulin using a *Pichia pastoris* yeast expression system. Spurred by this success in 2006, Biocon initiated its biosimilar strategy by establishing India's largest multi-product biologicals R&D facility at Biocon Park in Bangalore. Biocon biosimilar strategy has two critical elements which involve a) exploiting the success of insulin by expanding it in overseas market and parallel, b) developing technological capabilities for monoclonal antibodies (mAbs) and proteins used in treatment for diabetes and oncology.

Biocon has created significant capabilities for manufacturing of insulin through the indigenous learning process and became the second Indian company to launch human insulin in the Indian domestic market causing an almost 40 per cent drop in the price of insulin products. In 2005, Biocon started expanding in overseas marked by supplying human insulin to countries in Africa and the Middle East and now has approvals in over 60 emerging markets for its rh-Insulin and in over 20 emerging markets for its Insulin Glargine. In 2008, for €30 million, Biocon acquired a majority stake in the German pharmaceutical company AxiCorp GmbH (70%) to market and distribute its insulin biosimilar and analogues in the German market but dissolved this partnership in 2011 while retaining rights to market products in Germany.

In 2010 Biocon entered a landmark $350mn deal with Pfizer to globally commercialise several of Biocon's insulin products - Recombinant Human Insulin, Glargine, and Lispro. This deal signalled the coming together of Pfizer's strong marketing and commercialisation capabilities, especially in the highly regulated developed markets of the world, and Biocon's expertise in biotech R&D. Pfizer changed its strategy and pulled out of the deal in 2012.

In 2010 Biocon started setting up Asia's largest integrated insulins manufacturing facility in Malaysia at an investment of over $ 250mn, and currently, employs a team of over 400 people at this state-of-the-art facility in Malaysia. This is Biocon's first overseas biopharma manufacturing and research facility and has received the cGMP certification from the National Pharmaceutical Control Bureau (NPCB), Malaysia. Biocon also emerged as the first Indian company to have made inroads in Japan, one of the world's most stringent developed markets, with its Insulin Glargine. Further, Biocon is developing an insulin analogues portfolio for other developed markets like the US and Europe. In 2017 Biocon has agreed with Mexico's Laboratorios PiSA to develop and commercialise its rh-Insulin in the US market.

Unlike indigenous effort involved in the development of insulin capabilities, Biocon's development of technological capabilities for complex biosimilars involved internationalisation of R&D and overseas collaborations with MNCs. In 2006 Biocon entered a joint venture with the Cuban Institute of Monoclonal Antibodies (CIMAB), the commercial branch of the Center for Molecular Immunology (CIM) to develop antibodies and cancer therapies and followed that with a joint venture with Abraxix Bioscience to develop a biosimilar version of Filgrastim in 2007. In the same year, Biocon hired Dr Barve from a US biotech firm to lead its clinical research organisation and two years later promoted him to head of biotech R&D.

Under the leadership of Dr Barve, Biocon adopted an aggressive strategy of targeting emerging as well as advanced country markets and to achieve that, entered a range of collaborations and joint ventures. In 2009 Biocon formed a strategic joint venture with Mylan, an MNC generics firm, to co-develop four biosimilars and enter the global biosimilar market.

Over the years, this collaboration developed a strong portfolio of generic insulin analogues and biosimilars including monoclonal antibodies (mAbs) and recombinant proteins, with products on track for approvals with different regulatory agencies. During 2017, the Marketing Authorization Application (MAA) for a proposed biosimilar Trastuzumab was accepted by the European Medicines Agency (EMA) for review. This is the second biosimilar submission developed by the partnership that has been accepted for review in Europe. Earlier in 2017, Mylan's MAA for the proposed biosimilar Pegfilgrastim was also accepted for review by EMA. Further, the results of two pivotal Pegfilgrastim studies were have confirmed the comparability of the efficacy, safety and immunogenicity profiles of Pegfilgrastim versus the reference product (annual report, 2016). The third biosimilar Transtuzumab is in Phase III clinical trials while the global phase III clinical trial for Adalimumab is progressing well across multiple sites. The global phase I study for Bevacizumab is approaching completion while the ROW focused phase III trial is advancing.

Biocon's successful growth into a fully integrated biotech company with a strong biosimilar portfolio and an extensive presence in international markets was founded on a targeted programme of organic growth and investments in biotech R&D.

**5.3 Cipla**

Cipla was established in 1935 by Dr A K Hamied with the aim of making India self-sufficient in terms of its healthcare needs. Over the last five decades, Cipla has developed extensive capabilities in process R&D and has emerged as a global supplier of cheap generic drugs. Cipla's international generics strategy was boosted in 2001 with the launch of antiretroviral drugs (ARVs) in emerging country markets at comparatively low prices. By 2012 Cipla was credited with transforming the global HIV-AIDS treatment landscape, and it had also emerged as one of most successful Indian firms with an average annual growth rate of more than 20%.

