Technological learning and the evolution of the
Indian pharmaceutical and biopharmaceutical sectors

by

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ABSTRACT
The Indian pharmaceutical and biopharmaceutical sectors have been characterised by three features considered analogous to technological stagnation: low R&D investments, "copying" on-patent drugs (legal in India if a novel process is found) and manufacturing off–patent, generic drugs. Yet, some firms are innovating in drug discovery and development and the total number of firms is among the most numerous and export-oriented in the developing world.

This dissertation looks at patterns of technological capabilities using sector-wide indicators and firm-level cases in synthetic and biological pharmaceuticals. Common explanations for the sectoral capabilities are the country's process patent regime. However, a more detailed analysis shows this cannot be the sole cause. Although the patent regime was critical in helping firms develop skills early on, their process capabilities were honed by a variety of selection environments, of which the patent regime was one type. There were at least three distinct selection environments and at least three broad types of associated learning. The findings of external environmental influence and selection do not weaken the importance of national policy, far from it. However, studies that assign explanatory power for the sectors' advance entirely to national patent policies or rational firms miss the significance of the Indian story to date. The research also shows that there is scope for broadening debates on public health medicines to address technological learning opportunities in developing countries.

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Introduction

1.1 The puzzle-Indian innovations

Rapid advances in the biological and computational sciences have created immense new scientific and commercial possibilities across the globe. While a few advanced countries generated many of these innovations at the outset, a sturdy group of developing countries such as India, Brazil, South Africa and Egypt, has been exploiting these opportunities. However, India alone in the developing world has a pharmaceutical industry marked by intense competition, local ownership and export reach. This industry growth has occurred while other developing countries have struggled to build their capabilities and while their advantages, if any, have shrivelled against an onslaught of foreign firms entering their domestic markets.

This dissertation is concerned with economic development as viewed through a lens of industrial capabilities, technological learning and models of innovation. Learning and technological learning are used here inter-changeably to mean the dynamics of coping with both mature and new technologies. The technologies may be new to the firm in question, if not to the world (Schmookler, 1966, Nelson, 1992, Nelson and Rosenberg, 1993). Technological learning may involve both technical and non-technical components.[1] The dissertation uses a definition of innovation as "the processes by which firms master and get into practice product design and manufacturing processes that are new to them whether or not they are new to the universe, or even to the nation" (Nelson, 1992, p. 349).

Squeezed from above by technological innovations in advanced industrialised countries and from below by low-wage competitors, firms in developing economies are forced to reconsider their path of learning[2]. Technology transfer has been shown to be inherently difficult and costly, forcing these firms and their governments to develop (and some have developed) strategies to learn "differently". Technological change is speeding up in some sectors. In particular, the pharmaceutical and biopharmaceutical industries are generally viewed as advancing technologically (at the "frontier") in

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[1] The former may entail process chemistry and engineering, toxicology or clinical expertise, for example, while the latter requires the building of capabilities such as that involved in learning to file patents or drug applications in a different country or establishing marketing linkages abroad.

[2] From here on, "developing" will be used to describe countries that are not advanced industrialised ones. "Advanced" or "developed" countries will be taken to mean advanced industrialised countries or those roughly coinciding with member states of the Organisation of Economic Cooperation and Development (OECD). This reflects broad statistical categories of industrial composition and per capita incomes. They may hide institutional or micro-level similarities and differences between the two broad sets of countries or within them.

developed countries, and being largely stagnant in developing ones or competing on low-costs alone. Although developing countries do depend on advanced industrialised ones for access to products and tools, the evidence is still mixed whether there are opportunities for these countries to break away and create their own indigenous capabilities. There is little consensus on how these opportunities might arise and little systematic study into the conditions under which technological learning occurs.

The examination of the conditions under which India built a dynamic pharmaceutical and burgeoning biopharmaceutical sector, provides us some unique clues about challenges to drug discovery, development and manufacturing in a developing country. While the pharmaceutical industry arose from conditions of governmental protections that seemed unsustainable as the economy opened in the 1980s, it has evolved into one of the most dynamic of India's industries.

In the early 1900s India's first pharmaceutical company was incorporated. From there, onward to the 1970s, Indian companies were written off as "pirates" and "merely copycats". In the late 1990s, Indian companies were filing applications for New Chemical Entities in US markets and receiving patents. In Indian biopharmaceuticals, companies have made some impressive strides from "biogenerics" to vaccines. However, the learning is not uniform, and not all companies have become innovative.

A definition of innovation as a product or process new to the world market creates a puzzle. While the industry is both competitive and growing rapidly, it has been characterised in the past by three features which were considered analogous to relative technological stagnation: (a) low R&D investments, (b)"copying" on-patent drugs (legal in India if novel process is demonstrated) and (c) manufacturing generic, off-patent drugs. None of these features is characteristic of the conventional view of technological advancement and innovative firms. Why were Indian firms able to compete successfully in the world pharmaceutical market when they had neither proprietary technologies at the outset, nor always the lowest of wages worldwide? Why were they able to prosper when they lack the characteristics and environment that has typified success in the US and other advanced industrial countries, such as high R&D spending, or supporting institutions, such as venture capital? Why were some Indian firms, and not others, able to innovate and prosper?[3] While Indian firms have innovated and patented processes for much longer than products, a small number of Indian firms has innovated (in the conventional industry sense) through New Chemical Entities (NCEs) and by filing for an

[3] Throughout the various chapters, patents will be only one marker for innovation. Others will be expert evaluations in interviews and those products that immediately attract alliances for R&D and/or marketing.

increasing number of patents in the US and worldwide. Some firms are also developing bio-pharmaceutical drugs, which provide a new opportunity for developing countries with relatively advanced manufacturing skills. In particular, it's advancement is set against a rich policy backdrop, most publicised of which is the lack of a product patent regime (only process patents are allowed and for a relatively short 5-7 year period), which facilitated Indian-owned firms to achieve an enviable foothold against multinational companies in the domestic market. The process patent regime encouraged Indian firms to seek new ways to make drugs since the technique could be patented, but not the end product.

The debates surrounding pharmaceuticals in developing countries has centered on two related themes: intellectual property rights-particularly product patents, and the place of foreign (Western) firms as innovators. Current explanations for Indian advance are structured along the same line: they lay its success at the door of the country's intellectual property (process patent-only) regime, multinational companies, or its low costs. Certainly, low costs have been an important explanatory variable, but cannot explain why Indian firms have succeeded relative to other countries also competing on low costs, such as China, Egypt or Brazil, which have strong sectors, but do not appear to have the same density or export reach. Secondly, although other developing countries have had a similar IP regime, Indian pharmaceuticals have emerged as the undisputed leader in sheer numbers of competing manufacturing firms. Furthermore, while many advanced industrialized countries also had the same IP regime until very recently, they have been unable to either build the number or vertical integration of Indian companies. Thus, why India? The more enlightened explanations are still insufficient: they tend to depend too heavily on explanations of successful policies. However, these explanations do not explain why Indian companies did so well; after all, many other developing countries had similar policies, as did many industrialised countries. [4]

The dissertation shifts the focus to capabilities-based development over time. The central hypothesis explored in this dissertation is that process development *capabilities*, not the process patent regime or low costs alone, were at the heart of Indian advance. The term "Process Capability" will be used throughout to refer to the capability within a company of developing a viable manufacturing method

[4] In chemicals and pharmaceuticals, history suggests that many older firms in today's advanced industrialised countries indulged in industrial espionage and "copying" of products and processes during other patent regimes. Most present day success stories arose in large part by this ability. But the rules for developing economies have changed; pharmaceuticals and biopharmaceuticals have become characterised as a secretive, product-based, patent-protected industry

for a given proposed (product) outcome. In the pharmaceutical industry, process capabilities usually refer to process research, laboratory to factory scale-up and manufacture. This dissertation limits the focus here to include the skills of process chemistry and process engineering (including biotechnologies) related to the development of a viable manufacturing routine.[5] Those companies that discover drugs but cannot develop and manufacture them for commercial scale and speed, face considerable disadvantages.

The approach of this dissertation is to explicitly analyse the technological basis for advancement and to address developments from the 1950s to the present day against a backdrop of Indian and international changes. It attempts to contribute to an analysis of the innovation environment, which elements firms internalise and what dynamic motive force propels some firms forward. Furthermore, most economic analyses of pharmaceutical firms has been in advanced industrialised countries, particularly the US and UK, where generic drugs are seen as mature segments warranting little attention and the predominant focus is on 'blockbuster' drugs or more broadly, drug discovery. The impact of generic drugs has primarily been explained away as easy revenue streams because of the presumed ease of producing drugs that are off patent and codified.

The Indian case provides some instructive points. While the time from inception of the industry to the time of novel processes and product innovation has not been dramatically short by the standards set by the Asian "Tigers", the strength of the its lessons arise from the rich diversity of learning pathways in a single industry alone. This research focuses on the following specific aspects of technological advance: Why is the type of innovation (product or process) important? Is there a clear sequence from "imitation to innovation? How do government policies act to assist such advance? Some thought for policy is certainly called for: despite the impressive technological base of the industry and the rosy picture for some of its leading firms, most still lack (a) the ability to finance and conduct drug-discovery research compared to the US and other advanced industrialised countries (b) experience (in numbers of years and numbers of products) in applying newer biotechnologies in drug development and, perhaps more fundamentally, (c) the institutional environment to support innovation at enterprise and national level.

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[5] Other capabilities linked to the production process such as inventory management are not included, important though these may be in other settings. The categorisation of process capabilities used here differentiates technological skills from complementary skills, such as legal and regulatory strategies or marketing and distribution networks.

1.2 Scope and Structure of dissertation

The dissertation is an indirect product of several years of interest and research on economic development, innovation and health. This research tracks specific learning modes across two broad technological categories within industries associated with drug discovery, development and manufacture. The localised flavour of innovation arises from the choice of study of two southern Indian cities set against a common national policy backdrop. The data for this project includes over 50 detailed face-to-face interviews and phone and email communications with some of the nation's leading pharmaceutical and biopharmaceutical firms, some of its best scientists, engineers and entrepreneurs (many of whom have also been involved in recent policy making) and situated in two of its most technologically dynamic cities, Bangalore and Hyderabad. Some interviewees were located abroad, including some experts for informal assessments of firms. The data has been sourced from the standard primary and archival sources including academic journals, government reports, books, trade publications, company reports, analyst and investment reports, stock exchange filings and industry association, newspaper and magazine articles and interviews.

The intersection of studies on technological capabilities and developing countries is a sufficiently rich one that this dissertation can address only some facets of the subject. For example, it does not attempt to engage with elements of Indian advance such as infrastructure (better ventilation or refrigeration), production-related logistics (how different plants are connected, inventory management, or whether factory teams are made up of 25 or 50 or people) and informational improvements (such as faster computers, better Internet and telephone links between factory and laboratory). Moreover, although the paucity of drugs relevant to developing country populations such as drugs for malaria, tuberculosis or AIDS, is a distressing and urgent matter, this dissertation will not directly address this topic.[6]

This dissertation is structured as follows:

The current Chapter 1 Introduction, is followed by **Chapter 2: A Review of the Literature** and introduces the key concepts of technological learning and its link to economic development. The subsequent sections are primarily concerned with the theoretical dimensions of technological learning as described by firm-level studies, national capabilities and the role of public policy in development.

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[6] Thus, although some of the Indian firms profiled have been criticised for profit making from drugs relevant primarily for advanced industrialised countries, this research will not question this strategy choice. Perhaps the understanding of how firms learn will make us understand the conditions under which drugs for common illnesses will be pursued. I hope that more firms, once established more securely in world markets, will choose to focus their considerable capabilities on pressing local health needs. Indeed, some already do.

Chapter 3 Research Design and Methodology provides the logic of the specific methods chosen and focuses on two samples of firms (in pharmaceuticals and biopharmaceuticals), relying on extensive primary and secondary data to shape the analysis. **Chapter 4 Trouble in the Making: Process Development and Manufacturing,** presents detailed firm and industry data in Indian pharmaceuticals, and discusses the different core elements of how Indian firms advanced. It lays out the elements of the early environment and analyses manufacturing capabilities and the policies that induced firms to invest and upgrade in core segments. **Chapter 5 Learning by Proving through Process Development** explores the external environment that defines the pharmaceutical industry and the regulations surrounding drug development and manufacture, marketing and distribution. Indian firms have especially well grasped the basics of how to "prove" their quality in cGMP standards, but have also learnt to grapple with filing speed and patent challenges. International procurement policies have also been critical. **Chapter 6, Beyond Manufacturing: The Rise of Indian biopharmaceuticals,** studies cases of biopharmaceutical firms from the two Southern Indian cities of Bangalore and Hyderabad, where manufacturing capacity has been central to their story of learning and experimentation, but manufacturing alone is insufficient to advance with new technologies. The chapter explores the challenges that these firms face and the uncertainties regarding regulation. Thus, more mature segments such as public health vaccines have provided an avenue for experimentation. **Chapter 7 Analysis and Synthesis**, returns to the major themes of product maturity and learning environment, to show how selection environments acted in varied ways from the 1950s to create today's industry and allowed for some types of innovative skills to develop. It emphasises the link between public health and technological learning and provides some implications for policy.

Chapter 2 A Review of the Literature

2.1.Learning to develop: Industrial Evolution and technological learning

There are important analytical and policy reasons to model how innovation, technological learning and building capabilities takes place in developing economies, where firms are constrained by other low cost competitors at one end and high-technology competitors at another. [1] The debates of economic development that concern technology are diverse, but they rest on some common assumptions: that there is a limited amount of invention in the classical sense taking place in developing countries i.e. first introduction worldwide of a concept of product, and most efforts are concentrated among mature products, that appropriability conditions, specifically intellectual property rights, define innovation origins and that preferred vehicles of development in technologically complex industries are foreign firms. Moreover, much policy has been supply-oriented with a limited understanding of the demand-side of the equation that generates learning at firm level and industry-wide.

The approach taken in this research is akin to that of the National Systems of Innovation (NSI or National Innovation Systems, NIS) literature, which has gained currency since the late 1980s (Freeman 1987, Lundvall 1988). This NIS is seen to be the backdrop to diverse factors, some intended, others outside the scope of policy, against which firms innovate. There is some concept how national and other influences, both institutional and organisational, blend together to create a 'system' of innovation. From a policy standpoint, the NIS is an ex-ante, not ex-post concept (Arocena and Sutz, 2000), such that although technical innovation exists, it may require intention and policy action to create other factors to nurture or further the innovation, scale of innovation, or extent of regional spread of innovation. In "systems of innovation", the explanation for innovation rest in the abilities of societies to generate "systems" of learning that are the basis of development.[2] An innovation system is defined broadly to consist of units, agents and relationships that interact together to produce new and economically valuable knowledge. The "system" then comprises firms together with non-market institutions of which the public sector organisations of various kinds are a part (see Lundvall, 1988). A

[1] Economic development literature has presented multiple explanations for why technological gaps exist between advanced industrialised and 'developing' countries. Ever since Solow (1957) attributed the residual for productivity growth in the US economy to technical productivity enhancements, and Denison (1967) there has been an abiding interest in how to describe and disaggregate the sources of this technical change. Growth theory has highlighted the importance of endogenous technical change.

[2] Lundvall (1985) discusses 'innovation system', but without reference to the nation; Freeman (1987) discusses the national characteristics for the first time in studying Japan's growth. Although not explicitly mentioned as such, "national" characteristics were nevertheless implied in the works of Richard Nelson and others contrasting the US's S&T system with others.

caveat is necessary: some mappings of such systems do not translate easily to developing countries (see Arocena and Sutz, 2000), but do provide a framework for thinking, particularly in countries where national, more centralised planning history has been prevalent. While the public sector is by no means the only thrust behind firms' ability to compete, one useful way to integrate these often-complementary approaches is to grapple with how and when institutions like government play a role in endogenous science-based expertise and influence the ways in which geographic and social spaces of innovation as well as specific organizations evolve. Subsequent iterations of this literature looked at different scales and units of analyses-for example, regional systems of innovation (Cooke, 1996, Maskell and Malmberg, 1999) and technological and sectoral systems of innovation (Carlsson and Stankiewicz, 1991, Malerba 1992, Breschi and Malerba, 1997). Systems that "work," allow countries (and their firms) to grasp new technologies, adapt them, or generate new versions at home. Thus, for those smoothly running, closely intertwined and highly adaptable systems of innovation, both incremental and more dramatic technological changes are possible. Efficiency is not taken to be analogous to rigidity, and organisations and the institutions that bind such "systems" are used to explain economic development itself, not innovation alone. The primary thrust of such approaches rests in learning (and specifically technological learning) at the heart of economic change.

But what type of learning assists entire economies? How can we think of the variation in learning across institutions and organisations, and over time? Overall, the economic literature refers to three different types of learning situated in production experience: The first, learning-by-doing through changing the production environment and increasing efficiency of capital/production systems (Arrow, 1962, also interpretations of Nelson and Winter, 1982) occurs primarily as a matter of course in production without necessarily any deliberative attempts by firms to increase their knowledge stock.

On the other hand, there can be more deliberative forms of search, involved with the exploration of the scientific/technical space (universities or other non-profit research labs) or that subset associated with profitable activities (the firm being the obvious actor, which conducts R&D). In this sense, countries that can transform their learning institutions and mechanisms into productive technical outcomes are more likely to be able to economically direct their futures. Early writings such as David (1975) and Rosenberg (1976) have suggested that learning effects may be seen as more than either simple learning by doing, and in fact, more useful than cost reductions alone. These are manifested by learning-by-using through the use of complex systems (Rosenberg, 1982) and learning-by-interacting between producers and users (Lundvall, 1988 and demonstrated by Von Hippel (1988) and others). Malerba

(1992) elaborates and suggests six categories: 1. Learning by doing 2. Learning by using 3. Learning from advances in S&T 4. Learning from inter-industry spillovers 5. Learning by interacting 6. Learning by searching. The last refers to the more formal process of R&D within the firm.

Previous explanations for economic development such as that occurring in East Asia have rested on primarily resource explanations of capital accumulation on the one hand or varying abilities of firms and states on the other. Current explanations for technological advance largely consist of so-called "accumulation" and "assimilation" theories (Nelson and Pack, 1999), the first focusing on high investment rates as the driver of economic development, where higher output arises primarily from higher physical and human capital inputs. In such theories, technological advance emerges primarily as a by –product of the high investment rates. The "assimilation-ists" suggest that rather than static physical and human capital factor explanations, more dynamic learning strategies characterise the advances of some developing countries. The "assimilation" theories underline the importance of dynamic technological and organisational learning instituted in an environment of (often) State-led incentives.[3] [4] There is also an implied cumulative aspect to the latter approach. You can only move ahead by already learning at each stage. There can be no one single "leap".

Growth accounting exercises that recognised the unaccounted for residual also left largely ignored the issues of what accounts for differences in the knowledge base across countries and indeed, where knowledge comes from in the first place. Some have suggested that knowledge of markets were still largely confined by national boundaries and thus differences in innovative potential across countries could be explained by demand variations (Vernon, 1966). However, countries sometimes do specialise in industries that have no local demand base, such as Switzerland's marine engines and immense

[3] We can divide the growth literature into two main categories as evidenced by interpretations of the East Asian "miracle". On the one hand, Young (1995) and Krugman (1994) among others have argued that there is little that is surprising about the learning curves and outcomes of Korea, Taiwan, Singapore and other East Asian "Tigers"-it is mostly perspiration, through steady capital investments. I.e. there is, in fact, no "miracle". Those concerned with endogenous growth and building technological capability would argue that systematic investments in capital are themselves necessary but insufficient, that the "miracle" lies in the deliberate learning trajectory pursued by firms (and often aided by governments) in these countries of building 'knowledge assets' (Lall, 1987, Amsden, 1989, Wade, 1990 and others). The distinction between these two sets of approaches is the relative importance paid to factor endowments and how they develop- either through systematic resource-investments alone, or through accumulated knowledge stores that enrich multiple sectors.

[4] Furthermore, as Pavitt, 1985, Bell and Pavitt, 1993, 1995 suggest, entire economies can increase efficiency levels over a short period even if there is no indigenous invention or major technological change. This occurs through the adaptation and diffusion of external technologies, as did the East Asian Tigers in the early years. Thus, the relatively small number of "world-class" technological innovations (usually taken to mean US patents) should not be taken as a sole indicator of whether the sector overall is innovative or not.

pharmaceutical base (Pavitt, 2002). A path-dependent and cumulative mastery of certain types of knowledge (Nelson and Winter, 1982) then applied to other fields, might explain such examples.

But innovative potential is circumscribed to some degree by past industrial histories and relative positions in international labour pools. Because developing countries are often focused on or advised to focus on mature products, this dissertation concentrates on two main strands of literature concerned with technological learning: (a) Product maturity, specifically, source and type of innovation within the product's lifecycle and (b) the environment for learning and innovation.

2.2.Product maturity: innovation type and sequence

Within the technology advance literature, the main contrasts are (a) government versus markets as the "system" of choice or (b) technology-oriented views. The first category could more usefully be split into two sub-categories: firm-level studies (Stewart and James, 1982, Lall, 1986, Katz, 1987 for example) and sectoral and national writings (Gerschenkron, 1952, Evans, 1979, Evans and Gereffi, 1981, Krueger, 1973, Bhagwati, 1982, Lall, 1987, Johnson, 1987, Amsden, 1989, Wade, 1990, World Bank 1993, Bell, 1984, Teubal, 1996 etc.).

This dissertation focuses primarily on the technology-oriented views, which themselves draw on product life-cycle theory (Vernon, 1966, Abernathy and Utterback, 1978, Kim, 1980, Dahlman, 1985, Lee, Bae, Choi, 1988, Hobday, 1995, Kim, 1997 etc.). Data analysis indicated that there can be no *a priori* decision made about the appropriate institution for development without a more complete understanding of the technologies at hand, even if developing countries may need more active policy interventions. Nevertheless, whether State vs. Market debates or Technology debates, a shared theme in the literature has been the concept of product maturity i.e. developing countries look first to older products in world markets and use their wage advantage as an important leveraging factor to manufacture them. Some authors differ when they suggests that in addition to the wage advantage, latecomers succeed to the extent that they are able to develop knowledge within the firm and the extent to which the State is able to assist (Lall, 1987, Amsden, 1989, Wade, 1990, Lall, 1992, Hobday, 1995).

In developing countries, which more often than not concentrate on mature products, learning is situated mostly in process technologies. Incremental shifts in organisational form, production modifications for market conditions and new supply arrangements, can all lead to further

enhancements in production efficiency.[5] The policy implications to encourage such learning have usually been subsidies for importing capital goods or complete import substitution. In either case alone, the evidence is mixed for how firms learn and whether they are adaptable enough to rapidly changing technological and/or market conditions.

Although the early history of pharmaceuticals suggests that process innovations were at the core of advances such as penicillin and thus antithetical to product life-cycle theories, more recent changes in the industry have created a perceived dominant position for product innovation. Further, extensions of such theories contrast a typology of industrialised versus developing countries thus providing a lens into markers for advancement.

Economics tends to separate process and product innovations sharply, seeing the former as shifting supply curves through lowered costs, and the latter as shifting the demand curve through new products. The process of learning in the two are also seen as separate, that firms doing one tend not to do another, or even that process capabilities might be developed at the cost of product capabilities. Thus, learning at firm-level and industry-wide diffusion of innovation, must be situated squarely within the product's life cycle. For developing countries, this has usually been taken to mean that they should focus purely on mature industries and compete on the low cost (supply curve-shifting) advantage, while advanced industrialised countries plough resources into product innovation and shifting of demand curves. The data suggests that this is a false dichotomy.

The existing models of product-lifecycle theories reinforce the dichotomy. In this view, process innovation comes after product innovation and is used primarily to drive down costs. The original version (Vernon 1966, Abernathy and Utterback, 1978, and other life-cycle theorists) suggests that process development becomes more important as industries mature. When early phase in industry and new basic product concepts are being defined, product innovation outstrips process innovation. Later when both producers and consumers have gained experience with different versions of the product, a "dominant design" emerges and radical product innovation opportunities lessen. Another version of

[5] More empirical studies from developing countries on learning-by-doing emerged from firm-level studies in Latin America (Stewart and James, 1982, Lall, 1986 and Katz, 1987) and demonstrated convincingly that these firms are actively involved (and have to be) in absorbing, adapting and generating technologies. However, there was less attention paid to environmental stimuli and how policy instruments could shape industry-wide and nation-wide change. These latter themes were taken up by newer writings (Evans, 1979, Johnson, 1982, 1987, Haggard and Cheng, 1987, Evans, 1987, Amsden, 1989, Wade, 1990, for example) which suggest that "lateness"

this theory extends the model to a global production cycle (Vernon, 1966) and suggests that product innovations occur in advanced industrialised countries, and when the dominant design is well established and the product matures (by definition), the product moves over to being manufactured in lower-wage developing economies where process innovations further bring costs down. Kim (1997) suggests that latecomers such as Korea are relegated to the process innovation domain once mature technologies come their way but may leapfrog at later points in time.

Moreover, while the product life cycle and other learning models, are good at explaining innovation in many different industries, they have certain limitations. In particular, the product life cycle model has three assumptions that may not be always relevant: (for a similar discussion of the US case, see Pisano, 1997) (a) It assumes that the main benefit of process innovation is cost reduction, that companies take on process development focus only in mid-phase of an industry's life-when volume of production has risen and when product innovation opportunities are falling. It also assumes process development focus does not occur until product design is stable (b) Secondly, it assumes that organisational specialisation and abilities needed for product development and innovation are different in essence from process innovation and in fact, work against, those of process innovation. (c) Thirdly, it assumes that specialised process innovation is not necessary to do product innovation. In fact, it's seen as antithetical, because companies are supposed to be hesitant to introduce new products that make existing process technologies obsolete. I.e. new process innovations are not seen as a key to product breakthroughs.

While the discussions above pertain primarily to innovation "type" (i.e. product or process), there is a second issue that also relates to the capabilities of innovation: the particular sequence in which learning and innovation occurs. The literature suggests that countries work their way up from various forms of copying, reverse engineering, then 'creative' imitation to innovation recognised in its own right. Lee et al (1988) suggest that developing countries pursue technology trajectories in three stages of acquisition, assimilation and improvement (suggested by Kim 1980, extending Utterback's model) from mature, to intermediate and finally generate emerging technologies. Hobday (1995) states that developing countries thus reverse the direction (relative to industrialised countries) of technological capability and move from mature to emerging technologies. The implications are two-fold: *1.* That there is a certain identifiable sequence of learning from imitation to innovation and *2.* That catch-up or

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shapes the entire process of industrialisation and the ways in which firms learn, particularly through imitation, rather than innovation.

leapfrogging occurs when the speed of working through the sequence accelerates or certain steps are skipped entirely with the advent of new technologies.

The same process of innovation can be interpreted to result when systems that are rusty begin to work more smoothly. Reverse engineering or other forms of imitation are seen simply as varied ways in which learning occurs. Institutions that assist such learning (public research institutes, universities, or regulatory regimes, for example) are seen as part of the metamorphosis accompanying the learning process.

Thus far past research literature tell us that developing countries take on mature technologies, learn in different ways (by "doing", by "using", by "interacting" and so forth) to absorb, master and improve upon these technologies, and eventually (on an indeterminate and undoubtedly frustrating time-scale for many countries) will generate innovations if they do it 'right'. But how should these developing countries source core technologies or meet local demand when often they have limited resources and maladapted institutions for R&D? As the inexorable product life cycle rotates forth in each industry, manifested in levels of technological difficulty and value-added segments, developing countries must individually decide which technological segments to invest in, but are not told how the institutional niceties are to be arranged for this to occur.

2.3.An overly narrow view of the environment

What is the broader environment in which firms learn and choose particular technological paths? Does the State possess the capabilities to predict outcomes, target industries or specific technologies and accelerate technological learning in a field where the frontier is evolving less rapidly? Government policy was an important driver of early biotechnology and pharmaceuticals even in now developed countries, particularly in the early stages of research and in setting research priorities. (McMillam et al. 2000) How have other institutional forces such as patent laws, price controls, and regulatory approval sped or slowed the learning? There have been some very insightful studies on absorption and learning capacities. Kim (1997), as a representative example, refers to the firm situated in a "learning environment", while the now-classic contribution of Cohen and Levinthal (1990) suggests that skills are formed at a more rapid rate if the firm is also investing in in-house capabilities. As in-house capabilities develop, firms are able to source in information from the outside (their absorptive capacities). An understanding would prove useful of how the learning environment changes, and how firms absorb more as their environment shifts.

Some authors have described the environment, particularly selection environments as comprising markets, institutions and knowledge, broadly speaking (Wijnberg, 1994, Thompson, 1994, McKelvey 1996 and Murmann 2001). Wijnberg (2004) systematically explore valuation within selection environments in assessing a firm's capabilities .The "new institutionalists" suggest that institutions are the rules by which markets are organised (North, 1990) and the patterns of behaviour (Hodgson, 1988) that generate them. [6] The third dimension of the selection environment is seen as knowledge. However, while these authors (particularly McKelvey) acknowledge that these three dimensions tend to influence each other, there are insufficient examples, least of all from developing countries, that could shed light on these frameworks. This dissertation is thus an attempt to contribute to this empirical research agenda. In such thinking, market transactions are rightly typified as becoming only one dimension of selection. This dissertation argues for a more specific interpretation of knowledge (and technological acquisition) as being not independent, but shaped by the institutions within which it is developed. The firm is embedded simultaneously into both national and international selection environments that are intricately tied to the ways in which firms learn.

Undoubtedly, any static view of "the environment" cannot do justice to the adaptability of individuals and firms or the technological choices that they make. Products and process choices are made within this context, as are the capabilities each encourages. More importantly, the two are related. Technological choices are not independent of the political and economic environment, but neither are they entirely dependent on them. Technological specificity continues to be an important determinant of skills, paths and opportunities. After all, advances at firm-level occur in a broader environment that defines how the firm structures its strategies and how information flows to and from it. Past writings appear to have contributed significantly to views of the environment as primarily policy-driven, while others from the innovation system "school" do study the environment, but predominantly as an instrument of national or regional policies [7], as exogenous shocks (best represented by the trade

[6] Rosenberg and Birdzell (1986) argue that institutions coordinate economic behaviour, and thus can prove to be explanatory variables or different national performances. Neither knowledge nor market transactions alone are explanations; rather the ways in which institutions shape interactions between agents and organisations that matter. Others writing on this theme are Landes, 1969, North, 1993, Mowery and Rosenberg 1998. In all of these, institutions are used to demarcate rules of engagement. However, Lundvall (Ed.) 1992, Nelson (Ed.), 1993, Malerba (1999) explain differing performances at national level through specific innovation systems where institutions (predominantly in the rules and patterns sense) explain knowledge accumulation and differing trajectories of technology development at national and sectoral levels (Breschi and Malertba, 1997).

[7] Indeed, the use of innovation systems in analysing developing countries is still uncommon, in part because of queries raised about whether innovation (as seen as a first-time event) is applicable to most developing countries. However, even in the NIS literature, innovation has increasingly been defined broadly to include events and technologies faced by the firm or country for the first time, even if it cannot be seen as a worldwide first. As

literature) or primarily as entry barriers to firms. At the other extreme, a purely resource-based view of the firm can over-specify the internal capabilities of the firm with its level of agency and pay insufficient attention to the constraints and opportunities provided by external changes. By understanding the interplay of both national and international contexts for the specific industry, there are more likely to generate insights into the conditions under which firms choose specific paths of learning and gain both visibility and credibility in the marketplace, which itself is changed by their entry over time.

While firms can strategically adapt to their selection pressures, often pressures are difficult to recognise ex-ante, or even at firm-level. Selection and adaptation also co-evolve. Both rely on similar measures of surviving firms to draw conclusions and interpret survival as either optimal organisational form and practices, appropriate strategy or unique resources (see Volderba and Lewin, 2003, for a thorough discussion). Despite this, empirical studies continue to be necessary. Rationales for firm-level, or even industry-level performance without accommodating selection pressures leads to incorrect attributions of causality for success or failure, or even appropriate evaluations of whether the firm or industry has been successful or not. Most classical micro-economic and management studies are unable to interpret case-studies of technological change because of competing pressures over time, where some idealised production function or limited patent indicators may be a poor model to capture both selection and adaptation.

Learning attempts can be set against broader evolutionary dynamics. At least three stages of such dynamics exist (Aldrich, 1979, Baum and Singh, 1994 a,b, McKelvey, 1997): variation and heterogeneity (e.g. firm types, standards etc.); selection (both external and internal elements to firms or other organisations); retention or adaptation, which combines the ability of firms to identify traits which are selected for or against and adjust accordingly. The stages also partially mirror three separate, but complementary, streams of evolutionary research with different levels of analysis (see Durand, 2001 for attempted integration). They are evolutionary economics (Nelson and Winter, 1982), population ecology (Hannan and Freeman, 1989) and firm-level dynamic resource-based approaches (represented by Teece and Pisano, 1994 and Teece, Pisano and Schuen, 1997). All share the view that selection is recognised ex-post, that individuals cannot fully recognise selection pressures on populations as a whole, and that selection dynamics allow for causal ambiguity (Durand,

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Lundvall (1992) and others have suggested, an important goal of the NSI literature is an attempt to explain the level and direction of national capabilities and to this extent, its relevance is broader than OECD countries alone.

2001). The last creates special complications for policy-makers and firms alike, particularly because effects of selection occur with a lag after efforts have been put in place.

Thus, a promising analytical area for study emerges in this dissertation on the role of the environment and its selection pressures, with specificity to the technology and industry under study, with the caution that any one model on the environment is likely to have limited explanatory power. While it is certainly true that events external to the firm, particularly those as significant as national or international policy changes or crisis can lead to methodological challenges to control variables, the data for this dissertation suggest unequivocally that the environment in developing countries such as India, in which imitation or innovation occurs is much richer than these views alone. Of particular interest in this dissertation are the ways in which the environment (a) shapes the understanding, assimilation and exploitation of information and knowledge (including technology) and (b) moulds the imitation/innovation strategies and technology choices of firms[8] and (c) selects certain firms to propel forward.

This dissertation argues for a broader understanding of learning processes and capabilities when firms are faced with both older and newer technologies. Firms are thought to engage in more traditional learning-by-doing, but in reality, the process is much more interactive and any one industry shows multiple characteristics as the national and international context changes for the industry. Learning occurs with a selection environment, which in this dissertation shows some particular manifestations: (i) policy environment at national and international levels, and (ii) regulation and standards in the industry (iii) technological characteristics of the sectors.

Past contributions have been very useful in highlighting that the interactive process induces firms to engage with suppliers and users (for example, Von Hippel 1988, Schmitz and Cassiolato, 1992) or with their counterparts, other firms (Dosi et al 1988 and Lundvall, 1992, 2002). Systems thinkers have suggested that the broader institutional arrangement within an economy, encompasses social, economic-including markets- and political considerations that drive the success or failure of certain types of collective learning (Best, 1990, Nelson 1992, Lazonick 1993). However, many of the studies

[8] Indeed, this theme has arisen much earlier in economics writing, but has fallen into some neglect in recent years. Vernon (1966, p. 191) suggests correctly in the context of trade theory that "*.one cannot be exposed to the main currents of international trade for very long without feeling that any theory which neglected the roles of innovation, scale, ignorance and uncertainty would be incomplete.*" Vernon cautions that the discussion of trade and investment features of the product life-cycle refers in his case, solely to products associated with high wages and which are capital–intensive.

are strangely silent on how the environment influences firm choices at the international level and suggest that the determinants of firm trajectories are largely local, or primarily through national or regional policy instruments.

There have been useful reporting of changes in newspapers and other popular writings of Indian process capabilities, but relatively limited analytical structure given to the technological advance, public policy history and market entry for Indian (or other developing country) pharmaceuticals and biotechnologies. Some recent academic contributions and commentaries have been useful in highlighting specific facets of the pharmaceutical industry: engendering technological self-reliance and negotiation with multinational firms (Lall, 1986, Sahu, 1998), industrialisation with special reference to Indian pharmaceuticals (ranging from Chibilya, 1968, Ahmad, 1988, for example and later exemplified by Lall, 1974, 1982, 1984, 1987), descriptions of Indian biotechnology and policy (Lachke et al. 1988, Padh, 1997, Sharma, 2001, Padmanaban, 2003 and Jayaraman, 2003), drug supply (Phadke, 1998), tacit versus codified knowledge in technology transfer (Mourshed, 2000), comparative institutionalism (Felker, Chaudhuri and Gyorgy (WB Paper 392) and Gonsen (1998), collaborative potential (Chorghade, M.S, V.M. Chorghade, 1998), collaboration types and R&D potential (Visalakshi S; Sandhya G.D., 1997, Ramani, 2002) or primarily technical elements of actual implementation of manufacturing (Bhattacharya S.K., S. R. Tripathi, S. Kashyap. 1990, Mukhopadhyay SK, J. Dwivedy, A. Kumar, 1998, for example). A larger portion has focused on the product patent and World Trade Organisation decisions (Prasad, H.A.C and S. Bhat. 1993, Redwood, 1994, Keayala, 1996, Lanjuow, 1997, Watal, 2000). A recent study states that Indian firms which use technologies based on in-house capabilities developed under an inward-looking regime may thrive even under a liberalised one (Katrak, 2000).[9] The Forbes (1999) study suggests that the national innovation system of India only became fully international after 1991 and others situate India in the global industry (Thomas, 1996)..While this is certainly true for all sectors, it highlights how Indian firms prepared through process capabilities, low R&D costs and induced low costs of drugs through price controls, were able to seize opportunities abroad before the full-scale liberalisation of the 1990s. Indeed the literature on the positioning of Indian firms vis-à-vis multinational ones was very useful in

[9] The study emphasises that products made with the firm's own R&D efforts does not equate with reinventing the wheel, but may have benefited from foreign journals, exposure to overseas companies and trade fairs, as well as the firm's own history of past use of imported technologies. The point is in-house R&D instead of licensing or using standardised technologies alone. The study looks at chemical and allied products, electrical and electronic industries from 1991 (significant liberalisation) to 1998-'99. The author concludes that although production using in-house R&D began under a protectionist system, these products have lasted through liberalisation and have flourished.

building the narrative for early capabilities in the industry (Sahu, 1998, is typical). Where this dissertation aims to contribute is to shift the analysis away from units of impact as national policy or firm strategy alone, to building capabilities and the environment that shapes technological choices and hones certain capabilities more than others. It also hopes to contribute to linking pre-liberalisation analysis to new data on generic drugs and biopharmaceuticals, which have been left largely silent in other studies.

An additional debate around pharmaceuticals (and normally translated into debates on intellectual property) lies in the public health domain. Public health is usually analysed in terms of "public good" characteristics and by its dearth in developing countries (For a discussion of gaps in supply, see Mrazek and Mossialos, 2003) yet, there is little writing on how public health affects private technological capabilities in developing countries. The history of pharmaceuticals in advanced industrialised countries suggests that a closer look is warranted at such a link when public health needs are still significant. Indeed, the debate over public health needs such as drugs for TB, malaria or AIDS is whether supply meets demand, and who owns the production –whether multinationals or local firms provide the drugs. While this is a fruitful debate, it misses the mark with regard to technological upgrading. If firms in developing countries are to produce essential drugs for public health, what can they learn from the process technologically, and how can these capabilities in turn be upgraded to match changing public health needs?

The ability of firms to search for new demand for existing products, as well as new supply of features to existing products created a specific trajectory that allowed firms to see and reap rewards in new markets abroad. It remains to be seen in the Indian case whether the more illuminating unit of analysis will continue to be the lone Indian firm, or a broader, more diffuse set of knowledge networks, local and global that support innovation. (As suggested by various authors, more recently, McKelvey, 1999 Brusoni et al, 2001). This will give rise to certain methodological difficulties of its own.

2.4.Nurture versus nature for indigenous industry

Any analysis of innovation policies raises the question of whether and how governments should attempt to influence innovation processes and outcomes. One view is that states have to substitute for markets and push industrialisation along in developing nations where markets are underdeveloped (Gerschenkron, 1952, 1962 and supported by a vast array of later research). Public policies shape markets and other institutions within which selection occurs. Arrow's seminal work of 1962 on the economic implications of Learning by Doing elaborates on the assumption that learning is a natural

by-product of production experience. He also emphasised that facing similar problems does not do much for learning in the long-term. A changing production and selection environment that generates new problems to solve will result in technological progress, but mere repetition will not. While developing country governments and academics used this policy as a green signal for infant industry protections, arguing that such policies would bring the required certainty to returns in human and physical capital investments and generate positive industry-wide externalities, the actual impact of such policies has been mixed. It is now recognised that protections alone do not work and State-industry, Industry-society or three-way societal compacts must require performance levels (Evans, 1979, Evans and Gereffi, 1981, Lall, 1984, Johnson, 1982, 1987, Evans, 1987, Haggard and Cheng, 1997, Amsden, 1989, Wade, 1990, Hobday, 1995, among others). Institutional arrangements that encourage performance and punish lag, such as revocation of export permissions, rewards and public recognition for high quality products, preferential access to new technologies, can also be important drivers of the process of learning.

While the fact that firms learn and need supportive environments to do so is emphasised by the 'assimilationists', the environment tends to remain as an external incentive mechanism, not one that shapes innovation choices. The international context is particularly underemphasized. Even those writings that have emphasised a "learning" framework have focused on more "traditional" industries such as steel and automobiles. The story of electronics, while "high-tech" indicates entry points of developing economies at greater degrees of product maturity. Bio-pharmaceutical drugs are considered to be "science-based" (Niosi, 2000), presumed to be resting on abilities in product R&D and drug discovery. The question is, do the dynamics of innovation play out differently with such technologies in developing countries?[10] In particular, what is the policy basis for the technological and market advance, if any? However, assimilation of this kind while exemplifying firm level and policy efforts occurs in a larger technological, socio-political environment with access to markets and demand-side incentives as important. But demand alone will not tell the story of how indigenous institutions respond to this mix in what makes the "system" innovative.

Moreover, writings on trade theory in the last three decades, have emphasized the differences in viewpoints on the role of government in markets as protectors and in creating demand. Once the

[10] Furthermore, Amsden (1989) and Westphal (1990) highlight three types of technological capabilities that help technological learning within firms: (a) production capabilities (b) project execution capabilities and (c) innovation capabilities. But there is no clear-cut relationship of these capabilities with R&D functions of so-

argument was accepted that markets are inherently imperfect, although competitive, the role of government became more defensible, if not wholly so. Grossman (1988, 1990), Tybout (1992) and Rodrik (1994, 1995) have all reviewed the literature extensively and demonstrate the mixed evidence on whether or not, in what timeframe and how exactly state intervention improves the nation's welfare. Others have suggested (Harrison, 1994) that even with data, analysis and interpretation become challenging. From an empirical standpoint, it appears that no country other than Hong Kong, developed its industrial base without a series of infant industry protections of wide range (Chang, 2002, for example) Functional and selective government intervention (Lall, 1987) has been widespread in the histories of the UK, USA and Germany (among the early industrializing countries) and although it varied with time, it was expansive in its scope and international outreach. However, features such as the rate of technological change, the average size of firms and the need for capital investments, the need for relatively rapid social and institutional change (to create supply), all vary between those industrializing earlier and later. Furthermore, the later the industrialization, the shorter the time available for the principal elements of infant industry protections, export ramp-up and liberalization of trade (Shafaeddin, 1998, for a review).

The SAPPHO study and others identified success and failure in innovation across industries (Achilladelis, Robertson and Freeman, 1971) and identified factors influencing innovation. Seven broad areas of S&T advances, raw materials, market demand, competition, societal needs, government legislation and companies S&T and market specialisation were identified as influencing innovation. Achilladelis, Schwarzkopf, Cines, 1990, and Achilladelis, 2001 others have studied the chemical and pharmaceutical industry more particularly. The dichotomy of "S&T-push" and "market-pull" is insufficient to answer the specific pathways of countries. In particular, this trajectory, techno-economic paradigm or technological paradigm (Freeman and Perez, 1988, Dosi, 1982, Nelson and Winter, 1982, Rosenberg, 1976, for example) is historically unique in each case, but has some elements that can be generalized to other developing countries.