According to Capron and Mitchell (2012), Cipla's success in international generics markets lies in its business model, building a broad portfolio of products to achieve economies of scale in production and creating a network of alliances and licensing agreements with a wide range of other organisations with complementary skills and resources. However, the transformation of the Indian domestic market due to the strengthening of Indian patent act in 2005 and increased competition from global generic manufacturers has created new challenges for Cipla's existing business model.

**Processes involved in technological upgrading: Biosimilar capability development**

In 2000, these challenges forced Cipla to embrace biosimilars as a key area of future growth. However, to achieve success in the biosimilar market, Cipla had to overcome major hurdles in the form of R&D and manufacturing capabilities. Cipla had no previous experience of biotech R&D or innovative drug discovery R&D, and as a family-owned business, Cipla lacked the professional management required to succeed in the emerging biosimilar market. To overcome these knowledge gaps Cipla embarked on an ambitious strategy that involved acquisitions of biotech firms, entering inward co-licensing deals and hiring senior management professionals from competitor MNC firms to create top management teams experienced in international markets.

To accelerate biosimilar development, in 2004 Cipla in partnership with Avesthagen (an Indian biotech company), created Avesta Biologicals Ltd, a new biotech company. In 2007, Avesta Biological acquired Siegfried Biologicals, a biotech company based in Germany, to access biological R&D expertise. However, this did not lead to the expected progress on biosimilar R&D and in 2009 Cipla decided to dissolve Avesta Biologicals due to lack of progress in the development of biosimilars from Avesthagen.

To overcome this failure in 2010 Cipla acquired a 25% stake in MabPharm, an India based biotech firm and helped it to set up a state of the art biotechnology manufacturing facility in

India. In 2014 Cipla gained full ownership of the manufacturing plant by acquiring the remaining 75% share. In parallel to the MabPharm acquisition, Cipla invested $65 million to acquire a 40% stake in Bio Mabs, a Shanghai-based biotech aimed at developing ten monoclonal antibodies (mAbs) and fusion proteins against rheumatoid arthritis, cancers and asthma for marketing in India and China.

To complement these acquisitions, Cipla decided to build a biosimilar product portfolio through in-licensing. In 2013, Cipla launched its first biosimilar product, Etanercept, through in-licensing from China-based Shanghai CP Guojian Pharmaceutical Co, remarkably at a 30% reduced price over competitor brands. In 2014, Cipla in-licensed a second biosimilar, 'Darbepoetin alfa', by entering a co-marketing deal with Hetero Drugs, an Indian biotech company. Over the years, Cipla has created partnerships in manufacturing, sales and marketing with firms all over the world. In 2012, a new management team initiated a strategy to convert these partnerships into subsidiaries and joint ventures to bolster complementary capabilities. In 2012, Cipla acquired a distribution partner in South Africa, Cipla Medpro South Africa, for $512 million and followed that by increasing its stake in a Uganda-based joint venture, Quality Chemical Industries Ltd (QCIL) from 14.5% to 51.05% for $15 million.

To advance biosimilar development, Cipla set up of Cipla BioTec, a 100% subsidiary to research, development, manufacturing and marketing organisation focused on biosimilar products. In 2016, Cipla BioTec invested US$89 mn to establish a biosimilar manufacturing facility in South Africa. However, there are concerns about Cipla's biosimilar strategy as its core business differs significantly from the biosimilar and has raised issues of capital allocation to fund further expansion.

### 5.4 Lupin Pharmaceuticals

Dr D B Gupta started Lupin Pharmaceuticals Ltd in 1968, and over the years Lupin dominated the anti-TB market by becoming the largest producer and supplier of anti-TB drugs; Ethambutol and Rifampicin all over the world. By 2017 Lupin expanded its dominance over small molecule generic business in advanced countries by emerging as 4$^{th}$ in the US by prescriptions and six$^{th}$ largest generic pharmaceutical player in Japan (annual report, 2017).

Like Biocon, in 2011 Lupin established the Lupin Bioresearch Center (LBC) to conduct clinical and bioequivalence studies for generic products and branded formulations. These allow Lupin to develop complementary capabilities in regulatory R&D and establish collaborative linkages with overseas pharma companies.

**Processes involved in technological upgrading: Biosimilar capability development**

In 2008 Lupin entered the biosimilar sector by setting up the Lupin Biotechnology Research Group to develop biosimilars for India and other emerging countries. In 2010 Lupin hired Dr Cyrus Karkaria from a US-based biotech firm as president of Biological R&D to lead its efforts in biosimilars. By 2018 Lupin's biotech facility acquired a talent pool of close to 300 people, consisting of approximately 11 per cent PhDs and 63 per cent post-graduates. Under the leadership of Dr Karkaria, Lupin chose a strategy of targeting the products that are difficult to develop, have an entry barrier and therefore a larger competitive interest in the long run. Another key part of the strategy was to target regulatory approvals in Japan and EU before launching products in India as it will reduce expenditure on conducting India specific clinical trials. This might delay the product launch in India but it will also company to learn from other's mistakes (Rowchoudhari, 2018)