Demand-side policies have been investigated in various ways. However, the impact of demand deemed to be in the public interest has not been investigated as a tool for technological learning and not in developing countries, where such demand may be most acute. While this may not be easy to structure, it is useful to understand the socio-political and economic conditions under which such

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called science-based industries such as biopharmaceuticals, where innovation is invariably associated with R&D

policies can be constructed, and exploited. As Lundvall (1992) and others have suggested, an important goal of the NSI literature is an attempt to explain the level and direction of national capabilities. This and other economic literature (Hirschman, 1961 was one starting point) have highlighted demand conditions as an innovation-inducing mechanism, later highlighted again by Von Hippel (1988) on the importance of user-interactions with the innovator.

To conclude, product maturity and selection pressures of the environment, including policy, affect learning choices. While it is unclear what the fortunes of these industries will be in the long run, thus making challenging any assessment of the relative merits and de-merits of various developmental theories based on long-term models, there is sufficient data to suggest that existing explanations are missing the richness of the Indian story. Those views looking predominantly to foreign (western) firms for technological diffusion in developing countries, and to intellectual property-particularly product patents, as the prime determinant for Indian innovation, warrant refinement. These debates overlook important characteristics of the selection environment and the entry points for building capabilities that has shaped Indian advance and the diverse paths of learning. One-size-fits-all policies aimed at diverse industries with significantly different environments and technologies will not serve countries in their developmental goals.

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in drug discovery and early development, and not with manufacturing and commercialisation.

Chapter 3 Research Design and Methodology

3.1 Introduction

The choice of cases (and nested cases) was structured to track capabilities, specifically, process development capability, over time. Because the hypothesis was set against other causal explanations for advance such as patent regimes and low cost, a historical approach was used with nested cases at firm and sector-levels.

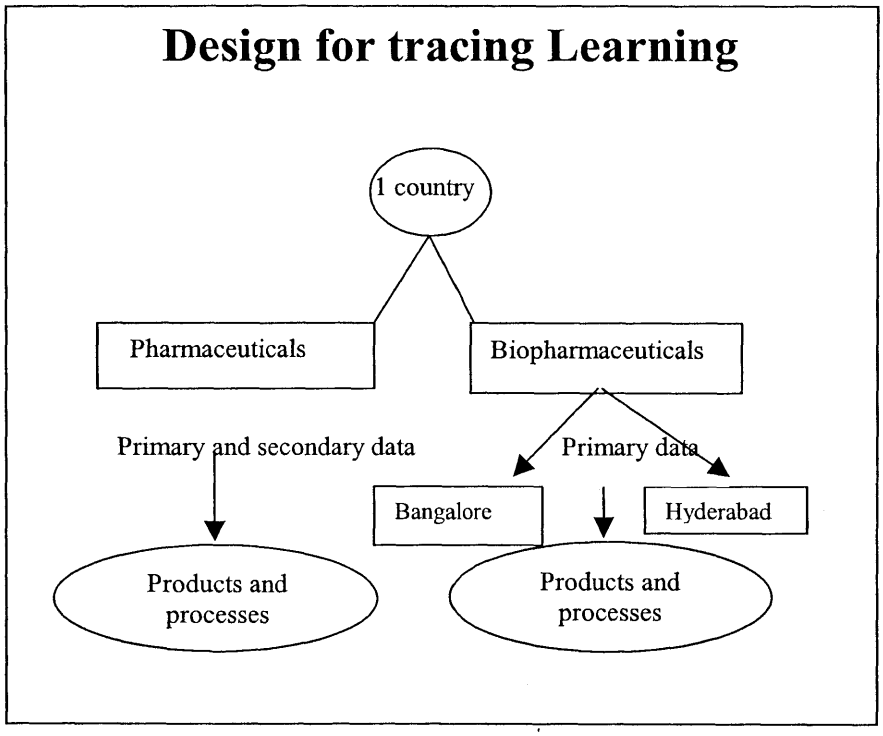
The emphasis is on pharmaceuticals and bio-pharmaceuticals or that set of scientific and technological tools and practices in research and development, as well as manufacturing, that are engaged with broadly (a) *therapeutics*: (drug discovery, development or manufacture) or (b) *diagnostics*. Both of these areas are included when the process or product or set of tools employed involves either small molecules ("traditional" pharmaceuticals) or large ones (recombinant protein chains and "modern" of post 1970s developments in molecular biology). Because recombinant DNA and genetic engineering companies are an important but not the only form of biotechnology utilised in these countries, a broader definition of biotechnology is necessary for the purposes of this study. The sector provides interesting disciplinary and industrial changes with the onset of the molecular biology "revolution" of the 1970s. Modern biotechnology, a set of process technologies, is usually defined with the onset of molecular biology breakthroughs such as the creation of recombinant DNA and of monoclonal antibodies in the 1970s. These advances heralded a change in the ways biomedical science and technologies functioned. Advances in bioinformatics capabilities, combining computational algorithms with the search for new genetic taxonomies, has also provided new avenues for growth. The structural changes in the industry have also led to new divisions of labour between various types of firms, providing new opportunities for firms (and their governments).

The focus was on the national system that builds innovation capabilities for two main reasons. Although Bangalore and Hyderabad are good examples of localised capabilities, their histories have, in large part, been driven by national policies. Secondly, while other units of analysis-regional, sectoral and so forth, are no doubt interesting and insightful for Indian pharmaceuticals, international pressures and opportunities in this sector are phrased in terms of national opportunities, even if exploited by firm-level competencies. Many of the institutions that support innovation in India have been nationally driven across diverse sectors, although some states have become active recently. Therefore, the nation state for the purposes of the research design is still a relevant and dominant marker for structuring the environment in which firms learn, even if (and precisely because) the international context varies.

3.2 Methods:

The research comprises a one-country (India), two sector study. The dissertation used a combination of (a) a study of innovation categories and products and processes over time and (b) a set of case studies . The primary data collection tool for the case studies was structured, open-ended interviewing with a list of sample questions included at the end of this chapter. Case-analysis was chosen because the focus of the dissertation was the intersection of three subjects areas: technological innovation, firm-level learning strategies and policy effects, whose combined effects are difficult to study statistically.

The figure provides a schematic of the research design, with a focus on indigenous firms.



3.2.1 Sample selection

The analysis focused on two firm samples: the first comprising a combination of primary and secondary data from India's 5 leading pharmaceutical firms in 2001 and the second consisting of primary data from biopharmaceutical firms in the two southern Indian cities of Bangalore and Hyderabad, considered to be India's up coming biotechnology centres. The second sample comprises 21 firms with research in biopharmaceuticals in Bangalore and Hyderabad, two of India's rapidly rising biotech centres, which were selected by criteria described in the previous chapter. The sample is too small to systematically investigate why some firms moved ahead faster than others or were more innovative, but the dissertation provides some insights into the characteristics of the leading firms that may be tested in later studies as causal factors.

First sample: All-India pharmaceutical leaders

In pharmaceuticals, 5 Indian-owned firms were selected for the sample by whether they were overall leaders in market share.[1] For these companies, systematic company histories, product and process innovations and industry-level changes were collected. Primary and secondary data of indicators are analysed for the top 5 Indian pharmaceutical companies by market share in 2001. Secondary indicators on their overall impact on the industry were used to confirm the choices, specifically technological innovation capability.

Second sample: Localised biopharmaceutical companies

In the case of biopharmaceuticals, localised firms were selected in the Bangalore and Hyderabad region from three main sources and their cross-listings: Department of Biotechnology publications, companies listing in biotech-related websites of the two states and mentioned in regional policy documents, those mentioned in TIFAC and other documents, and/or listed as collaborators with public research institutes (PRIs). The second sample comprises 21 firms with research in biopharmaceuticals in Bangalore and Hyderabad, two of India's rapidly rising biotech centres, which were selected by criteria described in the previous chapter. Their expertise is more varied than in pharmaceuticals, ranging from drug discovery to manufacture and bioinfornatics.

My cases differ on multiple levels. First, they vary by public sector influence –by policy type and by stage of influence. Second, they vary by technological focus, most prominently, two samples of firms in pharmaceuticals, and those in biopharmaceuticals. Third, they vary by product type. Fourth, I have selected the leading five pharmaceutical firms, but made a deliberate choice to focus the biopharmaceutical firms situated in Bangalore and Hyderabad, to give a localised flavour to innovation. The decsriptions at the end of the chapter provide a brief profile of the 5 leading companies of Sample 1 and the main characteristics of companies in sample 2.

Despite the dimensions of difference, there are some very important common characteristics to the firms described. All have shown some minimal level of process and product innovation in either synthetic or biological pharmaceuticals. All focus on the US market, some with greater focus on the UK or Western Europe. All have moved into the generic drug market. All of the leading five firms are large firms (over 500 employees). All the firms in synthetic and biopharmaceuticals samples alike are important in their respective segments and face the same pressures of low cost, high quality, high speed and high competition in their target markets.

Comments:

Choosing the firm sample was not a straightforward exercise. Faced with a trade-off of huge geographic spread for Indian pharmaceutical firms and a limited time frame and budget for data collection, the research was focused on two southern "biotech" cities of Bangalore and Hyderabad. This allowed an investigation of compisition, capabilities and growth of the sectors as reflected in the firms in these two cities, with Hyderabad being the home to almost 40% of Indian bulk drug production. Both cities had many public research institutes and universities associated with both sectors. No other city sample combination in close proximity could have afforded me the same firm sample coverage in both spheres of technology. Pharmaceutical firms lying outside these cities were interviewed by telephone, or analysed by secondary sources. Some biopharmaceutical firms were not available within the timeframe of the research or did not respond in time to set up interviews. The second sample is only partially representative of the population of such firms. This is for two reasons: first, many of these firms are new and are still defining their focus. Thus, knowing which firms are good comparisons within this set is tricky as are tracking births and deaths of firms. Furthermore, while these firms all have a biopharmaceutical focus, they come to the field with different focus, expertise, company histories and organisational sizes. Ideally, this set should be tracked over a much longer timeline. One significant problem that should diminish with studies following this one, is that well-established data sets on companies was scarce at the time of data collection.[2] Thus, preliminary conversations with various people in the field helped identify, by a 'snowball' effect, which companies to focus on, and these were then compared to secondary data to pick a final set. Although the sample size is relatively small, the detailed interviews provide insights into the learning process that a survey instrument or other statistical study would have been unlikely to obtain. For future research, more interviews will be used to test the hypotheses formed in this dissertation and will be combined with surveys of a large sample of firms in both pharmaceuticals and pharmaceuticals.

3.2.2 Hypotheses tests

Although the study is inductive in nature, hypothesis testing was done as findings emerged. The main dependent variables are speed to market (measured as the time lag between introduction of a product on the world market and the Indian introduction of the same or similar product to the world or domestic markets), cost of the drug and process and product improvements of the Indian –introduced drug. In addition, US and Indian Patent data is used.

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[1] Some multinational subsidiaries were also interviewed to obtain a different perspective on Indian firms.

[2] Since then, publications such as "BioSpectrum" in India have undertaken a ranking of leading companies. However, here again, all companies are listed, but not compared by expertise, but predominantly by sales, R&D figures and personnel, among others.

Interviews comprised testing hypotheses of process capability by studying(a) importance of in-house process versus product development and (b) the sequence of technology development in specific drug segments, (c) the relevance of the institutional environment in the development of technological in-house capabilities (d) the importance of national ownership, specifically with regard to alliances and access to technologies developed in the public research sector (e) lastly, I also tested the relative mix of in-house and outsourced R&D and services functions in the different types of firms. In all cases, I was assessing how much technological learning had been amassed in-house relative to acquisition, what sequence of innovation had taken place, if discernible, and at what stage of the company's development. The levels of sophistication were also checked with experts in the industry in India and in the US.[3]

3.2.3 Data sources, Indicators/metrics:

My empirical data for the dissertation comes from three main sources: (a) Qualitative data sources (Primary): detailed, structured and open-ended firm-level interviews (b) Quantitative sources (Primary and Secondary): economic indicators for firm-level, industry-level and national technological capability. Statistical information across countries. (c) Other secondary data sources such as company annual reports, financial record, stock market reporting, media profiles, various third-party ranking systems and more rarely (because of such few academic studies) journal articles or books. I also used case-study material where available developed by universities and from international organisations.

One way of measuring technological and market advance was to study the longitudinal performances of private Indian-owned firms[4][5]. A set of the firm's products and processes is taken as indicator of technological advance. In particular, while New Chemical Entities are taken as the ultimate indicator of product innovation, multiple paths to the same end product, increased speed of production and rapid generic filing are some of the non-exhaustive indicators of process innovation. Overall, there are three main types of indicators that were used for both background research and for building a framework of learning paths and the selection environment:

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[3] In the Indian case, I also interviewed bioinformatics firms, with their parent capability in the computing industry, to see how they were moving into biopharmaceuticals, especially drug discovery and development.

[4] Among most developing countries with pharmaceutical capability, India had the highest percentage of privately owned Indian firms in the top 10 by domestic market share. Thus, firm ownership was a central factor in sample choice. Government policies from the 1950s onwards have resulted in gains to Indian companies even today in newer bio-pharmaceuticals. Furthermore, where necessary to illustrate industry-wide learning, examples from the public sector effort are also relevant.

[5] The top five firms have changed over time, so in addition to these, to mitigate any selection bias, the background analysis also traced the histories of some that fell out of the top five, and some that were not market leaders, but are innovators (as measured by number of New Chemical Entities found, patents filed etc).

1. The first, sector economics, looks at the broad trends driving the industry as well as the growth indicators specific to the technologies used.
2. The second indicator, innovation timelines, deals with the micro-details of product and process development within each firm, or 'events' that highlight technological advance.
3. The third combined indicator, firm type, alliances, products, helps to explicitly model the relative advance, if any, by mapping technological and business outcomes.

Box 1 Indicator types and examples

INDICATOR TYPE	EXAMPLES
Indicator I: Sector economics	•Total sectoral output and growth •Increased market share in that sector •Increased exports in that sector •% of that sector's total output relative to total industrial output of the country •% of that sector's exports in country's total exports •% of people employed in R&D, No. of PhDs •R&D spending growth rates relative to capital investments •Amount invested in segment X relative to segment Y •No. of patents, inspections by regulatory authorities (import opportunities)
Indicator II: Innovation Timelines	Event timelines •Acquisitions, date when certain firm types enter sector, date when sector becomes independent in certain key functions, or first production of some specific product, or first attempt at process type A or B World timelines •Outlines when certain products and processes were introduced elsewhere, then in country X pharma sector. (e.g. When first introduced in the world, by whom, then when introduced in India, then when introduced in India or elsewhere by Indian company). Measure time lag trend, Filing of ANDAs and 180-day exclusive licensing period. •Manufacturing of generic to first establishment of licensing or contract manufacturing arrangement of an Indian company with an MNC.
Indicator III: firm type, alliances, products	•Domestic alliances versus international alliances (technology advances and sophistication of technology domestically-market opportunistic versus technology driven •Key events and institutional drivers, Development timeline for certain products, Patenting timeline, Strategic alliances by firm for key firms, Process or product type vs. Firm size, sources of initial technology, indigenous efforts to assimilate foreign technology •Differences with patented brand drug (get this from ANDA or from FDA, USPTO) •No. of public health versus other drugs •No. of new filings in different export markets •World's largest manufacturers of certain broad product categories: (also financing)•Position of Indian firms, Type of Indian firms, ownership structure within Indian industry •By product line and specific product and process categories

DESCRIPTION OF INTERVIEWS

Companies were first communicated with by email or phone asking if they would be willing to be interviewed. Only those who evinced an interest were communicated with and interviews were scheduled. Structured but open-ended interviews were carried out with scientists and engineers, academics (many of whom were scientists), CEOs, heads of R&D, senior executives, venture capitalists/bankers and policy officials. The smaller number of policy makers explicitly identified is misleading. An important strength of the sample is that many of the academic interviewees had held multiple positions, often in government or directly advising or leading government committees on industrial research or technology transfer, and so were able to provide both the details of the sector's history and provide perspectives from the State's standpoint.

Interviews lasted 1-2 hours on average. Hand-written notes were made of every interview. No taping, or typing was done during the interviews since they occasionally required touring of facilities while speaking, and many interviewees looked comfortable when they saw I only had pen and paper. 50 Indian interviews were carried out by August 2003 (47 in person with 3 additional telephone interviews) and 4 more by telephone by November 2003.

A challenge to the entire research was that in many cases, detailed descriptions of particular process innovations have had to be left out because it has been impossible to tell the story, fascinating though it is, without revealing the identity of the company (or the person) to a reader who is familiar with the two sectors. Thus references to people interviewed, even public officials, is represented as non-attributable quotes. Company names are mentioned directly only when the information used is in the public domain. On way to circumvent this difficulty for future research is to administer a survey in addition to case work, thus allowing aggregates to build a general typology of capabilities and their dynamics.

COMPANY PROFILES

Pharmaceutical firms

India's top five companies by domestic sales in 2001, Ranbaxy, Cipla, Sun Pharma, Zydus-Cadila and Wockhardt are described briefly below. Their advances are tracked as evidence of specific features of structural and technological change in the Indian pharmaceutical industry. Data obtained was a combination of detailed secondary data derived from industry statistics, and reports, interviews with CEO and R&D personnel, and supported by some phone interviews with India's leading firms. The second sample describes companies working in biopharmaceuticals in Bangalore and Hyderabad for whom primary data was collected through detailed structured, open-ended interviews. The first thus provides a lens on the pharmaceutical industry, and the second on more localised innovation occurring in the use of biological tools in the same industry.

1. Ranbaxy was India's largest pharmaceutical company by sales in 2003, and its second largest in 2001. It began in the 1960s and emerged as India's largest company by sales in 2002 by acquisition, inching past Cipla. It is an 8000 staff company and has become India's largest R&D investor by % of sales revenue, at 6% in 2002 It pioneered the break into the US generic drug market, ranking 9th in the US in 2002, 11th in the worldwide generic drugs market and growing faster in its US markets than US-based pharmaceutical companies (at over 120%).[6] It has announced the move to add one thousand more R&D staff into its Indian laboratories. It has moved into New Chemical Entity research and licensed out both promising molecules as well as platform technologies. Ranbaxy has exports into over seventy countries, a manufacturing presence in seven countries, and distribution or sales operations in over twenty five.[7] It has recently moved into cardiovascular, central nervous system and nutritional products. It also conducts contract manufacturing. The company has supported the introduction of product patents into the country.

2. Cipla has been India's largest pharmaceutical company for many years, and has built a presence mostly in generic drugs and contract manufacturing. Established in the early 1930s, it is one of India's oldest pharmaceutical companies. Its recent successes have been built AIDS, respiratory drugs and drug delivery systems. They have patented drug delivery platforms and stirred up controversies with MNCs through their AIDS cocktails, combining off-patent with on-patent drugs, a strategy legal in India. The company manufactures over 250 drugs from initial stages and has successfully commercialised many public sector research outputs. In recent years, Cipla has also been a strong advocate of keeping product patents away from critical public health drugs such as those for AIDS and has pioneered the introduction via manufacturing of many hitherto unavailable drugs into India.

3 Sun Pharmaceuticals was a relatively late entrant in manufacturing, beginning in 1983 with the psychiatry drug segments. It has since moved into chronic care areas such as cardiology, psychiatry, neurology and gastroenterology. In addition, this product diversification has been partly responsible for increased market penetration (as have numerous acquisitions, some from Indian-based MNCs) moving them from a rank of 107 in 1988 in domestic market share to 5th in December 2001 and to 3rd nationwide in 2002. It also retains its core expertise, ranking first nationwide by key customers for neurology and psychiatry. They have acquired many bulk drug facilities in recent years.

4. Zydus-Cadila is one company of the Cadila conglomerate involved in health care, information technology, agri-business and travel businesses. Cadila is also a flagship, multi-part company with various healthcare divisions. Cadila Healthcare Ltd is to launch a 5th division Zydus Neurosciences. It has a generic drug business. It was established in 1951 and has since developed a biopharmaceutical initiative and has an R&D staff of over 150 scientists. Its founder and director was credited as a champion of the

[6] IMS Health 2002

[7] Ranbaxy company website, http://www.ranbaxy.com

process-patent-only Indian Patent Act of 1970 and a director of the IDMA, the Industry association representing Indian-owned firms. Cadila was the first company worldwide to introduce a leprosy immuno-modulator, Immuvac. The company has 445 products registered in 50 countries, a presence in the US, Kenya, Nigeria and Russia and a sales presence in 43 countries worldwide. It has expertise in gastro-intestinal, cardiovascular, pain management, respiratory, gynaecological drugs and biological segments.

5. Wockhardt is India's 5th largest company by sales and is 2700 people strong. It specialises in anti-infectives, pain and inflammation, cough, psychiatry, medical nutrition and biopharmaceuticals. It focused its New Chemical Entities in anti-infectives and anti-Sepsis and has an R&D staff of over 300. It's R&D expenditure is now 7% by sales revenue, one of the highest nationwide. It is also one of two companies in the leading five with an ambitious biotechnology R&D program, having completed human insulin for market launch.

Biopharmaceutical firms

Some of the firms are drug discovery or service firms, others are drug development or manufacturing firms. Three firms which are drug-development and manufacturing-focused, are described below to highlight some of the common points emerging from multiple interviews. Findings from these and remaining companies are described without attribute for reasons of confidentiality. These 3 company profiles are sourced entirely from public domain information and thus are described here.

1. **DRL**

Dr. Reddy's Laboratories is a mid-size pharmaceutical company showing one of the highest rates of Indian innovation in new chemical entities and out-licensing of promising molecules. It comes from a history of bulk drug production and with a founder with experience in IDPL. DRL has grown rapidly, entering the top 10 Indian firms in the last two years, and focusing efforts on both NCEs, NDDS as well as the generic drug market. In addition, DRL has created an off-shoot, Aurigene Discovery, which combines drug discovery with contract research services in genomics, among other things. DRL can be listed under both pharmaceutical and biopharmaceutical categories. It remains one of Hyderabad's star companies and one of its biggest bulk drug manufacturers while still maintaining a smaller biopharmaceutical segment.

2. **BBIL**

Bharat Biotech is a new company, starting up in only 1983. It is a dedicated vaccine producer, being one of the first Indian firms to generate the Hepatitis B vaccine locally. It has the largest GMP manufacturing facility for vaccines in Asia and has recently produced streptokinase.

3. **Biocon India**

Biocon began in the 1970s and has evolved into a biopharmaceutical company with enzyme and fermentation expertise arising from catering to food and brewing companies. Using fermentation-based drugs as an entry point, and fermentation as a route for genetic engineering, Biocon has parleyed its strengths in enzyme studies into a drug manufacturing business, along with clinical testing and contract research arms. It has been innovative in stabilisation of conditions for genetic engineering, and has patented a solid state fermentation reactor which has resulted in higher yields. Biocon produces generic drugs as well, particularly Statins. Its profile is further developed in later chapters.

USING THE CASE STUDY

Technological innovation is often studied through patents and publications, but the history of economic development shows us that many developing countries have few incentive structures that rewards either patents of publications. This has been the case in Indian pharmaceuticals, which has only recently begun to patent vigorously. Indian publication data also poses mixed benefits, because while publication history exists, companies have published unevenly. I use both these indicators to further analyse my cases, as opposed to having them lead the methodology. Similarly, elements of firm strategy in building capability are difficult to capture through surveys, and impossible through statistics. Detailed interviews, however, do get to the heart of the matter. Finally, there is no better method of collecting historical data on the company's trajectory than interviews. Because of the codified and tacit nature of technology and the heightened competition between firms, surveys, no matter how rigorous, cannot capture information that is inherently proprietary, or the processes that resulted in specific technological and economic choices made. Although detailed interviewing cannot uncover all information, it is a research tool that comes closest to the means of understanding and describing incremental changes and dynamic equilibria. The case analysis has some disadvantages of its own: selection biases (particularly for surviving firms across history) as well as the relevance and generalisation of findings. To balance out the benefits and negatives, I have chosen the three types of indicators to track technical (process development) and non-technical capabilities.

The table below, modified from de la Mothe and Niosi (2000, p. 232) indicates the advantages and disadvantages of each secondary method. Thus a combination of available sources in addition to interviews was used to provide a more complete picture to test existing explanations than any one alone can provide.

Table 1 Secondary indicators

METHODS	ADVANTAGES	DISADVANTAGES	AVAILABILITY/CONCERNS IN INDIA
Patent analysis	Tracks location of innovation/inventor and close of knowledge	Assumes high propensity to patents, cannot capture the different economic values of different patents	Indian patent trends less intense than in OECD countries, problems of equating Indian and international patents in terms of economic value
Surveys based on samples	Can provide new knowledge about from structure and industry structure	Sampling errors, in any industry with proprietary and tacit information, there may be disclosure or description problems	No detailed surveys available on Indian pharmaceutical and biotech firms on technological and market advance, thus has potential to reveal new information
Publication citations	Can track important scientific supply and reveal networks of innovators	Same problem of surveys; proprietary and tacit information cannot be captured in publicly available documents	Good availability, but limited applicability to early trajectories of firms. They have potential in tracking technological assets in terms of founders, scientific officers
Databases, population surveys	Large population groups for firms covered	Population errors	Same as in sample survey case

LIST OF SAMPLE QUESTIONS

The interviews were structured but open-ended and a non-exhaustive list of sample questions is included below. Not all questions were used in every interview, but similar companies (in terms of size, technology and research experience) were asked similar sets of questions and in the same order to the extent possible. Biopharmaceutical companies were asked slightly different questions, because of the difference in technologies/tools used. Because their field is moving more rapidly than in generic drugs, for example, their strategies (and suitable policies to assist them) were different. Telephone interviews required fewer questions since the time available was shorter.

1. Tell me about your personal scientific/technical or business history.
2. Why has you company A been so successful in recent years? What distinguishes it from other firms B, C, D?
3. Do you perceive a " technological gap" between India and the US, say? How would you describe this and can this be reduced, if so, how? Can you give me an example of technological advance of this type within your firm?
4. What do you consider to be innovative? How do you evaluate this?
5. Are your company's challenges technological or strategic/business? Can you tell me how they are different?
6. What has your relationship been with Public research institutes?
7. How has technology transfer experience been in this drug segment-from MNCs and from PRIs? Can you give me examples of successes/failures?
8. How have you built process capabilities within the firm? Were the challenges in the laboratory? How did you scale-up to manufacturing the drug?
9. Why did you select the specific host culture? What were your choices? Who identified the paths available?
10. How have you combined your team to deal with this innovation? Where did you begin your search? What public domain information did you use?
11. What have been your challenges in entering the US market?
12. Which regulations are challenging? Why?
13. What historically, have been the government policies most useful to your firm?
14. Why did your company move into X product segment?
15. How did your company find a new way to make product Y? Please describe the process.
16. How important is intellectual property regime change in 2005 to your company's future in the US market?
17. Why did you select the transition country markets?
18. What is the trade-off between time to market and investment rates? How do you decide when some technology is worth making, versus buying?
19. Is there a difference in your approach between product development and process development? Why have you picked strategy S?
20. Which are your biggest markets?
21. What policies would most assist you today? Which assisted you most in your early history?
22. Which are the most promising areas for technological advance within your field?

Chapter 4 Trouble in the Making: Induced Process Development and Manufacturing in Indian industry[1]

4.1.Introduction

This chapter is grounded in a re-analysis of existing innovation categories, products and processes and buttressed by primary data from interviews and various secondary data sources. It builds the timeline from first national policy push in the public sector effort to the emergence of large-scale private capability in manufacturing, roughly corresponding to the period between the early 1950s and the late 1970s. In contrast to previous analytical writings on the Indian industry, the focus here is on the ways in which learning was induced and sustained. This manner of advancement allowed later stages of learning to emerge under very different environmental and technological constraints..

This chapter has three primary goals. First, it contributes a framework of understanding learning based on public health drugs within the context of technological "entry" points. This framework also emphasises that political vision and nationalistic principles of self-sufficiency were critical components of the industrial policies that allowed India's pharmaceutical industry to prosper. Although the vision was often preferentially applied, it was used to build indigenous capabilities. Without this socio-political defence, the industrial framework for pharmaceuticals is likely to have never taken off the way the history of other developing countries has shown. Divorcing the economic or policy analysis from national vision and political will is a misguided venture.

Second, the chapter shows that government-led research and development efforts combined with a massive push to build manufacturing capacity were important markers for the industry's inception, survival and growth. It confirms previous research that early protections to shield the industry from foreign competition –particularly through a process patent regime and restricted licenses for manufacture to foreign firms, were critical for many Indian companies.

Third, it highlights that process development and manufacturing capability was a critical pre-cursor to current innovation in the industry. Those companies that could scale-up from laboratory to factory were more likely to be both later imitators and innovators. However, process capabilities were built

[1] With due recognition to an excellent title, "Trouble in the Making: Pharmaceuticals", The Economist (US), August 31st 2002. As discussed earlier, the term "Process Capability" will is used here to refer to the capability within a company of developing a viable manufacturing method for a given proposed (product) outcome. In the pharmaceutical industry, process capabilities usually refer to process research, lab to factory scale-up and manufacture. Here they refer specifically to process chemistry/biology and process engineering.

(and could only sustain in the very early stages) within a tightly controlled selection environment. This theme sets the stage for the next chapter where process development forms the central bulwark for innovation capability, and which emerged, strengthened, into an entirely different innovation environment.

There were two distinct efforts between 1950 and 1980, one in the public realm, the other in the private one. In the early stages, the public sector acted as the repository of most R&D as one traditionally thinks of the term, with private firms engaged primarily in manufacturing in well-worn paths. In the classical sense, the public effort provided access to technologies and some search efforts that allowed private firms to learn-by-doing. However, the story was richer than this. The private effort, at various times in the first 20 years of the policy initiative, straddled a variety of interactive search and learning efforts, which later came to differentiate leading firms from others.[2]

4.2.The Indian pharmaceutical sector

There are many reasons to study the Indian case. India is the world's second largest country, has one of the developing world's most sophisticated pharmaceutical sectors, and is the 4th largest producer in the world and has a market value of about US$3.8 billion producing 8% of worldwide production volume, but presently only 1.1% in terms of value, or 13th worldwide (OPPI, 2000).[3] While industrial R&D in India is approximately 1/3rd of total R&D expenditure, of which half is financed by the private sector across sectors and has increased to about 70% of industrial R&D spending (Mani, 1999), the pharmaceutical sector has traditionally not spent heavily in R&D. Indeed, industry averages range from

The range of capabilities is uneven, but broad. It is one of the world's largest producers of bulk drugs (active chemicals) as well as formulations (the branded medicine sold to customers). Indian pharmaceuticals are growing at 14% or so per year and 58 foreign-owned multinational companies (hereafter MNCs) have manufacturing bases in the country, but account for less than 30% of market share in 2001. It is an industry characterised by huge volume, a large number of producers and competition. There are 3 main segments to the country's firms, which the Indian Drug Manufacturers' Association (IDMA, founded 1961), representing Indian-owned firms, indicates as being made up of

[2] This can be shown by the characteristics of the current successes, but there is a selection bias. Unfortunately the types of learning curves and improvements in search and productivity are unavailable that could contribute to a longitudinal study of firm efforts.

250 large manufacturing firms and 9,000 small-scale units alongside approximately 7,000 unregistered small-scale units in 1993 (cited in Lanjouw, 1997)[4] Other estimates are a total of 2,257 units in 1969-'70 and 20,053 in 1999-'00 (OPPI, 2000), and 12,000 firms, 2,900 large-scale units, employing almost 500 000 people (OPPI Annual Directory, 2000). All agree the market is competitive, which an observer could glean from the sheer numbers of units and from business reports and investment profiles of many publicly listed companies. The country also has a significant science and technology infrastructure, and after China, is the world's largest emerging market. Institutionally, India offers a mixed bag of national planning and socialism combined with capitalistic industries. It has had a rich and varied technological planning history, with pharmaceuticals and chemicals as core industries in this regard.

The sector also has global reach in more mature segments. Some Indian firms are generic drug leaders worldwide in specific products. India is the 17th largest exporter of pharmaceuticals in the world and had over 65 WHO certified production facilities and over 15 FDA facilities in 2000.[5] India is estimated to have the third largest scientific personnel worldwide in absolute terms. Almost 70% of India's high-tech exports is composed of pharmaceutical and inorganic chemicals.[6] Furthermore, Indian public research institutes (PRIs) are seeing large increases in external collaborations as well as commercialising PRI-led innovation in pharmaceuticals.

Indian pharmaceutical companies have strengths in generics product manufacture, particularly related to process chemistry and engineering, and have increasingly becoming more sophisticated about developing international R&D alliances. India's patenting profile is also primarily tipped in favour of drug process patents. In addition, there has been a recent spurt of activity in the "buy" versus "make" option for the latest technologies, with increasing acquisitions of manufacturing and research facilities in the US and UK by cash-rich Indian firms.[7]

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[3] This difference between manufacturing output and value is related to the fact that India is indeed, a large volume producer of "easier" (cheaper) drugs. However, it also hides the fact that it competes in the generic drug market of other countries, where the drugs are cheap, but not necessarily "easy" as Chapter 4 describes.

[4] The Organisation of Pharmaceutical Producers of India (OPPI) represents foreign firms in the country as well and was founded in 1965.

[5] Press Information Bureau, Government of India, Fact Sheet on Chemicals. Also at http://pib.nic.in/archieve/factsheet/fs2000/chemical.html

[6] The high-tech export statistics for India are for manufacturing and do not include one of the fastest export growth segments: high tech computer services.

[7] Ranbaxy for example, has manufacturing facilities in 7 countries, including China, Ireland, India, Malaysia, Nigeria, USA and Vietnam. It is currently the 9th largest generics manufacturer in the US after entering in 1995 and had one of the fastest rates of growth (131%) of any pharmaceutical company within the United States. (Company reports, citing IMS Health 2002). It is also the 11th largest generics manufacturer worldwide, exports

The learning by Indian firms in both mature and emerging product segments has been situated against a rich institutional backdrop of early government intervention. The country is unique among developing countries (indeed special among many advanced industrialised countries as well) in having a high percentage of Indian-owned firms competing with multinational firms (MNCs) in the top 100 firms. The relative performance of Indian firms versus MNCs is also highlighted by Pant (1995) who studied a sample of 218 chemical and 202 engineering firms and found no significant difference in the extent of export orientation of foreign firms (MNC affiliates) and Indian ones except in the pharmaceutical sector, where Indian firms outperformed foreign firms.

Lastly, while the world pharmaceutical industries show coalescence around core business skills derived from chemicals and developed in consumer products, the Indian pharmaceutical firms are mixed. Diversified business groups (DBGs) with varying backgrounds in telecommunications, petroleum, power and construction, made ambitious forays into drug discovery and development. Manufacturing still remained largely the province of medium-sized pharmaceutical bulk and formulation producers. Hyderabad city alone, in the South, produced more than 40% of the country's bulk drugs through mostly medium-sized manufacturing units.

The Indian pharmaceutical sector also provided a significant foreign exchange opportunity, in addition to being a source of technology exchange, with pharmaceuticals now being 4% and growing, of total Indian exports or totalling US$840 million in April 2000-March 2001 (OPPI, 2000). Furthermore, Indian companies exported to more than 100 countries worldwide and were aggressively expanding in transition economies, for example, being the second largest supplier of pharmaceuticals in Ukraine, second only to Germany.[8] This South-South market expansion in developing and transition economies represents almost 20% of potential world market share. (Scrip, 1998, p. 120) In recent years, Indian companies also became more aggressive in the generics or off-patent drugs market, moving quickly to assure exclusive licensing.[9] In the year 2000, Indian drug exports crossed the US$1.5billion mark for the first time and various projections placed the value of the industry to grow to about US$25 billion

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to over 70 countries, with field presence in 25 of them and manufacturing in the 7 listed above. In 2003 alone, upto October, Alembic bought a Dutch company, Aurobindo Pharma bought a Chinese pharmaceutical unit, Cadila Healthcare a French formulations business and Wockhardt bought C P Pharma (UK) (Centre for Monitoring the Indian Economy, CMIE and various news reports.)

[8] Compiled from Indian Embassy reports and trade reports of export councils.

[9] A recent success, for example, has been Dr. Reddy's Laboratories (DRL) receiving FDA approval to market Fluoxetine the generic for blockbuster drug Prozac from Eli Lilly for an exclusive 18-month period after going off patent. This generates large payoffs and a monopoly position for generics manufacturers.

in 2010. In biopharmaceuticals, statistics are more difficult to come by, although estimates of current revenues are US$380 million for all biotech applications to US$ 270 million for biopharmaceuticals alone in 2002-'03.[10]

The pharmaceutical industry in the 20th century has come to be characterised by a few notable company names, many large multinational companies from the US and Western Europe, some originating in the late 19th and early 20th centuries. Markets are segmented based on regulatory and patent regimes, per capita health spending and by insurance systems. The world pharmaceutical industry is characterised by certain economic traits: market structure (oligopoly and concentration and stability to the configuration), barriers to entry (product differentiation, economies of scale, predatory pricing), multinational dominance and global spread. Innovation is thus defined by who does it, what price or product/process strategies are adopted, how large their output can get and what barriers they face-economically, technologically and institutionally.

The pharmaceutical industry has moved from advances in chemistry: specifically, discovery, categorisation, and isolation of effective components of many age-old drugs such as the alkaloids, quinine and morphine; from serendipitous and persistent discovery of organic synthesis clues arising from by products of abundant industrial by-products such as coal tar; from advances in the fields of pharmacology and chemotherapy. (Drews, 1997) These led to rapid growth in the field and a swathe of new institutional arrangements for health insurance, university-industry relationships, and State funding of research. It is these very same institutional arrangement, specifically managed health care and costs of medicines (and those that will be reimbursed) that have significantly affected the direction of innovation in the industry today, particularly in the US. These changes have since affected companies in India since new policies introduced in the US to lower costs of health care, have opened the market to other (generic drug) entrants. In each sector, the companies that discover drugs may well be different from those that develop or manufacture them.

The largest market for most lucrative drugs remained that of the US, accounting for 42% of worldwide pharmaceutical sales, with a high per capita spending on drugs, and US ownership of seven of the leading ten pharmaceutical companies worldwide, and nine of the leading ten in biopharmaceuticals.

[10] Biospectrum, Vol 1, Issue 7, September 2003, p. 10, Corporate Office Gurgaon, Haryana, India. To put these numbers in perspective, these revenues are a fraction of the R&D budget of the world's leading pharmaceutical company, Bristol-Myers-Squibb, at US$5003 million or of the world's largest biotechnology (biopharmaceuticals) company Amgen, with R&D spending of US$865 million.

While the technological changes after the 1970s created new opportunities for firms, in reality the pharmaceutical industry worldwide looked remarkably static in terms of company names, company brands and national ownership patterns over the last century.[11] Worldwide, R&D spending in the pharmaceutical industry was US $30.4 billion in 2001, a rise of 17% from the previous year. There were also 48 blockbuster drugs, 8 of which recorded sales of more than US $ 3 billion each. The generics industry alone will account for a large portion of the market since over US$80 billion worth of patented drugs will go off patent in 2005. Structurally, mergers and acquisitions continued, with about 37% of structured around drug discovery arrangements. The alliances were primarily for therapeutic categories such as 21% for cancer, 19% for infection/anti-viral and 15% for neurological treatments. Overall, pharmaceutical outsourcing was estimated at US$ 8 billion.[12] Overall, biotechnology companies grew in size and in research spending, as did pharmaceutical companies.[13] In the last few years, the leading products worldwide were lifestyle drugs and those catering to diseases of predominantly urban, advanced industrialised markets.

4.3.Pharmaceutical technologies

The technological learning that firms engage in is not influenced by technological choices alone. Nevertheless, the technologies provide differentiated challenges and opportunities to firms and may limit them to certain types of product or process categories or to formulations or even packaging alone.

Firms face three main types of technology in the drug industry:

1. The discovery of new drugs, usually referred to as Product technology
2. The development of viable production methods, usually referred to as Process technology (note these may also include improvements to existing technologies) and
3. The use of multiple dosage forms (Formulations) and methods to store, transfer and distribute therapeutics (Packaging and storage technologies)

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[11] Besides mergers and acquisitions that concatenated their names, the leading companies stayed steady. Structurally there is a further division of labor, with pharmaceutical companies separated from biopharmaceutical companies. The top 3 worldwide pharmaceutical leaders by absolute R&D spending (often with their own biopharmaceutical divisions) were Bristol-Myers Squibb (US), followed by Pfizer (US) and Glaxo Smithkline (UK). Of the top twenty pharmaceutical firms, 11 were US firms (Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Abbott, Merck, Eli Lilly, Pharmacia, Wyeth, Schering-Plough, Medtronic and Baxter), two UK (Glaxo Smithkline and AstraZeneca) two French (Aventis and Sanofi-Synthelabo), two Swiss (Novartis and Roche), two Japanese (Takeda Chemical and Sankyo) and one German firm (Schering). (Source: "The Corporate R&D Scorecard 2002", Technology Review Magazine, December 2002/January 2003)

[12] All statistics quoted here from Ernst and Young, "Defining Issues in the Pharmaceutical Industry", January 2002-September 2002, Partners in Vision

Worldwide, countries are seen to either have all three types of technological capability, or to have specialised in one or other type. [14] Roughly speaking, many developing countries are primarily formulators and packagers, while advanced industrialised countries possess all three types of technological capability, but may focus mainly on product and process technologies.

The drug development cycle for both synthetic and biological drugs is complex technologically and prohibitive financially. The nature of innovation and the costs of undertaking it are significant. Some estimates put the cost of a new prescription drug reaching the market at US$802 million, while ten years ago the cost was $231 million, in 1987 dollars. (Tufts Centre for the Study of Drug Development, CSDD, and DiMasi et al, 1991, 200) A modern drug development cycle with distinct product development and process development sequences are shown below. The process development is also a three-step process from process research to prototype and pilot development to commercialization from lab to factory. In industrial biotechnologies, a typical 3-step process consists of preparation phases, fermentation phases and recovery and purification phases. In pharmaceuticals using biotechnologies, the stages are similar.

[13] Note, the high % of R&D spending of sales revenue for biotech versus pharmaceutical companies. Some biotech firms have R&D spending rates that outstrip revenue streams, pointing to dependence on pipeline drugs.
[14] Perhaps the dichotomy most evident in pharmaceuticals, matched in few other industries, is the importance given to companies who undertake product, rather than process, innovation. This dichotomy has been translated into the relative importance given to drug discovery findings versus companies that engage with process development and manufacturing. Innovation in the industry is projected in the media and in much academic literature on the industry primarily in terms of product technology, but process innovations are also important.. This is in part due to difficulties in measuring process innovation. Pisano (1997) shows the variation in importance of processes over products and lists pharmaceuticals as "process enabled".

Table 4.3.1 Typical modern pharmaceutical drug development cycle

PRODUCT DEVELOPMENT PHASES	**PROCESS DEVELOPMENT PHASES**	
	Broad process category	**Actual process contribution**
Lead compound discovery		Target, hit and lead identification
Pre-clinical development	**Process research** (Alternative synthetic routes, Routes scaled up for laboratory use, Lab-level production for clinical studies)	Lead optimisation and Candidate drug pre-nomination (Medicinal chemistry route)
Clinical development	**Process research** and **Prototype and pilot plant development** (Scale-up to pilot plant, Kinetics and scale-up uncertainties, Production for clinical trials, Design of plant equipment)	Concept testing (Early scalable synthesis)
Regulatory approvals	**Prototype and pilot plant development** and **Ramp-up from laboratory to plant** (Scale-up to commercial plant-level, Scale-up of processes for commercialisation)	End of early phase and start of Advanced scalable synthesis
Marketing and distribution	**Ramp-up from laboratory to plant**	Advanced scalable synthesis

Adapted from Pisano (1997) and Federsel (2003)

From the time of target, hit and lead identification, itself a process of many years of search and experimentation, the time taken until launch comprises investment in lead optimisation (upto 2 years), pre-nomination and nomination of potential candidates (less than a year), followed by testing of the concept-including proof of principle and concept- (upto 3 years), development for product launch and filing for registration with regulatory authorities (upto 2 years) and finally, launch itself (1 year approximately). However, overlapping these product development segments are the contributions of process R&D investments. These comprise medicinal chemistry work during the lead optimisation and candidate pre-nomination and nomination phase and approximately two segments of early and advanced scaling efforts. The first generation effort, of scalable synthesis, occurs during approximately three-quarters of the concept-testing phase. The remaining portion of this phase and

that of the development for launch and launch phases uses the advanced or second generation scaling effort.