In 2012 Lupin entered into a licensing agreement with Sydney-based NeuClone for proprietary cell-line technology to be developed into biosimilar drugs targeting the oncology segment and in May 2015 launched Filgrastim and Peg-Filgrastim in the Indian market. In the same year, Lupin entered a strategic distribution agreement with LG Life Sciences of South Korea to launch Insulin Glargine, a novel insulin analogue in the Indian market. This allowed Lupin to

expand its biosimilar portfolio and opportunity to work with leading South Korean biosimilar developer. In 2014 Lupin entered a joint venture with Yoshindo, a Japanese biotech company to form YL Biologics (YLB) to conduct clinical development of certain biosimilars including regulatory filings and obtaining marketing authorizations in Japan. YLB will be jointly managed by both partners and will in-license monoclonal antibodies (mAbs) from Lupin and partner with other companies for the Japanese market. Lupin's etanercept biosimilar was the first product to be licensed for clinical development to YLB, and it is currently undergoing phase III clinical trials on over 500 patients across Japan, India and Europe.

## 6.0 Analysis and Discussion

The case study narratives describe the processes involved in technology upgrading of the Indian pharmaceutical firms as they move from small molecule generic business to biosimilar.

Table 3 unpacks the case narratives and presents lists the key patterns of technological upgrading and their differences with small molecule generics by breaking down the technological capabilities into the sub-categories and matching them with nature and process involved in the technological upgrading.

**Table 3 Nature and processes involved in technology upgrading**

| **Capabilities** | **Nature of upgrade** | **Processes involved in the technology upgrading** | |
|---|---|---|---|
| | | **Small molecule** | **biosimilar** |
| R&D | Move from chemistry-based R&D to biological R&D | Built on existing process R&D capabilities by promoting non-infringe process development | Acquisition of new knowledge by hiring scientists based overseas experienced in biotech R&D |
| | | Links with public research institute as key source of external knowledge | In-licensing of technology from MNCs or other emerging country firms |
| | | Supplier arrangements with MNCs and overseas firms | Co-development agreements with MNCs and overseas firms |
| Technology | Development of organisational capabilities to manage a distinctive portfolio of generics | Assets exploiting acquisitions of generic firms based in advanced countries | Asset building acquisition of biotech firms based in advanced countries |
| Production | Manufacturing of large complex molecule and advanced production platforms | Small molecule manufacturing platforms with GMP certification and USFDA authorisation | Advance single-use biological manufacturing platforms with GMP authorization and greenfield investments in overseas countries |
| Regulatory | Move from bioequivalence to clinical trials | Strong in-house capability in bioequivalence or bioavailability tests | Outsourcing of clinical trials or collaborating with |

| | | | |
|---|---|---|---|
| | | | MNCs for clinical development |
| Market access | Move to high-value markets of biosimilars | Internationalisation focused on accessing advanced country markets | Target on the domestic market and other emerging countries |
| | | Competition with MNCs involving patent challenges | Collaborations and co-development agreements with MNCs and emerging country firms |

It suggests that internationalisation, collaboration with MNCs and hiring overseas Indian biology scientists as sources of external knowledge formed a core technology strategy for Indian pharmaceutical firms in their development of biosimilar capabilities (Table 3). These strategies have been elaborated in the following section.

### 6.1 Technology upgrading strategies

The Indian firms move towards the small molecule generics R&D represented a natural progression for Indian firms; it built on their superior process R&D capabilities and in-depth knowledge of organic and synthetic chemistry. However, in the case of biosimilars, Indian firms required technological upgrading to carry out certain functions and activities such as bioprocess development and cell-line development (interview data). These firms adopted combinations of four strategies to fill these technological gaps: 1) Internal investments and reorganisation; 2) Import of technology and knowledge; 3) Internationalisation of production, distribution and marketing and 4) Collaboration with MNCs.

#### 6.1.1 Internal investments: Setting up biotech dedicated R&D and manufacturing plants

The Indian firm strategies to develop biosimilar capability involved increasing the level of biotech R&D investment, building biological R&D facilities and setting up biotech as a separate business division. Majority of Indian firms have increased R&D spend over the past five years, in absolute as well as the percentage of sales terms. While absolute spend is still less than international generics MNCs but few Indian firms spend is higher in terms of R&D intensity (percentage of sales) (Table 4). Biocon and Lupin have also set up in-house CROs to develop their absorptive capacity in the areas of biosimilar commercialization where they perceive the significance of their own capabilities and sense cost advantages—e.g. in clinical trials. Both firms have exploited their process development skills to undertake contract research (in clinical research trials and process development) for MNCs.