The two sets of broad technology categories are therefore not independent from the product cycle's standpoint, although the division of labour between different types of firms may relegate product development and process development to separate organisational divisions within the same firm.

What characterises the process development in particular are the skills necessary to scale up operations from laboratory to factory, or the ability to take a lab-scale process and have it operate without hindrance in a production setting at industrial-scale.[15] Some common process technologies that were revolutionary in the pharmaceutical industry were those for fermentation, which enabled commercial penicillin to be produced. Biotechnology is fundamentally based on process technologies since it attempts to create proteins that are difficult to create through standard chemical synthesis. The specifics of each stage are shown below for pharmaceuticals and biotechnology, highlighting the 'old' (synthetic) and "new' (biological) ways in which drugs are manufactured. A fuller account of differences between old and new types of pharmaceutical development is presented in the later chapter on the rise of Indian biopharmaceuticals.

For this dissertation, the focus in interviews and in analysing secondary literature was on the elements of business strategy that depend on process development that related to process chemistry and bio-chemistry (the process research component) and the process engineering (the pilot development and commercial plant transfer and start-up component). While undoubtedly other important production-related skills are involved, such as mechanical engineering, computation, or even inventory control, these are not at the core of this dissertation.

Within drug manufacture itself, there are two types of technologies that firms need to incorporate. The main elements are (a) Bulk drugs (active pharmaceutical ingredients in drugs, API) (b) Formulations (the move from bulk drugs into finished dosage forms -tablets, capsules, ointments etc.). The primary source technology for production of pharmaceuticals is the technology of bulk drugs production. However, few developing countries possess the capabilities of being able to manufacture bulk drugs

[15] To use a now classic example, although acetylsalicyclic acid was first synthesised in a laboratory in 1853 with acetyl chloride as an acetylating agent, it took more than 40 years with acetic anhydride as an acetylating agent for a scalable, large-scale production system to be put in place. The result was the phenomenally successful drug Aspirin from Bayer.

from scratch from local raw materials. Bulk drug producers can be of various types, generic or specialised suppliers to other innovating firms.

Section I

Section I highlights that technological learning is representative of more than economic and cognitive activities alone. It is rooted in a socio-political framework that allows economic (particularly industrial policies) to seek legitimacy and that stalls opposition. Learning occurred here through manufacturing capabilities that were not built in all possible profitable segments simultaneously. They were developed in certain product categories linked to "essential" drugs deemed important for the public's health-particularly antibiotics, anti-infectives and vaccines. The link between public health and "entry" into the product life cycle is described by the early policy choices for drug development and manufacturing, and further developed by an examination of product profiles of leading companies today and by examining which niches of public health they have built on.

4.4.Public health, private learning: Market entry and capture

> *" Technological self-reliance in food and medicine was an important basis for decisions"*
> (Interview with policymaker, Oct 15 2003)

For the purposes of this research, public health drugs can be categorised as all therapeutic and diagnostic products that serve large-scale health needs in developing countries, but are not restricted to communicable diseases alone.

Neoclassical explanations for technology advance have tended to pay little or no attention to the socio-political dimensions of economic choice. In these models, all firms know the "frontier", and all firms make rational choices, based on their resources/factors of production, of which technologies to invest in. There is little analytical room for the influence of the environment, in selecting firms for market success that fit a specific national profile or set of capabilities. Analysis of past Indian data shows that the role of public health in technological learning has been vastly underestimated. Besides its expected socio-political function, it served to act as both an entry and market capture instrument.

While a few of India's leading firms today emerged after the most intense phase of intervention by the State, many cut their teeth on government assistance. The sections below address the findings on the key role of public health on a variety of fronts, most importantly, as a technology "entry point" to

domestic and foreign markets alike as well as a route to market capture of the large domestic market in the early years. It also demonstrates how public health continues to be an important driver of gains to Indian firms many years later, primarily through international procurement.

Before 1947, the country was heavily dependent on imports of essential medicines. The duration of World War II proved especially difficult with large-scale scarcity of critical drugs. The early 20th century patent regime appears to have primarily served the interests of British manufacturing firms, and the majority of drugs were imported from Britain into India. Post-1947, Indian policy-makers and nationalists across a wide domain of interests pushed for socialist medicine unsuccessfully though national health schemes. Although these were unsuccessful, calls became ever louder for access to medicines for all citizens.

Perhaps not surprising for a newly independent country, debates raged on the role that foreign multinational companies should play in the manufacture and sale of essential medicines. Technological self-reliance was seen as an extension of Swadeshi (indigenous) and Swaraj (self-rule). The public sector effort characterised the 1950s and 1960s, while the 1970s and 1980s comprised a critical second phase where nascent Indian-owned private sector capabilities had to be fuelled by the State, channelled into essential medicines, and to be pushed to compete against foreign firms. However, public health as a national goal, but subverted to build private indigenous companies is particularly well highlighted in the case where the government licensed Salbutamol to Cipla, instead of Glaxo.[16]

Indian independence in 1947 brought with it a nationalistic fervour for addressing its most basic needs, in food security and health, however, until 1983, there was no formal national health policy for citizens, nor was the public sector able to provide an impetus to the industry by itself. Nevertheless, the Indian republic post-1950s embraced a vision of access to medicines, even if its actual efforts to

[16] While this was being debated in the Indian Parliament, Glaxo protested the selective application of national interest clauses, *"Parliament stands for the right of the people to be heard on issues involving national interests. Yet it is now being seen to be spending more of its time and attention on the causes of private parties who wish to further their own economic interests. Certainly, decision taken in respect to individual companies, could in certain instances, have relevance to national policy. But when Parliament is drawn into protracted wrangles in which individual interests appear to be the main consideration, it is not surprising that some of its own members are provoked to voice their protest against the manner in which proceedings are conducted. Again, when the Government, in arriving at its decisions, appears to apply the rules of national good to one party and waived those very rules for another, national policies lose their meaning altogether."* Glaxo News, Bangalore Depot Special-a Glaxo Laboratories in-house publication, May 1982. Cited in J. S. Mazumdar, Background Paper in Sen Gupta (Ed.), 1986.

sustain an ambitious pro-poor agenda with public health infrastructure as a focus met with failure. The governments also sent out mixed signals about who could spearhead the effort for technological self-reliance. Symptomatic of this policy malaise,, even as late as the Sixth Five Year Plan, the government supported the public sector effort in principle but this was not reflected in its budget.[17]

Pharmaceutical technology straddles multiple levels of sophistication, from simply importing and repackaging imported medicines that are already fully manufactured to the ability to locally produce bulk materials from raw materials that are themselves locally available. While public health medicine supply can tolerate importing in finished medicines, public health drug security requires some significant degree of indigenous capability. Independent India with its twin banners of meeting basic needs as well as becoming self-reliant after a harsh colonial experience forged a new technological identity around public health access and drug supply.[18] Technology transfer experiences of the time had been unsuccessful (see Sahu, 1998, for example), and foreign firms were tolerated because of their access to the latest technologies.

Public health was a critical political economy instrument that channelled large-scale investments into State-structured categories of drug manufacture. The early years were characterised with a widespread fervour for access to medicines for the poor. But while "essential" medicines served to propel manufacturing license allocation to Indian-owned firms and provided incentives for increased plant capacity investments, the national focus on public health did something more. It created a system of demand and supply-side initiatives in which public health drugs acted as a technological and market entry point for Indian firms. Firms learnt by technology transfer (often via the public sector, which itself had negotiated transfers from other countries) and then scaled-up and manufactured, assured of significant local procurement and (later) exports. But the scale-up and manufacture was not always straightforward. Process patents encouraged firms to seek new ways to the same end drug, and the price controls forced this process to become ever more efficient. Thus the learning that firms were channelled into reaped dividends in terms of (a) process capabilities-chemistry and engineering, particularly in terms of yield for antibiotics and (b) more efficient plants (economies of scale over time).

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[17] The Plan indicates, "*the public sector should take a leading role*", but the allocation was Rs. 150 crore for the public sector and Rs. 250 crore in the private sector for drug production. (Rs. 1 crore = Rs. 10 million) Government of India, Sixth Five Year Plan document.

[18] In later years, at the 34th World Health Assembly of 1982 in Geneva, Switzerland, Prime Minister Indira Gandhi in a well-publicised speech, expressed an attitude common in the country at the time, "The idea of a

One interviewee stated:

> *"Public health gives big markets, large collaborative structures, thus steady advances."*
> (Interview)

In the 1970s, the concentration of formulation producers varied by category. Less technologically challenging categories such as Antacids had 12 firms while cardiovascular formulations showed 6, central nervous system analgesics 20 and, vitamins 16 and anti-pyretics 10. However, the most concentrated category for technological and public policy reasons was broad and narrow antibiotics, with 21 companies in this group alone.[19] The largest segment of market share continues to belong to antibiotics at 19.4% (Org-Marg) in 2000. The data indicates that Ranbaxy, Cipla, Zydus Cadila and Wockhardt all began their technological trajectory in anti-infective segments and have since diversified outward from this core area. For Ranbaxy and Cipla, anti-infectives provided the decades-old launch pad for exports and for the push into generic drugs. The public health policy focus on anti-infectives also provided a ready national procurement system and steady growth, although with increasingly lower margins. In very recent times, the antiterrorism alerts in the US have driven up the profile of antibiotics such as Ciprofloxacin, which constitute core products for Ranbaxy and Cipla.

Some companies like Ranbaxy have a sustained history in antibiotics, which has become a modern-day asset in the US market, with its recent bio-terrorism scares. Anti-tubercular are in principle, an attractive segment in all developing countries, where both TB and HIV (with patient susceptibility to TB) are prevalent. Lupin, one of the leading manufacturers, holds over 40% of the anti-TB market in the country, but has struggled to meet some efficacy requirements abroad.[20] However, TB medications only have 2.4% of the market. Foreign firms have traditionally dominated "non-essential" segments of the market and Indian companies like Ranbaxy and Alkem are positioned in the top 10 products due to their public health drug capabilities in Cephalosporins and quinolones. (Org-Marg, 2001)

The table below was created to demonstrate the continuing effects of older policies on the product structure and market orientation of India's five leading firms and some of the interviewed biopharmaceutical firms. The entries were made based on potential candidacy for procurement-not all companies have directly benefited from procurement. All come from significant process development

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better-ordered world is one in which medical discoveries will be free of patents and there will be no profiteering from life and death". (IDMA bulletin, 15, no. 25, 1984, p. 391).

[19] Singh (1985), pp.72-81.

histories, many have benefited from significant demand-side incentives, particularly procurement (P) for public health markets and some have directly benefited from past production allocation of manufacturing licenses. Their public health core has also been important in their market access strategies in the generic drugs market in the US and other advanced industrialised countries. Only Biocon and Sun do not have public health drugs as a significant part of their product portfolio, and the former emerged from a history of industrial applications, not health. All have significant plant capacities and almost all have invested in GMP infrastructure.[21]

Table 4.4.1 Public health legacy of leading Indian pharmaceutical companies

Company	Candidate for Procurement (P)	Market Access: GENERICS (G)/US or Other	Public health-core therapeutic segment (e.g. vaccines antibiotics or antibacterial)-*See next table*
Ranbaxy	Yes	G US O	Yes
Cipla	Yes	G US O	Yes
Sun Pharmaceuticals	Yes (some antibiotics)	G US O	No
Cadila	Yes	G O	Yes
Wockhardt	Yes	G US O	Yes
DRL	Yes	G US O	Yes
Bharat Biotech	Yes	G	Yes (Vaccines)
Shantha Biotechnics	Yes	G	Yes (Vaccines)
Biocon	Yes	G US	Yes (antibiotics)

[20] One study cites problems with Lupin's single drug rifampicin products sold in South Africa. The drug showed varied bioavailability and pharmacokinetic variation between patients. (International Journal of Tuberculosis & Lung Diseases (6(4):356-361, April 2002)

[21] Although the top 5 firms are profiled here, the dissertation research studied a vast number of other firms including some that no longer exist. In this section, as in other ones, the leading five are representative of a broader sample of learning techniques and capabilities. However, these other firms are differentiated from those who compete on cost alone and have no innovative products or processes as indicated by secondary data.

Table 4.4.2 Public health segments of leading companies

COMPANY	ANTIBIOTICS OR ANTIBACTERIALS[22]	VACCINES
Ranbaxy	Yes	Yes (planned)
Cipla	Yes	No (possibility of conducting clinical trials only for AIDS vaccines developed elsewhere)
Sun Pharmaceuticals	No	No
Cadila	Yes	Yes (launched)
Wockhardt	Yes	Yes (launched)
DRL	Yes	Yes (planned)
Biocon	Yes	No
Bharat Biotech	No	Yes (launched)
Shantha Biotechnics	No	Yes (launched)

Vaccine suppliers also abound where procurement is vital. India's pulse polio drive nationally can administer approximately 80 million doses in a day alone. In addition, as the domestic market crowds (as is occurring in Hepatitis B more recently), companies began to move into overseas markets. The Serum Institute alone exports products to over 130 countries, and is the leading producer in India for both DTP and MMR vaccines.

Although these are not large revenue segments for many of the companies, they have strangely enough found a new avenue back into the market for the same reason: a new need in advanced industrialised countries in particular, and not enough manufacturers. In particular, large multinational companies have moved out of these segments over time, providing opportunities for firms from developing countries, which may be able to manufacture to US FDA and other standards.

Furthermore, the core focus and use of public health as an entry point has allowed a form of collective learning with private firms and public research institutions (PRIs) coming together to commercialise (particularly) public health drugs. The table below indicates the extent to which diseases relevant to the Indian population such as vaccines for the rotavirus, rabies, malaria, TB, combined vaccines (pent valence and other), dosage and delivery form, have resulted in alliances with PRIs (both national laboratories as well as universities) and continue to be a source of competitive advantage for firms. Firms that engage in public health research also have access to R&D financing from the government

[22] A common distinction is that antibiotics are substances produced by living cells, while antibacterials (or antimicrobials) are synthetic chemicals used to fight against bacteria. However, this classification has its own problems since many antibiotic derivatives can themselves be partially or completely synthetic.

and international donor agencies, which will be discussed in Chapter 5. A further benefit to this core focus is that it provides almost automatic access for Indian firms to PRIs abroad as the table indicates from data collected on recent collaborations. However, linking to public domain research is not a guarantee of success. Even with barriers to transfer lowered, learning is not straightforward, as later chapters demonstrate when discussing data from biopharmaceutical firms.

Vaccines are an "ideal-type" for public health drugs and Bharat Biotech International Limited, a vaccine producer, among other specialties, is a classic example of how private R&D can be linked to public efforts and funding when the research focus is public health. The box below indicates its current portfolio of national and international public research linkages. Some are with national public health programs in the India and the US, others are with international initiatives for public health.

Table 4.4.3Sample collaboration with public research in 2003

National	Indian Institute of Science-Bangalore Centre for Biochemical Technology-New Delhi JN Centre for Advanced Research - Bangalore Institute of Biotechnology Institute of Human Genetics-Bangalore All India Institute of Medical Sciences - New Delhi International Centre for Genetic Engineering & Biotechnology (UNIDO) - New Delhi. Institute for Virology, Pune	Third generation Hepatitis B-Vaccine Vascular Epidermal Growth Factor, Development & scaling up of a Vaccine candidate against Malaria
International collaborations and grants	Centres for Disease Control-Atlanta (USA) National Institute of Health-Washington DC (USA) National Child Health Institute (USA) National Institute of Allergy & Infectious Diseases (USA) Stanford University (USA) Program for Appropriate Technology for Health - PATH Global Alliance for Vaccine Initiative - GAVI (USA) Malaria Vaccine Initiative - MVI (USA) Children's vaccine program- PATH Spread Program, World Bank	Rota Virus Infection Rota Virus Infection Rota Virus Infection Development & scaling up of a Vaccine candidate against Malaria Development & scaling up of a Vaccine candidate against Malaria Development & scaling up of a Vaccine candidate against Malaria Development & scaling up of a Vaccine candidate against Malaria

Source: Bharat Biotech International Limited company reports

Cadila alone has R&D collaborations with over 30 research centres in the country.

This focus on public health drugs to meet the large demand within the country and in other developing countries, has not been relegated to synthetic drugs alone. Many recombinant technologies for public health drugs in recent years have also been developed through collaborative efforts with public research partners and with some public funding.

Table 4.4.4 Public-private collaborations for recombinant R&D

PRI	Company	Recombinant product
International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, M.S University of Baroda	Biological E	Hepatitis B vaccine
Institute of Microbial Technology (IMTECH), Chandigarh	Bharat Biotech Cadila	Streptokinase
Indian Institute of Science (IISc), Bangalore	Cadila	Follicle Stimulating Hormone
Centre for Biotechnology, New Delhi, M.S. University of Baroda	Bharat Biotech Biological E	Epidermal Growth Factor
Indian Institute of Science, Bangalore	Shantha Biotechnics	Human Growth Hormone

Source: TIFAC "Recombinant DNA Therapeutic Products", January 2002, cited in "Biotechnology in India", Final Report, A. Maria, J. Ruet, M-H. Zerah.

In addition, public policies geared towards production of antibiotics for example, impinged directly on technological capabilities:

Table 4.4.5 The link between public health and manufacturing technology

Public health element	Relevant policy	Impact on Indian firms
Manufacture of essential drugs (e.g. Antibiotics)	Local production and allocation to Indian firms Canalisation of raw materials Public sector manufacturing companies Technology transfer of relevant strains to private sector Compulsory licensing and Controller's powers in setting the terms of settlement. Public procurement Drug price controls	Increased domestic market share in essential drugs Increased production capacity in antibiotics More private firms entering vaccine development Greater access to technologies for Indian firms Lowered risk, some technology upgrading Lowered prices in some categories, evidence for excess manufacturing of non-essentials and formulations

Companies such as Sarabhai Chemicals, heavily into antibiotics, ranked consistently in the top two between 1980-'86, and was since overtaken by companies such as Ranbaxy, Cadila, Lupin, Cipla and others. Ranbaxy and Cipla both developed considerable antibiotic and anti-infective portfolios and Cipla subsequently went into AIDS therapies as well. Lupin grew as one of the largest tuberculosis drug manufacturers in the world, and became the world's largest producer of ethambutol. Ranbaxy ranked first in total sales today, was 9th in 1983, twenty years ago. Its learning path has been structured around antibiotics, particularly Cephalosporins.

The learning pathway for most firms was therefore structured to adapt to national policy empathy for public health, even if many millions of Indians continued to lack access to basic health care. Prices fell in some segments, the industry grew larger, and process capabilities were enhanced, as subsequent sections demonstrate.

Section II

Section II lays the groundwork for introducing the policy environment in which the Indian pharmaceutical industry was born. Not only was State intervention high in the early years of post-independent India, but it continued at a high level of involvement for over a decade. The late 1960s and early 1970s were critical periods for building capabilities, but these alone were not enough. It attempts to anchor current capabilities in a historical climate where private firms were technologically unsophisticated, and where the public research infrastructure was established to create the basis for a later innovation climate.

4.5.1950s-1960s: A crucible for learning: the public sector effort

> *"IDBL and the public sector were critical in the Hyderabad story. People don't like to hear it but the public sector was very important."* (Interview, June 12th 2002)

The Indian pharmaceutical industry began in the early part of the 20th century. The archival history is sketchy on this front. Indian capability in pharmaceuticals arose predominantly from investments initially made within the public sector companies and research institutes (PRIs) and increasingly adopted and nurtured within the private sector. Indeed, in some cities like Hyderabad, the migration of people and their capabilities from public sector laboratories such as IDBL has defined the basis for the spurt in private sector pharmaceutical capability.[23] Post Indian economic liberalisation, beginning in

[23] Indeed, people like Dr. Anji Reddy, CEO of Dr. Reddy's Labs, were straight "imports" from public sector to private and served to create the defining vision for the private domain research and manufacturing capability. A

the mid-1980s and galvanised by the balance of payments crisis of 1990, forced previously distinct and largely isolated public and private sector R&D strategies closer together, the former because of funding constraints and a renewed mandate to work closely with industry, the latter because of the weight of the global regulatory regime for both patents and certification.[24]

The table below provides a chronological view of the development of pharmaceutical and biotechnological capability in India. Specific policy measures such as New Drug policy and the Patent Act appear to have had significant effects on firm-level learning as the chapter shortly discusses.

Table 4.5.1 Chronology of institutional change in Indian bio-pharmaceuticals

Period	Initiative and Effect
Pre-1947	British-friendly patent law. Imports dominate the market. Local production low and multinational companies thrive. 1901 First Indian pharmaceutical company reported open 1904-1907 British establish several research centres for tropical diseases. 1914-1918 World War I. Imports cut off. Local demand grows and local industry builds capability 1919 First drugs safety law enacted 1931 Drugs Enquiry Committee established to monitor prices and propose price controls. 1939-1945 World War II Imports cut off. Local industry continues to grow. India begins to produce conventional drugs as well as vaccines and serums. Dysentery and leprosy drugs begin.
1950-1970	Indian independence and creation of the Republic. Period of rapid industrialisation building on pre-World war II manufacturing experience. Establishment of public sector research centre network in key locations. Hindustan Antibiotics Limited (1954) and IDBL (1961), Hyderabad established, for example and becomes an industry pioneer. 1955-1960 Second Five-Year Plan. Government places pharmaceutical industry together with other chemical-based industries for integrated development planning. 1960-1965 Third Five-Year Plan. Government fuels public sector enterprises growth nationwide. Manufacturers produce penicillin, streptomycin and antibiotics of the tetracycline group. Firms establish foreign collaborations to acquire technical knowledge and develop synthetic drugs and alkaloids.

combination of advances in the public sector and its capabilities, and its inefficiencies, led to the eventual movement of skilled researchers out to seek their fortunes in the business sphere. However, these same people thus also recognise the ways in which effective public-private collaborations around R&D and technology transfer, can be structured.

[24] WTO rules for patent law harmonisation appear to have created new need for State intervention.

1970-1972	Drug Price Control Order 1970 serves to severely regulate the market vis-à-vis wholesale and retail prices. Serves to increase competition and number of smaller companies. Patents Act 1970 recognises only product patents and patents for production processes for 7 years. Serves to create protections for Indian firms while they learn and excel at process chemistry and engineering.
1978	New Drug Policy structures manufacturing capabilities through procurement and allocation
1980-86	1982 establishment of National Biotechnology Board. 1986, end of the Board's mandate. Identified focus areas for biotechnology and hurdles. 1986 Establishment of the Department of Biotechnology (still in existence) under the Ministry of Science and Technology to coordinate multi-disciplinary S&T capability building.
1986-1991	Objective to establish a network of biotech-competence in the country. Grants disbursed liberally. Creation of the Centre for Cell and Molecular Biology, Hyderabad Also creation of National Institute of Immunology, International centre for Genetic Engineering, New Delhi (with United Nations Industrial Development Organisation, UNIDO, assistance) Serves to deepen and widen the competence network and institutionalise biotechnology importance in the country
1990	Establishment of the Biotechnology Consortium of India BCIL, a public-sector company to provide public financing to industry in the absence of private venture capital.
1991	Balance of Payments crisis. India's New Economic Policy. Rethinking of State role. Funds crisis deepens for national laboratories. Liberalisation of the Indian economy continues (begins in the mid-1980s). Multinational firms increase presence with relaxed controls on foreign ownership. However, increased competition eventually forces some MNCs to exit the market.
1991-present	Continued DBT activity, including new Millennium initiatives to network private and public sector capability. CSIR laboratories continue to open up and work with industry. IISc and NCBS also open up and deepen links with private sector. State-funded research in national centres continues for public health remedies.

The story of Indian indigenous capability emerging through a strong Indian-owned private sector is a complex one. Against a backdrop of in-country paucity of antibiotics, vitamins and anti-diabetes drugs, a Pharmaceutical Enquiry Committee was established in 1953 to address industry-wide imbalances in supply and demand of essential drugs (antibiotics and synthetic bulk drugs). The history of essential drugs such as penicillin shows technological challenges in scaling-up and manufacturing large volumes.[25] The results were that industrial licenses were effectively tied to company agreements to locally manufacture bulk drugs from initial stages. However, foreign-owned firms were reluctant to do so. There appear to have been at least 5 distinct phases in India's move from dependence to

[25] The US war effort required large volumes of penicillin but firms lacked the ability to obtain large yields. Eventually, a "mission-mode" UK initiative led to the development of industrial-scale penicillin production to treat the ravages of war, Landau, Achilladelis and Scriabine (Eds.), 1999.

technological self-reliance.[26] In the first phase, Hindustan Antibiotics Limited (HAL), with technical and financial help from UNICEF and the WHO, and the Indian Drug and Pharmaceuticals Limited (IDPL), with assistance from the Soviet Union, manufactured on a large scale to become the largest producers in the Third World for antibiotics and for synthetic drugs of local supply. HAL and IDPL were at the forefront of the public sector pioneering effort in pharmaceuticals until a private sector emerged capable of investing in innovation. Their legacies have been mixed successes on technology imports, but robust advances in indigenous antibiotic production and essential bulk drugs. An important sector for indigenous activity was vaccines, where a series of Indian efforts in public research institutes and universities were jump-started by the government.

The story begins with the initial investments in public sector capacity, a predecessor of private sector capability today. The 1970 Patent Act did not act to create protection for domestic learning in a vacuum. Indian technological capability in the pharmaceutical sector had already been established early on with national research centres such as the Hindustan Antibiotics in Pimpri in 1954 and the Central Drug research Institute in Lucknow, and the Indian Drugs and Pharmaceuticals (IDPL) in 1961 in Hyderabad, and later, the Pune-based vaccines research focus. The network of public sector capability in pharmaceuticals was to reduce dependence on multinational companies (Singh, 1985).[27] While the public research institutes suffered from a variety of inefficiencies, they provided nevertheless an institutional mandate for dedicated resources in "mission-mode" for health research, particularly those of a public goods nature such as vaccines. Their ability to create nation-wide technological capability in manufacturing low-cost drugs, while also providing a platform for some pockets of high-quality scientific research, created the base for both the pharmaceutical industry as well as recent advances in biotechnology. They also provided an undeniable source of technically skilled, professional managers who migrated to the private sector and thus created a network of localised historical links between public and private R&D and manufacturing institutions. Indeed, many interviewees were of this category.

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[26] This differs from Sahu (1998) who studies four phases. The data shows public sector investments, building domestic manufacturing capabilities in the private sector, containment of foreign firms, further growth of Indian firms in capabilities and size, and finally, export-launches of Indian firms in multiple overseas markets.

[27] In addition, a variety of medical universities, teaching hospitals and a large, well-trained medical community, had created the institutional mechanisms for referral, diagnosis and distribution of prescription drugs. Although health insurance did not exist, a vast network of Central Government Health Service outlets provided the civil and military services with prescription drug coverage to some extent and has since expanded the private insurance and hospital markets to the middle-classes.

Technology was sourced into the public sector and the relatively advanced capabilities were built. In HAL alone, first-time process development advances were made in penicillin, streptomycin and gentamicin, among others. The sources of these technologies were varied, penicillin through the US via the World Health Organisation and later upgraded from Toyojozo in Japan, gentamicin again trough both the US via the WHO as well as the Hungarian company Medimpex (Sahu, 1998).[28] Process advances were also made in Streptomycin Sulfate and Ampicillin Anhydrous. The other major public sector laboratory, IDPL with five sites had distributed capacity ranging from antibiotics, synthetic drugs, and drug and chemical intermediates to formulations and surgical instrumentation. In Hyderabad, its centre for synthetic drugs and in Rishikesh for antibiotics, IDPL successfully manufactured 40% of India's bulk drug requirements as late as 1983. 24 drug technologies had process development and manufacture in-house and pilot-scale-up was completed for 14 others. While only 6 countries worldwide knew how to manufacture Vitamin B6, IDPL also accomplished this and provided consultancy services for many years to a variety of developing countries through the UN Industrial Development Organisation (UNIDO) partnership (Ibid.) Two decades after the founding of the public sector effort, almost 90 drugs were manufactured locally that had been previously unavailable. Categories of drugs needed across the country gradually became available, and at lower prices, such as antibiotics (synthetic), analgesics, antihistamines, arthritic medications, some nervous system medications, essential anaesthetics, some oncology drugs and routine vitamins, particularly important for public health programs.

HAL also grew from its entry point into a single antibiotic for bulk drug manufacture, to a producer of human and animal therapeutics and agricultural products. Its in-house R&D created Aureofungin (commercialised since 1962), Hamycin (commercialised since 1962) and Penicillin G-Acylase (commercialised since 1992). In addition to IDPL and HAL, with manufacturing capability, a variety of research efforts in chemical research were founded, such as the Haffkine Institute was founded in Mumbai around plague research, the Indian Institute of Chemical Technology (IICT), Central Drug Research Institute (CDRI) and the National Chemical Laboratory (NCL). Drugs like paracetomol[29], ethambutol, metronidazole, were subsequently manufactured in the country and exported. For high value added drugs like AZT, and cyclosporine indigenous technologies later became available.[30] CDRI has since also developed a one-a-week contraceptive pill (Saheli), the only non-steroidal contraceptive

[28] Schering (US), with best technology for Gentamicin, was unwilling to sell without equity in HAL Sahu, 1998).
[29] CDRI scientists found a new process for manufacturing the painkiller Paracetamol by using phenol instead of paraminophenol, which was scarce in the country.
[30] AZT, or Zidovudine, an anti-AIDS drug, was manufactured using a variant of the original process, by IICT and was subsequently transferred to Cipla for manufacturing.

pill worldwide. Local resources and skills were also nurtured to some degree, with commercial impact. Within Ayurveda, an Indian traditional medicine, new therapies were found. CDRI helped create entirely new drugs: *Guggulipid* for cholesterol reduction from the plant *Commiphora mukul* ("Guggul"), Memory Plus ™ using baculosides extracted from the "Brahmi" plant used extensively in Ayurveda, for memory enhacement, *Vincristine*, a high value-added oncology drug developed from *Vinca Rosea* plants ("Sadbahar")[31] Private firms speak even today of the effects of the public sector's importance in both research and development as well as manufacturing in the initial foray of entering the domestic market and capturing key segments for national production and national needs. Interviewees cited the importance of (a) public infrastructure, even if needing upgrading (b) public R&D advances, even if significantly under-commercialised (c) public sector personnel and their migration to the private sector.

The public effort in pharmaceuticals, arising as it was amidst significant heavy industry investments in industries such as petroleum, steel and chemicals, was an effort marked by significant long-term effects-both negative and positive. The public research and development network appeared to have been marked by some significant successes in both pharmaceutical and later, biotechnological, areas. It was also successful at building a relatively sophisticated physical and skill infrastructure for a developing country, and the skill-base in some sub-fields such as structural chemistry, for example, was equal to the best in the field worldwide. In pharmaceuticals in particular, as the next section demonstrates, the public effort was successful in pioneering the private sector foray into large-scale and numerous manufacturing efforts. It is here, in the induced learning process, that the public effort was most successful technologically, and through long-term professional development, and subsequent migration, that its impact was felt most. The private sector was transferred key technologies sourced through the public R&D units, then policies were geared in conjunction to induce private firms to invest in scale-up and manufacture, in many cases this being accomplished successfully for the first time in the public sector itself.

Nevertheless, the process was, perhaps not surprisingly, marked by considerable inefficiency and systemic contradictions. While the best skills were born in public laboratories, they were not nurtured in public research over the decades.

[31] Traditional Indian herbal names are shown in parentheses and quotation marks.

"The fact that the public sector was a driver for initial technology capabilities does not preclude the fact that it was also marked by lack of overall inventiveness and repetitive projects."

"In CSIR there are no younger people. I developed {XX} for drug discovery there. No information was available, efforts were isolated and my group was trying to reinvent the wheel" [32]*(Interview, July 5th 2002).*

That technology transfer is an inherently costly, uncertain and expensive process can be gleaned from the experiences of both public sector undertakings. For a variety of reasons, the transfers for antibiotics were problematic, leaving HAL no choice but to develop in-house capability with initial transfer packages being unfruitful. In addition, technology rapidly became obsolete, so in-house efforts were also eventually stymied in their search and experimentation timeline. In particular, the company was plagued by low yields in the fermentation process in antibiotic manufacture. Production scale also became a problem with government policy resulting in a fragmentation of plant capacity and unit size, resulting in inefficient yields. IDPL suffered with Soviet technology transfer and was reduced to holding on to obsolete technologies and languishing inventories of machinery and produced drugs. Substantial delays also took place due to problems sourcing raw materials, design and equipment alternations, and the plant began production in 1970, almost 11 years after the initial Soviet agreement. It continued for a long time to have idle installed capacity for obsolete bulk drugs and formulations, while India's private firms were beginning to ramp up in more modern technologies (Sahu, 1998) Obsolete technologies continued to be used, and in the 1980s and 1990s, some critical drugs such as cardiovascular ones such as streptokinase were still being imported, with no promise of public effort appearing likely.

This trend continued well into the 1990s when 'sick' public sector firms of all kinds were gradually placed on an auction block for privatisation.[33]

[32] Council for Scientific and Industrial Research and its 40-odd public research laboratories in industries ranging from leather to pharmaceuticals. The "XX" in parantheses in the quote was utilised for confidentiality reasons.
[33] The Indian government has recently given private companies 60 days to submit tenders for privatising HAL. In the state of Andhra Pradesh with Hyderabad at its core, with 40% of the country's bulk drug production, some of these public assets such as IDPL are now being converted into State and private consortia-run R&D units.

Section III

Section III devotes itself to a closer investigation of the policy process that allowed private sector capabilities to evolve and the ways in which foreign firms were contained while local firms grew. In particular, it develops a narrative about two important policies on patents and prices, the first of which is usually viewed as the primary explanation for advance in Indian pharmaceuticals. The ways in which local firms were protected by the government while they grew and the limits placed on foreign firms are described in Sections III and IV.

4.6.1970s-1980s: Process patents and price controls

The initiation of technological entry into important segments by the public sector was underway, but industrial production was complicated by a reticent and inexperienced private sector. Multinational companies overran the market and planners were troubled by the death of essential medicines and the cost of those that existed. To reign in foreign firms as well as to discipline local ones, the government pressed into service two strategic tools: process-only patents and price controls. Both were structured to transfer technological opportunity into the hands of Indian-owned firms and to build a vast number of Indian manufacturing units. Process development-new routes to old drugs in the simplest form, and new routes to new drugs in the desired form, were both objectives of the policy mix. The process patent regime allowed entry into hitherto inaccessible technology areas by issuing compulsory licenses, explicitly favouring process innovation, further driving down costs, but stepping up process development innovation in the industry. Price controls followed and were first initiated to prevent excess profiteering in essential medicines, but created significant pressures to drive down manufacturing costs and create process innovations so that retail prices would reflect this trend.

Process patents:
A pro-poor stand of the Congress government created the 1970 Patents Act of India, which generated protection for processes only, allowing Indian pharmaceutical firms to (a) provide versions of brand name monopolies at very low cost and (b) build up significant process chemistry capability.[34]

The high volume markets in India and in other developing countries made the last 30 years a particularly profitable time for Indian pharmaceutical companies, despite the low wholesale and retail costs of the drugs. The Patent Act made it more unlikely that foreign firms would conduct R&D in

India, but boosted process investments substantially in Indian firms and created the conditions for erosion of market power in foreign hands. A few years after the introduction of the Act, in 1976, for example, only 4 Indian firms ranked in the top 20 by sales, whereas by 1995, 13 of the top 20 were Indian companies and had cornered almost 85% of the market. In fact, of the top 50 sales revenue companies, 38 were Indian firms, and only 3 multination companies were in the top 10. (ORG-MARG, various years) The Indian Patent Act highlighted the fact that the government was not averse to licensing, which continued, nor to patents themselves, but was strictly against monopolies, which it saw affecting the prices of drugs for the masses. Product patents were not recognised, but patents for production processes were allowed patent production for 7 years. Furthermore, to prevent restrictive practices, the State could award compulsory licenses to other companies should the patent holder refuse to do so. The process patent-only regime had international repercussions and the Indian State held steadfast to its mission of technology transfer to private firms and access to affordable medicines. It was this dual purpose that carried the moral high ground that allowed private sector capability to eventually be built.[35] Unlike the perception that most drugs in the 'copying' phase were simply representations of piracy of a sort, in reality, the State-private sector compact had diverse characteristics: one the one hand, the State leaned on firms to upgrade technologically for "essential drugs" in exchange for key technologies linked to profitable markets, while on the other hand, the State structured markets to create indigenous capability in place of foreign firms. This latter set of policies however emerged only after many foreign firms balked at having to produce drugs for the "essentials".

However, the policy measures of the time, other than the patent legislation, and the resource constraints faced by firms created choices between products and processes in a manner that product life-cycle thinking does not straightforwardly suggest.

"We couldn't afford products, so we chose processes."(Interviewee)

While a series of policy measures were put in place to assist indigenous firms, the 1970s and 1980s reflected a growing repeated investment in processes rather than products. The public health push had created sets of technologies which could be improved upon through processes, and the patent regime

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[34] The Patent Act was unremarkable in its core elements: process patents and lack of recognition of product patents. Most countries in the world flirted with this combination of protections for decades, and many European countries in particular, moved out of this regime as recently as the late 1990s.

[35]The juxtaposition of access to medicines and company growth was brought to light in one interview: "*Patent law was intended to help to protect small inventors, but has been perverted by big pharmaceutical companies. I am a doctor also, so I feel this way*". (Interview, company board member, July 5th 2002).

reinforced this trends, providing further incentives for cash-strapped firms to invest in areas other than drug discovery, which most lacked both the technical and financial means to carry out.

In the early years, as both public and private actors appear to have faced each other with mutual suspicion as carriers of technological assets and capabilities, public health drugs or broadly categorised "essentials" acted to bring both parties together. The eventual re-structuring of the patent regime to patents for processes alone, was done with private sector profitability and public health access alongside.

> *"The generic drug industry told us, 'we don't have problems with product patents, per se, but we must be able to license key technologies. We don't mind paying royalties or sharing revenues.....don't cut us out of profitable markets'*
>
> *"....their R&D strategies came later".*
> (Interview with policymaker, Oct 15 2003)

The process patent years had significant effects on Indian capabilities.

> *"The patent phase was critical for Indian firms to develop capability. {Scientists} have to get experience and do it. If they are bright, they will spot opportunities and break away to do their own work."*
> (Interview, June 14th 2002)

On the one hand, it allowed Indian firms to license key technologies from foreign firms in the country; on the other, with greater long-term implications for learning capabilities, it provided Indian firms considerable incentive to find new processes to manufacture the same drug, which were then potentially patentable. The ability to scale-up and manufacture an existing drug thus became a natural path for many Indian firms, with search and experimentation over many years, putting them on a trajectory markedly different from their developing country counterparts and many in advanced industrialised countries.

Current explanations by scholars and some in the industry ascribe all subsequent successes to the process patent regime. However, as later sections describe, this period of protections and the creation of learning opportunities for indigenous firms, was primarily an initial and powerful pathway to market success. Only firms that could successfully scale-up and manufacture, and in some cases, compete with foreign firms, could thrive. These firms had to invest in distribution and marketing networks and continue to keep their channels of technology access open. What this period succeeded in accomplishing was to create a set of skills that could not be easily duplicated by foreign firms or

other local competitors. These were tacit capabilities that rivals could not quickly master unless they had gone through the same time-consuming search and experimentation process to find a viable path to an existing drug.

As with many other protections, the time finally came when international pressures to change the patent regime became marked. In the 1980s, as the first international intimation of the impending pressures emerged from the Trade in Intellectual Properties (TRIPS) of the General Agreement on Tariffs and Trade (GATT), Indian policy makers and private firms alike had to plan a time when product patents might be re-introduced. The TRIPS Agreement anticipates that all members of the WTO adopt minimum standards on patent laws and elaborates on the details of such laws, but rallies against the historically appropriate idea that a national patent system should be commensurate with a country's stage of development and evolve accordingly. A significant element of deliberation for developing countries emerged from the Doha Declaration on TRIPS Agreement and Public Health, adopted on Nov 14th, 2001, allowing each country the right to grant compulsory licenses (and determine the basis of such award) on key technologies/inventions if they pertain to public health problems.[36] For India, there are a variety of features that need modification in the existing patent regime to have it conform to the TRIPS requirements, among which are the increasing of the existing term for pharmaceutical patents from 7 years to 20 and outside pharmaceuticals from 14 to 20 years, thus extending the monopoly rights of companies. The Indian Parliament has enacted an Amendment to the patent regime through the Patents (Amendment) Act 1999 to provide for "mailbox" and exclusive marketing rights obligation, as well as the Patents (Second Amendment) Act 2002 to convert the 1970 Patents Act to comply with TRIPS during the 10 year transitional period from 1.1.1995 until 2005 when the full conversion to the TRIPS requirements occur. Before 2005, a Third Amendment will be introduced to provide a product patent regime for all areas of technology not presently covered by the 1970 Patents Act. More details on the TRIPS Agreement are provided in the following chapter.

Price controls:
The policy successes of the 1970s arose by the combination of market restructuring through changed appropriability conditions from the new patent regime, the skill-base that it engendered in process development, and the further learning forced on firms by creating price ceilings. An additional measure of preferential licenses also allowed firms further opportunities to learn.

[36] WTO/MIN(01)/DEC/2

Price ceilings have been commonplace in many countries in this industry. Underlying the Indian push for public health and 'essential' drugs was the concern that drugs be cheap and accessible by all citizens. The Drug Price Control Order (DPCO) was instituted formally in 1970 and subsequently revised in 1979, 1987 and 1995, and more recently in 2002, when greater numbers of drugs have been removed from price controls.[37] While the DPCO, 1970 indicated that a firm's pre-tax profit from sales of pharmaceuticals should not be greater than 15% of its sales from pharmaceuticals, firms could set their prices accordingly, since any excess revenue had to be given to the government. The concern was with overall margins, not on a by-product basis. The revisions in DPCO, 1979, made the process significantly more cumbersome for companies since the Order required price limits on 370 specific categories of both bulk drugs and formulations.[38] The Kelkar Committee of 1984 recommended revoking price controls on many drug categories so as to liberalise the system and allow the sector to grow with greater profitability. This resulted in the DPCO, 1987, which reduced the number of price controlled substances from 370 to 142.These ceilings on prices resulted in extremely low drug retail prices in many categories, and its legacy has been largely positive. While the decade had begun with Indian drug prices for essential medicines among the highest worldwide, the following decade concluded with drug retail prices among the lowest.[39] Besides mark-ups on drugs being restricted, the controls were strict because they set normative numbers (not directly associated with the cost of production) on price ceilings, thus drastically reducing profit margins and forcing firms to find cheaper processes to the same end. Overall profitability in the industry fell from approximately 15.5% in 1969-70 (just before the introduction of the Patent Act) to 8.8% in 1980-81 (just after the introduction of price controls) to 4% in 1985-'86 (just before the first wave of drug price liberalisation in 1986 after significant industry lobbying). Nevertheless, the controls on the industry were still significant.[40] In recent years, low pricing levels also have curtailed market growth. In 2000, volume

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[37] Until the early 1960s, India had no price controls of any form. The Chinese invasion in 1962 prompted policy makers to worry about the costs of medicines under a state of Emergency. The Drugs (Display of Prices) Order was promulgated in 1962, followed closely by the Drugs (control of Prices) Order in 1963 and the Drug Prices (Display and Control) Order of 1966, by which time all producers had to gain government permissions for any price increases (*History of Drugs Price Control, Role of NPPA in Drug Pricing*, National Pharmaceutical Pricing Authority.)