**Table 4 R&D intensity in Indian firms**

| | **2013** | **2014** | **2015** | **2016** |
|---|---|---|---|---|
| Biocon | 8.8 | 6.1 | 7.5 | 11.5 |
| DRL | 6.6 | 11.8 | 11.5 | 13.9 |
| Cipla | 4.6 | 5.6 | 6.3 | 7.6 |
| Lupin | 8.4 | 8.7 | 11.7 | 13.5 |

#### 6.1.2 Import of technology and knowledge

Indian firms have focused on the import of production technology, final products and scientists in their effort to develop technological and managerial capabilities required for the development of biosimilars. The key focus in biosimilar development is highly complicated biological production process. Contrary to the highly predictable chemical production processes, the biological production process is more complicated, and that creates managing manufacturing process a continuous challenge for the biosimilar developer. In response, some

Indian firms have transitioned from use of stainless steel to single-use technology. In 2017, DRL imported single-use technology platform from General Electric to employ at their manufacturing plant in India. This production platform enables DRL to enhance flexibility and efficiency in their manufacturing set-up. Single-use technologies facilitate multi-product manufacturing and improve productivity by increasing the number of lots manufactured. Highlighting the benefits of the technology, Stelis' CEO Joe Thomas comments,

> "We believe that single-use technologies will dramatically improve quality and compliance to regulation by eliminating the possibility of cross-contamination through the use of disposable components. Also, high level of process controls through automation eliminates manual intervention and enhances traceability of process parameters giving greater comfort to regulatory authorities. The higher batch cost on account of disposables will be offset by the reduction in batch failures, faster changeover between batches, no cleaning validations, lower utility cost and greater capacity utilisation. This should certainly attract more global manufacturing into India."
>
> (Stanton, 2017)

Gradually some other Indian firms are moving towards the use of single-use technology for manufacturing of biosimilars. For example, in 2017 Stellis Biopharma, a leading Indian firm in collaboration with MilliporeSigma, Merck KGaA's life science division opened a 'Joint Process ScaleUp Lab' employing the 'single-use technology' at its biologics R&D facility in India.

**The hiring of overseas scientists, managers and engineers**

In the case of biosimilars, Indian firms lacked an in-house knowledge base. Indian firms are trying to acquire specific knowledge (in biosimilar production, development and regulation) by hiring Indian scientists working with MNCs and biotech firms in advanced countries. All case study firms show evidence of the development of biosimilar R&D capability through the hiring of scientists. A head of the business strategy at the Indian firm comments,

> "One of the biggest challenges that we have right now is talent scarcity. That remains so, but we are unique as we have a presence in India, presence in Basel, presence in New Jersey. The company's global organisations give us access to that kind of talent pools. For example, if you look at the senior leadership of this organisation, apart from the head of biotech R&D, other four VPs that are leading the product development are also from the US. They are based in different regions around the world; our head of clinical development is based in the UK, head of the commercialisation is based in Basel, and head of manufacturing is based in Singapore. These kinds of global talent we access. This trend will continue, and it will pay off in the future because in India there is a scarcity of talent."
>
> (author interview, 2016)

Indian firms attract these scientists by offering leadership positions and providing scope to develop their biological business (Table 5). These scientists have been instrumental in establishing the biotech R&D facility with the goal of developing and producing biosimilars for the global market. For example, Dr Cyrus Karkaria set up Lupin's biotech R&D and built scientist teams to work on biosimilar development. A head of biotech R&D from leading Indian firm comments,

> "The other big thing is that India is growing, but it is not like IT sort of business. In pharmaceutical expected, biological skill sets are limited especially at the middle level. They have not been exposed to correct ways of doing things, and I would say that people are very hungry to learn. However, it is our responsibility to train them so that they can acquire the required skills."
>
> (author interview, 2016)

This managerial upgrading is a significant part of the technology upgrading at the Indian firms as it allows firms to internalise external knowledge and build local teams. These scientists also contribute significantly to scouting for collaboration and acquisition deals by bringing some science intelligence as well as their networks to internationalisation activity of these firms. Dr Cyrus Karkaria comments,

> "We negotiated with each global authority and are" doing the spade work" looking for partners for the US market."
>
> (Rowchoudhury, 2018)

**Table 5 Hiring of Indian biotech scientists from overseas**

| Firm | Year | Current role | Previous overseas connection |
|---|---|---|---|
| Biocon | 2010 - 2015 | Dr Abhijit Barve, R&D President | Working with Astellas, a US biotech company as a Global Development Project Leader |
| Biocon | 2015 | Dr Narendra Chirumule, Sr Vice President, Head of R&D | Executive director, Amgen (2007-14) and Director, Merck (2000-2007) |
| DRL | 1999 | Dr Cartikeya Reddy, Head Biologicals division | Working with Genetech Inc., as a Group Leader in Cell Culture Process Development |
| Lupin | 2010 | Dr Cyrus Karkaria President, Biotech Division | Leading a biotech company in the US |
| Cipla | 2012 | Subhanu Saxena, CEO | Head, Global Product Strategy, Novartis Pharma AG |

In some instances, these scientists revived and catalysed the development of biosimilar in Indian firms through their networks of scientists in overseas countries, understanding of biosimilar business and providing guidance on the collaboration activities. A head of manufacturing at the Indian firm comments,

> "When I came here there was the limited scale of efforts and largely around the first generation of biologic. Mostly I would say the products that were not very industrial in their scale. We started there and built on that".

This is also clearly evident in the example of DRL. Sudrendran (2016) points out that DRL struggled with the development of biosimilars in its first attempt. In late 1990 DRL's biological business suffered a significant setback when original patent holder Roche pointed out that DRL's version of filgrastim had a different sequence of amino acids compared to its own and that the copy could not claim to be the same drug. This resulted in the departure of head of biotech R&D in 2003 with no leadership of biotech division at DRL. The business was again revived in 2004 after Dr Cartikeya Reddy came on board. Dr Cartikeya Reddy was working with Genentech as a Group Leader in Cell Culture Process Development. Dr Anji Reddy offered him an opportunity to lead DRL biological R&D as an independent integrated business unit. Dr Cartikeya Reddy is credited with developing DRL's biosimilar capabilities and playing

an instrumental role in putting the building blocks to the long-term sustainability of biosimilar business by entering a partnership with Merck Serono.

### 6.1.3 Internationalisation of production, distribution and marketing

In the post-1990 era, Indian firms invested to ensure compliance with Good Manufacturing Practices (GMP) standards for the manufacture of small molecule generics. This was a key requirement for FDA approval and access to generics markets in advanced countries. Indian firms also acquired production facilities in advanced countries. Building on these complementary capabilities, Indian firms have made greenfield investments in overseas countries for manufacturing of biosimilars and supplying to other emerging as well as advanced countries. For example, Biocon production facility in Malaysia was commissioned in 2010 and was certified by Malaysia's National Pharmaceutical Regulatory Authority (NPRA) in 2015. This facility is dedicated by the Biocon to supply insulin glargine – co-developed with Mylan – in Europe. Biocon received the big boost in 2017 with a contract from the Malaysian government for supply of its rh-insulin and pen delivery device to local firm CCM Pharmaceuticals for distribution to service primary health care clinics and hospitals across Malaysia.

The leading Indian firms have established a strong marketing and distribution presence in small molecule generic markets all over the world including advanced countries. This has created significant complementary capabilities (Teece, 1986) and an in-depth understanding of overseas markets, facilitating the entry of Indian firms into international biosimilar markets. Similar to the entry into small molecule generics markets, in the case of biosimilars, the Indian firms have focused on the emerging country markets and collaborating with local firms to de-risk their investment. Biocon, DRL and Cipla are also collaborating with overseas firms based in emerging country markets to access markets overseas. A head of biologicals from an Indian firm suggests,

> We basically have a business-to-business model in biosimilar markets; we access various regions of the world through commercial partners. For example, to pick up the Latin American region we work with the local pharma company to get access to that market. We still haven't built up the strength ourselves in understanding nuances of the domestic biosimilar market. For example, going to the Latin American market and understanding how the regulators work, understanding how the prescriber players behave there, setting up the distribution network, this kind of nuances. Instead of investing in those ourselves it is easier for us to find a like-minded partner to take us to market quickly and bring us those capabilities right away.
>
> (author interview, 2016)

It is quite evident that Indian firms collaborating with other emerging country firms are focused on gaining market access in contrast to linkages with MNCs in advanced markets which are aimed at capability building.

### 6.1.4 Collaboration with MNCs and emerging country firms

The Indian firms chose to collaborate and interact with overseas research institutes and firms in advanced countries to fill knowledge gaps and reduce development costs. These firms entered different types of collaborations with MNCs. In some cases, these collaborations involved co-development of biosimilar while other collaborations involved in-licensing of biosimilar and technology transfer (Table 6).

Indian firms' co-development agreements with MNC leverage their strong development and manufacturing capability and MNC's strength in managing regulatory filings and commercialisation. These co-development collaborations are specifically focused on the commercialization of monoclonal antibodies as the regulatory pathway for biosimilar mAbs is

longer, the physician acceptance is expected to be lower, and competition from innovative products is high (Jonker-Exler, 2014). A typical strategy involves Indian firms handling product development, manufacturing while MNC takes the lead in late-stage clinical trials and commercialization in advanced markets. An R&D head at a leading firm commented,

> "Now we are focusing on more global development efforts so we are investing in technologies, investing in partnerships that can give us some late-stage capabilities and that can help us access markets like the US and Europe".
>
> (author interview, 2016)

**Table 6 Key R&D collaborations for biosimilars (Annual reports, company website)**

| Year | Indian firm | MNC | Nature of alliance |
|---|---|---|---|
| 2004 | Biocon | Vaccinex (USA) | Co-develop at least four therapeutic antibody products |
| 2006 | Biocon | Cuban Institute of Molecular Immunology (Cuba) | Development of antibody for treating cancer |
| 2007 | Biocon | Abraxis (USA) | Out-licensing of Peg-Filgrastim to Abraxis for regulatory development and commercialisation in the US and Europe |
| 2009 | Biocon | Amylin (USA) | Co-development of novel peptide hybrid for treatment of diabetes. |
| 2009 | Biocon | Mylan (USA) | Co-development of six Monoclonal Antibodies (mAbs) (Trastuzumab, Pegfilgrastim, Adalimumab, Bevacizumab, Etanercept and Filgrastim) |
| 2010 | Biocon | Pfizer (USA) | Insulin and analogues (Pfizer: marketing and sales) |
| 2011 | Lupin | Neuclone (Australia) | Access to cell line technology to develop biosimilar drugs used in cancer treatment |
| 2012 | DRL | Merck Serono (Switzerland) | 3 mAbs (joint development) |
| 2014 | Lupin | Yoshindo (Japan) | Co-development and commercialisation of etanercept |
| 2016 | Biocon | Lab PiSA (USA) | Co-development and commercialisation of rh-insulin in the USA |
| 2017 | DRL | Amgen (USA) | In-licensing of 3 biologicals |