[38] The actual pricing formula was Retail Price = {Material Cost (MC) + Conversion Cost for the dosage form (CC) + Packing materials cost (PM) + Packaging Charge (PC)} X (1+ Maximum Allowable Post Manufacturing Expenses (MAPE)/100) +excise duty. Note: MAPE was a mark-up on costs, allowed to cover sales and distribution, and covered retail and wholesale trade margins. The 370 drugs were split into 3 categories, each with a different MAPE, with essential drugs having the least at 40% MAPE and Category IV with 60% MAPE.

[39] The Hathi Committee Report of 1975 stressed the importance of the public sector's role in the pharmaceutical manufacture and availability and the DPCO revisions in 1979 reflected this concern to some extent.

[40] Profitability here is measured before tax and as percentage of sales revenue. All figures from the Hathi Committee Report, 1975, RBI Bulletins, OPPI various years.

growth was about 8% while price growth was just over 2%. Profitability on average is estimated to be only about 8% where profit is calculated before tax as percentage of sales .

The classical thinking on microeconomic effects of price controls predict that if the price of a good is artificially set lower than the equilibrium price in the industry, the supply should shrink-since some firms find the process to be unprofitable, and demand exceeds supply. However, in the Indian case, price controls were not a lone policy initiative. They were combined with earlier process patents and later New Drug Policy measures, both of which created incentives for increased supply by indigenous firms. While data was unavailable to show the number of firms that became unprofitable, the eventual numbers show a significant rise in the total numbers of manufacturing units and their lowered average profitability[41]. Although price ceilings were introduced, they were selectively introduced for medicinal products deemed 'essential" by the government, and exempted for small-scale units, and acted in conjunction with process patent initiatives to spur process development skills, this time to lower cost. Thus the traditional interpretation of process development acting primarily to cut costs can be rejected in this period, as process capabilities took on a variety of goals, only one of which was to reduce drug costs. Even this latter measure acted to further enhance process skills as firms acted to find additional process techniques to cut costs. Largely due to a variety of policies spurring indigenous supply, the salutary effect of price controls was felt in increased competition and a proliferation (helped along by policies favouring small scale units) of small industry which was exempted from price controls as an incentive in certain drug categories, Production of certain drugs like paracetamol was since also reserved for the small scale organised sector. The intense competition led to Indian firms gradually pulling back from formulations (which witnessed greater growth for a period and larger number of entrants because of low price controls) and moving into bulk drugs (where MNCs had pulled back). Formulations were also an area of branded inertia favouring incumbents, and Indian firms lacking brand labelling, were at a disadvantage. Between 1970 and 1984, formulations grew by 12.5% while bulk drugs were growing at a higher 19.5%.[42]

The Indian market became characterised by intense competition due to the stringent price-control measures. Manufacturers scrambled to recoup investments once the price controls came into place, and a large number of small units that were exempted from the DPCO sprang up to service the significant

[41] One problem is that secondary sources of data on industry profitability show averages across all product categories. Therefore, the effects of price controls only on specific product segments (the "essentials") where the controls were particularly strict, cannot unequivocally be demonstrated. Overall, however, the industry grew in numbers of firms but showed reduced gross profit margins.
[42] Sahu, 1998, p. 80.

market demand. Many larger companies skirted the restrictions by focusing on "non-essential" drugs that were out of purview of the DPCO.[43] Gross profit margins, while quite low, overall, allowed some companies which could invest in scaled up plants and more sophisticated, faster and in the long-term, more profitable production technologies, to take a dominant position in the Indian market. The favourable conditions within the DPCO for smaller units, led to a current estimated 18,000 manufacturing units in the country, and over 3 million employed (in manufacturing, pre-and post-production areas). Of these, about 2,900 are large –scale units (Agarwal and Saibaba, 2001). Various industry estimates put the percentage of modern medicines consumed domestically and produced domestically at 90%.

While the controls led to increased process capabilities in mitigating price controls on profitability, they could have led to even greater technological investments and upgrading of capabilities in antibiotics, antidiabetics and the like. However, their success was mixed. With significantly lowered prices and process capabilities, they also brought with them shortfalls in highly controlled drug segments, especially essential medicines. The DPCO initially controlled prices on 347 bulk drugs. Of these more than 220 were produced in India. The 347 drugs were split into four categories: (a) Category I: Essential drugs[44] (b) Category II: Essential drugs (c) Category III: Non-essential[45] (d) Category IV: Non-controlled.[46] Private Indian and foreign firms alike increased their profit margins by openly moving into non-essential and unregulated segments. Category IV formulations, in particular, without price controls of any kind, flourished and India became an example of excessive formulations of dubious utility. One estimate suggests that in the 1980s the country was producing between 40,000 and 60,000 formulations.[47] By deliberately trying to increase access to essential medicines to the poorest, the price controls had perverted the system to increase production of dubious therapeutics at

[43] The importance of public health as an entry instrument into manufacturing prowess, market gains and access to key technologies is not incompatible with the fact that some Indian firms have avoided essential drugs and have themselves not substantially invested s in discovering drugs for many common Indian and developing country illnesses. Potential large volume sales do not necessarily cover the costs of drug discovery and development when more assured market segments are available. In fact, the significance of public health as a technological and market entry vehicle lies in its link to antibiotics and basic vaccines. Only recently have Indian firms developed in-house variants on existing drugs for AIDS and TB.

[44] The prices refer to wholesale prices and the mark-us was taken to include manufacturing profit margins, trade commissions, advertising and marketing costs and distribution. Mark-ups for Category I was set at a ceiling of 40% and at 55% for Category II. All calculations and figures from Drug Price Control Order, Government of India, 1970, 1979

[45] Mark-up for the less essential drugs in Category III was allowed upto 100% and Category IV was altogether unregulated in price.

[46] Drug Price Control Order, Government of India, 1970, 1979. "Essential" drugs was a controversial category, with both Indian and foreign firms alike disagreeing with the government on what should be considered essential and to what extent the price of the drug be controlled.

much higher prices. Since then, the DPCO has gradually reduced in stages the number of drugs whose prices it monitors and controls. Companies like CIPLA gradually gained recognition because of the low Ciproflaxin and AIDS drugs costs. While prices were still out of the reach of most developing country individuals, their public health cause provided a forum to question monopoly patents and the enormous riches that accrue to large companies while certain critical drugs for tropical diseases remain unavailable.

Indian advances have often been described primarily in terms of the process patent regime without a full understanding of why such a regime proved useful beyond "copying" opportunities. Most developing countries had similar policies, but only India built such an extensive pharmaceutical sector because of its multi-pronged approach and its "entry points" that could be defended. Many of today's advanced industrialised countries had similarly structured patent regimes in the recent past, but only India was able to build such robust growth over two decades. Indian policies to create a self-reliant nation were generated shortly after independence in 1947 and continued well into the late 1970s. Indeed, if anything, this is a lesson in sustained efforts by both policy makers and the nascent Indian private sector to ensure that their respective aims were fulfilled. Additional policy measures to build the industry are now described.

4.7.Monopolies, MNCs and accelerated Indian learning:

Learning does not occur without significant changes made to the environment within which firms reside and draw their resources. A protected environment for learning required the curbing of foreign firm dominance in the domestic market. These policy measures have led to measurable discrepancies between Indian and foreign firms in their investment profiles, with legacies dating back to this period where foreign firms were less willing to invest in R&D lest their products be immediately copied by Indian firms. It also shows how many Indian firms have since advanced in both technology and market share relative to their foreign counterparts. A sizeable ethical yardstick of company performance was applied to firms by policy-makers, the medical community and social activists. These were measured for each company primarily in terms of (a) the extent of bulk drug production (b) the investments in "essential" drugs (c) the technology-intensive profile of products.

Indian competition law dates back to the Monopoly Enquiry Commission of 1964. Its mandate continued to influence policies such as the Industrial Policy Resolution of 1956, the Industrial Development and Regulation Act and all planning undertaken through the national Five-Year Plans.

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[47] "Farce of Drug Policy", EPW, March 8-15, 1986, p. 409

The Commission concentrated on generating high levels of production while ensuring the greater social good, consistent with the directive principles of State Policy of the Constitution of India. These centred on the desire to control ownership and material resources to best serve the common good and to work against concentration of wealth and means of production to a few. The Monopoly and Restrictive Trade Practices Act, 1969, arose directly from these influences and from the workings of the 1964 Commission and was influenced in large part by corresponding legislation on prices, monopoly and fair trade in the UK, the US and Canada, among others.

The MRTP Act had the following goals: (a) The prevention of concentration of economic power to the common detriment (b) control of monopolies (c) prohibition of monopolistic trade practices and (d) the prohibition of unfair trade practices. (e) To ensure an environment conducive to healthy industrial growth, fair trade and competition. While the Act was modified a number of times, it was only in 1991 that size became de-linked from tensions of market power and monopoly status.

The tensions in sourcing technology from foreign firms also created the patent policies. While the MNC's reduced presence is in part due to the lack of product patent coverage, in reality, many re-entered the Indian market, despite the same patent regime, after economy-wide liberalization in the early 1990s resulting from India's Balance of Payments crisis. Indeed firms such as Hoechst Marion Roussel made the decision to start introducing new products in the Indian market despite the almost immediate imitative manufacturing by Indian firms, such as three new products in 2002 (anti-diabetic Amaryl, cardiovascular Cardace-H and Tavanic, an anti-infective). While many took advantage of the new market opportunity, only some, such as Aventis (List others) have invested in local R&D, claiming that Indian companies would copy the results outright. Certainly, the patent regime and price controls have acted to favor Indian-owned firms. The MNCs therefore survived on sales of branded drugs and of mature product lines, many in low-technology segments such as cough syrups and cold medications.

India's relationship to the MNCs was driven by two competing goals (a) to reduce national dependence on them in essential drugs and (b) to source new technologies from them. While one favoured curtailing their powers, allocating production away from them in essential medicines and reducing their size, the other was geared to allowing them to profit in return for technology transfer in antibiotics and vaccines. The move to allocate manufacturing licenses preferentially to Indian companies emerged only after attempts to induce MNCs to manufacture locally and in essential categories had largely failed.

The 1970s Patent Act combined with preferential allocation of manufacturing licenses for Indian firms also served to change the tide of fortunes for Indian-owned companies. Multinationals overran the market before the 1970s with almost an 85% market share. Local production was not required and most MNCs manufactured elsewhere, imported their drugs and sold at a sizeable profit to the captive Indian market. By the end of the 1990s, however, Indian companies dominated the market 60:40 and many MNCs had to introduce local production to compete. The extent of Indian penetration into the ranking of manufacturing firms is shown below for the top twenty-five companies in the domestic market in 1998

The table below shows recent market shares of leading Indian and MNCs alike in the domestic market, with shaded portions indicating Indian ownership.

Table 4.7.1 Indian and MNC domestic market share in Indian market in 2001

2001 rank	Company name	% Domestic market share
1	Glaxo-Wellcome (MNC)	5.7
2	Cipla (Indian)	4.7
3	Ranbaxy (Indian)	4.0
4	Hoechst Marion Roussel (MNC)	2.8
5	Sun Pharma (Indian)	2.5
6	Zydus Cadila (Indian)	2.4
7	Knoll Pharma (MNC)	2.3
8	Wockhardt-Merind (Indian)	2.3
9	Pfizer (MNC)	2.1
10	Nicholas Piramal (Indian)	2.1
		Total: 30.9%

Source: Operations Research Group-Marketing and Research Group (ORG-MARG), 2002 India.

The noticeable features are that only 10 foreign firms feature in the top 25 firms. Furthermore, the market concentration is sizeable while no single company exceeds 7% market share. In addition, some Indian firms are domestic product leaders even if they are below the no. 10 rank (For 1997-'98, e.g. Alkem for Cephalosporins was outside the list and Lupin, for TB bulk drugs was at no. 8). High R&D

spenders relative to sales are also well below no. 10 (for example, Dr. Reddy's Laboratories). (ORG-MARG Research Ltd. India Pharma Market, for rankings between September 1997-August 1998)

The market restructuring that protected Indian firms in the early years, combined with price controls, created a competitive environment, with indigenous firms slowly taking market share from foreign ones. The market was also marked by concentration of the largest firms, but considerable flux in their positions. Today, the leader holds a tenuous 5.7% and the top 10 combined hold 31% of the total market. While most known MNCs operate in the country, only 4 of them hold a place in the top 10. In 1976, for example, only 4 Indian firms ranked in the top 20 by sales, whereas by 1995, 13 of the top 20 were Indian companies and cornered almost 85% of the market. In fact, of the top 50 sales revenue companies, 38 were Indian firms, and only 3 multinational companies were in the top 10. Indian companies are pushing further into the top 10 list, with companies being replaced often in this ranking.[48] While Glaxo-Wellcome holds first position, its market share has decreased slightly over the last 5 years, while Cipla and Ranbaxy, both Indian-owned companies, have increased theirs.

Indian companies flourished relative to MNCs since the 1970s when a series of far-reaching policies were initiated to assist Indian firms. In 1998, Indian companies occupied 68% of market share, UK companies had 10% of the market, the US and German companies had 9% and other Europeans had 4%. (ORG-MARG Research Ltd., various years). However, Indian advancement in market share did not preclude high competition. In the same year, the top 5 companies held 19% of market share, those occupying 6-10th rank shared 11%, 11-15 10%, 16-20 9% and 21-25 6% and all others 45%.

Process patents without product patents allowed Indian firms to rapidly create drugs developed by foreign firms if the were able to find a new route to the drug. This created a disincentive for some foreign firms to remain in the Indian market; others stayed to enjoy the market's size. Foreign firms, especially multinational companies (MNCs), were not persuaded to manufacture from bulk drug stages. Various instruments of coercion such as the Monopoly and Restrictive Trade Practices Act, were used to limit the power of MNCs. At the same time, policies were constructed to allow them enough freedom so they remained as a source of superior technologies, although many MNCs enjoyed dominance with outdated products in the local market since local competitors were few at the outset.

[48] That competition is heavy is also evidenced by the fact that market share leaders in the Indian market are not necessarily the same as product leaders in the domestic market. Alkem, for example, an Indian-owned firm, has

But the far-reaching effects of the Patent Act and the New Drug Policy had implications beyond R&D and into manufacturing. Some leading MNCs did not conduct R&D in India nor were their manufacturing facilities USFDA approved, since they did not export significantly out of the country, unlike Indian firms.

Traditionally, MNCs depended on the parent company for capital requirements and thus their local capital base was quite low. They also depended heavily on the parent's product portfolio and other proprietary assets, rarely conducting R&D abroad. This was the case in India, where MNC local offices conducted hardly any novel work, and whose R&D budgets as a percentage of total operational income was low relative to leading Indian pharmaceutical companies. In addition, they had no drug discovery programs or biotechnology efforts to speak of relative to the leading Indian firms. Glaxo, Aventis and Pfizer had no significant locally-based research in India in late 2001, while at the same time their Indian counterparts were actively upgrading their research capabilities. Ranbaxy had already entered drug discovery in anti-infectives, respiratory, urology, cardiovascular and oncology segments, other technology platforms and biopharmaceuticals. Cipla had no biopharmaceutical element, but was attempting some drug discovery and development in anti-fungal, antihistamine and AIDS areas, while Dr. Reddy's Laboratories was conducting discovery research in diabetes, oncology, anti-infective and pain management. It had also begun search efforts in vaccines and biopharmaceuticals.

The tables below indicate the relatively low levels of R&D intensity of MNC subsidiaries in India compared to leading Indian firms and the limited extent of drug discovery, platform development or biotech investments. Companies like Astra Zeneca are examples of a change in this thinking.[49] As an indicator of the relative vigor in recent years of Indian firms, even those not among the top 10 by market share, and the corresponding stagnation of foreign ones, a comparison is useful between Pfizer (India), one of India's leading MNCs and Glenmark Pharma, a mid-size Indian pharmaceutical company. Both had comparable operating profits of 18-20% in 2001-'02, but the Indian firm had substantially higher operating revenues from the previous year (+39% versus 11%), primarily driven by an expanded product portfolio and new product launches by Glenmark, particularly in diabetes drugs. Pfizer performed well on low dependence on raw material sales. [50] But its performance is less

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the 6th most sold product, Taxim, a Cephalosporin, but the company does not rank among the top 10 firms by market share.

[49] AstraZeneca has recently invested approximately US$11million in its Bangalore R&D facility for furthering research in tropical diseases, most notably tuberculosis.

[50] Raw materials form a small proportion of sales at 31% and Pfizer has also lowered this through cost cutting over a long period.

attractive overall because its interest costs in particular, are low relative to Glenmark. [51] However although its net profit is low, Pfizer's return on Net Worth (RONW) is high because of low capital employed and ready-to-use brand names among others.[52]

Some of the reasons for the growth of Indian companies are the targeting of both domestic and export markets, increased R&D expenditures by Indian companies and thus increased expectations from the market, increased generic drug opportunities, out-licensing to foreign companies, increased patenting by Indian firms and targeting of high margin therapeutic categories such as cardiovascular and diabetes. In particular, exports have fuelled Indian companies rise. There has been a recent further rise of exports from 26 firms over 5 years from 1997-2002, coinciding with a time of increased R&D spending as well. Data from the Bombay Stock Exchange demonstrates that sales of these 26 leading Indian firms had almost doubled while local MNCs saw sales rise slightly. Profits for the Indian firms were also significantly higher on average, their R&D spending growth going from an absolute total amount of Rs. 50 crore in 1997-'98 to 240 crore in 2001-'02, a rise of 380%. There was a very slight increase for foreign firms. Exports also rose 230% in the same five-year period, although most foreign firms were only beginning to revisit the possibility of using India as an export base for their products. Finally, market capitalisation rose sharply for the 26 Indian firms (Ranbaxy more than doubled, Dr. Reddy's up 431%, Cipla up 4 times) while except for Pfizer, all other foreign firms saw a decline.[53]

Undoubtedly, both the absence of product patents and the price controls imposed by the Indian government on many drug segments kept MNCs away, but the rate of most MNC investments worldwide in R&D locally have been low by most accounts. Furthermore, Indian firms have shown high profitability even with controls of certain drug segments. However, neither the MTRP nor requirements of local production induced MNCs to move into essential bulk drugs locally. The Indian government forced the hand of both Indian-owned and foreign firms alike through process patents and price controls by making the former move into technologically new and complex antibiotic and anti-infective segments. At the same time it created conditions where the latter were forced to hand over key technologies or where local firms were encouraged to find new routes to the same drug. The years spent grappling with dependence on MNCs for technology, yet seeking the growth of local industry defined India's vision that technological capabilities could not remain neutral to firm ownership.

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[51] Local MNCs cannot take advantage of tax benefits for overseas sales.
[52] Business Line, The Hindu, "As Different as Chalk and Cheese", July 14th 2002.

Section IV

Section IV further investigates the continued growth of Indian firms and the Drug Policy measures that allowed the eventual consolidation of private sector capability through a series of protected spaces for learning that excluded foreign firms from some drug categories. In particular, it explores the hypothesis that large size benefited companies to upgrade technologies. It also uses varied indicators from business reports to demonstrate that Indian firms emerging from their particular policy environment have recently managed to create a competitive advantage around manufacturing ability and R&D investments relative to foreign firms in the country.

4.8.Trouble in the making: The New Drug Policy, production and size

Building private sector manufacturing capability

> *"The public sector cannot be a substitute for in-house technology capabilities"* (Interview, July 6th 2002)

While the public sector had initiated the technology acquisition, adaptation, diffusion and creation, private skills had been uneven and their access to technologies limited. The restructuring of the selection environment begun with the process patents and price controls, continued with the introduction of the New Drug Policy in the late 1970s. Until then, foreign firms had been tolerated. However, the preference for indigenous firms as manufacturing hubs and for production of key technologies became complete with this policy measure.

The Drug Policy of 1978 saw as its goals the following:

i. To develop self-reliance in drug technology ii. To provide a leadership role to the public sector iii. To aim at quick self-sufficiency in the output of drugs with a view to reduce imports iv. To foster and encourage the growth of the Indian sector v. To ensure that drugs are available in abundance to meet the health needs of our people vi. To make drugs available at reasonable prices vii. To keep a careful watch on the quality of production and prevent adulteration and malpractices viii. To offer special incentives to firms which are engaged in Research and Development ix. To provide other parameters to control and rejuvenate this industry as a whole with particular reference to containing and channelling the activity of foreign companies in accord with national objectives and priorities.

(source: Government of India, Drug Policy, 1978)

[53] Business Standard article, "Desi vs. MNC pharma battles, Desi success", citing Bombay Stock Exchange indicators, 5th June 2003.

Foreign firms were under considerable pressure to manufacture essential drugs and to introduce new product varieties into the country. However, most continued to make non-essential, but highly profitable tonics, concentrating heavily on formulations at the cost of bulk drug, most of which they imported in. Indian policy-makers had to grapple with technology dependence on foreign firms on the hand, with the absence of widespread private sector manufacturing capability of bulk drugs on the other.[54]

The primary technology for production of pharmaceuticals is the technology of bulk drugs production. However, very few developing countries possess the capabilities of being able to manufacture bulk drugs from local raw materials. In addition, this has historically been the province of multinational companies. MNCs rarely produce bulk drugs from locally available raw materials, and thus Indian policy was structured to advance technological learning through this route. The government recognized that bulk drugs manufacture had become a monopoly of foreign firms and policies were explicitly geared to prevent this, as well as to prevent abuses of transfer pricing when MNC local subsidiaries bought materials from the parent company to manufacture bulk drugs locally. One explicit policy was through the "canalisation" of bulk drugs, the importation of bulk drugs through a government-initiated corporation, to (a) prevent transfer pricing by the MNC (b) to ensure a steady supply in the Indian market and © to ensure a steady price to Indian producers. (Sahu, 1998 also documents this measure superbly)

Buoyed by policies that kept foreign firms at a distance, and that reduced uncertainties for indigenous firms, Indian companies began to participate in larger numbers in an upgrading process. While not all firms attempted this or succeeded, policies induced them to step through the grades below until they could bulk manufacture from locally available raw materials.

1. •Import finished medicines and repackage
2. •Import bulk materials and formulate them
3. •Import penultimate and intermediate products in bulk and formulate them
4. •Import basic raw materials and produce bulk drugs from various stages
5. •Produce bulk drugs from locally available raw materialsCapability of very few countries, particularly DCs

[54] Companies like Cipla, operating since the 1930s were the exception, rather than the rule.

The New Drug Policy (NDP) imposed by the Janata Party Government in 1978 was instrumental in categorising and allocating production licenses for three categories of drugs- 17 essential ones (public sector only)[55], 27 drugs (Indian firms only) and 64 items (open for all applicants).[56]

The table below highlights the drug production reserved for the Indian sector-public and private alike in the middle column.

Table 4.8.1New Drug Policy (1978) production allocation lists

(In alphabetical order)

PUBLIC SECTOR-ONLY DRUGS	INDIAN SECTOR-ONLY DRUGS
Analgin	Ampicillin
Folic Acid	Bephenium Hydroxynaphthoate
Gentamycin	Caffeine (Natural)
Morphine	Chlorpropamide
Oxytetracycline	Diazepam
Penicillin	Diethylcarbamazine Citrate
Phenobarbitone	Doxycycline
Polio Vaccine	Erythromycin
Quinine	Glybenclamide
Streptomycin	Griseofulvin
Sufadimethoxine	Halogenated Oxyquinoline
Sulfadimidine	INH
Sulfaguanidine	Metronidazole
Sulfamethoxy-Pyridazine	Nicotinamide
Vitamin B-1	Oxyphenbutazone
Vitamin B-2	Paracetamol
	Pethidine
	Phenylbutazone

[55] For the list of "Highly Essential and Life-Saving Drugs" of the Drug Policy, Category I formulations included items such as Aspirin tablets, DPT vaccines, insulin injections, Penicillin injections (including Procaine, G and Benzathine Penicillins), Streptomycin injections. Category II formulations included Analgin and Amodiaquin tablets, Chloroquin salts, Phenobarbitone tavles, Tetanus toxoid injections, Tetracyclines in different forms. For the 17 essential bulk drugs, some listed were Vitamins a, B12, C, Penicillins of various types, Insulin, Tetracyclines and Prednisolone (Source: Background papers of the National Convention on Economic Independence and Pespective of Drug Industry, New Delhi, 21 December 1974, pp. XLIX, cited in J.S. Majumdar, 1986 in Sen Gupta (Ed.)

[56] That ownership origin is significant was clear. Even with the clear demarcation of three categories of drugs, some controversies emerged of preferential allocation of licenses to Indian firms. In a famous case, Glaxo (India) was denied a license for manufacture of an effective anti-asthmatic drug, Salbutamol, and Cipla was awarded production rights on the basis of indigenously developed technology.

	Phthalyl Sulfathiazole
	Piperazine
	Sodium PAS
	Sulfacetamide
	Thiacetazone
	Tolbutamide
	Vaccines and Toxoids
	Vitamin C
	Xylocaine

Adapted from: Government of India: New Drug Policy, 1978, Ministry of Chemicals and Fertilizers and Sahu (1998)

Note that categories were further divided; polio was on the public sector-only list of vaccines, whereas all other vaccines were available for licensing to Indian private firms. No vaccines were allowed to be produced by foreign firms. Technologically more sophisticated therapeutic segments such as cortico-steroids, Vitamins B-6 and B-12 and other vitamins and drugs such as Cyclophosphamide were open for local production by foreign firms. Even here, however, restrictions were placed on equity holdings by foreigners who chose to manufacture "low technology" drugs. Those with investments in higher technologies, were allowed equity of greater than 40%, but were then forced to mix product types and bulk drug availability (a) such firms were forced to a strict ratio of 1:5 (bulk drugs: formulations), while Indian companies enjoyed 1:10. (b) 50% of their bulk drug production was then available for formulation companies to utilise. (Indian firms were subject only to 30% out-use, the rest could be used within the firm. Public sector firms were subject to higher ratios of 40% to other formulators, 60% for use in-house). (New Drug policy, 1978. GOI and Sahu, 1998)

While the New Drug policy and its elaborate licensing structure suffered many of the same problems as other "License Raj" policies, it was successful at inducing manufacturing capability into the private sector through a combination of production allocation and government procurement and through the explicit sidelining of MNCs in key drug areas. The table below shows the progression from the 1950s to the 1990s of Indian indigenous bulk drug capability and the gradual metamorphosis of the economy from being one primarily dependent on imported formulations to one manufacturing and consuming bulk drugs from locally available raw materials.

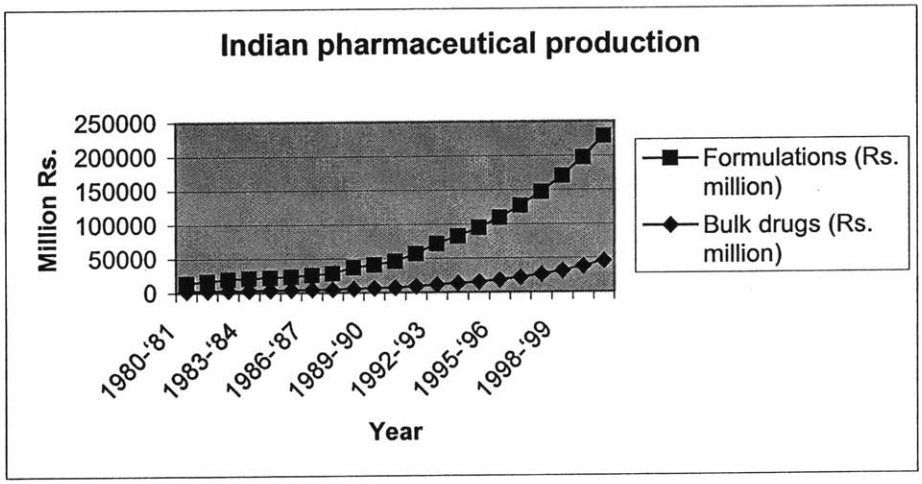
Table 4.8.2 Increased self-sufficiency of Indian pharmaceuticals

YEAR	PRODUCTION TYPE	STATUS
1950s	Formulations	Mostly imported MNC dominance
1960s	Formulations	Domestic endeavour on imported bulk drugs
1970s	Formulations Bulk drugs	Some imports. Indigenous manufacture by domestic companies
1980s	Formulations Bulk drugs	Marginal imports (<5%). Significant indigenous manufacture (based on domestic R&D)
1990s	Formulations Bulk drugs	Significant exports, minimal imports (< 2%) Self reliant (exports > imports)

Source: Ministry of Chemicals and Fertilisers, Department of Chemicals and Petrochemicals

Between 1995-2001, exports have considerably exceeded imports. By the 1990s, India had become a net exporter of both bulk drugs and formulations, although formulations continued to be produced at higher rates in recent years.

Figure 4.8.1 Twenty years of Indian pharmaceutical production



Source: WIPO, 2002

The Indian industry is the largest by volume and in numbers of companies in the developing world. It leads worldwide in the manufacture and export of drugs such as ibuprofen, and anti-TB drugs such as ethambutol and Rifampicin. It is also the world's second largest producer of Hepatitis B vaccines developed through an indigenous process. Of the leading bulk drug manufacturers in 2000-'01, Ranbaxy and Dr. Reddy's Laboratories have also emerged as innovative drug firms in terms of their NCE and patenting profile.

Since the mid-1990s, the imports of bulk drugs into the country lessened in part because the quality of local manufacture has significantly increased, leading to MNCs using locally manufactured bulk drugs instead of importation. Remaining imports were primarily due to patented molecules which were either provided to an MNC subsidiary by its patent-holding parent, or because Indian manufacturers were unable to produce the same. In some cases, imports are made on price margins from China, where certain bulk drugs are manufactured much more cheaply than in India, as in the case of Captopril bulk molecules, which is bought at a tenth of the Indian price. This combined with the fact that Indian companies are beginning to become preferred vendors for specialty "customised" bulk drugs (on specifications from an innovating firm), indicates that Indian firms do not compete on cost alone. The industry evolved such that it manufactured at all stages of the value chain. It now has a repertoire of approximately 350 bulk drugs from most major therapeutic categories. It has production capability for all dosage forms: capsules, liquids, tablets, orals and injectible drugs.

Size as a strategic tool for national self-reliance

The subset of companies that could thrive in this environment explicitly structured by industrial policies was further reduced to those that could scale-up operations. The 1970s were marked by sectoral policies favouring large size. While national industrial policies favoured the small-scale sector overall, based on Gandhian influences of returning economic power to small (cottage) industries, sectoral policies were explicitly geared to creating bulk drug capability and building plant capacity in the private sector with the hope that nation-wide shortages of essential drugs would become an artefact of the past.[57] While size is often interpreted as one representing dynamic economies of scale, in the Indian case it appears to indicate in part problems within the external environment which many firms avoided by sourcing internally and in part the ability to increase internal speed and scale of operations. Nevertheless, it is not surprising that even India's largest and most successful firms are as yet unable to develop a drug from discovery to market.

> *"None of the companies yet have the muscle to establish drug development....they have to do this abroad and have to license this to big pharma"* (Interview, June 14th 2002)

> *"DRL couldn't afford the cost of development, therefore it had to license to the US. It thus generated in-house expertise and has now moved further up the value chain or close to approval"* (Interview, June 27th 2002)

[57] Indeed, many of India's pharmaceutical policies ran afoul of this small-scale industry bias and minor modifications were made from time to time to further include small firms.

Yet, a few companies that have paid their manufacturing dues and built scale have also benefited from revenue streams that allow them to move closer to discovering drugs themselves.

> *"Hyderabad-based companies have made so much money that now it's simply a money issue combined with priorities, and they can take any expertise and capital and develop really innovative products!"*(Interview)

The type of learning that Indian firms managed to embark on was related to the financial, infrastructure (including equipment) and human resources they could devote to the process. Manufacturing was a capital-intensive process, while process chemistry and engineering required skilled personnel. Those firms that were able to invest in buying new technologies or upgrading existing ones were more likely to be large. Plagued by quality control problems, firms also grew in size to ensure in-house sourcing. Indeed, in recent years, different technological and organisation challenges have generated the need for external collaboration. Some firms expressed the desire for greater cooperation, especially those moving into biopharmaceuticals.

"We do too much in-house" (Interview, June 27th 2002)

The Industries Development and Regulation Act (IDRA) first brought into force in the 1950s continued to exert a powerful force to shape indigenous production. It allowed drug manufacturers to both diversify into new products as well as increase production by up to 25% thus setting the stage for advances through economies of both scale and scope. The economies allowed drug makers to invest in back integration into critical essential technologies associated with bulk drug manufacture. While in the 1950s no indigenous private sector expertise existed to manufacture bulk drugs, by the 1980s, Hyderabad city alone in Southern India was manufacturing upto 40% of India's bulk drug intake, much of it produced by entrepreneurs with past histories in the public sector, often the local IDPL.[58] The diversification allowed into new products

If the IDRA acted to encourage all firms to diversify and invest in production, there could be little doubt about where the government intended to go next. In 1970-, the Government of India withdrew permission of diversification from foreign –owned firms. This was followed in short order by the now well-known Indian Patent Act in 1970, and by further encouragement of economies of scale and scope in 1972 by allowing Indian firms to further increase their licensed capacities of production, while simultaneously diversifying upto 100%. Production of bulk drugs for companies in the organised

[58] Dr. Reddy's Laboratories, one of India's most innovative firms today, was begun in this fashion.

sector was licensed versus projected demand for the following year. While production of most antibiotics met demand projections, other categories, such as antidiabetics, particularly insulin production, an essential, was in shortfall, showing that such a strict licensing system with government setting projections, was not necessarily the most efficient way to meet clearly pressing health needs in the country.

The table below highlights some important policies related to size. Except for the Monopoly and Restrictive Trade Practices Act (MRTP) which limited market power (usually related to size), the other policies were only indirectly size-related, but had long-reaching effects on the growth of Indian firms. In particular, the IDRA and the New Drug Policy initiated considerable capacity expansion in Indian-owned firms, and allowed diversification in products for upto 100%. By doing so, firms were being channelled into significant back-integration into bulk drugs.

Table 4.8.3Chronology of Indian government policies regarding drug manufacturing

Year	Policy	Effect
1951	Industries Development and Regulation Act (IDRA)	Varied. For pharmaceutical production, licensed manufacturing out to public, private and foreign firms alike, by quota system based on national plan targets.
1969	Monopoly and Restrictive Trade Practices Act (MRTP act)	Curtails growth on companies with dross assets greater than Rs. 20 crores or with a dominant undertaking of market share greater than 33% (1982) and 25% (since)
	No amendment to IDRA.	Drug manufacturers were allowed to diversify into new products. Also allowed increase in production by 25%
1970	Government withdraws diversification permission to foreign firms	
1970	Indian Patent Act	Restrict monopoly by multinational firms Reduced patent validity from 16 to 14 years overall, and in drugs to 7 years, raised royalties needed to renew licenses and did away with product patents, increased grounds for compulsory licensing, gave the Government unrestricted use of patents for its own use,
1972	Indian firms allowed to increase their licensed capacities and to diversify up to 100%	
1973	Foreign Exchange Regulation Act (FERA)	Restrictions on foreign equity holdings upto40% in non-core industries. Pharmaceuticals seen as "core", the Act allowed companies exceeding MRTP and FERA clauses to nevertheless participate in pharmaceutical growth.
1978	New Drug Policy (NDP)	Divided drugs into three main reservation items for selected allocation and production (17 for public sector, 27 for Indians, 64 open to all). Linked FERA to upgraded technology and manufacturing requirements.

As the table shows, the concerted policy push died down after the late 1970s and Indian firms found themselves in a newer domestic environment in the 1980s. The diversification allowances were also carrots to companies to provide them larger profit margins through the sale of formulations (finished dosage forms -tablets, capsules, ointments etc.), There were additional rewards for bulk drug (active ingredients in drugs) production through procurement and preferential allotment of manufacturing licenses and sticks (primarily price controls). The main goals were the move away from formulations into bulk drugs. From 1948-1968 there was a MNC monopoly, from 1969-1978, policies were explicitly geared to removing the MNC monopoly, 1978-1985 was the period of the development of a strong national sector and significant numbers of process improvements and some product innovations and 1985-2003, innovations in both products and processes.

A policy measure that rebelled against the large size of leading Indian firms and foreign ones alike was allocation of certain drugs for production in the small-scale sector, such as Antibiotics (Chromphenical powder and palmitate, Ampicillin trihydrate, erythromycin, amoxycillin, rifampicin, ciprofloxacibn, cephalexin), Antibacterials (Trimethoprin), Sulpha drugs (Sulphamethoxazole), CNC stimulants(Caffeine), Vitamins (Nicotinamide) and Tranquilizers and sedatives such as Diazepam. (Sen Gupta (Ed), 1986)

While economies of scale in production of bulk drugs certainly also contribute to size, large companies have dominated the pharmaceutical sector worldwide in part because of the financial and production requirements for clinical trials and advertising. In India, these factors were differently moulded by policy measures of the 1960s and 1970s. Indian firms were not forced to invest in drug discovery at all or as much in clinical trials, and sold their products in segmented markets, not globally. Price controls also removed the incentive to invest in advertising to the same degree. Thus the reasons for large firm growth differed in India, where production targets and allocation and procurement incentives worked towards creating larger firms. However, an important additional reason (and one that subsequently plagued Indian biopharmaceutical work) was the lack of reliable supply networks and quality of materials. This created pressures on firms to vertically integrate to ensure standardisation of materials and routines.

Institutionally, the thrust of the DPCO and the Patents Act, was to create an environment in which process research and development was rewarded, shortened patent protection periods served to fuel competition and lack of a product patent regime served to bring down costs on existing MNC drugs

within the country. Furthermore, the preferential status awarded to small-scale manufacturing units served to fuel the growth of almost 18-20,00 Indian manufacturing firms and a vast supplier network to the more research-intensive large-scale firms, both public and private. The proliferation of such a large number of manufacturing sources also served to increase the possibilities of process experimentation, diffusion of new techniques, and the lowered costs of new routes of manufacture. But most importantly, it allowed both technological challenges to new routes to the same end, as well as the medically complex requirement to show continued efficacy and safety at similar levels. The process technologies also served to create economies of scale in investments in chemists, chemical and mechanical engineers and integration across firm investments in manufacturing ability.

Part of the difficulty was persuading foreign firms to manufacture bulk drugs locally. While some of these firms were willing manufacturers of the less technology-intensive formulations, they were slow to manufacture bulk drugs as the table below demonstrates.

Table 4.8.4 Foreign firm reluctance in bulk drugs

Company	Founding year in India	Year of commencing formulation production	Year of commencing bulk drug production (As of 1978)
Abbott Laboratories (India)	1946	1960	Not produced
Anglo French Drug company (Eastern)	1923	Not before 1955	Not produced
Roussel Pharmaceuticals (India)	1956	1956 and after	Not produced
Smith Kline and French (India)	1950	1963	Not produced

Source: Adapted from Chaudhuri, 1986

The Indian sector –public and private combined dominated the bulk drug production and the foreign firms the formulation production, by a huge margin. The public sector's contribution was significant in technology sourcing, transfer, development and production. The table below shows actual numbers in the critical years when the State was attempting to curb the dominance of the MNCs. In the middle 1980's, some years after the first institution of the New Drug Policy, the industry continued to be concentrated. For 48 product groups, there were 21 firms with monopoly power in more than one drug category, and for 17 product groups, 13 firms with duopoly power in more than one drug category. (Singh. 1985) High levels of concentration existed in almost all segments and even where large numbers of producers existed for similar goods, price competition was not necessarily the main factor,

and companies compete on promotion/advertising expenditures. Price competition appears to have been higher in the small-scale industry segment. (Abrol and Guha, 1986).

A criticism of Indian drug policies has been the de-linking of the industrial growth side from the actual health needs of the people. While the normative standards on price and production volume have had their benefits, the disadvantage to such a policy has clearly been the lack of correspondence with actual drug intake requirements. The assessments were made on past production and growth trends and future growth projections of the industry, rather than health statistics per se (except for the requirement of drugs in national health programs) (Maitra, 1986) Since pharmaceuticals as an industry lies with the Ministry of Chemicals and Fertilisers rather than the Ministry of Health, this institutional gap is undesirable, but hardly surprising.

While product differentiation can be considered one proxy for some innovation, it can also degenerate into the production of irrational drugs. The regulatory mechanism is meant to ensure that novelty is always worthwhile clinically. However, even so, each producer has a host of brand names and combinations of similar drugs attempting to compete on the basis of brand, not price alone or least of all efficacy. Some of the increased combinations can also prove dangerous as they increase the risk of unsafe drug interactions.

In 1986, there were over 60,000 formulations in the Indian market, of which 9000 formulators differentiates their brands minimally to be noticed in the market. This compared unfavourably to the WHO Essential Drug List of the time, which described 7 fixed dose ratio combination drugs out of its total 250 essential drugs and recommended that essential drugs only be marketed in generic form. (Abrol and Guha, 1986)

While segment allocation had its benefits by providing incentives for Indian companies to develop abilities in certain strategic areas, the table below shows that the legacy of these policies (especially price controls) lingered unattractively in the extent to which "non-essentials" captured market share. The table indicates the share of tonics, vitamins and cough and cold preparations in the domestic market. Note that particularly high percentages are also produced by MNCs. For example, between 1980 and 1986, the turnover (in Rs.) of MNCs in the top 20 companies by market share in antibiotics was only 38%, while Indian firms-public and private-was 62%. Among the top 85 companies, the MNC contribution was similarly static at 35% and Indian firms produced 65% in Rupee terms. However, in simple formulations and vitamins, MNCs produced 73% and Indian firms only 27%.

(ORG Survey, cited in Sahu, 1998). The Indian Patent Act of 1970 also created incentives for Indian firms to find new processes for existing drugs, but also reduced incentives for MNCs to introduce more sophisticated drugs into the country (other than the requirements forced on them through the later New Drug Policy of 1978) since the drugs could quickly be produced by Indian firms using different means. Some have argued that even with 40% equity, companies have been granted the same footing as Indian companies and that should change since in other countries, companies with even 10% foreign equity are characterised as foreign companies. (Abrol and Guha, 1986).

The instances of non-essentials and hazardous drugs selling well in the market are numerous. Becosules (B Complex) ranked second in 1984, Baralgan (deemed a hazardous antispasmodic) ranked 5th. (ORGMAT, 1984 May). This type of market inertia and the relatively low levels of regulation in the domestic market continue to work in favour of companies that spent more on advertising.

The fact that price regulations continued to be problematic in channelling efforts towards non-essential drugs was further evidenced by lack of enforcement. MNCs in particular, in the mid 1980s, continued to over-charge on some of their highest selling products (usually formulations) with the help of legal filings against government orders. The over-pricing ranged upto almost 45% in the case of Becosules (20s pack) from Pfizer and various Glaxo tonics at 90-100% (Guha, 1986). The data also confirms that price controls on essential drugs created a perverse situation where non-essential medicines such as tonics, supplements and sough and cold preparations, with higher profit margins, ended up with larger market share. National policies skewed in favour of Indian firms were justified by the fact that foreign-owned companies dominated the market in non-essential drugs.

4.9.Summary:

While being late to the use and adaptation of a set of scientific and technological advances brings definite costs, the gains can also be substantial as pointed out by Gerschenkron in 1962. In the pharmaceutical sector, Indian companies have profited by sticking to mature segments and by manufacturing both bulk drugs and formulations. They have exploited the generics market and in recent years have begun to use modern biotechnologies to enter new product markets, create new processes for manufacturing drugs and to diversify further into process-based innovation in the related food and chemical sectors. In this chapter, three particular policies with far-reaching impact on the industry, process patent-only regime, price controls and the New Drug Policy were discussed, the latter highlighting the significance of a recurring theme in Indian policies: access to medicine.

PHASE	POLICY MEASURES
Sub-phase I: 1950s-1960s (The Public Effort)	Entering the domestic market: technological capability and the public sector Entry/capture points through public health and "essential" drugs were important for learning.
Sub-phase II: 1970s-1980s (The Private Effort)	Process patents, price controls and production allocation licenses.

These contributed to significant learning measures while *simultaneously* restructuring the market to allow this to happen. Other countries that held expectations of their indigenous firms to compete against foreign multinational companies were to be disappointed The Indian policies acted as selection mechanisms to nurture capable firms, but they also created an environment in which an entire industry could be indigenously built. This period demonstrated that there was nothing 'natural' about the conditions under which the private sector grew at its earliest phase. Although companies had existed from the early part of the century, it was only in the nationalistic post-independent period, where an entire industry could be made to thrive. Learning occurred at firm level in conjunction with considerable environmental restructuring, suggesting that firm-based explanations alone are insufficient. Furthermore, patents, although extremely important for this industry, are also an insufficient explanation since a variety of other important measures were also in place. The selection environment structured by the State through strict price controls, selected public sector allocation for certain therapeutic categories and public procurement, all drove the prices of drugs down, rewarded new routes to the same end, and create competition in both input supply and manufacturing. India emerged with strong capabilities in process engineering, chemistry and manufacturing. However, while the process capabilities are seen to be important, they are depicted in some interviewees as a somewhat embarrassing vestige of an outdated patent regime, not as a competitive advantage that has buoyed Indian products more recently. The next chapter further highlights the limitations of patent regime explanations.

While market access-first domestic, then foreign, has determined technological learning trajectory for Indian firms, this has been far from a free-market conforming path. Key prices of drugs neither reflected true scarcity, but instead reflected targeted demand projections of Indian planners. Production allocation, similarly, was structured to reflect desired standards in self-sufficiency, rather

than actual capacity. Indeed, this often resulted in inefficient production shortfalls and lack of investment in certain key therapeutic areas. However, the combination of structured entry points in antibiotics and vaccines, along with the deliberate building up of plant capacity through government incentives, largely determined Indian technological trajectory. The disciplinary carrot and sticks employed were associated with price regulation and incentives for domestic market access. Thus, Indian firms were gradually pushed into core technologies while at the same time foreign firms were forced into local production, higher technology investments and smaller market shares. Indian firms were also rewarded with additional production licenses for indigenous technology developments, such as Cipla's Salbutamol technology. However, Indian firms were not subject to strict revocation of licenses for not meeting demand, or for inertia in investing in new technologies. Another problem that arose was that serious shortfalls in some essential drugs resulted from the combination of ceilings on drug prices and restrictions on who produced the drugs. The price controls alone made production of certain essential drugs an unsustainable business venture, and allocation criteria by ownership meant that unless public sector labs could produce and upgrade to keep up with technology changes and demand shifts, the production of certain essential drugs remained well below target.

Overall, however, Indian policies were successful in wresting control of the domestic market away from MNCs and placing it in the hands of Indian-owned firms. Many policies, especially the New Drug Policy, the Patent Act and Price Control Order, all acted to induce manufacturing capability into Indian firms and channelled through public health drugs. Large firms emerged at the helm. The New Drug Policy in particular, had far-reaching consequences, with Indian firms establishing a dominant position in certain key categories such as antibiotics. Both price controls and process patents acted in the same direction as far as technological entry was concerned into critical drug segments by making it easier for Indian firms to seize critical technologies, while they acted in misaligned ways as far as incentives for entry into those segments by making it less profitable in those segments. Price controls had their disadvantages and critics were correct in their assessment that such policies also led to allocation inefficiencies. Unwittingly, they also appear to have forced some firms abroad to seek higher profit margins. The changed selection environment in which these firms found themselves and the ways in which this environment structured their further learning is the story of the next chapter.

The achievement of early Indian S&T policy is not technological advancement relative to leading companies in the US or UK, *per se*, although that has occurred in some instances, but industry-building in number, scope and size of establishments. It also suggests that policies cannot be easily compared across countries since the trajectory has been inspired by different sets of national priorities

and local skills. India's strategic hand was public health access, even if it was an unevenly developed policy. It allowed some nurturing of Indian firms against multinational presence. In recent years, these policies have also allowed the move into newer technologies and the strengths (admittedly, also problems) of the public research institutes and some universities. Overall, the growth of manufacturing companies has permitted increased revenues, which have then given rise to increased R&D spending and the further absorption of newer technologies. This selection for success has permitted more Indian owned firms surviving and prospering than would most likely have occurred, although the null hypothesis can only be proven by the untimely demise of indigenous pharmaceutical firms in other developing countries.

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Chapter 5 "Learning-by proving" through process development

Section I

5.1 Standards and Regulations as tools for learning

In product life cycles, the progression from emergence to maturity occurs without mention of entry. The graded technological learning path alone did not show how Indian companies entered the market. In analyzing the Indian case in Chapter 3, it became clear how significant the entry point was: public health drugs, buttressed by preferential allocation and significant procurement possibilities, both national and international. These reduced demand-side uncertainties, allowing firms to invest resources in upgrading technological in-house efforts. Since then, firms have moved out of "essential" drugs and into a wide range of non-communicable and profitable segments such as cardiovascular, neurological and "lifestyle" drugs. Here we discuss learning, entry and growth from the viewpoint of export markets and their associated regulatory standards. This corresponds to a "Learning by Proving" phase, with tiered learning, from approximately 1980 to the current day. There were three types of novel learning mechanisms in export sub-phases: one associated with tiered cGMP compliance worldwide, another associated with vaccines procurement, and the third with the more publicized generic drugs market.

Technological learning and advances in process capabilities have not occurred in a vacuum in this industry. Not only is the pharmaceutical industry worldwide typified by a series of regulations, it is also considerably different from one country to the next as governments and medical agencies choose to monitor the health sector closely and adapt it to their own national priorities. Drugs also fall under the purview of ingestible substances and thus Food and Drug Administration agencies (FDAs) exist across the globe, each with their own institutional histories and monitoring purviews. Furthermore, the pharmaceutical and biopharmaceutical industries have additional sectoral characteristics that mould the environment within which firms strategise, such as health insurance, price regulation, safety regulations and immunisation protocols. The conventional view of regulation is that it complicates the workings of "free" markets and creates more barriers of entry for firms. Since the pharmaceutical industry is particularly regulation-prone, it provides an excellent example of how Indian companies respond to regulations of various types and a useful contrast to the newer biopharmaceutical industry, which is explored in the following chapter.

Indian firms moved abroad partly in response to price controls in the domestic market, which made export markets ever more attractive. Unlike the 1950-'60s where government policies appear to have had clearly directed goals for technology acquisition, creation and transfer from public to private sector, or the 1970s when significant efforts were made to protect indigenous firms and build their manufacturing capability, the 1980s were characterised by a relative lack of policy vision for this sector. In particular, a series of relatively unforeseen events of the mid-1980s and early 1990s set impromptu tests of how well Indian firms had learnt the lessons of yesteryear. This chapter describes how some of today's leading Indian pharmaceutical firms traversed a regulated path from one country to the next in their export-push.

This chapter is divided into two sections. Section I deals with the regulatory and standard-setting environment in which technological learning has occurred in the Indian pharmaceutical industry. The section draws on a combination of reinterpretation of existing data from the industry and insights drawn from primary data interviews with leading firms. It concludes by laying out a framework to analyse a specific path for firms led to the position they now find themselves in. A case is built for how regulation has compelled Indian firms to meet standards, at the same time that it has honed past process capabilities. Thus, the environment (here, selection on the basis of "proving" certification quality) rewards those firms that respond rapidly to standard-setting and regulation. The selection environment here is shown to be a complex mingling of national and international events that set in motion a set of opportunities that firms "endogenised" through past process capabilities. This is demonstrated by (a) describing three environmental characteristics often described in the language of one-time "shocks" (and subsequent perturbations)-the US Wax-Hatchman Act, the WTO TRIPS Act and India's Balance of Payments crisis (b) showing progression of Indian firms from one tier of regulatory standards to another (c) data on FDA compliance by Indian firms, particularly to the US FDA and cGMP standards (d) the importance of public procurement in vaccines and sera linked to strict technology standards at international level. The underlying dynamic of process development capabilities allowed firms to advance within this selection environment. Firm-level capabilities were on part of a richer story of global institutional and export opportunities.

"Learning-by-proving" provides an additional dimension to past thinking on learning types. While many useful contributions have recognised the importance of demand-led technology upgrading, there has been little analysis to show sequence of changes, and the ways in which learning is linked to product maturity in developing countries. The chapter attempts to draw the reader's attention to how capabilities can be nurtured by a selection environment when a judicious mix of steady demand mixed

in with both high levels of competition and some integration of technology upgrading can be sustained. In this chapter, two specific variations are discussed of export market demand-side triggers for firm-level learning. The first, international procurement, dodges some of the pitfalls that can characterise poorly-run national procurement programs, and blends assured demand and immense markets, with some level of international competition and high quality standards. The second, the generic drugs market, mixes heavy competition with strict regulation, with an added fillip given to innovation where it can be demonstrated even in mature segments. In particular, the evidence argues for a broader interpretation of ways in which the production environment is structured, such that firms face standards with varying parameters that provide "new" learning over time. This type of learning is linked to information symmetry since regulation here provided Indian firms a means of common information with international competitors, particularly in the generic drug business. Information symmetry has also been a necessary, but not sufficient measure, to ensure high quality vaccines. However, regulation and standard-setting is technology dependent, and the later chapter on biopharmaceuticals highlights how information asymmetries can continue to be problematic.

Section II is devoted entirely to how Indian firms have produced some innovations even in the mature generic drug industry and how a variety of other, non-technical advances have been made. The section analyses how process development capabilities within a sub-segment of leading firms, assisted by previous decades of assistance from government nurturing, evolved into instruments for global competition in the generic drug industry. Contrary to the conventional thinking, data analysis shows that both technical and non-technical types of learning occur even in mature product segments and innovation did not have to rely on cost reductions alone. But with the opportunities from the opening up of the US generic drugs market also come uncertainties of future paths. The chapter underlines that the environmental conditions under which Indian firms have advanced is changing, even as firms adapt to them, leaving the future optimistic but insecure nevertheless. Learning at firm level is being shaped by impending changes to the Indian patent regime, institutional changes to contain rising costs in the US health industry, and the changing nature of regulation arising from unexpected effects of newer methods and technologies.

5.2 Export-led learning in the 1980s-1990s: "endogenizing" external opportunities

The economic environment of the 1970s in which Indian firms had built basic capabilities in manufacturing was to be affected in the coming decade by three major events. The first, external to the country, in 1984, was a landmark change in the US pharmaceuticals market by the introduction of the

Hatch-Waxman Act. The second, in 1985, was the initial pressures for IPR homogenisation at the Uruguay Round of GATT. The Trade in Intellectual Properties (TRIPS) agreement was to gradually come to dominate the debate on the pharmaceutical industry in developing countries. This coincided with a third, internal event, and a partial liberalisation of the Indian economy commencing in the middle 1980s.[1]. All three events of the decades served to increase pressures on Indian firms to upgrade their process development and manufacturing capabilities.

1. The Drug Price Competition and Patent Term Restoration Act, 1984 (Waxman-Hatch Act)

Estimates are that the average clinical trial process took at least 7 years and the cost of the drug from start to finish ranged from 100$ to $500 million. For generics drug manufacture, when the patent expiry date was reached, producers needed to go through a similar process to manufacture and market generics. Even though the generics drug producers did not have to support sunk costs to do market surveys and technical feasibility studies, they still needed to support the expense of the safety and efficacy tests needed by the FDA.

All this changed when the US Congress passed the Waxman-Hatch Act in 1984 that was created to compromise between providing generic drug companies with greater access to the prescription drug market (and lower prices to consumers), while at the same time restoring patent life to innovating companies for products who lost patent life during the FDA's regulatory process. The implications of the changed environment for Indian firms is discussed in detail in Section II.

2. The Trade in Intellectual Properties (TRIPs) agreement, Uruguay and Doha

Much has been written about the TRIPs agreement and how it will revolutionise the industry worldwide. Indeed, there has been little else in the worldwide press on this industry. Various authors such as Singh (1985), Keayala (1996) and Lanjuow (1997) in their analysis of patent laws and their effects, have taken up where much earlier discussions in the late 1960s and early 1970s ended, when India's Patent Act was being discussed. While the jury is out on what the actual impact will be on Indian pharmaceuticals: higher or lower drug prices, more or less access to basic medicines by the poor, more or less innovation (particularly on public health drugs), more or less R&D spending, more or less competition, more or less MNC participation in the domestic economy; the interviews showed

[1] Although the Balance of Payments crisis is seen to have heralded in India's economy-wide liberalisation in 1991, in reality, some degree of liberalisation (in the specific sense of lifting of licensing regulations) was occurring across multiple sectors in the mid 1980s.

an interesting response to this question. Leading firms have already begun preparation for the change to a product patent regime in 2005.

Discussions are underway in Indian government and industry regarding the core elements of the "Scope of Patentability" provisions within TRIPS, where analysts (see Keayala, 1996) have suggested that India tighten the use of the word "invention" so no frivolous claims can be filed, that "product" should only apply to New Chemical Entities and not to formulations, dosage firms, new uses or new combinations of off-patent products. As this dissertation goes on to suggest, although TRIPS acts to limit the future policy options to developing countries, the diversity of learning paths and the extent of capabilities that have been developed indicate that some flexibility in policy-making may yet be available.

5.3 Proving standards

The pharmaceutical (and biopharmaceutical) industry is characterised by a vast array of regulatory instruments. Considerable variation exists across countries and drug types. In particular, what varies are the relative efficacy of reporting requirements, enforcement and the institutions that monitor the industry. Also different are the supporting institutions that allow firms to grapple with the costs of regulation, such as public funding or venture capital, and those that assist firms in obtaining information on regulation (patent offices, information bureaus in professional associations or nation-wide standards for common practice for manufacturers, pharmacists, doctors or hospitals).

The inspiration of pharmaceutical industry regulation in most countries arise from the idea that:

1. Safety is paramount since the product is directly ingested, injected or applied topically. Since the drug can make the difference between life and death in many cases, the interests of the patient need to be safeguarded, including the hopes of the patient.
2. The consumer often has the product selected for him/her by a doctor; the consumer himself does not necessarily make a rational choice. Information asymmetries are significant between producers and consumers, with the latter not having specialised information necessary for judging the product.
3. Indeed, even health care workers are often not trained to judge many of the qualities of the product. (Advertising may be restricted, for instance, among other measures)
4. Depending on the existence and structure of the insurance industry, price effects can vary hugely and their impact on consumers is highly specific to the type and coverage the insurance provided.
5. Furthermore, to ensure quality, efficacy and safety, manufacturing guidelines can be stringent, as exemplified in Good Manufacturing Practice. When manufacturing hiccups, the end product may contain either too little actual medicinal value, or too much contamination, leading to lack of efficacy or toxicity. Because laboratory scale processes are directly

converted to commercial scale where possible, there are problems with uniformity in safety and efficacy that emerge at industrial level.

Indian firms face a fragmented standardisation and approvals system within the country. The burden of proof in worldwide standards has fallen to individual firms. One interviewee stated, :

> *Standardisation and reliability are poor in Indian labs. ...People haven't stored valuable serum samples for later studies. Ethics committee review boards from India are not taken seriously abroad even though they comprise good clinical doctors and good case loads."*
> (Interview, July 6th 2002)

The standardisation of quality is also a challenge for Indian companies from the input supply. Firms have to find local sources where possible, and costs of setting up cGMP facilities and certified supply routes can be expensive.

> *"In the case of contract research, it isn't just like the IT industry. Reagents and equipment is imported. Therefore, it is actually more expensive to set up a service in India"*
> (Interview, July 6th 2002)

Although the regulatory system is fragmented, companies nevertheless acknowledge the involvement of the government and the efforts to streamline the process. The scale of the Indian market also requires controls as product impact and liability are multiplied manifold.

> *"Governmental functions come into play with regulatory issues when you market to one billion people"*
> (Interview, July 6th 2002)

5.3.1 The Practice of Good Manufacturing: GMP/cGMP

Current Good Manufacturing Practice (cGMP) provides a certification for manufacturing companies in pharmaceuticals and sets standards for the industry. As Indian firms moved abroad, many eventually set their sights on entering the US market for generic drugs. An example of the most highly regulated market for pharmaceuticals, the USA, requires the following broad conditions be satisfied before drugs can reach the market. The constraints that the FDA places on companies involve the extent of regulation of the process (and setting standards) through the entire product development cycle from drug discovery to market. At each stage the company files relevant material with the FDA to prove compliance (in the event the company specializes in the entire chain) or the specialist company files in any one or more segment.

Manufacturing companies face particularly stringent hurdles and must show a variety of well-established standards. This requires not only compliance with existing regulations, but also the ability

to change internal organisational structures rapidly. The following section lays out the FDA manufacturing guidelines.

Any human therapeutic or vaccine protein using any biotechnology method are called "biologics", or biological pharmaceuticals and come under the regulatory purview of the Food and Drug Administrations (FDAs) of various countries. The US FDA, in particular, requires firms to comply with particularly strict guidelines for how biologics should be manufactured and produced for sale.[2] Recombinant human proteins are of specific interest as they are often intravenously or by injection consumed by human beings.[3] "cGMP" or **Current Good Manufacturing Practice** straddles the range of "Manufacturing, Processing, Packaging and Holding of Drugs"[4] and includes requirements of workers, physical infrastructure, equipment, the actual manufacturing process (production and process control), packaging, labeling, holding (storage) and distribution (as well as handling returns). It also specifies guidelines for company records and reporting mechanisms, quality control monitoring and documentation.[5] Thus, for many companies, the most relevant cGMP guidelines are for

1. Tools and processes-such as fermentation or upstream processing, purification or downstream processing and quality control
2. Descriptive documents, data collection documents and numbering systems
3. How to establish validation protocols for a new protein, new infrastructure or entirely new facility altogether.[6]

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[2] For a full description, see http://www.fda.gov/cder/

[3] See also Walsh, Gary and Denis Headon. 1994. Chapter 4. Therapeutic Proteins: Special considerations, in Protein Biotechnology, John Wiley and Sons, New York.

[4] These refer to FDA regulations, listed under the Code for Federal Regulations (CFR) 21, CFR 210 and 211, also 21CFR600 and 610.

[5] Documentation alone includes (a) standard operating procedure guidelines and descriptions, protocols of various kinds for process and production controls, master production records (b) data collection formats such as forms, batch production records, log books (c) numbering systems-equipment part numbers, lot numbers, form numbers etc (d) data files for everything ranging from equipment history to files that track products, parts and equipment and allow traceability at all times.

[6] Thus Indian companies are having to establish validation protocols, many for the first time, which have 3 components (a) installation qualification (IQ) including equipment identification information, equipment utility requirements-such as services of water, gas, nitrogen, drainage and exhaust etc, and equipment safety features, such as pressure valve releases, alarms and appropriate triggers. (b) Operational qualification (OQ) calibration requirements, such as measurable parameters, methods of measurement, monitoring and the appropriate range, triggers and limits such calibration parameters, pre-operational activities, operations and acceptance criteria and (c) performance qualification (PQ) to create reliable and reproducible working performance even in extreme conditions. This includes preliminary operations, performance qualification procedures and performance qualification acceptance procedures and criteria.

For example, the USFDA thus requires that not only companies establish Standard Operating Procedures (SOPs), but also that they act as written commitments that the company specify the (a) procedure (b) assigns responsibility (c) reasons for the task (d) constraints and parameters of the task (when it can be or should not be applied). Finally, FDA inspections occur to check that the company complies with these standards.

In addition, Process Validation[7] itself is a complex set of procedures. It is a requirement of Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals,[8] and includes, but is not limited to, sampling and testing of in-process materials and drug products (Section 211.110) and control of Microbiological Contamination (Section 211.113).[9]

Interview data and secondary data analysis demonstrate that GMP guidelines are a useful tool both for the study of productivity increases, and for ways in which it coerces firms into achieving certification and ramping up production. The skills needed to achieve GMP are not simply in the realm of obtaining certification as proof, but lie in the ability to demonstrate quick-turn around time to getting a product certified for specific markets, for undertaking contract manufacturing, and importantly, for persuading regulatory authorities that samples are not only of high quality, but that they are of high consistency, and that future trials will not be jeopardized by the inability to manufacture in quantity for the market once approval is granted. These two themes, of quality, consistency and quantity all ensure speed to market and national reputation of the industry.

5.4 Indian responses to regulation: tiers, "consolidation plateaus"

Unlike the histories of export-propelled growth as a core element of NIE industrial policy, the Indian pharmaceutical industry went through stages of development abroad. The pharmaceutical industry thus differed significantly from other Indian ones by the intent of industrial policy. Import substitution was

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[7] Process validation is defined by the USFDA as *"process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics"*. (see http://www.fda.gov/cder/guidance/pv.htm)

[8] 21 CFR 210, 211 and GMP for Medical Devices, 21CFR 820.

[9] In particular, in an area of relevance to much product differentiation from Indian companies, different tablet forms, process validation procedures are integral to the quality and efficacy of the final product. As the guidelines state, *"for example, in the production of a compressed tablet, a firm may switch from one type of granulation blender to another with the erroneous assumption that both types have similar performance characteristics, and, therefore granulation mixing times and procedures need not be altered. However, if the blenders are substantially different, use of the new blender with procedures used for the previous blender may result in granulation with poor content uniformity. This, in turn, may lead to tablets having significant differing potencies...In this example, revalidation comprises installation qualification of the new equipment and performance qualification of the process intended for use in the new blender"*. "Guideline on General Principles of Process Validation, May 1987, Dr. Arthur Shaw, Food and Drug Administration.

clearly intended though primarily two elements (a) backward integration of bulk drugs and local production (later mandated through local content requirements, but initially through requiring MNCs to manufacture bulk drugs locally). (b) Similarly, import substitution was catalysed through the process patent allowance that generated process development resulting in new ways to make drugs only available abroad. However, export orientation emerged as a peculiar offshoot of Indian planning. Profit margins, squeezed extraordinarily low by price ceilings on "essential" drugs forced two paths (a) firms, Indian and others, moved into production of non-essential drugs (although Indian firms were provided production allocation licenses and procurement opportunities in the essential drug domain and thus appear to have moved relatively less frequently than MNCs into non-essential categories). (b) The second trend was more spectacular and less deliberate in Indian policy: firms moved into export markets to increase profits, which were unattainable in the same categories at home.

While the guidelines on standards and regulation can be described through lists of criteria, the interview data captures the challenges and benefits more completely. As described in previous sections, the entry point into the product's life cycle was predominantly through public health segments. Below a framework is developed for analysing technological and market advances based on the innovation environment. Firms had been born in a relatively unwieldy and inefficient regulatory climate. Guidelines had been in disuse and in need of an upgrade for some time. Approvals were cumbersome and slow. This is where export markets have been so important.

> "*"The greatest obstacle is GMP and regulatory hurdles. At least 25 other companies fall into this same category. For Indians, formulations and process chemistry are like ABC now, formulations we can now learn to do the next day, process chemistry in less than 12 months".* (Interview, October 2003)

Interviews elicited a surprising similarity in responses among pharmaceutical firms and different (from pharmaceuticals), but self-similar responses in biopharmaceuticals. Companies appear to have found the Indian regulatory process time consuming and procedurally complex. Yet, despite the inexperience, a subset of Indian firms learnt rapidly in export markets and grew in size and market reach. Furthermore, more recently, GMP compliance, for example, can further reward larger companies that make the investment in complying.[10] The coming sections construct a path for Indian firms which has linked learning (technological and otherwise) to regulations and standards.

[10] Various estimates suggest that because of their opening of highly regulated markets, GMP compliant manufacturing facilities are 25-30% more valuable to Indian companies than facilities that do not receive GMP

5.4.1 Tiered markets: Interrupting the product's life-cycle:

Markets are not all of one ideal type: they take national, regional or other forms with considerable barriers to entry and plagued by information variations. Indeed, in the pharmaceutical industry, considerable segmentation exists within the "world" market. This sub-section describes the variation and the pathway of leading Indian firms.

A typology of three main types of export markets can be constructed, each with varying degrees of regulation-both in patents, but also in GMP. The patent regime of the tiers is less uniform, and less clearly correlated to advance. The first, the Tier 1 markets, signify the lowest levels of regulatory requirements, and are labelled "unregulated". In reality they are loosely regulated by GMP, and often allow products on-patent elsewhere. Many Indian firms began their ascent out of the Indian market and into the world, first through unregulated markets with quality standards and efficacy and safety standards at similar, or lower; levels than in India. The table below shows Indian firms and the graded markets they moved into. Unregulated markets of significant market potential (Tier 1) were the first destination. Tier 2 and Tier 3 are regulated markets, the first corresponding to transition economies of Europe, and Tier 3 to the highly regulated markets of the US and UK. The evidence is two-fold, tracking export reach of companies and their compliance with GMP requirements of various national authorities.[11]

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certification. However, the investments required upgrading or constructing facilities to achieve compliance prices out most companies. Thus large companies become larger.

[11] Although compliance determines which countries the firm has access to, it is not a perfect one-to-one relationship between GMP standards and country list since some countries have (a) minimal or (b) unclear regulatory requirements and thus a firm with "higher" levels of GMP capability simply enter with no difficulty or (b) don't enter until the regulatory climate can be clarified.

Table 5.4.1Graded market access

Company	Indian	Unregulated or minimally regulated Tier 1	Regulated-Tier 2 (Transition Economies Including Former Soviet Republics)	Highly Regulated-Tier 3
Ranbaxy	Yes	Yes	Yes	Yes
Cipla	Yes	Yes	Yes	Yes
Sun Pharmaceuticals	Yes	Yes	Yes	Yes
Cadila	Yes	Yes	Yes	Yes
Wockhardt	Yes	Yes	Yes	Yes
DRL	Yes	Yes	Yes	Yes
Biocon	Yes	No	No	Yes
Bharat Biotech (Vaccines and recombinants)	Yes	Yes	No	No
Shanta Biotechnics (Vaccines and recombinants)	Yes	Yes	No	No

The fact that some of these companies were also suppliers to other countries through partner companies does not discount the fact that they began by trying to capture a significant share of the India first, albeit with considerable policy assistance.

On the basis of the regulatory standards, one can construct a taxonomy of learning levels and can categorise (and test) three main types of Indian manufacturing firms based on their target markets:

1. Those that target the domestic market
2. Those that target the domestic and unregulated export markets
3. Those that target the domestic unregulated and regulated export markets.

The technological learning process appears to be sharply different in the production process between regulated and unregulated markets, where current Good Manufacturing Practice becomes a critical differentiator of quality, and affects speed to market. Indian cGMP-certified firms gain upwards of 25% in margins relative to non-compliant firms.[12] Although many Indian firms continue to export primarily to markets where regulatory standards are lower, leading Indian firms have been gradually learning to challenge foreign firms in regulated markets and in profitable therapeutic segments.[13] Thus, an Indian firm that can demonstrate quality, and can develop APIs both for internal consumption as well as for niche exports, stands to gain market share. It becomes a specialised generic drug player and can begin to challenge first comer firms for certain API categories.

[12] Interview data and confirmed from secondary interview quotes.
[13] See for example, "Indian generic drug firms step up patent battle", Saritha Rai, New York Times, Friday, December 26, 2003

An important element of the learning is that the tiered structure of export markets created "consolidation plateaus" where firms expand markets laterally (in countries with the same or similar regulatory requirements) without having to advance technologically at the same time. Thus, important revenue streams were brought into the companies at each tier, which could then be used to invest in GMP compliance, and process capabilities to enter the next tier.

The table below was created to demonstrate the combined effects of entry and expansion for leading companies. It shows the continuing effects of older policies on the product structure and market orientation of India's five leading firms and some of the interviewed biopharmaceutical firms. Procurement here was listed as a potential benefit reflecting their products, not whether companies have actually benefited in recent years. However, an even more important common characteristic is the extent of similarity in market access and GMP facilities (usually USFDA or UK MCA). All companies have significant plant capacities and almost all have invested in GMP infrastructure.

Table 5.4.2 cGMP compliance and generic capabilities in India or abroad

Company	Market Access: GENERICS (G)/US or Other	CGMP facilities
Ranbaxy	G US O	Yes
Cipla	G US O	Yes
Sun Pharmaceuticals	G US O	Yes
Cadila	G O	Yes
Wockhardt	G US O	Yes
DRL	G US O	Yes
Bharat Biotech	G	Yes
Biocon	G US	Yes

The progression of leading Indian companies into the highly regulated markets (Tier 3) has occurred in three ways: (1) GMP certification by the Tier 3 country authorities (2) marketing and distribution networks established in Tier 3 countries and (3) R&D connections (often scientific advisory presence or CEOS from Tier 3 countries), as the next two cases demonstrate.

Large companies such as Cipla, with a long history of exports, have approval from the State Institute for the Control of Drugs, Slovak Republic, National Institute of Pharmacy (NIP), Hungary ,ANVISA, Brazil, Medicines Control Council (MCC), South Africa, Therapeutic Goods Administration (TGA), Australia, Pharmaceutical Inspection Convention (PIC), Germany, Medicines Control Agency (MCA), UK, the Food and Drug Administration (FDA), USA and the World Health Organisation (WHO).

5.4.2 Case I Ranbaxy

The Drug Price Control Order thwarted large profit margins at home and created an urgency to search abroad for higher profits. Ranbaxy, like other Indian companies, moved abroad. For ten years starting in 1986, the company exported APIs/bulk drugs at an average annual rate of Serum Institute of India% mainly to other developing countries. (WIPO/PCT/MRU/01/10). Exports of APIs was begun to Europe in the 1990s and total exports constituted approximately 40% to total revenues by the middle of the decade. Ranbaxy then began moving into the export of finished drugs and collaboration through joint ventures abroad. It also began moving overseas to establish manufacturing and sales.

The case of Ranbaxy, India's largest pharmaceutical firm by sales demonstrates the development cycle of capabilities and the importance of manufacturing and process engineering in the move into generic drugs as well as drug discovery. The company began in 1961 and in the ensuing 40 years went from a manufacturing firm to one innovating in new chemical entities, drug delivery systems, and to out-licensing its products to transnational companies. The Indian patent regime was beginning to face overhaul when the Uruguay Round of negotiations began in 1991 at the World Trade Organisation. By 1993, Ranbaxy and companies like it had reoriented their strategy to expand internationally as "research-based" companies. Ranbaxy itself began moving out of the protections awarded through the Indian Patent Act and into the newer domain of non-infringement that its Ceflacor successes had wrought. It alone accounts for almost 27% of total pharmaceutical sector R&D spending in 2002. Its recent business strategy has reflected in part its historical trajectory, four segmented markets, with exports approximately 60% of total revenues today, in over a 100 countries, with sales presence in over 25 and manufacturing in 7 of them. The US market is its second largest market after India.

The analysis of firm-level profiles shows that India's leading drug firms all have some antibiotics and anti-infective capability, and a few have it as their continued major revenue stream. In fact, Ranbaxy, India's leading firm continues to enjoy advantages developed through anti-infective capability. Its presence in the US market has allowed it to expand its antibiotics portfolio where most other generic drug firms, even US firms, have phased out their antibiotics production facilities. In this sense, even past sluggish markets for obsolete or unsophisticated drugs (many antibiotics, for example) have found a new lease on life.

Furthermore, the investments in manufacturing and research into new drug systems evolved concurrently and the emergence of Ranbaxy's new drug discovery capabilities arose out of process

experimentation to find new benefits to existing drugs and new routes of manufacture, as in the case of the once a day oral dose of Ciprofloxacin, in such demand recently in US markets after the anthrax bio terrorism scare. From the business end, Ranbaxy also evolved from being an Indian company, to being forced to find new overseas markets (50% of revenues come from exports). It then moved on to setting up JVs first for manufacture, then marketing, public listing on foreign stock exchanges, then foreign acquisition of manufacturing sites, capture a piece of US generics market, sales of its branded products in US, then filing multiple investigational drugs applications and beginning clinical trials.

Ranbaxy was listed among the top 20 most competitive Asian companies in a 1997 Arthur D. Little study of 4500 Asian companies. Its history is consistent with a staged path through tiered regulatory environments. It is also consistent with a move from manufacturing to drug discovery over time, with clearly overlapping phases when both process and product research was ongoing (and still continues to be). Infrastructure to build visibility, quality and compliance with GMP standards has also shown a steady progression. The table below shows how Ranbaxy, one of India's leading R&D spenders in the pharmaceutical industry, has built its presence overseas through GMP certification and facility approval (at Indian sites and subsequently acquired foreign sites), sales presence in the US and strategic marketing alliances and finally, a gradual push into R&D visibility abroad.

Table 5.4.3 Example of technological milestones for Ranbaxy

YEAR	MAIN BUSINESS MILESTONE	MAIN TECHNOLOGICAL MILESTONE
1961	Company incorporated	
1973	Company goes public	Begins Active Pharmaceutical Ingredients (APIs). Multipurpose chemical plant established in Mohali.
1977	First foreign JV in Nigeria. Penetration of African markets.	
1983		Modern dosage facility begun in Dewas.
1985	A second pharmaceutical marketing division is begun.	The Ranbaxy Research foundation is started.
1987-'88		Modern Active Pharmaceutical Ingredient (API) production plant opened in Toansa. Ranbaxy thus becomes country's largest antibiotics manufacturer. The antibiotics plant received US FDA approval
1990		Received US patent for Doxycyline
1991		Modern Cephalosporin facility begun in Mohali. Received US patent for Cephalosporins.
1992	First JV with TNC: agreement with Eli Lilly to market some of Lilly's products in India	
1993	First JV in China. Corporate mission to evolve into a research-based and international pharmaceutical company.	
1994	Regional HQs begun in Raleigh (USA), London (UK) Ranbaxy's first Global Depository Receipts listed on the Luxembourg Stock Exchange.	New Ranbaxy Research Centre opened in Gurgaon. A pilot fermentation plant is begun in Paonta Sahib.
1995	Acquisition of US-based Ohm Laboratories' manufacturing units.	Commissioned new FDA-approved new manufacturing wing at Ohm laboratories.
1997	Ranbaxy crosses sales of Rs. 10,000 million and exports of Rs. 5,000 million.	
1998	First entry into US pharmaceutical market under branded product names Ranbaxy emerges publicly positioned as a drug discovery company	Company completes successful pre-clinical studies and files first Investigational New Drug (IND) application in India to start Phase I Clinical Trials
1999	First out-licensing/reverse technology transfer for drug development. Bayer AG signs an agreement with Ranbaxy for exclusive development and	Ranbaxy commences Phase I clinical trials for RBx2258

	worldwide marketing rights to an oral once-daily Ciprofloxacin.	
2000	Company's first TNC acquisition: Buys Bayer's generics business in Germany, named Basics. Company enters South America's biggest market, Brazil, sales top US$2.5 million in Brazil alone.	Company completes successful pre-clinical studies and files IND application for RNx4638, an asthma molecule
2001	Move into East Asia: Ranbaxy begins new US $10 million manufacturing facility in Vietnam Company passes 2001 turnover of US$600million Surpasses sales of US$100 million and becomes fastest growing US-based pharmaceutical company.	
2002		Files IND for Oxazolidinone RBx 7644, an antibacterial.

Sources: Indian Infoline 2002, http://www.indiainfoline.com, The Hindu, various months, company records, Times of India, various months, US Patent Office.

Its research accomplishments have also been impressive. In the recent past over 50 products launched in India and in Chemical Research, a technology for more than 40 APIs developed over the last 3 years. But the firm is not the only unit of analysis for tiered growth. The selection environment represented in this phase of the industry's evolution by fragmented regulatory markets worldwide, also induced tiered product launches and some associated technological learning (but largely compliance-particularly with patents). More than 100 process and product patents have been filed, of which ~50 have been granted. Over 450 patent filings have occurred in the USA, Brazil, UK, Germany, China and elsewhere. The table below underlines the strategy to patent in segmented markets and shows the extent of process patents and API capability relative to New Drug Discovery.

Table 5.4.4 Patent Status of Ranbaxy as on 31st July, 2002

Type	india		usa		europe		PCT	
	Filed	Granted	Filed	Granted	Filed	Granted	Filed	Published
PROCESS	115	29	53	27	25	6	52	32
APIs	78	25	39	22	18	6	36	21
PDR	37	4	14	5	7	0	16	11
NDDS	29	6	13	4	5	0	16	9
FERMENTATION	4	2	1	0	1	0	2	2
NDDR	23	0	17	6	0	0	17	8

Source: Ranbaxy company reports, various.

Bulk drugs formed about 38% of revenues in 1998 and are internally consumed in the manufacturing of formulations, thus giving the company a cost advantage for the final product.

The table below shows the gradual progression of the company into manufacturing sites abroad.

Table 5.4.5 Ranbaxy's tiered country entry

COUNTRY	YEAR OF ENTRY
India	1965
Nigeria	1979
Malaysia and Thailand	1986-'86
China	1992
USA	1994

Source: WIPO, 2002

The next table below shows major target export countries, with Tier 3 countries explicitly shaded.

Table 5.4.6 Indian pharmaceutical exports and leading 15 countries, 1995-2000

(Tier 2 countries shaded)

COUNTRY	1995-'96	1999-'00
USA	4238	6718
Germany	3418	3252
Russia	3036	4932
Hong Kong	1919	3562
Netherlands	1436	2192
Nigeria	1199	2577
UK	1142	2568
Vietnam	885	1413
Singapore	868	2452
Sri Lanka	825	1242
Spain	765	1287
Italy	721	1514
Iran	634	1796
China	361	1371
Brazil	170	1627
Total to leading 15	**21617 (62.8%)**	**38503 (58.1%)**
Total exports	34432	66310

Source: Adapted from 39th IDMA Annual Publication, 2001

All three tiers continue to be attractive markets, the rate of growth of exports in the years 1995-2000 to the US lower than those to "easier" Tier 2 countries, but increasing.

The product launches have been tiered as well, with small improvements made to the drug depending on the regulatory requirements and the potential market.

Table 5.4.7 Ranbaxy export product launches

Ranbaxy Product molecule	Generic version of brand name	Countries
Keflor MR	Ceflacor	Cefaclor
Sporidex AF	Cephalexin	India, USA, SA
Coriem XL	Diltiazem Hcl	India, Malaysia, Myanmar
Difnal DR	Diclofenac Sod	Malaysia, Singapore
Roletra D	Loratadine Pseudoephedrine	India
Altiva D	Fexofenadine Pseudoephedrine	India
Romesec DR	Omeprazole	Malaysia, Singapore
Cifran OD	Ciprofloxacin	India; Licensed to Bayer AG for further development
Zanocin OD	Ofloxacin	India
Riomet OD	Metformin	India

Source: Adapted from company reports, website and press releases

Manufacturing firms have later used the acquisition route to establish a more global presence within the tiered markets. The importance of regulatory requirements on firms is demonstrated by the level of investments of Ranbaxy in acquiring key firms for their manufacturing capabilities approved by regulatory authorities in their respective locations. Ranbaxy prepared for further advances in the US and European markets by acquiring technologies from Crosslands and Gufic, and acquiring certified manufacturing facilities for immediate product launch. The table below shows the acquisitions, particularly those of Vorin in India, Rima in Ireland, and Ohm in the US. In addition, Ranbaxy like other Indian firms is obtaining US FDA and other manufacturing certification across a wide range of its own manufacturing facilities at home.

Table 5.4.8 Ranbaxy's acquisition pathway

COMPANY ACQUIRED	CAPABILITIES ACQUIRED INTO RANBAXY	EFFECT
Crosslands Research	Dermatological expertise relevant to dermatology, orthopaedics and gynaecology.	Diluted the heavy dependence on antibiotics and antibacterial. Entry into four new segments of ant fungal and anti-inflammatory, orthopaedics, ophthalmologic and gynaecological medicine. With this acquisition, Ranbaxy becomes the largest pharmaceutical company in India.

Gufic	5 major brands acquired (Mox, Suprimix, Exel, Zole and Roxythro) and semi-synthetic penicillin and anti-helminthes, among others.	Biggest selling brands in these segments. Amoxycillin capability relevant for US market increased.
Vorin Laboratories	Bulk Ciprofloxacin manufacture	Increased market share
Rima Pharmaceuticals	200 product manufacturing portfolio acquired	Entry into Europe for generic dosages of Rima's portfolio and as an export entry vehicle for Ranbaxy's own Amoxycillin and others.
Ohm Laboratories	Anti-inflammatory drugs, OTC analgesics focus	Increased generic drug market share and greater global presence for highly regulated markets

5.4.3 Case II Sun Pharmaceuticals

The learning path is characterised for most early entrants by manufacturing experience that brought in the revenues, which were then invested in acquisition and R&D investments. While most of today's leading Indian firms traversed the manufacturing path, gradually assimilating capabilities and revenues, and patenting and launching products in a tiered fashion, regulation has also motivated recently manufacturing firms to choose acquisition directly instead of manufacturing alone, as a rapid path to growth. Such firms acquire drug specific manufacturing sites for later certification, or buy those already certified as cGMP compliant. The table below shows major acquisitions by Sun Pharmaceuticals (begun in 1983), India's fastest growing pharmaceutical company in 2002-2003. The acquisitions combine brands with often corresponding acquisitions of certified facilities in key regions to cater to specific markets.

Table 5.4.9 Acquisition pathway of certified manufacturing facilities for Sun Pharmaceuticals

PLANT ACQUIRED	DISTINCTIVE FEATURES
Tamil Nadu Dadha Pharma's plant, 1996	Oncology specialization
Knoll Pharmaceuticals	Bulk manufacture of APIs in Ahmednagar
Gujarat Lyka Organics Ltd, equity 1996, merged 1999	Bulk manufacture of active cephalexin for international sales
MJ Pharmaceuticals, Ltd, equity stake 1996	Insulin manufacturing plants. Approval for many dosage form lines (sterile dry powder injections, small volume injections, tablets, capsules, liquids and ointments, soft gelatine caps and aerosols). UK MCA approval. Filing for US FDA approval shortly.
Caraco Pharmaceutical Laboratories, equity stake 1996, acquisition 2002	US-based manufacturer of generic pharmaceuticals, US FDA approved plant. 5 ANDA approvals received in the last year, and 5 more products await approval. Caraco to source APIs from Sun's plants (one plant is USFDA

	approved, another awaits FDA inspection) to compete as an integrated manufacturer. [14]
Pradeep Drug Company, 2000	WHO cGMP approved site for manufacturing APIs and intermediates for India and the neighboring markets
Natco Pharma, 1999	A basket of brands (turnover-Rs50cr) for high-value segments of respiratory, gastro-enterology, orthopedics, anti-infectives and pediatrics
Milmet Labs, acquisition, 1999	Acquired brands in ophthalmology.

Source: Adapted from Sun Pharmaceuticals company reports, website and press releases.

A more detailed analysis of Sun's learning path highlights the intertwined focus on manufacturing with acquisitions of key technologies and the push into tiered markets-India, Asia, Russia, Canada, USA. Scientific breakthroughs were not at the heart of this learning path. Mature brands in psychiatry are bought, and then manufacturing commences at a modest scale. Region al expansion occurred and complementary assets in distribution and marketing are developed. The first product diversification into cardiology drugs begins. The first significant manufacturing milestone is the acquisition of the MNC Knoll Pharmaceutical's manufacturing plant.

[14] ANDA refers here to the Abbreviated New Drug Application of the US FDA.