Other types of collaboration have involved in-licensing of biosimilars and biological drugs for MNCs to market in domestic and other emerging markets. For example, DRL entered into a collaboration with Amgen for in-licensing of biosimilars and biological drugs. Some of these deals have also involved significant technology transfer along with the in-licensing of the biosimilars. Ipca, an Indian firm collaboration with Oncologics, a US-based biological firm involves in-licensing of biosimilars but also requires Ipca to create a new R&D facility in Mumbai that will be modelled on the Oncobiologics facility. Furthermore, Oncobiologics, in its joint venture, will be offering specialised biologics training at its R&D site in the US for certain Ipca scientific staff as the two firms look to build a bio-manufacturing plant in India. Oncobiologics VP Business Development, Stephen McAndrew points out,

> "The design infrastructure, training and know-how will occur via direct transfer in the US initially. Over time the manufacturing will be 'tech transferred' to India so that biologics manufacturing costs can be minimised, but only after establishing high-quality expertise (via onsite training) and establishing appropriate quality control systems."
>
> (Stanton, 2017)

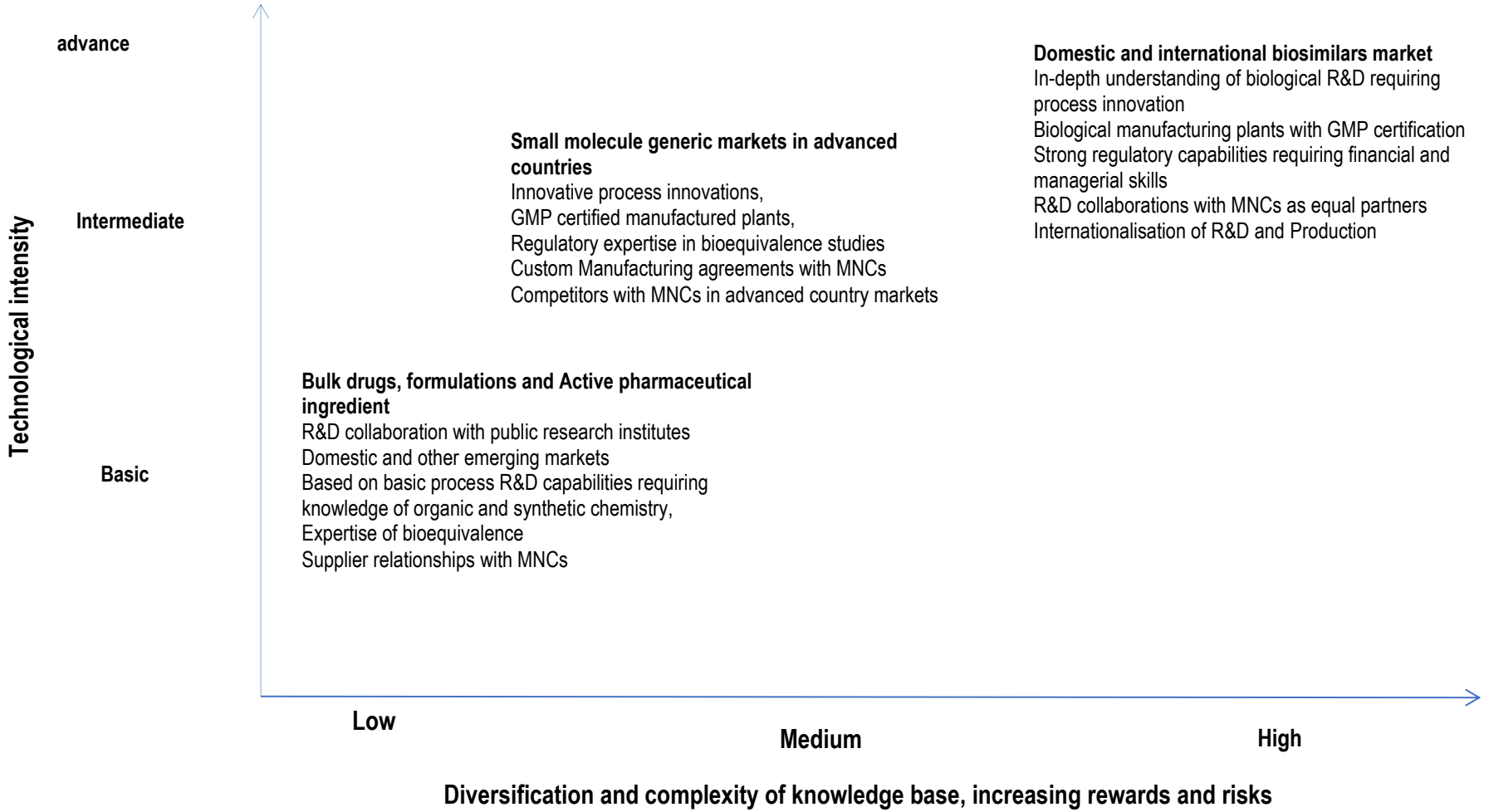
These co-development agreements bridge key technological skill, managerial capability gap and financial weakness of Indian firms and allow them to target highly competitive advanced country markets.