Table 5.4.10 Acquisition and advancement path for Sun Pharmaceuticals

Year	Milestones
1983	Sun Pharma starts operations with 5 psychiatry-based products. Initial coverage is limited to Calcutta. Within a year the company expands to cover all eastern states. A small manufacturing facility for tablets/capsules is set up in a shed at Vapi.
1986	Administrative office is set up in Bombay. Coverage extends to Western India.
1987	Marketing operations are expanded nation-wide.
1988	Initial products in cardiology are launched. The company is reported in a market audit by the prescription tracking company, ORG* for the first time- rank 107th, 0.1% Market share.
1989	The corporate office is shifted to Baroda, in the western state of Gujarat. Products used in gastroenterology are introduced. Exports begin, with marketed to neighbouring countries in Asia.
1991	A proposed research centre, SPARC, is constructed. Rank 70th.
1993	SPARC is inaugurated. Moscow, Toronto offices opened. Products registered in 10 markets.
1994	After an IPO in October, the company is listed on stock exchanges in India. The company's first bulk drug plant at Panoli starts production. A dosage form plant at Silvassa starts production. Major expansion at the existing plant in Vapi is completed. One product now features among the top 250 pharma brands in the Indian market. A separate division, Synergy, is created to market Psychiatry/ Neurology products.
1995	A division, Aztec, is begun for cardiology products. Inca, a new division to market critical care medication to intensive care units commences operations. International marketing is strengthened with offices in Ukraine and Belarus.
1996	A bulk drug unit at Ahmednagar is acquired from Knoll Pharma. A stake is acquired in a generic dosage form manufacturer; the Detroit based Caraco Pharma Labs. An equity stake acquired in Gujarat Lyka Organics Ltd.; a manufacturer of cephalexin bulk active with a USFDA approved intermediate. An equity stake acquired in MJ Pharma, a manufacturer of several dosage form lines with a UK MCA approved plant. The company ranks 27th with 2 products ranking among the country's top selling 300 pharma brands. Product registrations are now in place across 24 countries.
1997	TDPL, a company with a diverse product offering (oncology, fertility, anaesthesiology, pain management) is merged with Sun Pharma. The company's second R&D facility is established for dosage forms and supporting documentation for North America and European generic drug markets.
1998	Brands acquired from Natco Pharma. For entry into opthalmology, Milmet Labs is merged into Sun Pharma. The company's new formulation plant at Silvas commences operations.
1999	Rank is in top 10 in the domestic market. The bulk cephalexin manufacturer Gujarat Lyka Organics is merged with Sun Pharma. 6 brands now feature among the leading 300 pharma brands in India.
2000	Ranked 5th among all companies in the domestic market. Pradeep Drug company, a Chennai based bulk active manufacturer is merged with Sun Pharma. The company announces a dedicated research campus for NCE initiatives with investments of Rs. 40cr over two years.

Source: Adapted from Sun Pharmaceuticals company reports, website and press releases.

Although much of the evidence shown here has been drawn from domestic market leaders, the story of tiered advance is richer than this. Capabilities in certain therapeutic categories have also shown tiered growth, shaped by the selection environment (and demand) of that product set. Although the competition in the top layers of the domestic market is intense, it does not reflect that market leaders may not be segment leaders or vice-versa. For example, Alkem leads in Cephalosporins but is not in the top 10 companies by total market share. Neither is Morepon Laboratories, which is the second largest generic manufacturer worldwide for the non-sedative, antihistamine Loratadine, which is the 4th largest drug worldwide in terms of market size (estimated at about $3 billion). Morepen exports to over 50 countries. It also exports to the more difficult regulatory markets of North America and Western Europe.

One can test the tiered structure further. Bulk drug manufacturers such as Aurobindo Pharma and Orchid show a relationship to this tiered path. Indeed, the challenge in recent years for Indian firms has not been exports, but the high levels of investments necessary to sustain speed of adaptation to regulatory requirements. Their target markets and the associated institutional climate have affected the technological growth paths of these three types of companies, in particular, the extent of technological intensity of manufacturing itself and the desire to build proprietary assets. But both steps 1 and 2 often lead to 3, as larger customer bases provide search and experimentation opportunities for dosage forms, clients and volume markets for APIs.

For 1 and 2, Indian companies have developed extensive marketing and distribution expertise, only in step 3, do companies link up significantly with foreign companies to distribute and market Indian pharmaceutical products. However, as Indian companies gradually move through the "manufacturing push" to invest more heavily in drug discovery and development, later costs for clinical trials may also be born by more established foreign companies.Those companies that cannot move from Tiers 1-2 or 2-3 suffer as their knowledge base stagnates and their wage advantage shrivels.

5.5 International public procurement: demand-led learning

In the previous chapter, we saw how public health afforded some entry points for Indian firms into the domestic market and the previous section underscored how learning was linked to graded regulatory paths. This section analyses how the ideal-type public health drug, vaccines, have been supported and upgraded by procurement at international levels. Those firms that could adapt their learning to regulations abroad and could meet demand were rewarded. Indian firms had emerged from benefiting from the public health focus of government policies and the volume sales in the domestic market.

Although profit margins were sharply lower after price controls were introduced into the "essential" segments, firms were still assured of two elements: (a) large domestic volume sales direct to customers and (b) public procurement through the government particularly for vaccines.

This section shows that another significant form of regulatory impact on learning has been international procurement of public health drugs through international agencies. While vaccines and sera have specific paths for procurement, also important are drugs considered to be in the public interest such as antibiotics and anti-infectives. These are usually high-volume and low cost products and have a significant place in public hospitals and clinics. Although procurement within countries has often been criticised for its inefficiencies and linked to protectionism for domestic firms, international vaccine procurement has provided a thought-provoking variant of infant industry protection. Here, vaccine suppliers from developing countries have a potentially immense market, but which are linked to high quality standards. It also encourages some level of innovation on the part of these firms since the procurers have an incentive to assist current suppliers to adapt to new public health concerns and increase production to supply to lesser developed countries.

> *"These programs have played a huge role in sustainability and supply of vaccines because they do not have large commercial markets. At the same time GMP requirements keep changing, so companies need procurement to really make the process viable. This is a guarantee to us and to others to have markets available. It also recognizes companies and thus makes new collaborations possible, while also helping with the standardization of platforms. "* (Interview, June 2002)

Vaccines and sera are not like other drugs. Their quality and control considerations are significantly different, and thus their procurement guidelines also differ. For vaccines, procurement cannot be made on the basis of price since quality considerations are of utmost importance. Vaccine efficacy and safety cannot be determined solely in the laboratory, thus making the uncertainties and technical challenges for manufacturers acute. Only a few companies worldwide make vaccines of high enough quality to be procured internationally for expanded immunisation programs (EPI). The fact that vaccines are highly temperature sensitive means that both the manufacturer and the procurement agency rely on considerable support infrastructure to keep the vaccines effective and safe.
The box shows the social and economic characteristics of vaccines, which make them, requite special consideration in manufacturing and procurement.

Box 1 Special characteristics of vaccines

National impact: Vaccination coverage is designed for all infants and thus has an immense national impact on public health. 2. **Biological product**: Since vaccine production is a biological process with living organisms as inputs, so production/quality control require cGMP and good laboratory practice (GLP) compliance. Lab testing alone cannot determine a vaccine's safety ad efficacy. 3. **Captive consumer**: Vaccination is generally mandatory and the consumer has neither choice nor (usually) the ability to judge the quality of the vaccine. 4. **Semi-captive market**: The worldwide vaccine market is characterized by less than 20 vaccine exporters. 5. **Difficult handling:** Vaccines are heat-sensitive with a limited shelf-life (two years maximum).
6. **Credibility/quality:** The burden of proof on vaccination programs is high. Public acceptance of vaccination is vital and depends on the safety and efficacy of the treatment. The more people decide not to get vaccinated, the greater the risk of disease spread to the rest of the population. 7. **Low cost**: Traditional vaccines are cheap per dose and are often provided free. This can result in lowered perceptions of value of vaccines.

Source: Adapted from WHO/VSQ/98.05

On the one hand, theory predicts that 'easy' markets and government protection will result in firms stagnating and suggest that competition and free markets are the solution. Others suggest that procurement has its place in helping firms learn. Public health procurement is unique for the global scale in which acquisitions are made. Only a limited number of industries allow such possibilities.[15] However, some examples exist in other parts of the health industry (medical equipment, for example, in public hospitals), the energy sector, defence and related industries (bomb detonators, land mine clearing machines etc) and education sectors, thus opening up technology procurement as an important potential tool for technology access and upgrading.[16]. The interview data for this dissertation provided a unique opportunity to question firms about international procurement, a case where firms compete with others internationally to bid for procurement by the international agency. Therefore, the standard critiques of protectionism do not apply straightforwardly to such schemes, but they nevertheless do provide a system by which firms can find reliable (and large) markets. The firms, however, must demonstrate high levels of product quality, consistency of batches and the ability to supply large volumes on demand. In more recent years, this procurement role has been significantly taken over by

[15] Public procurement by private supply can occur in some sub-sectors of energy, education, public services such as waste removal or recycling, and defence. While public procurement is often automatic for public suppliers, the focus here is on procurement for private companies, where technological learning and upgrading requirements can be linked to the demand for products. In vaccines, for example, both public and private suppliers exist in India, but the data focuses on private suppliers of vaccines as primary recipients of the "learning-by-proving" advantage.

[16] While any public agency can, in principle, be a consumer (example, book supplies, garbage trucks, or hospital equipment) it is of particular value for developing countries that the procurement be linked to standards of increasing levels of sophistication.

international organisations. They have two functions. First, they provide a launching pad into new markets by the former's certification system for public health procurement, particularly for vaccines and secondly (and more importantly) they act to procure large volumes of certified drugs from strictly selected manufacturers. Interviewees stated repeatedly the importance of public procurement for vaccines, and guaranteed markets (despite slow growth) for antibiotics.

Two international agencies with large procurement programs are the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF). UNICEF alone supplies vaccines to 40 per cent of the world's children.[17] UNICEF spends US$220 million on vaccines and immunization supplies (the largest group expenditure on commodities) out of a total budget of $541 million worth of supplies for children in 162 countries and territories. (UNICEF reports).
One interviewee, reflecting the importance of these agencies said,

> *"In particular, the Serum Institute of India showed all companies the potential importance of institutional buyers in vaccines."* (Interview)

Three elements in particular are vital for procuring agencies: quality, reliability and availability. Thus a high quality manufacturer, who cannot deliver large quantities of the vaccine at short notice, also fails the test on availability. An additional concern is that clinical trials need to be rigorous in methods and testing as well as conducted on appropriately sizes trial populations. Suppliers pre-qualify by registering in their home countries through the National Control Authority (NCA)[18] and through an International Competitive Bidding (ICB) procedure[19]. They also furnish additional information to the NCA and WHO/UNICEF.[20] [21] The technical challenges can be considerable depending on the type of vaccine, the extent of use and the speed of response time needed for supply. They also depend on how stable the vaccine type is to external conditions. The role of the international procurers is also to

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[17] UNICEF works with both governments and other partners to strengthen and increase in scale and scope existing immunization programs and has co-founded the Global Alliance for Vaccines and Immunization (GAVI), "a partnership dedicated to strengthening immunization systems and increasing access to new and under-used vaccines" and goes to the poorest nations and includes hepatitis B, Hib (for some types of meningitis and pneumonia) and yellow fever. "Priority is given to the 40 nations where routine immunization coverage is lowest and to the districts within those countries where children are least protected."

[18] See "Regulation and licensing of biological products", *WHO Technical Report Series* No 858, 1995

[19] The NCA reviews all bids and acts as a selector.

[20] The supplier must be a manufacturer (or importer of bulk product for filling, labelling and repackaging) and must provide a 1. Certificate of registration /licensing in country of origin 2. Documentation on quality control (QC) and sampling procedures 3. Copy of most recent GMP certification. 4. · Production and quality control summary protocols. 5. Certificate of analysis from NCA in country of origin. 6. Statement of licensing status in other countries. (Source: WHO/VSQ/98.05, "Guidelines for the international procurement of vaccines and sera", Global programme for vaccines and immunization, Vaccine supply and quality, World Health Organization, Geneva 1998). For UNICEF, companies must show qualification for - EN ISO 9001 / EN 46001 and EN ISO 9002 / EN 46002 standards.

coordinate worldwide agreement and uniformity on methods, substrates and virus strains; supply and demand, licensing, standards setting and regulatory guidelines for packaging, distribution and return, among others.

The vaccine industry is compartmentalized into 5 segments by manufacturers: US and European MNCs, OECD local manufacturers, emerging worldwide suppliers and developing country local suppliers and biotechnology companies. The importance for the mandate of international agencies in sourcing vaccines from developing countries has gained in importance. In 1986 there were 7 suppliers of 4 vaccines and 0% were located in developing countries/emerging economies. Ten years later in 1996, through deliberate procurement policies, there were 14 suppliers for 5 internationally procured vaccines and 50% were located outside the First World. This number has continued to increase to 58% for 6 vaccines, but the suppliers have dropped to 12, partly a function of stricter guidelines.[22] In addition, there is a shortening lifespan of product development cycles for pediatric vaccines (For example, in the US, DTP introduced in 1948 took 48 years to find a replacement DTaP, while DTP-Hib introduced in 1993 took only 7 years to be replaced by DtaP combination vaccines. The shortest period of replacement was 2 years for Hib polysaccharide introduced in 1985 to be replaced by Hib conjugate).[23] The table below shows vaccine types with intent to highlight technological and process capabilities necessary. It should be read in conjunction with the subsequent tables to identify lack of capabilities on the Indian aide, despite accomplishments. The reasons for the gap in capabilities for some categories are diverse: lack of process capabilities, lack of local relevance for some sub-categories of capabilities, lack of infrastructure, lack of demand, for example. However, there are other developing countries that do have capabilities in these other areas, even if the number of their firms or the spread of their capabilities is much narrower than India's.

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[21] See also WHO/GPV/VSQ at www.who.int/gpv-supqual/unprequalprod.htm

[22] Milstien, J.B., S.N.Glass, A.Batson, M. Greco and J. Berger. 2001. "Divergence of vaccine product lines in industrialised and developing countries", unpublished manuscript, presented to the Strategic Advisory Group of Experts, Department of Vaccines and Biologicals, WHO, cited in "Technological Development of Vaccine: Projections to 2015", June 2003. Ministerio Da Saude, Fiocruz, Fundacao Oswaldo Cruz.

[23] Ibid. DTP=Diphtheria and tetanus toxoid, DtaP= Diphtheria and tetanus toxoid with acellular pertussis vaccine, Hib=Haemophilus influenzae type b, TT=Tetanus toxoid

Table 5.5.1Vaccine types considered and processes involved

VACCINE TYPE	SPECIFIC TECHNOLOGICAL GOAL	PROCESS DETAILS
Attenuated microbial cells	Growth and purification of microbial cells adapted or engineered to delete pathogenicity, retaining immunogenicity.	Fermentation in defined media; recovery of whole microbial cells by centrifugation/washing or ultrafiltration methods; formulation, filling.
Live microbial vector	Growth and purification of non-pathogenic microbial cells carrying added gene for an immunogenic protein.	Fermentation in defined media; recovery of whole microbial cells by centrifugation/washing or ultrafiltration methodology; formulation, filling.
DNA vaccine	Extraction and purification of plasmid DNA from bacterial cells containing desired gene in the plasmid.	Fermentation in defined media; recovery of whole microbial cells by centrifugation/washing or ultrafiltration methodology; cell lysis and removal of cell debris (filtration, centrifugation or expanded bed chromatography); removal of host impurities, RNA, genomic DNA, proteins and endotoxins (salting out, PEG precipitation); concentration (ultrafiltration methodology, PEG precipitation); purification of plasmid DNA by IEC and/or SEC; concentration and buffer exchange; sterile filtration of final bulk; formulation, filling.
Purified protein, excreted or cell associated	Growth of recombinant bacteria, yeast or cell culture where recombinant protein, cell lysis (for cell associated proteins), isolation and purification of the protein.	Fermentation in defined media; removal of microbial cells by centrifugation or filtration; mechanical disruption of cells, removal of cell debris, solubilization (if necessary); concentration of soluble protein by ultrafiltration methodology; protein purification by chromatography, concentration, buffer exchange, sterile filtration and stabilization; formulation, filling.
Conjugated polysaccharides	Growth of bacterial culture, extraction and purification of capsular polysaccharides, preparation of carrier protein, conjugation to carrier protein.	Fermentation in defined media; primary recovery of cells; isolation/extraction of polysaccharide by chromatography or precipitation; chemical characterization of the polysaccharide; concentration and drying of bulk. Purification of carrier protein (see

		purification sequence described above). Chemical modification of polysaccharide; linker if required; chemical processing of carrier if required; conjugation; separation of conjugated from un-conjugated species by chromatography; concentration of bulk conjugate, sterile filtration and stabilization; formulation; filling.
Live attenuated viruses	Growth of cells (from cell banks of continuous cells or isolation of primary cells), infection with attenuated virus, isolation and purification of virus.	Cell culturing (risk free medium) in bioreactors, roller bottles, hollow fiber, cell cubes, flasks, or microcarrier culture with various types of feeding; virus infection; cell controls; removal of cell or cell debris by centrifugation or ultrafiltration methodology; purification of virus if required, concentration; stabilization, formulation; filling.
Multiple antigen peptide vaccines	Linking of synthetic peptide antigens to a synthetic backbone (eg polylysine).	Peptide synthesis and purification; backbone synthesis and purification; linking of antigens to backbone; purification of multiple antigen peptide product.; sterile filtration; stabilization; formulation; filling.
Virus-like particles	Growth of cells, infection by virus or recombinant virus producing non-replicating, non-infectious, particles with intact immunogenic antigens, isolation and purification of the virus-like particles.	Cell culturing (risk free medium) in bioreactors, roller bottles, hollow fiber, cell cubes, flasks, or microcarrier culture with various types of feeding; virus infection; cell controls; removal of cell or cell debris by centrifugation or ultrafiltration methodology; differential separation of virus-like particle from virus if required, purification and concentration; stabilization; formulation; filling.
Live viral vectors	Growth of cells, infection with genetically engineered replicating non-pathogenic viruses containing added gene of interest, isolation and purification of virus.	Cell culturing (risk free medium) in bioreactors, roller bottles, hollow fiber, cell cubes, flasks, or microcarrier culture with various types of feeding; virus infection; cell controls; removal of cell or cell debris by centrifugation or ultrafiltration methodology; purification of virus if required, concentration; formulation; filling.

Source: column text reproduced verbatim from WHO, Initiative for Vaccine Research (IVR), 2003

The interviews suggest that both national and international procurement resulted in large revenues for companies. In national procurement for antibiotics, they provided steady demand for otherwise sluggish growth segments[24]. More importantly, they reduced the risk for Indian companies investing in greater anti-infective production, for example, and assured their sales to the government. The table below shows the list of Inactivated polio vaccine (IPV) and Oral Polio Vaccine (OPV) Manufacturers to the WHO vaccines and biologicals unit as of October 2002. The number of Indian manufacturers in this category is the highest from any single country.[25][26] Public sector companies like Haffkine Bio-pharmaceuticals have also become active suppliers again. In 1999, WHO-GMP certification was awarded to the company for oral polio vaccine blending facilities and the company subsequently obtained a UNICEF procurement order for supply of oral polio vaccine in India.

[24] For many antibiotics, technological obsolescence has characterised Indian efforts.

[25] Despite many able manufactures of vaccines, India still imported some polio vaccines in 1995. The scenario for imports has changed for Hepatitis B since many companies now indigenously manufacture it. Furthermore, the New Drug Policy of 1994 lifted price restrictions on genetically engineered vaccines produced by recombinant DNA technology and specific cell/tissue culture targeted drug formulations for 5 years from date of manufacturing to provide an impetus to the private sector to ensure adequate national supply.

[26] A newer organisation, the Developing Country Vaccine Manufacturers Network (DCVMN) helps companies upgrade and meet procurement requirements.

Table 5.5.2 Worldwide Inactivated Polio Vaccine suppliers to WHO

COMPANY	COUNTRY
Glaxo Smithkline Biologicals	Belgium
Scientific Institute of Public Health Louis Pasteur	Belgium
Bio-Manguinhos	Brazil
National Vaccine and Serum Institute	China
Kunming Institute of Medical Biology	China
Statens Serum Institut	Denmark
Egyptian Organisation for Biological Products and Vaccines	Egypt
Aventis Pasteur	France
Agence Francaise de Securite Sanitaire de Produits de Sante (AFSSAPS)	France
Chiron Behring	Germany
Bharat Immunologicals and Biologicals Corp. Ltd/	India
Haffkine Bio-Pharmaceutical Corp. Ltd.	India
Panacea Biotec Lt.	India
Serum Institute of India Ltd.	India
P.T. BioFarma (Persero)	Indonesia
National Agency of Food and Drug Control	Indonesia
RAZI Institute	Iran
Institute Superiore di Sanita	Italy
Japan Poliomyelitis Research Institute	Japan
Birmex	Mexico
National Institute of Health	Pakistan
Institute of Poliomyelitis and Viral Encephalitides	Russia
Dong Shin Pharmaceutical Co.	S. Korea
Green Cross Corporation	S. Korea
Korea Vaccines Co. Ltd.	S. Korea
SBL Vaccine AB	Sweden
SVM	The Netherlands
Evans Vaccines	UK
Poliovac	VietNam
Institute of Immunology and Virology Torlak	Yugoslavia

Source: Adapted from "Vaccines and Biologicals, Access to technologies", II WHO/UNICEF Consultation with IPV/OPV Manufacturers, Bharat Biotech April 2003, Geneva

Other Indian vaccine companies are Biological E (TT, DTwP and working on DTP-Hep B), Panacea Biotec (Hep B, DTP-Hep B, OPV), Serum Institute of India (Measles, mumps, rubella, TT, DT, DTP, Hep B), Shantha (Hep B, working on Hepatitis E, Typhoid, Tuberculosis, Combination vaccine against Hep-B + DPT), Bharat Biotech (Hep B, single-shot typhoid, working on malaria and rotavirus).[27]

[27] The challenges to developing vaccines using biological materials are detailed in the case studies developed in the next chapter.

The Indian governmental requirements for the Immunization Programme Department requires six different vaccines for infants and for pregnant women. The following table lists some of the leading vaccine providers to the Government of India with their annual dosage capacity

Table 5.5.3 Procurement from leading Indian vaccine suppliers

Vaccine	Name of manufacturing unit[28]	Annual Capacity (In million doses)
Tetanus Toxoid	Biological E	120
	Serum Institute	96
	Haffkine Bio-Pharmaceuticals	71.2
	Central Research Institute	30
	Pasteur Institute of India	30
	State Vaccine Institute	10
DT Vaccine	Biological E	24
	Central Research Institute	20
	Pasteur Institute of India	15
	Haffkine Bio-Pharmaceuticals	10
DPT Vaccine	Serum Institute of India	97.5
	Biological E	80
	Haffkine Bio-Pharmaceuticals	44.8
	Pasteur Institute of India	40
	Central Research Institute	25
Measles Vaccine	Serum Institute of India	100
BCG Vaccine	Unit of MOH(FW), Tamil Nadu.	35
Oral Polio Vaccine	Radicura Pharma	540
	BIBCOL	300
	Haffkine Bio Pharmaceutical	240
	Biomed	156

Source: Ministry of Health and Human Welfare, Government of India, also at http://health.nic.in/vaccines.htm,

Data compiled from the WHO's databases also shows that 6 Indian companies are compliant with WHO requirements for vaccine production, and some have specific specialties for process development varying with the biological under consideration.

Table 5.5.4 Quality, Capacity and Background of WHO Vaccine Manufacturers from India

Company	Functional National Regulatory Authority[29]	GMP compliance certificate	GMP clinical batches
Bharat Biotech International	Yes	Yes	Yes
Bharat Immunologicals and Biologicals *(public sector)*	Yes	Yes	Yes
Biological E	Yes	Yes	----
Panacea Biotec	Yes	Yes	Yes
Serum Institute of India	Yes	Yes	Yes
Shantha Biotechnics	Yes	Yes	Yes

Source: Adapted by the author from the WHO, Initiative for Vaccine Research (IVR), Vaccines, Immunisation and Biologicals, Database on Contract Manufacturers. Also, http://www.who.int/vaccines-access/quality/contractmanufdb/index.htm

The Serum Institute, a Pune based company, is also the country's largest manufacturer of MMR (100% of local measles vaccine needs) and DPT vaccines (60% of local needs). Their quality assurance and regulatory compliance profile highlights the challenges in scale, with DTP vaccine batches ranging between 2-4 million doses.

For the Asia region, for example, the table indicates that for DNA vaccines alone, some specific capabilities are available, but the gaps in capabilities (or the time lag in registering for these capabilities) are evident. These are skills not offered relative to other Asian (predominantly public sector Iranian and Indonesian institutes) and European and US private suppliers indicating that there is some learning that has not occurred.

[28] Some are public sector units at national level, others run by State governments.
[29] The WHO requires functional NRAs to be able to produce guidelines, systems and enforcement to ensure siz critical functions: 1. a published set of requirements for licensing 2. surveillance of vaccine field performance 3. system of lot release 4. use of laboratory when needed 5. regular inspections for GMP; and 6. evaluation of linical performance.

Table 5.5.5 Contract manufacturers in Asia and their capabilities for vaccines and biologicals[30]

Source: Adapted by the author from the WHO, Initiative for Vaccine Research (IVR), Vaccines, Immunisation and Biologicals, Database on Contract Manufacturers. Also, http://www.who.int/vaccines-access/quality/contractmanufdb/index.htm)

Services	Attenuated microbial cells	DNA vaccines	Live microbial vectors	Purified protein	Conjugated vaccines	Live attenuated viruses	Multiple antigen peptide vaccines	Virus-like particles	Live viral vectors
Product development	2	1	2	3					
Process development	2		2	3					
Cell Banking GMP	2		2	2					
Analytical Development	5		5	5					
Fermentation	3		3	5					
Downstream processing	3		3	1					
Final Bulk (clinical grade)	2		2	2					
Formulation and filling	5	5	5	6	6	2	6		
Animal test facilities	4	4	4	4	4		4		

[30] Since this database was first developed, more Indian suppliers have met other category requirements.

This unprecedented access to first world and third world markets alike is analogous to privileged access of Taiwan and Korea into the US market, for example. These were important elements of their growth, particularly when viewed as part of a changing selection environment. Third world market access and the certification of quality from the WHO have guaranteed procurement, while the introduction of these manufacturers into new countries via the WHO has also resulted in new markets for other non-WHO certified drugs directly to consumers. These "voluntary' regulations of quality provide a powerful incentive for Indian firms to produce for the world public health market and upgrade technology and infrastructure to this end. From an international procurer's standpoint, the following list captures the main advantages of Indian companies.[31]

Table 5.5.6Advantages of Indian companies:

Skill type	Competitive advantage
Ability to manufacture APIs	Low cost, local sourcing, proprietary base, vertical integration and self-reliance, good quality
Process development capabilities:	Alternate routes, high process patents, rapid engineering to new drugs
Low cost for high skills:	Low manufacturing, research and regulatory costs
Rapid adaptation to regulatory requirements	Strong manufacturing history, strong technical skills, infrastructure, low regulatory costs, good quality

As the table on comparisons of Indian and European or US vaccine providers demonstrated, there are some technological gaps for Indian vaccine suppliers. Not all vaccines with local relevance are being pursued with equal alacrity, nor are all capabilities for local vaccine needs completely indigenous, in part the reason why international collaborations continue to be attractive. Furthermore, a tiered path for vaccine development using recombinant technology is less than straightforward as biological substances have different standards and monitoring guidelines relative to synthetic drugs. The segmented markets and suppliers established through WHO guidelines, also places some limits on market expansion in the long-run. Nevertheless, international procurement continues to play an important demand-side role to promoting upgrading and some gradual innovation, while it also increases export reach for indigenous vaccine suppliers. Such programs provide a promising variant on traditional technology procurement at national level.

[31] No international procurers were interviewed. This list was catalogued from interview statements of suppliers and scientists working on vaccines.

To broaden the understanding of two different elements of export demand as manifestations of the later selection environment, the chapter now turns to a close cousin in learning effects, but a distant relative of public procurement as a policy instrument: the competitive generic drug industry. As Indian firms waded into foreign waters, the biggest market opportunity presenting itself was from generic drugs. These arose after significant structural changes were put in place in the US market intended to induce more competition while still protecting an innovator's incentives. As another instance for how the selection environment propels certain capabilities to the fore, regulatory standards related to the generic drug industry have moulded firm strategies as they walk the fine line between "imitation" and innovation.

Section II

5.6 Generic yet Innovative: Process development and generic drugs

This section uses a variety of primary and secondary data on patented and other products in the generic drug industry, highlighting how some Indian firms have used many of the same pathways for advancing (dosage/formulations) that today's leading firms have used in the past. However, India's generic drug advances are primarily further manifestations of process capabilities. Many of these opportunities have evolved out of core strengths in public health drugs outward into higher value-added "urban" drugs for cardiovascular, lifestyle and cancer treatments. Importantly, generic drugs have proved to be a challenging learning path for firms, not technologically, but in the "learning-by proving" that the generic drug regulations require from firms. This has brought learning of a different kind: horizontal and vertical product differentiation opportunities for off-patent drugs and providing a small windows for Indian firms to patent products that can be shown to be sufficiently different from the incumbent's. I

This chapter attempts the following: First, to show that even mature product segments have considerable learning opportunities for developing country firms if market advance is linked to upgrading and quality standards. Second, that learning is not automatic. Clearly many firms chose not to enter this path (or could not) and both technical and non-technical components of learning occur side-by-side. Third, process capabilities have been further honed by the strict requirements of regulation, and novelty has arisen out of considerable product differentiation skills. All the evidence underscores how dependent on the specific environment evaluation (and valuation) of how innovative a new product is.

5.6.1 A second demand-driven opportunity: lowered barriers to entry

The early regulatory environment until the 1980s placed considerable burdens on firms to show novelty, safety and efficacy. However, these came with considerable rewards when these standards could be met. The Waxman-Hatch Act, in its attempt to increase competition, reduced the regulatory hurdles to introduce generic drug competition into the market. The New Drug Application for entirely new molecules was reduced (Abbreviated) and did not require the extent of clinical testing to show safety and efficacy. It was deemed sufficient that the drug be shown to simply be bio-equivalent to any previously approved drug by the US FDA. This change in procedure had the effect of considerably reducing the time (although still substantial) and expense required to file a drug application. Indian companies took advantage of this new regulatory system to enhance their speed to file, (and thus to market) when their application was approved. It however, required Indian firms to be able to demonstrate that they could manufacture immediately on approval, and that they could manufacture consistently and to meet market volume demands. The Act also initiated opportunities for those firms that had mastered APIs and formulation creation, and could thus concentrate their energies on demonstrating the (minimum) standards for novelty, and perhaps, a patent challenge.

Generic drugs are cheaper for two reasons: (a) the generic drug manufacturer does not have to bear the costs associated with drug discovery and development undertaken by the brand name company[32] -the costs include R&D and marketing expenses (b) as patent expiry occurs, multiple manufacturers may be approved for the generic drug, thus increasing competition and reducing the price further. However, generics still need to meet the same facilities requirements for manufacturing approved by the FDA.[33]

> "A generic drug is identical, or bio-equivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use." [34]

Interviews revealed some important features of technological and non-technical learning. Although generic drugs are a mature product line (possibly "the" most mature, by definition since the product

[32] Although in the case of patent challenges, a non-infringing method of manufacture is one of the criteria for application.
[33] The Congressional Budget Office of the US Government estimates that consumers save approximately US$8-10 billion yearly at retail pharmacies by buying generics, and hospitals save much more. (Office of Generic Drugs, USFDA).
[34] Office of Generic Drugs, U.S. Food and Drug Administration, Centre for Drug Evaluation and Research. Also, http://www.fda.gov/cder/ogd

has reached some maximal standardisation), the challenges are still significant for firms to gain market entry, introduce product arrays, show novelty and challenge incumbent firms.

The generic drug industry provides a specific cross-section on firm-level learning in mature product segments and the highly regulated (although less so than for entirely new products) environment in which this learning occurs. Alternate processes have been developed, leading to new products such that patent challenges can be launched. But generic drug manufacture is an inherently diminishing returns game unless one can be the first to market, in which case the US market allows a 180-day exclusivity incentive. For this period of time, the market is essentially a duopoly, between the original brand-name manufacturer and the generic drug challenger, and profit margins can be very high, even if the price of the drug is already lowered due to the onset of competition. Thus, Indian firms have had two ways to advance. First, they attempted to be the first to market, still rare or they created additional novel properties for existing generic drug categories.

Furthermore, although generic drugs are a potential opportunity for all pharmaceutical developers, in reality only a small fraction of drug manufacturers are able to exploit this market opening. This is primarily because firms have to be first to file, to develop speed to market, the ability to produce non-infringing manufacturing processes, ramp-up capability, and marketing and distribution links. Only those firms who had most if not all of these characteristics, are able to compete.

However, the ANDA still requires considerable investments for the firms ahead of the approval process and uncertainties regarding approval itself along with the fact that the FDA can also approve other firms for the same generic drug in order to stimulate increased competition on the incumbent, thus lowering drug prices. What this means is that generic drug producers need to (a) reduce the prospect of FDA rejection or requirement of submitting further information to satisfy regulatory guidelines and (b) attempt to be the first to market the generic drug itself, thus leaving behind the other FDA-approved producers and securing a close to monopoly position among this secondary market for a short time. (Recall that the original drug manufacturer-the original patent holder also stays in this market anticipating future price reductions, but still earning revenues on their brand name out in the market). To satisfy (a), the producer not only has to have a complete, sophisticated and technologically and scientifically rigorous dossier for the FDA, but also that to reduce the possible time taken for approval, the producer needs to ensure that its own submission must be considerably superior to

rivals', in the absence of any information of how far ahead they may be. The average approval time requires 2-3 resubmissions and can take on average 19 months. (Scott Morton, 1999)

The generic drug must duplicate the active pharmaceutical ingredient (API). In addition, those firms that can show superior efficacy or other novelty can also apply for a patent challenge.

For FDA approval, a generic drug has to meet the following requirements:[35]

1. "Contain the same active ingredients as the innovator drug (inactive ingredients may vary)
2. Be identical in strength, dosage form, and route of administration
3. Have the same indications
4. Be bio equivalent
5. Meet the same batch requirements for identity, strength, purity and quality
6. Be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products."

Furthermore, generic drug manufacturers have to compete with the incumbent directly. Brand name firms are linked to approximately 50% of generics, and make copies o their own patent-expired drugs and sell them under the generic name. (USFDA, Centre for Drug Evaluation and Research).

A New Chemical Entity (NCE) can only be manufactured and marketed after the producer has received a New Drug Approval (NDA) from the US FDA.[36] Not only does the drug have to go through the expensive, time consuming and scientifically rigorous process of clinical testing to FDA specifications, but it also means that producers work in a climate of high uncertainty, unsure if their drug will ever reach market and make a substantial return on in-house investments in the early stage of drug discovery and/or drug development.

Generic drugs present a particularly attractive market opportunity for developing countries. The table below shows some patent-expiry timelines of some well-known drugs, which provide a significant market and technological learning opportunity. In the last years of the 20th century alone, many high value drugs have seen patent expiry. Between the years 1990-'99, about $17 billion worth of brand

[35] US FDA, http://www.fda.gov/cder/ogd

[36] Although the regulatory processes of many different countries are similar, the US FDA approval process is described here because it is seen to be the amongst, if not the most rigorous of all the regulatory processes worldwide, and because the US represents the target market of choice for most Indian drug companies.

name drugs lost patent protection. The more lucrative breakthrough is occurring now with approximately US$42 billion worth of branded drugs facing patent expiry between 2002-2005. The normal calculation is that generic drugs are priced at about 20% of the brand name drug, thus estimating that the generic market is now valued at US$8.5 billion and is estimated to grow to about US$60 billion in 2005. Even at a limited 10% of market share of this potential pie, Indian firms could still make about almost US$1billion. Between 2002-'04, for example, 27 cardiovascular and central nervous systems treatments, 16 oncology drugs and 11 respiratory drugs lose patents.[37]

While the Waxman-Hatch Act provided some incentives for innovation to first movers companies, it also stimulated competition in the US pharmaceutical industry and simultaneously gave a tremendous new market opportunity to producers worldwide. For the first time, generics drug producer faced a simpler regulatory process, the Abbreviated New Drug Approval (ANDA), needing now to only show bio-equivalence of the intended generic drug to any drug previously approved by the FDA. The ANDA applies to drugs first marketed after 1962 and is much cheaper than the NDA, thus causing many new producers vying to be the first to introduce a new generics drug once the patent expiry date for a specific drug had passed. Between 1976-'82, only two of the top 13 drugs appeared to face any generics entry in the first year, whereas after the passing of the Act and studied in the period 1990-'93, 11 had seen generic drug competition within two months of approval.[38]

5.6.2 Indian paths of "generic innovation": a guarded yes to novelty

A signature element of governmental strategy emerging in the 1960s, and consolidated in the 1970s, was the push to create private Indian-owned firms that could back-integrate into bulk drug capability while also enjoying economies of scale and scope. The increased investments in both plant capacity as well as product diversification, allowed firms to corner the domestic market while simultaneously moving ahead in formulation markets built on low-cost advantages secured in in-house produced bulk drugs.

While product diversification allowed Indians firms to preferentially enter different product markets, the introduction of process patent protections also spurred firms to develop multiple paths to the same end product. This resulted in intense competition, lowering the price of existing drugs for which

[37] Figures from USFDA, Ernst and Young, 2001, Kheria, 2002.
[38] For the 1976-'82 period, see Cook (1991) in Caves, Whinston and Hurwicz (Eds.) and Cook (1998) for the period 1990-'93.

multiple production paths were created, but also resulted in increased competition in newly entered product markets.

Pharmaceutical companies had low levels of R&D investments in 1976, two years before the New Drug Policy that gave such a spurt to manufacturing. Nevertheless, even shortly after the policy was enforced, Indian companies were investigating new routes for process development, but not new drugs, and their R&D investments stayed relatively low, ranging from Rs. 105 million in 1976-'77 to Rs. 500 million ten years later, Rs. 1850 million in 1996-'97 and rising to Rs. 3700 million in 2000-'01.[39] Only in very recent times has the R&D expenditure of a few companies as a percentage of sales exceeded 5%, while comparable levels by leading global pharmaceutical companies are in excess of 15% of sales revenues.

The learning trajectories offered by generics are richer than most analysts have given them credit for, since they are usually dismissed as 'copies'. In fact, these drugs are often not exact copies, and because of India's continued process patent regime, different processes for the same end chemical composition or bio-equivalent version are patentable, thus leading to many new search and experimentation learning options for firms. Furthermore, on-patent drug filings give the bare bones of the composition and in the more modern filings, entire families of molecules can be patented, leaving developing country firms (and also generic drug manufacturers in advanced industrialised countries) no option but to use entirely new sets of molecules an non-infringing processes in many cases to devise the same end product. Data from interviews and supplemented by secondary data indicates that Indian firms in both traditional pharmaceuticals and biopharmaceuticals have faced challenges by (a) "reverse engineering" through process development, which was allowed under the Indian Patent Act (b) finding new processes so as to benefit from the process patents awarded as well as to work around price controls (i.e. which limited profit margins. Thus firms had incentives to also bring down costs by innovative new processes) (c) scaling up processes to factory floor so as to benefit from industrial incentives such as reserved licenses for certain drug categories. Even for 'straightforward' generic manufacturing, a certain level of experimentation always exists for in-house process development.

In the early environment when even leading Indian firms were predominantly attempting to search for processes that 'reverse engineered' a new product patented elsewhere, firms nevertheless had some element of search and experimentation to conduct. As the patenting trends became more strict (in part

[39] WIPO (2002). All figures in absolute unadjusted terms.

to curb this very tendency of firms to imitate new products), firms had to conduct more in-house efforts to move past the last patented step of the process.

But for Indian firms to earn significant revenue streams and advance technologically, the learning-by-doing production system must change, or else companies face diminishing returns manufacturing identical copies over time. The challenge is to achieve slight changes in production parameters which can provide continual learning-by-doing. Thus even in generic drugs, there are two main ways to add value and enhance technological capabilities.

The first has to do with modifying an existing molecule in such a way as to show new features and therapeutic value. These are patentable in themselves, such that although the entry lies with a relatively straightforward generic opportunity, the financial reward and learning is high if new technological features can be added. For example, the shelf life of most liquid suspensions is short. Keeping with its history of strong dosage form capability, Ranbaxy has created effervescent liquids. This dosage form accomplishes two things (a) by creating an amorphous state, the drug's shelf life is effectively increased and (b) increases uptake efficiency when the patient consumes and liquefies the effervescent medicine.

The second lies in New Drug Delivery Systems (NDDS). Here Ranbaxy alters the frequency of dosage form, which has two main effects (a) reduces cost to consumer and to manufacturer (b) increases effectiveness of overall dose. Ranbaxy has done this by altering the molecular structure in the generic drug so as to exhibit these properties when provided in an altered dosage form and frequency.

Those companies that can accomplish one or both of these innovations in the generic drug market and manage to compete in regulated markets on basis of low cost for high skills and speed to market, have a clear competitive advantage. Indian companies now dominate worldwide the Drug Master Files (DMF) and ANDA filings with the US FDA[40]. For the last quarter of 2003, there were more DMFs filed by the Indian companies than by any other national group. The larger number of ANDAs is to also to assure a higher chance in the 180-day exclusive marketing approval lottery. Including the last quarter, there were an anticipated 112 Indian ANDAs in 2003 (up from 40 ANDA filed in 2001 and lower than 392 filed by Indians in 2002). In master files, the progress has also been brisk. 58 DMFs

[40] All data from "Indian firms set to dominate drug registrations with FDA", Hindustan Times, Chandigarh edition, November 23rd 2003.

were filed in the first six months compared to a total of 50 filings in 2001 and 86 in 2002.[41] However, many drugs in this category are not novel, technologically, and only a few appear to challenge the companies' abilities.

Biotechnology companies such as Biocon have also entered high-value segments such as Statin production from their traditional base in biological extracts.

Table 5.6.1 Biocon US DMF submissions

DATE	DRUG MASTER FILE SUBMISSION
JUNE 00	LOVASTATIN USP
JULY 02	PRAVASTATIN SODIUM
JULY 02	COMPACTIN
AUGUST 02	SIMVASTATIN USP
AUGUST 02	LOVASTATIN TECHNICAL(SFP)
JANUARY 03	MYCOPHENOLATE MOFETIL
JANUARY 03	MYCOPHENOLIC ACID
JANUARY 03	PIOGLITAZONE HYDROCHLORIDE

Dosage forms provide one way in which firms can continue to add incremental new features while extending older product lines. Both Ranbaxy and DRL, for example, have introduced an array of new tablet and capsule dosages that reflect intelligent marketing as opposed to new technologies.

In the case of Fluoxetine (brand name Prozac), Dr. Reddy's Laboratory simply invested in creating a 40 mg dosage because it had discovered that the most highly prescribed dosage for Prozac was two 20 mg tablets. The company's burden of proof was then to show that its 40 mg tablet dosage form could have the same therapeutic effect. It emerged as the first Indian company to receive a 180-exclusive marketing approval from the US FDA in July 2001.

The patenting profile of all leading Indian companies lies squarely in the domain of process developments, with only some minor efforts at new product development. However, the process developments and the search activities to find new ways to enter the US market, have resulted in some ingenuity. The publication record also demonstrates the importance of process development capabilities.

[41] This must be offset against the reduction in patent expiries beginning mid-way through the coming decade.