The evidence presents a strong association between internationalisation and technological upgrading in the Indian firms. However, it also shows that Indian firms' internationalisation and R&D collaboration strategies in biosimilar differed significantly from small molecule generics market. In small molecule generics focus of internationalisation was clearly built to assess exploiting behaviour by leveraging process R&D capabilities and low-cost manufacturing. In contrast, evidence shows that in biosimilars these firms are entering collaboration and embarking on internationalisation process to achieve world-leading process R&D and manufacturing capabilities.

### 6.2 Dimensions and paths of technology upgrading in the Indian pharmaceutical industry

Evidence from case studies suggests the development of biosimilars is shaping the evolution of new capabilities and strategies in Indian pharmaceutical firms. Radosevic and Yurik (2015) conceptual framework is modified and employed to track the technology intensity, paths and width of technology upgrading in the Indian pharmaceutical industry (Fig 1).

**Fig 1 Dimensions and paths of technology upgrading (author modification of Radosevic and Yoruk., 2015)**



In this model complexity of the knowledge base, risks and rewards are plotted against different levels of technological intensities and capabilities. Based on Bell and Figueiredo (2013) a basic level of capability is taken as the ability to make minor adaptations to production and assimilate technology into a firm's environment. The intermediate capability is the ability to generate incremental technical change in product design, quality and production processes; it also includes the ability to search and evaluate external sources of technology. Advanced capabilities refer to the ability to catch up with the international technological frontier and closing in on leading global incumbents, perhaps with differing directions of innovation. With biosimilars, a significant degree of risk is evident in the projected future growth of the market, the evolving regulation and the position of emerging country suppliers.

Technology intensity is activated based on the criteria of domestic behind the technology frontier towards world frontier technology efforts. In the global generic business, manufacturing of active pharmaceutical ingredients, formulations and bulk drug represents the basic capability and behind the technology frontier activities while small molecule generics in advanced countries and biosimilars can be viewed as world frontier activities. However, the complexity of the knowledge base, the need for managerial and organisational capabilities to handle more onerous manufacturing, regulatory and marketing demands, and technology intensity associated with biosimilars make it a truly world frontier technology and advanced capability. It indicates that a technology upgrading process is being followed that will eventually allow firms to accumulate capabilities to enable them to produce novel biologics.

Further, Singh (2015) points out that currently, an estimated 150 biosimilars are under development, and many of large firms such as Amgen, Boehringer Ingelheim, Merck, Novartis, and Pfizer. For example, Pfizer is gearing up for the biosimilar market with its purchase of biosimilar manufacturer Hospira, while Amgen has at least nine biosimilars under development and yet to launch its first biosimilar in the US market. It suggests that biosimilar is an emergent market segment where Indian firms and leading MNCs are at similar stages of product development (table 7). In this context, for Indian industry, development of biosimilar capabilities represents competing at the technological frontier of global generic business.

**Table 7 Competitive landscape and Indian firms' biosimilar regulatory filings in advanced markets**

| Molecule | Biosimilar Development pipeline | | | |
|---|---|---|---|---|
| | Pre-clinical | Phase I | Phase II/ filed | Approved/marketed |
| Peg-filgrastim | Pfizer | **DRL** | **Biocon,** Apotex Coherus, Sandoz, Cinfa | |
| trastuzumab | Oncobiologics, **DRL** | Meiji Seika | **Biocon, C**elltrion, Samsung, Amgen, Pfizer, Hanhwa | |
| insulin glargine | | | **Biocon - EMA,** Samsung | **Biocon – Japan,** Eli Lilly – EU, US, JP, CAN Samsung - EU |
| adalimumab | Epirus | | **Biocon,** Samsung, Sandoz, Boehringer Ingelheim, | Amgen |

| | | | | |
|---|---|---|---|---|
| | | | Coherus, Momenta, Pfizer, Fresenius, Fujifilm-Kirin - EMA, Oncobiologics | |
| bevacizumab | Celltrion | Sandoz, Daiichi, Oncobiologics, **Cipla** | **Biocon**; Amgen, Boehringer Ingelheim, Pfizer, Samsung, Fujifilm-Kirin/Astra Zeneca, **DRL** | |
| filgrastim | **Biocon**, Pfizer | | Apotex | Sandoz; Teva, Apotex, Hospira, Fuji |
| etanercept | **Biocon**, Celltrion | Hanwha | Coherus, **Lupin - Japan** | Samsung, Sandoz |
| rituximab | | **DRL - FDA** | Mylan, Pfizer, Teva, | Sandoz - EU, Celltrion – EU, Mundipharma - EU |

Evidence also highlights the significance of complementary capabilities as small molecule generics have created key knowledge bases, understanding of generics business and global networks of suppliers and retailers. However, this research also reveals that some pre-existing capabilities learned through experience with small molecule generics markets constrained the development of biosimilar R&D and regulatory capabilities. All firms under study invested in setting up new R&D infrastructure, organisational practices and regulatory capabilities as existing infrastructure and practices became secondary, though not completely obsolete in the new environment. Studies of other industries suggest that some resources, processes and capabilities that served firms well in the past become obsolete where there is a new technology and discarding these activities forms important aspect of adding new knowledge (Leonard-Barton, 1992). Biosimilar capabilities are therefore being developed in parallel with small molecule generics.