But what leads companies from processes to products? Is there such a pathway? The gradual move of the industry's process capabilities appears to have been some combination of the process patent regime, which encouraged new process routes for the same end drug, and stricter product patents, which forced greater search efforts among leading firms to a non-infringing path. These were part of a broader selection environment that made some technological choices (processes rather than products)

One interviewee expressed support for stricter product patents that induced firms to be more innovative:

> *"Foes of this change are people who aren't capable of doing something novel"* (Interview, June 17th 2002)

Specifically, the trend to patent appears to have induced some level of intensity of recent effort among academics and public research laboratories. Another interviewee stated, :

> *"The patenting trend is useful. We have too many armchair scientists"* (Interview, June 14th 2002)

However, it is unclear whether the trend simply reflects past efforts that are being formalised through patents, or any new research efforts. This is unlikely to be measurable for some time to come.
A handful of Indian companies have made the first ventures into novelty by introducing sufficiently differentiated products and by challenging existing patents through "Para IV" filings and through new chemical entities. In the case of early innovations arising from Indian pharmaceutical firms the novelty was to provide new formulations, new platform processes or new process development pathways, as was the case of Compos from Ranbaxy (Valium) and Salbutamol from Cipla.

Table 5.6.2Early private sector successes for alternate processes

Company	Indian name	Patented brand name	Generic name	Drug product
Cipla	Salbutamol	Ventolin (GlaxoSmithKline)	Albuterol Sulfate	Anti-asthma
Ranbaxy	Calmpose	Valium (Roche)	Diazepam	Tranquilliser

Generic drugs emerge as a singular learning path for how developing countries can advance technologically. "Generics" have been seen primarily as 'copies', but as this section emphasizes, generic drugs afford an unusual opportunity in a specific institutional setting, for technological advancement. In particular, they highlight entry conditions and how firms can advance their market

share once they have entered a particular drug segment. For developing countries, the path holds special significance because of entry barriers, regulatory hurdles and incumbent security of the patented product. Furthermore, the generics drugs market allows multiple firms entry for the same generic drug, which means firms enter without knowing how many others have also applied for the same approvals, and although they are sequenced in turn through the approval mechanism, they create high costs and uncertainties for firms, particularly those who may be relatively new to a particular drug segment, even if the date of patent expiry and type of drug segment is known in advance.[42] In addition, the number of producers of the generic drug is linked less to the price of the drug at a given time and more to the anticipated rents from the particular drug segment.[43] What this means for Indian firms, is that information of what rents to expect is an area of some concentrated effort and so speed to market is also of the essence.

Indian firms have been decreasing the time required to introduce a patented drug to market in countries that do not have a product patent regime. They have also reduced the time to introduce off-patent drugs to market, often because they have already been selling the drug in the Indian market, or exporting the specific drug to countries with no product patents. Indeed, because of the diversity of regulations worldwide, with different national systems adopting policies for local needs, there may be no lag at all, but lead-time, with Indian firms launching the product in India many years before patent expiry, and waiting to launch in international markets. Often, the product is launched immediately and some Indian-owned firms have been the first worldwide to receive approval to launch and/or to receive exclusive marketing approval for limited time from the US FDA.

Indeed, relative to China, the patent profile appears distinctly focused on process innovation within this industry relative to others, and showing the preponderance of innovation around existing chemical entities. Furthermore, a closer look at Indian firms such as Ranbaxy shows the patenting profile follows closely that of its peers. As a patenting leader, its publication and patent profile below indicate how much the focus is manufacturing (scale-up) and process chemistry.

The table below indicates the short introduction lag for India's leading generic drug firms, and an introduction lead where Indian approvals (based on the no-product patent regime) have come before the patent expiry date. Note the variation in product types, showing a gain in diversity as process

[42] However, the FDA simultaneously approved 3 generics drug producers in Oct 1993 for alprazolam and 9 generic drug producers in December 1993 for naproxen. (IMS health data and FDA)

development skills improved over time. The high lead time of 10-12 years in many cases, also indicates that technologically, there is little preventing Indian firms from producing these drugs (as they have already introduced them in the Indian market). A few, such as Ciprofloxacin, have shown novel properties-predominantly a viable dosage form (once a day), that has resulted in the brand name company seeking an alliance with the Indian generic drug firm in question.

Table 5.6.3 Select examples of development timelines for Indian generics

(In alphabetical order)

DRUG	FIRST INTRODUCTION	PATENT EXPIRY	INDIAN APPROVAL/MARKETING (APPROX.)	TIME LAG FROM FIRST INTRODUCTION (APPROX.) AND LEAD (BEFORE PATENT EXPIRY)
Aciclovir	1981	1997	1988	7 (9)
Albendazole	1974	1995	1988	14 (7)
Asternizole	1983	1999	1988	5 (11)
Captopril	1980	1997	1985	5 (12)
Cefaclor	1979	1994	1991	12 (3)
Ceflazidime	1983	2000	1988	5 (12)
Cefotaxime	1980	1997	1988	8 (9)
Cefotaxime Sodium	1980	1997	1988	8 (9)
Cefuroxime Axetil	1988	1997	1990	2 (7)
Cefuroxime Sodium	1978	1994	1988	10 (6)
Ciprofloxacin	1986	2001	1989	3 (12)
Enalapril Maleate	1984	1999	1989	5 (10)
Famotidine	1984	1999	1989	5 (10)
Ketoconazole	1981	1998	1988	7 (10)
Netimicin	1980	1994	1988	8 (6)
Norfloxacin	1984	1998	1988	4 (10)
Ranitidine	1981	1997	1985	4 (12)

Source: Author's calculations, Keayala (1996) and Lanjouw (1997)

While the lead and lag times act as one indicator of advance, the following case study of a generic drug firm emphasizes that while not technologically sophisticated, generic drugs are nevertheless not without effort. They require revenue streams and the ability to shoulder considerable risk and uncertainty. While the firm benefits from low local R&D labour costs, it faces considerable GMP investments.

[43] For more on modelling of how competition evolves in the generics drug market, see David Reiffen and Michael Ward, 2002, "Generics Drug Industry Dynamics", Report prepared for the Federal Trade Commission.

5.6.3 CASE: In-house R&D, generic drug and biopharmaceutical investments

> *"It is the ability to know and extrapolate what the remaining 10% of the patent information is....."* (Interview).

Company X is a leading Indian pharmaceutical firm, beginning more than two decades ago and having entered the market through capabilities in antibiotics, anti-infectives, among others. It has since moved into biopharmaceutical research, although this continues to be a small portion of its revenues. It began manufacturing products patented elsewhere and remained open to alliances for technology transfer and contract manufacturing with both Indian and foreign firms. It also committed itself relatively early to investing in in-house R&D capabilities and has since shown considerable advance in process, platform and some product innovation. Company X feels that any Indian company can easily develop processes for drugs developed elsewhere because of the country's health needs, past process patent laws, as well as because skilled labour is cheap and plentiful for this industry. In particular, it feels that although antibiotics and other public health drugs are mature segments, they will always sell easily and allow the company to invest in other areas of research.

Furthermore, it stresses strongly that India does not have a low-cost manufacturing advantage, but a low cost R&D advantage because people, not capital requirements, are inexpensive. This advantage is likely to erode over time, as MNCs choosing to conduct R&D in India are likely to hire from the same pool. *"We're still enjoying our R&D cost advantage, but not for long"*. The technological learning, company A feels, was accomplished much earlier in the company's (and nation's history). It, and other companies like it, are now facing an uphill task to learn and adapt to new regulations and new business environments.

Process capabilities are central to its success, and it went down this route because" *"we couldn't afford products, so we chose processes*." It adds that people write off generic drugs as mere copies. However, although technological challenges are now minimal, they were surmounted through gaining market share by adding minor novelties-dosage form, lowered frequency, fewer side effects etc.-all the time. These do not present interesting technical challenges any more, but huge financial and regulatory ones. *"People think that generics is a zero investment business. But it is very investment heavy in comparison to rewards when prices drop. The R&D depreciation is a very, very heavy percentage in generic drugs. No one has really measured this well. The only saving grace is that no sales and marketing is needed in this segment."* Thus, a firm that wants to be innovative in products as well, needs to learn to cope with these other challenges. *"The greatest obstacle is GMP and regulatory*

hurdles. At least 25 other companies fall into this same category. For Indians, formulations and process chemistry are like ABC now, formulations we can now learn to do the next day, process chemistry in less than 12 months".

While it is undoubtedly easier to modify an existing design than to create the design in the first place, it is still a technologically challenging task given the patent barriers surrounding the innovation. In addition, the tacitness of the procedure is itself protection even were a patent not in place. Innovative advances that skirt patent barriers or that tweak certain parameters of the design, process or product to introduce a new variant of design, process or product on the market, demonstrate a form of technological learning that is not necessarily bounded. I.e. there is no automatic ceiling to this type of learning and firms in this path are not necessarily doomed to be forever imitators.

Levels of technological capability in generics manufacturing range from manufacturing ability to modification of APIs, formulation changes and drug delivery changes, among others. This requires not only the ability to distinguish and search around patent families, but also the ability to meet regulatory requirements of the specific authorities. In addition, patent applications can be filed for[44]:

1. Engineered excipients
2. Individual or combined delivery devices
3. Preferred API salts, active metabolites or approved APIs
4. Unexpected results from API mixtures

The task of the firm is then to outline all possible patent families, which then safeguard future revenues.

During the era of stringent production licensing and price ceilings, many firms circumvented this process and profited from non-essential drugs such as tonics and dubious preparations. Even then, companies gained from process capabilities in creating formulations and dosage forms. In more recent years, firms that targeted the generic drugs market built their market advance on dosage forms. The Tables below indicate examples from the late 1990s of Indian firms that have introduced differentiated products in the US market. These products are often different in dosage form, some demonstrating additional efficacy or better delivery. In each of these cases, the case for novelty has been made to the US FDA. The patent profile of Indian firms has also evolved in a similar direction, represented in the

[44] "API Management Practices", Contract Pharma Magazine, Jan/Feb 2003

concentration of papers and patent applications focused on process improvements and modifications of existing drugs. (Mani, 2002)

Case Ranbaxy

In the case of Ranbaxy, the foray into manufacturing began in 1965. Its manufacturing successes began with Calmpose, the generic version of Valium from Roche, and was followed by further gains through Roscillin (1971), generic of Ampicillin and Gramoneg (1974), a formulation of Nalidixic acid. Because Ranbaxy had built up capability in anti-infectives in the late 1960s and early 1970s, it was particularly ell positioned to grow through critical policy shifts of the early 1970s, particularly the Patents Act, making its generic business easier. The policy shifts allowed it to consolidate its hold in domestic market share, and to move into novel processes for blockbuster drugs. In particular, its ability to develop non-infringing processes for existing drugs was a successful strategy despite the fact that the Patent Act allowed it to do otherwise. It launched a novel process for Doxycycline manufacture in 1978 and for the biggest seller of all, Ranitidine in 1985. Seven years later in 1992, Ranbaxy developed a non-infringing process for Ceflacor. The Ceflacor case launched Ranbaxy into a different league altogether. The non-infringement meant that a new form of innovation was occurring, and signalled to pharmaceutical companies abroad that Ranbaxy was a company to monitor. Eli Lilly, the patent holder on Ceflacor established a relationship with Ranbaxy for contract manufacturing of Ceflacor, thus thwarting direct competition. The signal was not the non-infringing process development alone. It was the scale-up capability of Ranbaxy and its ability to take the laboratory process to factory scale immediately that was threatening. Large Indian companies had thus emerged on the incumbent firm's radar. This process confirms different forms of scale economies, with the last being unique to firms from developing countries.[45] Large firm size in this case is thus institutionally preferred and rewarded as technological learning occurs and investments re made in plant capacity and in-house skills in scale-up and manufacture.

A typical story of simultaneous process and product innovation is demonstrated by the varied generics drugs speedily brought to market by Ranbaxy, one of India's leading pharmaceutical firms. Indian innovations like those of Ranbaxy are that these drugs provided minimal side effects or more controlled release relative to the patented drug. Some also showed new therapeutic effects for other treatments because of process innovation. A typical example is the generic version of the drug Ceflacor, which not only exhibited product ingenuity through incremental product innovation, but also

[45] Amsden (2002) highlights information, signalling and transaction cost economies of scale, differentiated from production-related costs and fixed costs of design, the more "standard" scale economies.

showed process innovation. Process innovation here related to (a) studying the patent filing from the parent company (b) devising an in-house lab-level process to duplicate the final product, but not process (c) devising an in-house manufacturing process suitably scaled-up to do the same, (d) pushing the drug studies past the 56 steps that Eli Lilly had completed and patented[46]. In general, leading Indian pharmaceutical firms have developed mechanisms that have brought in a profitable flow of revenues from generics, rapidly catching up with expiry dates and aggressively launching in both the US and India.

Many of the company's advances on processes and products were concurrent, or with no obvious sequencing. In addition, the company benefited from institutional parameters that allowed in-house development of sophisticated process capabilities and a vast infrastructure of manufacturing facilities that satisfy stringent certification requirements. Ranbaxy's case is symptomatic of the typology of differences between the different types of innovation described in the literature.

The table below shows that even in generic drug segments, the chances of product differentiation with far-reaching consequences (usually substantial market share, important joint venture, technology exchange agreements or contract manufacturing revenues) are substantial. In each case, the technology is only partly known. Some elements such as purification or yield are more tacit than others, where the only barrier is patent expiry. Some of the drugs below are not manufactured in large scale such as venom antidotes, but demonstrate the point that considerable process innovations exist in the Indian case and are examples of the ability to scale-up production from lab yields to large-scale manufacturing. Indian firms perfected the art and science of product differentiation while more recently attempting to patent the novel properties of so-called copies. Even a company such as Cipla, which has not been considered an innovative firm, has demonstrated some level of product differentiation and indigenous firsts.

[46] Note that size again was crucial because large revenue streams were essential to pay for this investment, but also because only when Ceflacor was developed through a non-infringing process and ready for large-scale manufacture, did the brand-holder register the signalling mechanism based on size.

Table 5.6.4 Examples of some recent innovations from Indian-owned firms[47]

Company name	Drug/technology platform	Type of innovation
Cipla	AIDS 3-drug cocktail, with two on-patent drug (but exported to countries with no process patent-only regimes) and one Cipla generic.	AIDS kit with easy-dosage form. Cocktail offered at less than half the cost. Steady supply ensured.
Ranbaxy	Ciprofloxacin generic	Oral once-a-day dose compared to multiple doses needed presently by Bayer's patented drug.
Dr. Reddy's Laboratories	Prozac generic Fluoxetine	Shows some novel properties. In arrangement with patent-holder Eli Lilly for out-licensing and production.
Shanta Biotech	Hepatitis B vaccine	Significantly lowered cost, alternative culture for preparing the vaccine
Bharat Biotech International	Hepatitis B vaccine	Significantly lowered cost, alternative culture for preparing the vaccine (distinct from Shanta)
Biocon India	New fermentation reactor for enzyme culture use din pharmaceuticals	New fermentation technology used Novel solid state mechanism to control fermentation conditions
Vittal Mallya Foundation	Snake venom antidote	Made through culture from poultry eggs
Reliance Life Sciences	Stem cell research	Uses novel methods for harvesting.

A significant investment of technological ability rests in the ability of a firm to demonstrate that a given drug does not infringe on the patent-holder's intellectual property. In particular, process and product need be shown to be sufficiently different, while the product still needs to be sufficiently close in therapeutic characteristics that it can compete with the incumbent drug.[48] The table indicates different categories of drug introductions by Cipla into the domestic market. The fact that product differentiation can continue to be strategic advantages for such firms is demonstrated by the table below. In particular, note that as discussed earlier, Cipla's Salbutamol was preferentially allocated a license for indigenous development under the New Drug Policy.

[47] Because of India's process patent regime, some of these drugs are process engineered differently from on-patent drugs, while some are generics of off-patent drugs.

[48] Often the market leader may itself be a once me-too drug, now facing generic competition of its own. For example, Zantac was the largest-selling prescription drug treating heartburn and ulcers. It was produced by Glaxo Wellcome (since Glaxo SmithKline, ironically), a "me-too" version of the initial "revolution", SmithKline's Tagamet in 1977. Because Zantac could show non-infringement, it filed a patent of its own (multiple patents, in fact, to protect the drug). Subsequently, when its patents expired, Novopharm was awarded rights to market ranitidine, the generic chemical version of Zantac. Yet Zantac continued to enjoy significant brand name, incumbent market power. Zantac's prowess was in establishing a product differentiation strategy buttressed by significant revenues to spend on marketing and distribution.

Figure 5.6.1 CIPLA first-time introductions in India

DRUG CATEGORY	DRUG
Antihypertensives	Propranolol
	Doxasozin
	Metaprolol extended-release (Metolar XR)
Anti anxiety	Lorazepam
HIV	Stavudine
	Lamivudine
	Zidovudine (AZT)
Cancer	Vincristine sulphate (for acute leukaemia)
	Vinblastine sulphate (for palliative treatment of cancer)
	Etoposide (for various cancers)
	Bicalutamide (for prostate cancer)
	Ondansetron (for cancer-induced emesis)
Asthma/Respiratory	Montelukast Sodium (for bronchial asthma)
	Salbutamol sulphate (for bronchial asthma)
	Salmeterol (for bronchial asthma)
	Deferiprone (world's first oral iron chelator for use in thalassaemia)
	Clofibrate (for hyperlipidaemias resistant to diet)
	Gugulipid (for cholesterol reduction)
	Norfloxacin (broad spectrum antibacterial)
	Famcyclovir (for herpes infections)
	Apraclonidine (for glaucoma)
	Finasteride (for benign prostatic hyperplasia)
	Fluicasone porionate (topical corticosteroid)
	Alendronate (for osteoporosis)
	Misoprostol (for NASAID induced gastritis)
	Tamsulosin (for BPH)
International patents	CFC-free metered dose aerosol inhaler
International patents	Rotahaler and Zerostat spacer

Source: Adapted from Cipla company reports and website

Table 5.6.5 New Cipla introductions

Drug category	Drug	Novelty
Chronic Obstructive Pulmonary Disease (COPD)	TIOVA (Tiotropium bromide)	Dry powder inhalation with 18 g cause improvement in lung function and reduction in symptoms than ipratropium bromide given 4 times daily, Show superior bronchodilation and symptomatic improvements when compared to twice-daily salmeterol.
COPD	Asthalin	First-time combination of Salbutamol, a potent bronchodilator with a safe and effective mucolytic, Ambroxol, for nebulisation.
Anti-hypertensive	Fosinace	Unique dual elimination rote (50% renal and 50% hepatic) for 24 hour blood pressure control
	Budesal Respules	Combination of corticosteroid budesonide with a bronchodilator Salbutamol,
Anti-HIV	Odivir Kit (world's first antiretroviral kit)	Simplifies therapy, specially packed strip with contains once-daily does of 3 antiretrovirals that are commonly used as a triple drug regimen. Contains Efavirenz 600 mg, Lamivudine 300 mg and enteric-coated Didanosine 250 or 400 mg as separate pills.
Anti-acne	Isotroin (synthetic Vitamin A analogue)	Only drug that acts on all four factors responsible for the pathogenensis of acne.
Anti platelet therapy	Clopivas AP	Combination of two antiplatelet agents clopidogrel and aspirin
	Metolar XR (extended release metoprolol) launched for first time in India	Multiple extended release (MXR) technology. Capsule with multiple pellets, each of which acts as a separate delivery over 24 hours.

Source: Cipla Annual reports and website

The data from Cipla, Ranbaxy, Dr. Reddy's Laboratories, Sun and Wockhardt, and supported by various secondary documents on other leading firms, indicates that a clear sequence of "imitation" to innovation appears to break down. While most firms were able to produce the mirrored sequence of process steps, one-by-one, which speaks to their imitation activity, in some cases the process developed to "reverse engineer" the product was itself sufficiently new worldwide, as to suggest some innovative capabilities as well. In other cases, such as that for Cefaclor, the company proceeded to map each step of the brand name company's efforts until at last, a new step, all its own, could be patented. In the Ceflacor case, Eli Lilly had patented up to 56 steps of the development process for the drug and Ranbaxy, attempting to develop a non-infringing method for the same drug, had to persist to the 57th step, wherein its differentiated process emerged and could then file for a patent of its own.

As the following narrative describes, the regulatory climate influences the valuation of innovation and the stage at which innovation occurs in a company such as Ranbaxy and is determined in large part by a combination of technological intricacies and the patent coverage awarded to the original innovator.

"...When all factors are considered Ceclor (cefaclor) should remain a viable product for Eli Lilly beyond expiration of the patent" (President, Eli Lilly pharmaceuticals, Feb 1991).

"The Ceclor synthetic route is so long and so complex' that it will be difficult to duplicate...a legal end-run seems extremely improbable". (President, Eli Lilly research labs).

"56 processes were under patent (with Lilly) and we found the 57th". (Ranbaxy executive).[49]

This could be characterized as tenacious, rather than innovative, if the other evidence from Paragraph IV challenges did not also support the innovation hypothesis. Some Indian companies, through "minor" novelties, are demonstrating a product differentiation strategy which in a previous era of patent regulation, would have warranted new patents altogether. The growing confidence of companies is reflected in attempts to increase speed of ANDA filings and Paragraph IV patent challenges. In 2002, DRL filed 11 drugs in the US out of a total filing of 13 worldwide. 8 out of 11 were patent challenges in 2002.[50]

Table 5.6.6 Recent "blockbuster" patent challenges or infringement lawsuits for Indian firms

COMPANY	FOREIGN FIRM	PRODUCT PATENT CHALLENGED	INFRINGEMENT LAWSUIT	STATUS
Dr. Reddy's Laboratories	Pfizer	Norvasc (hypertension drug, estimated worldwide sales 2002 US$3.8 billion)		Challenge in lower court successful. FDA approval received for manufacturing. Pending higher court.
Dr. Reddy's Laboratories	GlaxoSmithKline	Zofran (for treating post-operative , chemotherapy and radiotherapy induced nausea and vomiting		
Ranbaxy[51]	Pfizer	Lipitor (cholesterol reducer)		
Rambaxy[52]	GlaxoSmithKline		Augmentin	

[49] All quotes taken from Lanjouw (1997)

[50] "Litigation in large doses", P. T. Jyothi Datta, Business Line, (The Hindu), Wednesday, Sep 18, 2002

[51] On patent challenges: *"Indian companies have definitely arrived on the global scene and litigations only ensure that the challenging company does its homework well. The onus of an honest challenge is on the generic,"* Bimal Raizada, Senior Vice-President, Ranbaxy Laboratories, quoted in "Litigation in large doses", P. T. Jyothi Datta, BusinessLine, (The Hindu), Wednesday, Sep 18, 2002

Source: adapted from various news reports and company press releases

The next sub-section underscores the far reach of integrated bulk drug manufacturing. As companies learn to adapt to regulations and standards, they face new opportunities in custom synthesis to innovator companies -some in India.

5.6.4 Launch readiness: Catching up before the race begins?

One significant feature of time-to-market is not the speed at which a drug gets through the FDA or other regulatory process but by the speed at which the company can respond to demand for the drug once it is launched. A high-profile example of the failure to meet market demand and the subsequent fall in the company's ranking as a provider for that drug category is Immunex in the year 2000. The company announced that for its blockbuster drug for arthritis, Enbrel, it did not have sufficient capacity to meet public demand. Besides the loss estimated at $250 million in potential revenues, the company's stock price also took a battering. While Enbrel is the patented drug, the ability of the first-company to profit from the tardiness of Immunex lies in its ability to ramp up at short notice, while dealing with problems of unexpected volume demand and price pressures.

Both bulk drug capability and the adaptation to the generic drug regulatory selection mechanisms has allowed Active Pharmaceutical Ingredients (APIs) to emerge as a critical source of profitability and proprietary assets. Both "innovators" and generic drug manufacturers in advanced industrialised countries have historically sourced APIs from other such countries. The patent regime allows Indian firms with formulation, dosing and API manufacture capabilities much greater familiarity with a given product by continued exposure over a longer time than their counterparts in other countries where markets are regulated through product patents. The strict regulatory environment has prompted further proprietary API relationships such that innovating companies in advanced industrialised countries search for suppliers who are able to manage proprietary chemicals and processes. Thus, API manufacturing has emerged as a source of proprietary innovation and tacitness. The sources of Indian API expertise range from the low cost of inputs and development to chemical synthesis capabilities, GMP compliance and speed of development.[53]

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[52] On infringement lawsuits: "*We take legal advice and respond appropriately. But we will not lose sleep over it. It is something that one has to live with, if one has to do business in the US.*", D. S. Brar, CEO and MD of Ranbaxy Laboratories, Ibid.

[53] Dr. Reddy's Laboratories-Cheminor (since acquired) argued that its advantage is a development speed almost twice that of any competing European or US firm.

For instance, new opportunities have arisen where Solvay, a Swiss company, normally sourcing from Lonza, another Swiss company for Teveten/Eprosartan mesylate (anihypertensive sources indirectly the same API from Dishman, and Indian firm. API manufacturing capability, inclusive of its proprietary processes and speed to market, is itself, although not a product innovation, the source of multiple product innovations both in-house and to innovating clients. While thus far API assets have been central to the patent challenge and have been known to be a barrier to entry, the Indian case demonstrates that they have evolved into proprietary assets. The greater the niche product, the faster to market (or a combination of the two), the more likely the API manufacturing capacity becomes a proprietary asset in itself.

While the previous sections have highlighted the product differentiation pathway of generic drugs, we now turn briefly to a recent change in Indian companies, their production of new products.

5.7 New Chemical Entities and New realities: Arbitration on novelty

Part of the reluctance of Indian companies to search for new drugs is the cost associated with it. In recent years, India's manufacturing firms, buoyed by successes in mature product lines, have invested the money into drug discovery. The change of the Indian patent regime in 2005 has also been a spur for such investments, but the example set by Dr. Reddy's Laboratories, in particular, has stood out. Its CEO has stated more than once than Indian companies can find new molecules faster and more cheaply than anyone else and is attempting to prove it.

Table 5.7.1 Ranbaxy New Chemical Entities

NCE Pipeline		
	Clinical	RBx2258 : Selective 1μ antagonist for BPH –undergoing Phase II Studies RBx7796 : Novel VLA4 antagonist for Bronchial Asthma - undergoing Phase I studies RBx 7644: Anti Bacterial - Oral & IV - Phase I
	Early Discovery	RBx 6198 : Other BPH molecule RBx 9611 :Overactive bladder RBx 8700 : Anti-infective , Tuberculosis
	NDDS - Achievements	4 Platform Technologies: Aerogel Gastric Retention PH Independent Micro encapsulation & particle coating

Source: Company reports and website

But the fundamental link between process capabilities and the gradual increase in launches of products, is the increased ability of Indian firms to differentiate products through different processes, gain revenues by manufacturing, and invest in new drug discovery and development. Product differentiation also brings with it a host of complementary assets such as market research, better marketing and distribution and faster regulatory compliance.[54] The skills developed in process development at early synthesis stages, also assist firms in their drug discovery and development studies.

A few firms have been entering higher value-added segments through drug discovery programs of their own, introducing New Chemical Entities (NCEs) into the certification and regulatory process. While some of these firms began the process of technology acquisition through links with MNCs, this has been the exception rather than the rule, although increasingly, with newer technologies, technology alliances have become more common.

The NCE table below also indicates that in a few instances, advanced stage pharmaceuticals from Indian firms have also been out-licensed to MNCs, reversing a technology transfer trend to developing countries. These same firms have then moved from generics into more profitable urology, cancer and diabetes drugs. [55] In addition, by developing state of the art facilities, Indian firms are increasingly becoming manufacturers and developers of choice for MNCs and foreign governments, as well as the WHO. For example, Reliance Life Sciences (a spin-off of the Indian conglomerate Reliance) has been designated by the US National Institute of Health as one of 10 worldwide preferred suppliers for stem-cell cultures.[56] Indian –owned firms have also benefited from global pandemics such as AIDS[57] and tuberculosis as well as from bio terrorism scares such as Anthrax.[58].

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[54] In the case of a drug under patent, the patent may specify how the drug is released and absorbed into the body. The cholesterol-lowering drug Lovastatin is now off-patent (the original brand name was Mevacor from Merck) but was patented as an immediate-release product. Thus, Andrx, one of the world's leading generic drug manufacturers, was able to come up with an extended-release version, Altocor, which is not considered a generic copy and can be patented. This "super generic" or "branded generic" is seen as vertical product differentiation, and automatically obtains a three year period of marketing exclusivity in the US, but also comes with a higher price since it can no longer go through the abbreviated approval process.

[55] The most visible of these was the licensing of Ranbaxy's Ciprofloxacin to Bayer, with once-a-day dosage properties, that Bayer, the patent-holder, was not able to create.

[56] This not only noted RLS as having state-of-the-art facilities, but also registered its sophistication in research.

[57] At the start of the 1990s, the cost of an AIDS treatment combination for an individual was about $8500 a year in India, but when Indian-owned Cipla began production in 1993 of Zidovudine as a generic, and followed it with Stavudine, Lamivuidine and Nevirapine-they had succeeded in creating the relatively successful AIDS cocktail for US$600 per year/patient and provided it at US$1/day to charities like Medecins Sans Frontiers,

Table 5.7.2 Examples of Indian New Chemical Entity pipeline

Company	Molecule	Category	Development Stage
Ranbaxy	RBx2258	Urology (BPH)	Phase II
	RBX6198	Urology (BPH)	Discovery
	RBx5736	Urology (BPH)	Discovery
	RBx4638	Respiratory (Novel VLA-4)	Phase 1
	RBx7635	Anti-fungal	Discovery
	RBx7644	Anti-bacterial	Pre-clinical
	RBx7643	Overactive Bladder	Pre-clinical
Dr. Reddy's Laboratories	DRF-2725	Diabetes and Dyslipidemia[59]	Phase III
	DRF-2593	Diabetes	Phase II
	DRF-4158	Diabetes	Pre-clinical completed
	DRF-NPPC	Diabetes	Pre-clinical completed
	DRF-1042	Cancer	Phase I
	DRF-1644	Cancer	Pre-clinical completed
	DRF-3188	Cancer, Viral infections and Immuno-stimulation	Late pre-clinical
	DRF-4832	CV-PPAR HDL Elevator	Late pre-clinical
	DRF-4714	CV-PPAR HDL Elevator	Pre-clinical
	DRF-2937	CV-anti hyper lipoprotein	Pre-clinical
	DRF-4848	Inflammation	Late pre-clinical

Source: Adapted by author from company reports and from analyst reports, Piyush Kheria (2002)

Firms have had to first identify what other companies have commercialised compounds similar to their own target molecule or intermediate, what starting materials or modification thereof are required to obtain a final desired product, how to maximise drug purity and quantity, and minimising impurities and variability. Syntheses have to be designed to yield the highest probability for commercial scaling-

causing a stir worldwide and forcing multinational pharmaceuticals to significantly lower their prices. Cipla exports anti-AIDS drugs to more than 35 countries. In March 2002, the World Health Organisation listed Cipla as one of the preferred international suppliers of Anti-AIDS drugs. Cipla is presently in talks with South Africa's largest mining company to sell a three-drug cocktail of the drugs for $350 per patient per year. Of the cocktail, Cipla has registered one generic (of Glaxo-Smithkline Beecham's Lamivuidine) in South Africa. The cocktail consists of three products, Lamivuidine (brand name- Lamivir), Stavudine (Stavir from Bristol-Myers Squibb) and Navirapine (Nevimune from Boehringer-Ingelheim). Cipla's stock has risen considerably after the withdrawal by 39 transnational companies of a patent suit for AIDS drugs against the South African government.

[58] The recent anthrax scare in the US highlighted the low cost of Ciprofloxacin generics made by Cipla pharmaceuticals in India, which was selling the drug for about 10 US cents, compared to Bayer's monopoly price of US$6 (both are retail prices). This caused some US senators to try and contact Cipla for access to cheap Cipro, (despite US patent laws prohibiting importation of a patented drug from a company other than the patent holder) resulting in Bayer reducing its price to 95cents.

[59] Since withdrawn from trials after carcinogenicity studies showed tumours in rats and mice.

up. This overall process development starts with route selection and design, on to kilo lab trials, pilot laboratory scale-up and finally, commercial scale-up.

While TRIPS requirements emerge in full force in 2005, Indian paten laws are also being changed as discussed in earlier chapters, with Amendments in 1999, 2002 and one coming up shortly before 2005. Among the issues being revised are the introduction of product [patents, of duration of patent monopolies and the scope of patentability.[60] Keayala (1996) stresses that the government should introduce restrictions on "product" applying only to NCEs and not to dosage forms or combinations of existing off-patent products, for example, as have been awarded worldwide in the past to some famous drugs such as Aspirin in 1973 (Soma compound, W Codeine) from Wallac labs, whose patented dosage/formulations were Aspirin 325 mg+ Carisoprodol 200 mg + Codeine Phosphate 16 mg, and whose patent expires 13/8/2002, or Aspirin 325 mg+ Carisoprodol 200 mg, whose patent expires 13/8/2002. Other famous examples of patents being given to dosage/formulations are Ranitidine Hel (1995), also called Zantac (150,300) from Glaxo for which patents range in expiry from the same year to 8 years later for Eq. 150 mg base tab, Eq. 300 mg base tab, Eq. 15 mg base/ml Syrup, Eq. 25 mg base/ml inj., and Eq. 50 mg base/100 ml inj. (in order of dates of expiry). (Ibid.) These patent awards brought considerable fortunes and market power to their parent companies. What new patent restrictions imposed by the government could entail is a much higher burden of proof from Indian companies, many of whom have until now, made formulations and dosage forms a fine art, but have not shown "an inventive step" or "an important technical advance".[61] Indeed, many companies interviewed agreed that much of what they accomplish requires no significant technological sophistication. Yet, this is similar to what many of today's leading pharmaceutical firms continues to undertake.

The Indian findings are in fact consistent with one typology of how innovation now occurs in the pharmaceutical industry. Incrementally modified drugs (IMDs) account for 2/3 of all drugs approved

[60] A comprehensive discussion is found in Keayala (1996).
[61] The Patent Act of 1970, Section 2 suggests that novelty is necessary but does not specify the "inventive step". The Joint Parliamentary Committee suggests inclusion of a new clause (ja) "Inventive step" means a feature that makes the invention not obvious to a person skilled in the art. Keayala's response is "Inventive step": means a feature of an invention that involves an important technical advance as compared to the existing knowledge and/or having considerable economic significance and which makes the invention not obvious to a person skilled in the art." (Ibid.)

between 1989-2000, with old active ingredients.[62] This type of innovation (IMDs) has arisen because of the following reasons as the table shows, based on the US market.

Table 5.7.3 Incremental drug modification dynamics

Category of incentive to create IMDs	Market manifestation	Reason
Legal	Patent expiry	Companies try to protect their winning drugs by attempting to improve upon them
Technological	Horizontal and vertical product differentiation	Companies move into new markets or garner greater share in same markets. Lesser and greater technological differentiation (based on market characteristics or those based on minor improvements to the drug)
Regulatory	Regulatory incentives to innovate incrementally	Companies can get a drug to market faster if they can show that a new version of an old (approved) drug is available (the 505(b) pathway of the USFDA), for example extended release drugs, new ways of administering the drug (pills versus injectibles) or purified drugs from molecular mixtures)
Competitive	Strategic ways of entry barriers in generic drugs	Companies facing patent expiries of selected drugs try to patent new features of the IMD and may be able to obtain 3 years of exclusive market access of they show either an entirely new version of the earlier drug or an entirely new use for an existing drug.

Source: Adapted by author from "Changing Patterns of Pharmaceutical Innovation" (2002.)

While this typology is useful for understanding why IMDs are increasing as a percentage of total drug approvals in the US, it presents a slightly different conceptualisation for IMD proliferation in India, where firms are challengers, not incumbents. It highlights the changes in innovation criteria as the selection environment changes with regulatory changes. Indian companies are creating significant numbers of IMDs that in a previous era might have been considered new products.

[62] "Changing Patterns of Pharmaceutical Innovation", A research report by the National Institute for Health Care Management Research and Educational Foundation (NIHCM), May 2002, Washington D.C.

This is reflected in the statement by the K. Anji Reddy, Chairman, Dr. Reddy's Laboratories Limited:

> *"When I looked tat the number of new drugs that were launched the world over, I found most of them to be analogues of the leader molecules, or the so-called me-too molecules and second-generation molecules.....Look at Roche's tenoxicam structure, Roche has replaced "phenyl" in piroxicam (Pfizer) with "thienyl", and the result is that we have a new drug with a longer half-life and has one-a-day advantage over piroxicam. There are many such cases, the well-known examples being Cimetidine, Ranitidine, Norfloxacin, Ciprofloxacin, Lovastatin-Simvastatin".*[63]

Nevertheless, reflecting changes in selection, firms now face higher thresholds in demonstrating novelty of their outputs.

5.8 "Learning–by-Proving": a special skill-set emerges

The prevailing wisdom is that developing countries should concentrate on mature product segments, but that the primary innovation is targeted to lower costs since the dominant design has been achieved. The Indian experience demonstrates that firms further honed their process capabilities since product development, specifically drug discovery, was too expensive. Secondly, even in mature product segments, some innovation existed which was lucrative. "Learning-by-proving" in export markets occurred in 3 modes: through tiered cGMP compliance, through vaccines procurement, and through generic drugs. The modes explain why structural elements (cGMP) are closely linked to market entry, and thus to incentives for further product differentiation and innovation. It has also provided many competitive skills required from today's marketplace: rapid filing of applications for novelty, filing challenges against incumbents and rising to litigation coming from incumbents and other generic drug competitors. In addition, Indian firms began to use custom API synthesis as a means to increase revenues by contract manufacturing. CGMP was a means to the end of both in-house and contract manufacturing upgrading and signalling to companies the ability to scale-up, speed up and custom create specialty chemicals.

The table below shows the internalisation of learning through external selection.

REGULATORY CHANGES IN EXTERNAL ENVIRONMENT	3 SUB-CATEGORIES OF TIERED LEARNING
Waxman Hatch Act 1984 TRIPS/WTO 1985 First wave of Indian liberalisation mid 1980s and BOP 1991	1. Tiered worldwide cGMP worldwide 2. International procurement 3. Generic drugs

What my industry profile and sub-cases demonstrate is that in addition to these forms of learning, a clearly different manifestation of learning has arisen from facing regulatory hurdles in a tiered manner (referred to as "learning by proving"). This type of learning certainly has elements of learning by interacting and learning by searching, but it is more: This type of learning is in fact driven in part by facing specifications that are externally determined at the outset, but absorbed rapidly into the internal workings of the organisation and technological routines. They also need to adapt to new specifications at short notice, but further, to actively speed up the internal processes of the firm, from laboratory to final manufacture, filing and drug launch. Companies in India-in both pharmaceutical and biopharmaceutical categories have learnt to litigate and face litigation.[64] However, it cannot be developed at the first encounter with regulation, it is build on a long, cumulative path of abilities based on (a) yield advances (b) changes to the scale of the production process (c) changes to the organisation itself-R&D functions, contract services, shifts in internal hierarchies etc. (d) horizontal product differentiation (especially using process innovations across multiple product categories) (c) vertical product differentiation.

India's initial economic reforms began in the mid 1980s and were propelled into crisis in 1991 with the Balance of Payments debacle. Indian industry's wooing of overseas markets began by companies being forced abroad by price rigidities at home, but was assisted by three structural changes: liberalisation of the economy, changes in the US institutional environment for the pharmaceutical industry (specifically, the Wax-Hatchman Act) and the TRIPS homogenisation initiatives. But these technological windows were not purely exogenous constructions of opportunity, but appear to be

[63] ,Quoted in his speech "The agony and the ecstasy of Drug Discovery", Foundation Day Lecture, CRIPS Vol. 4, No.1, January-March 2003.

[64] Interviewees spoke about product liability, industrial espionage that had since been prosecuted, the need to find non-infringing routes quickly, and the importance of acquiring in-house legal expertise for both patent challenges as well as defences. In 2002, 8 of 13 filings by Dr. Reddy's Laboratories were patent challenges in the US market.

dependent on both the prior capabilities of Indian firms in process development and in core entry points of public health.[65] In addition, evidence from interviews suggests that the extent to which pharmaceutical and biopharmaceutical firms are able to appropriate new types of technologies and knowledge of practice are shaped by the selection environment in which they place themselves (as highlighted more generally by Wijnberg, 2004 forthcoming). For example, interviewees cite the relative advances with which they can now advance in generic drug segments where the selection mechanism is mostly known in advance, but not in "bio-generics". However, even within the same selection mechanism, firms use appropriation in different ways. Furthermore, since the valuators of the innovations were different in each case, (since the selection mechanism and evaluations were different), different demand characteristics emerge in each broad phase: state-led domestic phase, regulation-led and procurement led export phase, and the new technology-led, biopharmaceutical phase, which is discussed in the next chapter.

Trade is structured around the basis of differences in factor endowments of various sorts, including knowledge. History has shown quite convincingly that all firms (and all countries) neither have access to the same bodies of knowledge nor sets of technology. Vernon (1966) and others have further argued that while scientific principles underlying technologies were relatively well understood and managed internationally, markets were not, thus differences in access to knowledge and the adaptability to markets explained why variations across countries occur in innovation levels. The Indian story is certainly consistent with this explanation. Regulations as well as procurement, both acted to standardise information, pool knowledge across sets of technology in vaccines and generic drugs and create new markets responsive to adaptive firms. This fuelled demand-side pressures on technological learning and innovation, as well as complementary learning. However, before this export-push, the demand-side story and its impact on innovation is less clear. The State acted instead to boost supply of technologies and capabilities in the face of projected public health demands. Thus a more complete explanation is that cumulative abilities were forced into existence and then nurtured by changes in a selection environment, first by the state, then by foreign markets. Regulatory changes in this phase beginning in the 1980s, also highlight the positive role that regulation can play for developing country firms. Indians benefited from procurement and generic drug policies that made known cGMP requirements worldwide, that provided information on technologies (to some extent) and on competitors. Procurement provided worldwide credibility to Indian firms and global markets through

[65] This is consistent with Rosenberg (1974) that determinants of technological opportunity can be seen as endogenously determined and often arise from changes in scientific and technological developments (also see

the WHO and UNICEF, and generic drugs allowed firms to experiment extensively with minor product differentiation and more novel feature additions. Phase II was distinctive: the 3 types of learning occurred facing regulations that were voluntary for firms. Those firms that chose to invest in these capabilities, further pulled away from the rest of the sector, and prepared themselves for further selection criteria.

Furthermore, from the 1980s onward, what constituted novelty changed, as did the burden of proof on generic drug firms. The move of some Indian generic drug manufacturers into the US market recently coincides roughly with the heightened US worries of terrorism and the greater attention being paid to antibiotics and vaccine procurement. Health care costs, particularly those of prescription medications and managed care needs have worked to drive down costs, benefiting the generic drug industries. Although this is a mature product segment, process development capabilities have allowed innovation to occur to some extent. The government is debating the elements of the burden of proof required of Indian companies on what constitutes novelty, inventiveness and a product deserving patenting. This is creating additional challenges for interviewed firms to increase in-house R&D efforts.

The following chapter discusses the advent of "new" biology tools and their impact on the Indian biotechnology sector by bringing biology and its models of health and the human body to a chemistry-dominated Indian industry. The specific challenges, opportunities and institutional tensions are highlighted as the selection environment changes yet again with new scientific breakthroughs.

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discussion in Pavitt, 2002).

Chapter 6 Beyond Manufacturing: The rise of Indian biopharmaceuticals

6.1 Changes in scientific and technological paradigms: The rise of biopharmaceuticals

Biopharmaceuticals are simply the use of biological elements in creating medical therapies. For three decades now, the field of therapeutics has been revolutionized by breakthroughs in molecular biology of the early 1970s. Biology, chemistry and computation have surged ahead given the impetus from these breakthroughs.

Nested within these changes, the Indian therapeutics and diagnostics industries were also metamorphosing. Biopharmaceuticals brought newer product opportunities as well as newer characteristics to more mature products. In addition, the elements of the selection environment that affect firm choices have also changed with the onset of newer tools, products and processes. In this sense, "biotechnology" is all about process technologies and their development. Thus placed against earlier paradigms within the industry, this industry's institutional characteristics gain prominence.