### 6.3 Role of government policy and internal markets

Amann and Cantwell (2012) suggest that in the studies of technological upgrading attention must be paid to the regular interaction between firm-level capability building and policy-making as a co-evolutionary process, as opposed to a set of separate actions. In case of biosimilars development, the Indian pharmaceutical industry proactively worked with the government to set up regulatory guidelines for biosimilar approvals in India. They argued for guidelines, scientific principles and approaches to be like those of the EMA (European Medical Agency) and USFDA. As a result, in 2012 the Department of Biotechnology (DBT) in consultation with industry and scientists, devised guidelines for biosimilar products titled 'Similar Biologics: Regulatory Requirements for Marketing Authorisation in India'. These guidelines cover the regulatory pathway regarding the manufacturing and quality aspects of biosimilars in India and list the pre-approval regulatory requirements for the comparative quality, safety, and efficacy as demonstrated by the comparative quality, non-clinical and clinical studies. These strict regulations in the domestic market coupled with the technological complexity of developing a biosimilar made it harder for Indian firms to produce and market their biosimilars in the domestic market. These resulted in only a few Indian firms entering the Indian biosimilar market, and these firms had to make significant investments along with greater R&D and market effort to succeed in the domestic market. This shows that the challenging domestic

market played a key role in the development of significant technological upgrading in the Indian pharmaceutical industry. This is important point as it is contrary to the conventional thinking in the literature focused on the technological capability building in late-comer firms which suggest that the export market is more demanding and more conducive to the acquisition of advanced technological capability.

## 7.0 Conclusion

Over the last three decades, the Indian pharmaceutical industry has dominated small molecule generics market based on skills in chemical synthesis and advanced process R&D capabilities. However, saturation and reduction of value in small molecule generic markets in advanced countries have forced Indian firms to look at complex biosimilars, creating a need for a new knowledge base and an alternative path to the upgrading of technological capabilities. Using the case studies of four Indian pharmaceuticals firms, this paper explores the factors and processes involved in the development of biosimilar capabilities in the Indian pharmaceutical industry. This paper shows that the technological upgrading process in the Indian pharmaceutical industry consists of advanced technological intensity and high diversification and complexity of the knowledge.

Employing the 'dimensions and paths' conceptual framework developed by Radosevic and Yurik (2015), this research examines the movement of Indian pharmaceutical firms from 'small molecule generics towards biosimilar segment in the global generics market. This shows that development biosimilar capability represents an up-gradation of Indian firms capabilities throughout the production process; starting from an upstream expansion of the knowledge base and re-orientation of R&D to a downstream enhancement of regulatory and marketing capabilities in emerging and advanced country markets. Thus, this development of biosimilar capabilities points towards the movement of the Indian domestic industry from behind technology frontier effort towards world frontier technology efforts in the global generics industry.

Indian firms' presence in small molecule generic markets in advanced countries and competition with MNCs has created an understanding of regulatory challenges, and that has influenced their relationship with overseas firms in the emerging area of biosimilars. Evidence presented in this paper reveals a strong role of internationalisation and R&D collaborations with MNCs in the development of biosimilar capabilities. It is also evident that Indian firms collaborating with other emerging country firms are focused on gaining market access in contrast to linkages with MNCs in advanced markets are aimed at leveraging regulatory costs. Significantly, Indian firms' collaborations with MNCs specifically involved the development of complex products such as mAbs and proteins but relies on indigenous learning process for manufacturing of less complex biosimilars such as insulin. This highlights that the relationship between capability building and internationalisation is complex, firm-specific and dependent on the institutional environment and prevalent modes of international connectedness.

This paper shows that Indian firms adopted distinctive strategies to develop biosimilar and these strategies fall into three broad categories: technology acquisition strategies, accessing international markets and managing regulatory requirements essential for biosimilar product approvals. Indian firms hired of biotech scientists working in advanced countries increased R&D investment and reorganised R&D to create an absorptive capacity and internalise external knowledge. These scientists made a significant contribution by helping to set up the biotech R&D facility, development of business models, training the workforce and scouting for M&A deals. This finding highlights the processes involved in the coupling of global knowledge flows with firm-level innovation efforts.

This research also highlights that developing biosimilars for the domestic market was technologically more challenging and also involved greater market effort. This is contrary to conventional thinking about technological capability building which has usually suggested the

export market is more demanding and more conducive to the acquisition of advanced technological capability. The findings from this research have implications for pharmaceutical firms based in other emerging and developing countries.

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