The previous chapters laid out the history of manufacturing capability, process improvements and learning to deal with regulations that has characterized the Indian pharmaceutical industry. While the story of process capabilities and the environment in which this occurred unfolded from early post-independence days to the early part of the 21st century, the narrative did not capture an important paradigmatic shift occurring in the field of biology in the late 1970s. India invested in recombinant DNA technologies in the 1980s, early relative to the advent of these technologies on the world stage in the previous decade. Nevertheless, the majority of commercialization existed in more mature, less technologically sophisticated technologies such as high-yielding seeds, vaccinations and industrial fermentation and enzyme manufacture. However, its traditional strengths in agricultural technologies had led to significant advances in plant tissue culture, micro propagation, animal husbandry, diagnostics and vaccines.

While pharmaceutical firms underwent a learning process of their own, much of it was structured within an environment built by the Indian state in the early years and honed by a clearly demarcated and accessible (at least to richer firms) regulatory and standards regimen characterizing their exporting wave. Leading pharmaceutical firms advanced and learnt through a manufacturing push, with process

capabilities, scale up and manufacturing revenues gradually fuelling a move into the realm of early stage drug development, and even drug discovery, both more expensive endeavours. Thus, Indian process development and manufacturing capabilities were developed with industry protections and honed by regulatory pathways. As the newer tools emerged, they brought forth a further focus on process development to capitalize on these biological advances. However, the shifts in the science base of these technologies also required a new configuration of interactions between companies and their environment. The time between the first advances in the field worldwide, and their adoption in India, was relatively compressed, and firms in India faced many of the same uncertainties that firms in the US faced, for example. Thus, besides uncertain regulatory environments and rapid technological change, firms, public research institutes and policy makers alike faced uncertain institutional models. Specifically, the tensions present between business and scientists as the pharmaceutical industry developed were brought into stark relief here as science took on added prominence in the emerging field and interdisciplinary work became *de rigueur* in many sub-fields. These were occurring at the same time that universities and research institutes in India were facing considerable institutional uncertainties and opportunities of their own.

Thus, manufacturing capabilities alone were insufficient. Firms (and public research efforts) have had to move beyond a focus on process scale-up and manufacturing capability and question the institutional basis on which their relationship to science (and commercialization of the science) is premised. As the numbers of scientists –turned-entrepreneurs increases, and as the number of businesses with scientific knowledge increases, the schisms that exist today (and the stereotypes that pervade the industry) between business and science may be bridged in the future.

This chapter has two main purposes: to lay out the changes in the Indian landscape that accompanied the worldwide technological shifts, thus analyzing how the selection environment has changed, particularly with regard to standards and regulations. Second, to demonstrate how a newer field has created diverse industrial entry points by firms but also raises learning challenges of its own. In both themes, selection environment and product (im) maturity, in this newer field, the role of information gathering in building knowledge again gained visibility. Yet, the embedded nature of the firm in its local environment precluded the possibility that all search paths were readily available or equally costly. Resource-constraints, as in the pharmaceutical case, affected initial search choices, process development paths and final innovation.

When previous chapters discussed learning, it was situated against a backdrop of relatively mature product lines, but nevertheless required considerable investments by firms (even in generic drugs, perhaps assumed to be the "easiest" segment to learn from). The analysis continues in biopharmaceuticals by highlighting some distinctive cases of how learning takes place at firm level, the challenges and the methods by which advance has occurred.[1] Here too, the fact that a product is known to the world has nevertheless initiated a learning process in a firm facing the process development for the product for the first time. The rise of capabilities in this sector is a new phenomenon, and the chapter maps out the variation in environments and paths accordingly.

6.2 Emerging technologies: process development revisited

Within the drug industry, the technique of choice and the paradigm for drug discovery was random screening before the 1970s where serendipity, large samples and systematic search were seen to result in the occasional promising drug candidate. In pre-1970 period, "discovery" related to random screening which led to specific compounds being selected out for further work based on properties that seemed promising. Furthermore, this resulted in classification opportunities when molecules with new therapeutic qualities were discovered. No explicit therapeutic biological models were used to understand why certain molecules might have a certain efficacy. The search was primarily characterized by chemical properties of the candidate molecules.

The 1970s brought new breakthroughs in genetics and cell and molecular biology. A new way of looking at the human body and disease emerged, and with it, new techniques and models of disease and possible therapeutic candidates. Rational drug design signifying a higher level of understanding to "design" molecules with certain characteristics allowed for less labour intensive searches and a higher "hit" rate. In the post-1970s period, with HST and drug design, the researchers began backwards from the known disease and sets of molecules were designed to fit the needs of treating a certain disease. Although they are actively "designed", this is the equivalent of the "discovery". However, the methods are often not either drug design or random screening alone, but a combination of both.

With these technological changes came organizational restructuring. It also resulted in a division of labour with large pharmaceutical firms taking over almost exclusively full development of promising drug candidates, marketing and distribution functions, while drug discovery began to occur with higher frequency in dedicated biotechnology firms. Not just therapeutics, but diagnostics as well was

[1] As discussed in the chapter on methodology, data collection was complicated by the confidential nature of many of the exchanges. Thus, some useful case illustrations could not be developed fully because the company

affected by this change. Pharmaceuticals have since been changed, both in the processes that lead to new products, and in the product characteristics themselves. Biotechnology used in pharmaceuticals, is species specific since they are characterized by new uses of genetic manipulation. In modern pharmaceuticals, these processes may range from applied genetics (traditional or modern), genetic engineering (of which rDNA is most commonly used), cell-fusion technologies (of which hybridoma to make monoclonal antibodies is the most common) to protein engineering. Furthermore, traditional industrial processes such as fermentation, have been given a new lease of life through modern biotechnologies, and pharmaceuticals, which depend on fermentation for chemical synthesis, have now returned to this revitalized process in modern biopharmaceuticals. The ability of pharmaceutical firms to control enzyme culture through the fermentation process, for example, critically determines their path to some types of drug development.

Generally, three generations of products exist: the older methods of farm and industrial scale production of cheese making and brewing; a second generation primarily using fermentation with end products of enzymes (in food and related industries) and antibiotics (in health); a third generation using modern biotechnologies, such as vaccines of various kinds, human growth hormone and genetically produced insulin. The table below shows products developed using biotechnologies, and classifies them by user industries. Many processes are shared across sectors. For example, the process of enzyme immobilization has important technological learning effects and consequences for both industrial applications and biopharmaceuticals.

Table 6.2.1 Examples of biotechnology products

SECTOR	PRODUCT	WHETHER INDIGENOUSLY PRODUCED
Pharmaceuticals	Alpha and gamma interferons	Yes
	Erythropoietin	Yes
	Hepatitis B vaccines	Yes
	Human insulin	Yes
	Interlukin-2	Yes
	Gm-CSF[2]	Yes
Diagnostics	AIDS kits	Yes
	Aquaculture diseases detection kits	Yes
	Hepatitis kits	Yes

could be easily identified if the particular details of the product/process were discussed.

[2] GM-CSF = Granulocyte Macrophage Colony Stimulating Factor, AIDS = Acquired Immune Deficiency Syndrome

In addition, various indigenous diagnostic kits have also become available: (a) commercial applications: HIV (using agglutination ELISA[3] and Western blot techniques), Heptatis C (ELISA), Cysticercosis (ELISA) and (b) those under development: Tuberculosis, (PCR), Leishmaniasis (PCR), Malaria (ELISA/Dipstick, HLA (PCR/ELISA) and Typhoid (ELISA) (Padmanaban, 2003).

In particular, the process development characteristics vary between synthetic and biological therapeutics. Furthermore, process development has different elements of lab to factory scale-up in biopharmaceuticals as the table illustrates.

Table 6.2.2 Process development in pharmaceuticals and biotechnology

EXAMPLES OF PROCESS DEVELOPMENT	NARROW CATEGORIES
Pharmaceuticals	**Process research:** Alternative synthetic routes Routes scaled up for laboratory use Lab-level production for clinical studies **Pilot development:** Scale-up to pilot plant Kinetics and scale-up uncertainties Production for clinical trials Design of plant equipment **Commercial plant transfer and start-up** Scale-up to commercial plant-level Scale-up of processes for commercialization
Biotechnology	**Process research** Develop Analytical methods Cell line routes **Pilot development:** Small-scale purification Scale-up to bench level Pilot batches **Commercial plant transfer and start-up** Scale-up for commercialization

Adapted from Pisano (1997)

[3] ELISA = Enzyme-Linked Immunosorbent Assay, PCR = Polymerase Chain Reaction, HIV = Human Immunodeficiency Virus, Agglutination refers to a technique in rapid diagnostic testing based on the cohesion of white or colored latex particles, gelatin beads dyes, colloidal particles, or preserved mammalian/avian blood cells to carry antibodies or antigens.

6.3 The Public effort of the 1980s-1990s: galvanizing an industry (again)

> *"For pharmaceutical firms, scale-up is obvious, for biotech firms, scale-up is not obvious. ....This is not just about throwing money; trouble-shooting ability and scale-up are critical for biotech..... Companies need technologies that differentiate them and also revenue streams."* (Interview)

India's move into biology-based products, was driven in large part by external scientific and technological advances, but depended on accumulated process capabilities built up in chemistry, biochemistry and certain fields of biology, such as structural biology for example, where significant worldwide breakthroughs such as collagen modeling, were made. It also depended to some extent on advances in agricultural biotechnology and the levels of confidence of scientists that advances using the 'new' biotechnologies could be successfully applied to challenges of human (and animal) health.

India had already invested in recombinant DNA technologies in the 1980s, although the bulk of its present commercialization is in mature segments such as high-yielding seeds, vaccinations, industrial fermentation and enzyme manufacture. Its traditional strengths in agricultural technologies had led to advances in plant tissue culture, micro propagation, animal husbandry, diagnostics and vaccines. India's biotechnology capabilities straddle different industrial sectors and a varied assortment of "old" and newer biological and chemical general-purpose tools.[4] (see also Lachke et al. 1988, Padh, 1997, Sharma, 2001, Nagaratnam, 2001, Padmanaban, 2003).

[4] The Department of Biotechnology (DBT) of the Indian government uses a sweeping definition of biotechnology that leaves many ambiguities: "biotechnology is an application of recombinant and non-recombinant technologies in biological resource utilization for product and process development aimed for commercialization" (for a full discussion of classification problems, see Chaturvedi, 2002). Even biotechnology patents have not been segregated into different types. One problematic feature is the differing definitions used by various ministries of the government in their internal reporting. Some efforts for consolidation of the data collection exercise have now commenced. The OECD definition is "The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods or services". (OECD ad hoc committee) The meeting uses 5 categories to develop a list-based definition of biotechnology: 1. DNA (Genetics, pharmaco-genetics, gene probes, DNA sequencing/synthesis/simplification, genetic engineering) 2. Proteins an molecules (Protein/peptide, sequencing/synthesis, lipid/protein engineering, proteomics, hormones, and growth factors, cell receptors/signalling/pheromonics) 3. Cell and tissue culture and engineering (Cell/tissue culture, tissue engineering, hybridisation, cellular fusion, vaccine/immune stimulants, embryo manipulation) 4. Process biotechnologies (Bioreactors, fermentation, bio processing, bio leaching, bio-pulping, bio-bleaching, bio desulphurisation, bioremediation and bio filtration) 5. Sub-cellular organisms (Gene therapy, viral vectors). Source: OECD, cited in Chaturvedi (2002).

The country has achieved some level of success in innovation in the following fields: Basic Research: (a) establishing the helical structure of collagen, assisting therefore in solving for protein structures. (b) Sequencing of Arabidopsis and rice genomes (c) gene identification (d) drug delivery systems (e) diagnostics (e) recombinant vaccines (f) computational biology, Sharma (2001). The government of India established the National Biotechnology Board in 1982 and the subsequent creation of the Department of Biotechnology, Ministry of Science and Technology, in the early 1980s was intended to propel innovation across industry, medicine and agriculture. Specific recent focus as been on increasing productivity in agriculture (in the seed sector, as in the Green Revolution biotechnologies as well as in veterinary products), industrial biotechnology, bio informatics dealing with newer gene techniques, and environmental biotechnologies, particularly bio pesticides and bio fuels. (Sharma 2001)[5] In bio informatics, India's progress in information technology and computer software and services has supported a focus on genome research and applications, drug design and the development of a molecular taxonomy. Computational biologists have linked up with computer scientists to find new life in drug discovery and development.[6]

Many successes have been on the agricultural biotechnology front, but some scientists still feel that this area had far more potential than has been realized and that prioritizing health biotechnology to the detriment of agricultural biotech was incorrect.[7] On the food and livestock area, India has changed from milk-scarce to becoming the world's largest producer of milk. This "White Revolution", had its institutional base in a revolution in dairy co-operatives in the West of India, and became synonymous with a revolution in collection, transportation and distribution of milk and profits to million of small and marginal farmers. However, an important component of this revolution was supported by the biotechnological development of vaccine kits and of the institutional innovation of livestock medicine franchises for their propagation.

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[5] There has also been some effort to involve NGOs to take up the use of innovations in small bio industries, particularly for women. India has also explicitly created the Biotechnology Consortium of India Limited (BCIL) and is working with the Swiss Development Corporation as intermediary and institutional donor to foster relations between and pool resources of public and private sectors.

[6] An Indian government mission, the Jai Vigyan Mission, has been established to develop genomic databases. India's Department of Biotechnology has developed a nationwide bio informatics network with 10 Distributed Information Centres and 35 sub-distributed information centres. Also distributed round the country and graphics centres (Sharma, 2001). The Government of India also has 48 approved (accredited) Master of Science, Post-doctoral and MD biotechnology training programs in almost all states and union territories. Fellowships for students to go abroad, shorter training programs, training at other Indian institutes, and the development of a popular lecture series on biotech, are all part of a recent package adopted by the government. There have been some attempts to focus particularly on encouraging and rewarding women in the biosciences.

[7] As one scientist said, *"Government should have pushed the agricultural biotech area. We tried to do what the Western world did. We should have done differently"* (Interview, 7 June 2003)

Explicit early attempts by government to establish tissue culture pilot plants in Pune and Delhi have resulted in considerable success, and these have been converted into Micro-propagation Technology Parks with the explicit aim of transferring technology to entrepreneurs. Success has been visible in cardamom and vanilla tissue culture research. The National Plant Genome centre in Delhi has provided some promising leads in transgenic cotton, moongbean, potato and brassica. In health, important advances have occurred in protein studies in mosquitoes and in the demonstration of transfer of genes in a site-specific way of the reconstituted viral envelopes containing F proteins of the virus (Sharma, 2001). Both have come from university laboratories.

In 2002-'03, biopharmaceuticals had revenues of Rs. 1275 crores[8], around 70% of the biotechnology market (excluding various suppliers and hybrid seed companies), followed a distant second by industrial biotechnology at Rs. 235 crores (13%), services companies[9] Rs. 135 crores (7%), agricultural biotechnology Rs. 110 crores (6%) and bioinformatics Rs. 75 crores (4%). When all categories including suppliers and hybrid seed companies are included, biopharmaceuticals account for 55% of the total industry sales revenues. The vaccines market comprised 57 percent of the total biopharma segment, with total sales of Rs 725 crores, therapeutics with 32% and diagnostics with 8%.[10] There appear to be at least 176[11]biotechnology firms in the country and possibly more than 200 active ones. [12] The same geographic regions with large concentrations of public research institutes are also areas where multinational companies have clustered or outsourced computer services and which are concurrently vibrant IT service centres. Many of those are now biotechnology hubs (either pharmaceutical or other types-particularly agricultural biotechnology) such as Bangalore and Hyderabad. About 60% of the Indian biotech sector is made up of pharmaceuticals and human health industries, closely followed by agri-biotech. (Ernst and Young, 2001).[13] Other initiatives to drive the growth of the "sector" have included the establishment of facilitative organizations such as The

[8] Rs.1 crore=Rs. 10 million
[9] Some of which may have pharmaceutical R&D being conducted in-house.
[10] Data from Industry Overview, Biospectrum, Vol 1, Issue 7, September 2003, p. 10, India
[11] The Department of Biotechnology (DBT) established the Biotech Consortium of Indian Limited (BCIL) as a public company. Its 2001 directory surveys all firms in various user industries.
[12] Biospectrum, Vol 1, Issue 7, September 2003, p. 10, India
[13] There is an urgent need for classification and measurement within biopharmaceuticals, and the biotechnology sectors more broadly. For example, Chaturvedi (2002) looks at variation across reports on sizes of various Indian sub-sectors from the Confederation of Indian Industry (CII), the Department of Biotechnology (DBT) and the magazine The Economist. The Indian biotechnology industry is estimated to be approximately US$ 2.5 billion (CII), US$1.9 billion (DBT) and $US 1.5 billion (Economist). The same types of large variation exists across

Biotech Consortium India Limited (BCIL), a public limited company founded by the Department of Biotechnology (DBT), Government of India, in 1990 with a corpus of Rs. 5.37 crores (Rs.53.7 million) with the explicit aim of accelerating the commercialization of biotechnology in the country through technology development and technology transfer and acting as a link among all Indian research institutes, firms, government and funding bodies. Financial institutions provided the corpus across the country such as the IDBI, ICICI, IFCI, IFCI Venture Capital Funds, UTI and pharmaceutical firms such as Ranbaxy, Cadila, Glaxo India, and SPIC. Its Board comprises scientists from public research institutes such as the Central Drug Research Institute, Institute of Microbial Technology, Indian Council of Agricultural Research, financiers from ICICI and from IDBI and company CEOs such as those from Dr. Reddy's Laboratories and Bharat Biotech International.[14]

The total R&D budget outlay of the last decade of major R&D funding has risen and for biotechnology alone, the budgets are also increasing from the Department of Biotechnology (DBT). Under the Ninth and Tenth Five Year Plans, governmental allocations for biotechnology have also increased from Rs. 6,215.42 million in the Ninth Plan to Rs. 20, 750 million in the Tenth Plan, an approximately 233% increase.[15] (DBT, GOI, various years). Three newer initiatives, the Drug Development Program, the Technology Development Board (TDB) and the New Millennium Technology Imperative (NMITLI), have attempted to build scale of efforts and provide incentives to the private sector and to collaborative research. Much of the same impetus that gave rise to a vast public research infrastructure for the pharmaceutical industry has also acted as an umbrella for research in the life sciences. The Council of Scientific and Industrial Research was founded in 1942 as India's largest network of public R&D laboratories.

Some of its wings are now actively involved in biotechnology, but the integration of biology into the supremacy of existing chemistry-based research centres has not always been easy. Under a combined onslaught of liberalization-induced economic crises in Indian laboratories and faced an impending product patent regime, CSIR has been actively patenting in recent years, and seeking industry partners. It has 101 biological science patents, of which 64 are US patents and 34 Indian patents with a total of

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biopharmaceuticals (defined as Diagnostics/Vaccines only for comparisons) US$420 million (CII), US$150 million (DBT) and US$375 million (Economist).

[14] From BCIL's reports.

[15] This outlay includes facilities, Centres of Excellence programs and other program support, R&D outlays, Biotechnology for Societal Development and Bioprocess and Product development (both of which are mostly new allocations in the Tenth Plan). These outlays also include international cooperation, human resource

2605 patents since 1976, of which 896 patents in all scientific fields have been obtained from 2000 alone (author's calculations from CSIR patent database).

Despite India's considerable investments in science and technology over the years, its universities and public research institutes continue to be hindered by outdated models, a search for newer vision and difficulties collaborating within public research and with industry. Thus, biopharmaceutical research has provided some significant challenges, and impetus, for institutional change. At the same time, the compression in timeline at the onset of the new technologies of the 1970s to the frequency of innovation in the field also has blurred the signposts for the field. The next section underscores the varied learning challenges for firms in a new selection environment, and suggests that innovation strictly defined as invention, or first introduction worldwide of a scientific or technological feat, misses much of the remarkable diversity of learning to innovate and the extent to which it depends on its localized environment.

6.4 Where signposts are blurred and the map is new: learning paths in biopharmaceuticals

> *"Hepatitis B being a known technology is like saying missile technology is known or the atom bomb is public domain. We still need ways to construct it and to take it to market and compete."* (Interviewee)

By the end of 2003, there were six indigenously developed biopharmaceutical products being sold in the Indian market and with some markets abroad: recombinant Hepatitis B Vaccine, recombinant human insulin, recombinant Streptokinase, Interferon Alpha 2b, Erythropoetin and GCSF and others are being developed. None of these products is new worldwide, but in some cases Indian firms have still been distinctive in their recombinant efforts. For example, Bharat Biotech is the second largest Hepatitis B producer worldwide and one of the few to manufacture recombinant Streptokinase. Wockhardt is the 4th manufacturer worldwide of human insulin and the first Asian company and Shanta Biotech is the first Indian company to receive WHO certification for Hep B. Wockhardt is the first WHO-GMP approved Hep B product from India,

The nature of innovation within the industry is captured in the following table, many of which are for products and/or processes introduced into the Indian market for the first time, and some as a new worldwide introduction. The innovations range from new versions of older products characterized by

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development, bioinformatics, funding of actual autonomous institutes (not those under the CSIR mandate) as well as the actual workings of the DBT itself. (Also, see Chaturvedi, 2002, p.6)

fewer impurities, side effects and greater benefits, new processes to obtain higher yields for known

DRUG	TYPE OF INNOVATION
AIDS 3-drug cocktail, with two on-patent drug (but exported to countries with no process patent-only regimes) and one Cipla generic.	Changed formulation, easy to use kit. Steady supply ensured. Cocktail offered at less than half the cost.
Ciprofloxacin generic	Oral once-a-day dose compared to multiple doses needed presently by Bayer's patented drug.
Prozac generic Fluoxetine	Different dosage. Shows some novel properties. In arrangement with patent-holder Eli Lilly for out-licensing and manufacture.
Hepatitis B vaccine	2 alternative cultures for preparing the vaccine. Significantly lowered cost,
New fermentation reactor for enzyme culture	New fermentation technology used. Novel solid state mechanism to control fermentation conditions
Snake venom antidote	Made through culture from poultry eggs
Stem cell research	Uses novel methods for harvesting. Associated institutes in India have also used ophthalmologic cells.

cultures, and application of older processes or concepts to entirely new applications, particularly those with India-specific biological resources (plant or human). As an example of a company able to move between manufacture of known drugs and vaccines to one able to innovate in-house, Bharat Biotech's process development capabilities have taken a variety of forms: (a) in-house production process with platform technology for more refined vaccines with worldwide patents[16] (b) serotype for vaccines using new production process[17] (c) development and scaling up for new vaccines and development of regionally specific bovine and human strains[18] (d) discovery and development of new molecules for existing infections through new in-house method for recombinant proteins [19] (e) first in country to manufacture new generation vaccines.[20]

The coming sections highlight specific learning challenges and structural problems facing the industry. The new institutional characteristics of the firms and the ways in which they absorb knowledge is visible in two main ways: the diversity of learning paths and the niche research opportunities they pursue. Perhaps most importantly, they highlight the breadth of complementary learning strategies employed under constrained resources and search horizons. The diverse learning also underscores the diversity in industrial actors who have emerged in the biopharmaceutical realm. A variety of

[16] First Cesium Chloride free (CsCl) vaccine worldwide manufactured using a patented innovative in-house production process.
[17] Serotype for Hepatitis A with new production process.
[18] Rotaviral vaccine candidate attempts, in collaboration with various US-based public and private research institutes.
[19] A new molecular entity for Lysostaphin against Staphylo coccus aureus infections and for r-strpetokinase.

technology paths have intersected, giving rise to shifts in industrial reconfigurations, such as brewing companies with expertise in fermentation (which uses biological agents) which they then utilise in developing therapeutics and diagnostic kits.

6.4.1 Technological and regulatory challenges: narratives from companies

The entry of Indian pharmaceutical and other companies into newer biological products particularly recombinant proteins arose in part because of the dire need for cheap vaccines for common diseases. Companies like Bharat Biotech International Limited and Shanta Biotech made national headlines for initiating a competitive drive to manufacture a recombinant hepatitis B vaccine, the first such Indian vaccine appearing on the market in 1997 and costing 20 times less than the existing multinational company product from SmithKline Beecham. Since then the public and private initiatives have been to build capability in erythropoietin, stimulating growth factor, and insulin, among others. These companies developed their own manufacturing technologies suited to local conditions, and created a variety of process and production technologies for these known vaccines, while attempting to meet world-class standards for the end product. Thus the fact that the product was known worldwide did not prevent a learning process from taking place.

The Indian capability in bio-pharmaceuticals has been built in a shared, but not coordinated way, by two powerful sets of actors: the first is the state, and the second, mid-size and small Indian firms. The story of the pharmaceutical companies is a different one from the biotech companies to the extent that they show a particular technological path of advancement from chemistry to biotech. Although an increasing number of pharmaceutical companies have invested in in-house biopharmaceutical capability, broadly speaking, "biotech" companies are a motley crew of smaller companies with capabilities being built around genomics, but in applications as varied as brewing, bioinformatics, seed genotyping, phage therapies and "bio" insecticides. Their story is one of building technological capability around relatively mature, proven concepts and their innovation is then one of process improvement and the search for new applications. An important additional factor warranting more research is the notable presence of foreign-returned (usually from the US) scientists and engineers in this industry, many of who were connected at various times with centres of biotechnology R&D (and thus venture capital funding as well) near San Francisco, San Diego and Boston in the US.

[20] For single-shot typhoid vaccines

The industry comprises a diversity of firms, from development and manufacturing firms to drug discovery, bioinformatics and equipment supplier and materials supplier firms.[21] In recent years, Hyderabad companies like Shanta Biotech[22], Bharat biotech[23] and Dr. Reddy's Laboratories[24] have succeeded in entering the drug development and manufacturing domain, and have adopted biotechnological tools to produce vaccines and other drugs. At the drug discovery end, Bangalore-based companies like Strand Genomics[25] (starting with bioinformatics), Avesthagen[26], Dr. Reddy's and Aurigene[27] have all invested in building their genomics capability to look at a variety of challenging drug and agricultural biotechnologies. Furthermore, the Hepatitis B learning path, and that of other recombinant products, has required close collaboration with universities and public research institutes who conducted some of the initial work on the vaccine. Companies stated that it was important for industry to speak the language of science. Shantha Biotechnics, for example, continues a range of efforts with public research institutes.[28] While institutional changes have been complex, process development and especially manufacturing ability continues to play a dominant role in Indian biopharmaceuticals. Even though such collaborations exist, and transfers of technology may take place into companies, the latter must be able to contend with process scale-up problems ranging from

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[21] Because "new" biotech applications are relatively recent, the classification of companies is difficult since the learning process involves diversifying into new areas, adding organisational segments and changing business strategies.

[22] The company aims to "achieve break throughs in modern biotechnology leading to development of products and services that address critical healthcare needs. (They) have the competence to provide high quality contract R & D services ranging from molecular cloning to process development and formulation." (Company website)

[23] The company is engaged in "the field of developing Next-Generation Vaccines and Biopharmaceuticals through original and collaborative research." (Company website)

[24] DRL is a pharmaceutical company, but its biotechnology division "deals with therapeutics, vaccines and diagnostics. Molecular biology, cell culture, fermentation, downstream processing and hybridoma technology are the focus areas. Dr Reddy's core competency is in the recombinant proteins technology platform." (Company website)

[25] The company is "a leading life sciences informatics company focused on software for drug discovery and development" (Company website)

[26] The company applies "it's integrated technology platform for novel seed development offering nutriceuticals to complement its disease specific medicinal plant based drug discovery and plant based solution for chronic health problems where no existing effective treatment exists today." (Company website)

[27] "Aurigene is a Boston-based drug discovery organization, with state-of-the-art research facilities in Bangalore, India. With a combination of internal discovery programs and sponsored research activities, Aurigene accelerates discovery by providing products and services that specifically address chokepoints in the discovery value chain." (Company website)

[28] The company was launched from a base in the Centre for Cell and Molecular Biology (CCMB) in Hyderabad- after beginning research efforts at Osmania University in the same city, and has continued to build on its public partnerships for drugs that have broad use. For example, it collaborates with CCMB in Hyderabad, the Indian Institute of Science (IISc) in Bangalore, Jawaharlal University in Delhi, the Bhabha Atomic Research Centre (BARC), Mumbai, Institute of Chemical Biology, Calcutta, among others complete list of public and private collaborations around specific products is available in the report of French Embassy, New Delhi, RUET, Joel, ZERAH Marie-Helene, MARIA Augustin, GIRAUD Pierre-Noel, (2002), "Biotechnologies in India", Report commissioned by The French Embassy in India

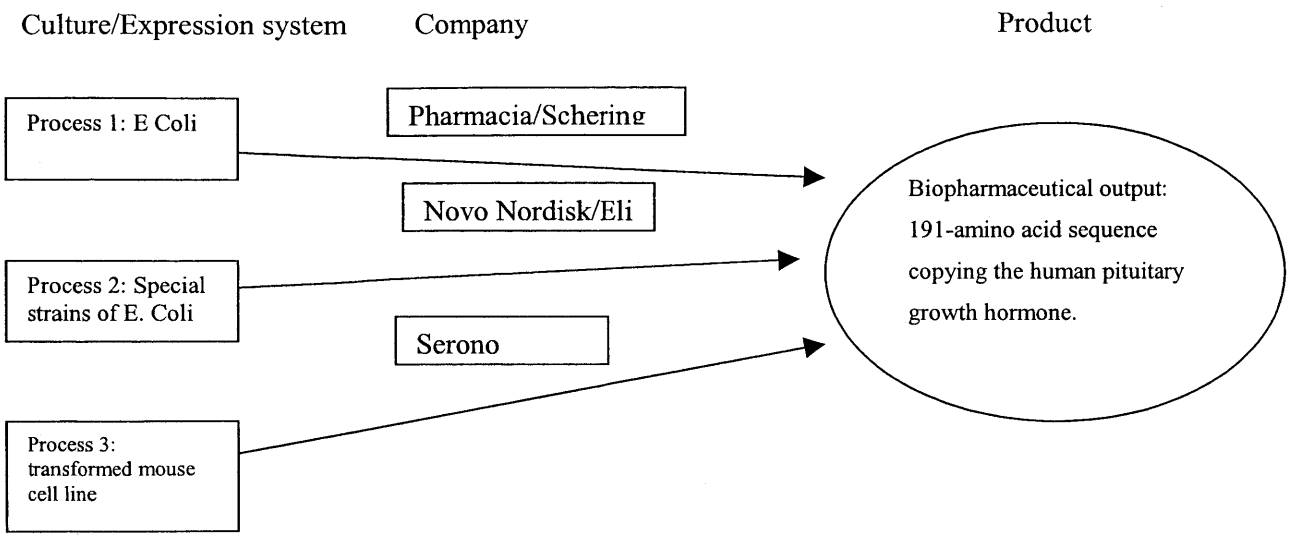
usability of host cultures, to regulatory problems and attempts to synchronize their in-house efforts with client R&D.

6.4.2 Case 1 Expressions of advance: approval mechanisms and brands

The Hepatitis story illustrates the challenges facing firms because even though the technology now lies in the public domain, it has a host of tacit characteristics that only in-house search, experimentation and mistakes will decipher. It also raises the issues of media exposure and national expectation lying heavily on the shoulders of fledgling companies. [29] This case briefly highlights an additional problem faced by a few companies in the sample. It is posed in general terms because of data confidentiality from the companies interviewed. In this, different paths to the same end drug through different host cultures are not straightforward. In the example below, posed in general terms of an actual known non-Indian case, three leading companies used three different cultures to express the same drug form. In each case, the process had to be approved by regulatory authorities by demonstrating a host of species-specific and efficacy studies. The fact that the end product may be identical appears to suggest that the process differences should not determine the product, that there are many ways to the same end. There are 5 distinct European processes with different expression systems that have led to the creation of an identical human growth hormone.[30]

[29] One company said. "The first time was much easier. The more well known you are, the harder it will become"." (Interview)

[30] If this characteristic of biological development of therapeutics if regulated as such, there may be more promise than now currently appears for Indian companies, who have limited resources and high levels of process development.



Source: Adapted from Contract Pharma magazine, Nov/Dec 2003,

In process engineering in this subsector, companies may have multiple ways to achieve the end result (i.e. drug). However, the analogy with pharmaceuticals ends here. The example shows three ways in which major companies created the human growth hormone. Each process is associated with a specific choice of culture/expression system in which the process is directed and controlled. However, demonstrating that the end product is similar is insufficient a proof of product efficacy or safety. Because of species specificity, among other things, the company must also show that the process sequences are similar on a variety of dimensions.

The interview data demonstrated cases where the very first element of the token search, their cultures, was not a given. Companies were constrained in terms of their access to comparable cultures or access to approved cultures. In one case, the interviewee indicated that the host had presented high yields and a variety of studies had shown the safety and efficacy of the end result. Yet, the company was to discover that by US FDA guidelines, the culture wasn't approved and thus the process could not be taken further. In another case, the company was unsure of the product liability implications if a specific culture was pursued and the end product were to cause undesirable effects. In a third case, public research laboratories and private companies alike were continuing to manufacture vaccines for local use with a sheep brain culture.

In such instances, the variation in regulations and the uncertainties regarding US FDA regulations for certain categories of biopharmaceuticals as well as litigation and product liability uncertainties for vaccines, have all made search activities not an entirely open-ended operation. Companies have to

select from what they can afford to pursue, and within this, what they can anticipate being able to have approved, even if they can extract high yields for the particular process.

6.4.3 Case 2: International ladders, international uncertainties

Company 2 began as a vaccines supplier and only later emerged with a formulations base. It emerged from its old ownership with a few very competitive brands. Although some of its portfolio could have created very easy revenues, they chose not to focus on low technology, easy revenue segments such as cough medications. Other bulk drugs companies had emerged from antibiotics groups such as Cephalosporins. These were hugely competitive in India. For these companies, formulations had been a lesser priority. Company 2's own existing bulk drugs portfolio has existed for decades.

The animal health vaccine market in India is fragmented and viruses keep changing so companies are forced to keep up with technologies. But their partnership with a specific foreign company ended when it sold the animal health products division to another company, and company 2's access to technology in this area ended. They tried another company to link up with; again, they sold their division to another company.

Company 2 claims a certain pride in working with the State and in creating vaccines that assist children. In vaccines, not all products are technology transferred. They were never interested in Hepatitis B, but have been interested in combination vaccines. They have focused on technology platforms for preventive reasons. E.g. rDNA and very interested in WHO/UN markets, where public procurement is important, and they push for public procurement advocacy, with new developing country vaccine initiatives. Global EPI vaccine programs are almost 85% provided by developing country pharmaceutical companies. These directives have been criticized by developed countries. However, CCMB with their work on stem cells, and All India Institute for Medical Sciences (AIIMS) with their work on the AIDS vaccine, have both done some path breaking work. Also, one of the worldwide leading biotech firms had chosen Company 2 as an AIDS vaccine provider, but this turned out not to be a workable solution. Company 2 is not that interested in biotechnology apart from vaccines, and not in industrial enzymes, even if the technology is close to in-house abilities.

The WHO (and initiatives such as GAVI, the Gates Foundation and the Rockfeller foundation) have recognized the efforts of Company 2 and its work in vaccines has been equated to the Expanded Program of Immunization (EPI) programs and their standards. These programs have played a significant role in sustainability and supply of vaccines because the end products do not have large

commercial markets. At the same time, the cGMP requirements have also kept changing, so companies need procurement to make the process viable. This is a guarantee to Company 2 and others of assured demand in foreign countries that come under the purview of these immunization programs. The recognition of companies by such international programs for R&D and procurement makes new collaborative opportunities possible, as a signaling mechanism to other firms. Its effect on platform standardization assists Company 2 and others like it in their export path.

Because they have had such a long history of vaccine development, their technological commitment is clear. All companies and governments in developing countries have learnt to make vaccines around the same time, so this itself is not a differentiating factor. But big changes emerged with Hepatitis B vaccines through the recombinant B vaccine. Combination technologies have been used to develop both recombinant B and combo vaccines (multiple vaccines) and these are process and platform driven. For Company 2, regulatory issues surrounding their products drove the decision to buy existing products and technologies instead of facing the uncertainties and costs and developing products in-house. This makes it easier for the company to get products to market. The Department of Biotechnology had licensed the new yeast medium, but they never pursued this fully in-house since they never quite felt they had enough time to do full development in-house.

Company 2 is now dedicating about 30% of internal resources for the future in terms of both R&D investments as well as to technological alliances with public research institutes. These options are not as expensive as buyouts of companies or their products. In some cases, the link with PRIs has been for key technologies, in some cases purely for infrastructure. Furthermore, when links such as these exist with PRIs, some other aspects of getting to market simplify because assistance is available: such as financial assistance, quicker import of equipment, assistance with meeting regulatory policy, overall speed in getting to market). PRIs have been most helpful when the problem is encapsulated. This has allowed Company 2 to emerge again in global vaccine program initiatives. Earlier, MNCs such as Merck, Aventis and SmithKline Beecham used to supply about 100% of WHO's supply, but now they have dropped to les than 15% since they also have invested less in capabilities for hexavalent and pentavalent vaccines. On the other hand, Indian EPIs, African EPIs etc have been critical for companies like company B. Even 15% of the pentavalent market, for example, is greater than 6 times the total EPI market for India, so it viewed as very much worth getting into since the "Big 4" companies in the pharmaceutical realm working on vaccines are not going to fight for this share. So it

is not that technology, per se, is needed for catching up, but getting to the market is harder. Both physical GMP models (compliance) are expensive, as are other regulatory hurdles.

Company 2 also stressed that it does not know how big FDA hurdles are going to be for biologicals. Even in the US market, these hurdles are unknown, so they have built an in-house team to deal with all aspects of the biotech markets. Furthermore, it is unclear what product liability will be in biologicals. In the case of Wyeth, for example, a serious vaccine controversy emerged. 50 children died because of a reaction to the vaccine but the company got off relatively unscathed because the US FDA had licensed the technology to them. Also, the biological specificity means that Phase 3 work is intensive and that national control agencies of all countries will be working hard-for example, such as the agency in India in Khasauli where specified random sample tests on the batches are carried out.

In terms of advances in Company 2's core fields, overall drivers are broad perspectives in health such as those that drove the Human Genome Project. One core problem is that upcoming process technologies (conjugation reagents, micro arrays) are all patented and these are critical input technologies into vaccines. The obstacles for Company 2 are thus monopolies on key input process technologies, having a market presence in core areas for long enough, while having money at the same time to invest in technological learning.

If A is the initial culture and three different strains of yeast are used to get to B, the Hep B product, the process patent drives the process. The host cell is patentable, but it has taken a long time to find, stabilize, test and demonstrate that the vaccine can be found here, and finally working all the way to market. So the process requires that Company 2 (and others like it) needs to patent the yeast medium (the Aventis strategy) and then see if they can get other products out of this medium. Pursuing the one method for making Hep B alone does not make much business sense.

Besides the access that the relationship with PRIs buys for Company 2 and information on the regulatory structure and hurdles, there isn't any real difference between India (local) public domain information and that obtained elsewhere. In fact for vaccine research, Company 2 has developed links with a variety of foreign universities and research institutes. Thus local academia does not always have to be so critical, unless one is trying to use links with the government for scaling up, or got getting researchers with specific regional diseases or other expertise. Successful companies know exactly what to obtain fro m their relationship with PRIs-time-specific encapsulated problems are best, not

exploratory work. Only a few Indian companies have in-house scaling-up capability for R&D and only these are truly able to benefit from links with the public sector. Thus, the public sector cannot be a substitute for in-house technology capabilities. If there is no real knowledge base in the company, in-house retention of scientists in the long-term is a nightmare.

6.4.4 Case 3: Pursuing high-quality and local traditions

Company 3 is an arm of a larger company that investigates pharmaceutical and biopharmaceutical lines of research. The parent company has pursued this investment as an exploration into possible future profits. The research arm, which is referred to here as Company 3 (although within the same company, but acting independently), has developed multiple innovative new processes and some differentiated products using both chemistry and biology as routes. The head of Company 3 the public research institutes as having been critical in amassing capabilities, but lacking the abilities to commercialize their findings, while industry has had little appreciation for scientific and technological advances and feels this is symptomatic of much of Indian industry which needs to think more long-term.

In the nutriceuticals realm, a public research institute had identified a strain of a compound for the first time almost four decades ago. An MNC became interested in this compound, particularly in the animal studies. Company 3 recognized that this compound was central to health care stores in the US. Its contribution was to create a pure soluble salt of this compound and has subsequently patented this in India, Europe and the US and has completed both animal and clinical studies. It finds that although the intended benefit shows less dramatic results, a highly significant side benefit has been found and pursued-cholesterol reduction. They now have built links with other Indian organizations for clinical studies. While the parent company is global and has much marketing and distribution experience, they have no expertise in this area. So company 3 finds itself having to learn the export markets itself. They have found a contract manufacturing partner close by whom they trust to discuss proprietary technologies. They have taken the process and manufactured 1 ton of the compound a month. Exporters buy this for almost a third of their price but at 50% purity, whereas theirs is 95% pure, but people are unwilling to accept their higher price. Part of their work now is to convince customers that the higher price is worth the cost. They are pursuing these soluble salts and their tests since if they come through, immense revenues may be in store. They have found markets in Indonesia and Japan. Two companies received information about the product through old employees and combined this with public domain patent information and created the product at a lower price to undercut them. Now

company 3 has also learnt to litigate. Although it doesn't have the powers to commercialize the technology, they simply license it out and put the earned royalties back into their R&D.

Company 3 also discussed 4 other products, discussing the inability of most of Indian industry to appreciate the technological challenges in process research, scale-up, commercialization. They even developed a fermentation control process using a sophisticated algorithm that may have benefited some companies, but were ignored. They have since developed an Indian patent for this. They are now pursuing marketing links directly with foreign companies abroad so as to advance their products. They are looking for products that are profitable to India, then to the US. Resource constraints have created this blend of expertise in house. Another additional difficulty is the cost and procedures involved with patenting. A US patent costs about 30-40 thousand dollars, but now their own patent lawyer in Delhi does all the work and sends his counterpart in the US the final materials. Thus, the patent costs are brought down to about 10,000 USS$. Company 3 then described a series of other products and challenges of technological learning, regulatory hurdles, cost of development, and the slow development of links with other companies in India and abroad for marketing links. They see increased public-private interaction now.

In most of these products, there is a common technological theme, where one process capability (in this case a specific soluble salt) is developed and improved continuously and applied in different contexts. For example, they are investigating known pharmacological off-patent compounds which are no longer effective (i.e. resistant drugs) and then attempting to add local natural products that have antibodies and creating very innovative products. They are also looking at specific genes cloned in yeast, which do not appear to have a specific biologic activity. They are working on this with a small company with specific expertise (founded by a former company executive) and working on company X's site. If they get good yields and good biological activity, then they will have some combined marketing benefit. Although yeast expression has been done before there continues to be a large demand for such yields. They have a process patent in the US now.

6.4.5 Case 4 "From Brewing to Biotech": lateral learning and industrial reconfiguration

> *"...(From a) Company focused on manufacturing enzymes by fermentation into being a Fermentation Company focusing on Enzymes and Pharmaceuticals production."*
> *(http://www.biocon.com)*

When Biocon began its journey into Statins, the route was indirect. Its past user industries ranged from brewing industries to textiles. It first began investigating enzymes through the food industry, and then struggled for some time to find an alternate non-infringing route to manufacture at industrial scale Koji enzymes, ordinarily available only from Japan. After considerable search and experimentation in Bangalore, Biocon was able to prepare these enzymes by itself, the success launching a large line of processes and products depending on this input. It also created new urgencies for platform technologies that stabilized the conditions under which enzymes were manufactured and could act. This resulted in the launch of it's patented (worldwide patent) for the Plafractor, a solid-state system. Statins, an off-patent biological therapeutic were an attractive segment to manufacture in.

Given that almost 7 of the world's top 20 best-selling drugs are fermentation –based, it allows industrial companies such as Biocon, originating from a non-pharmaceutical route, with expertise in enzyme manufacture and fermentation, to enter and gain market share in the pharmaceutical industry through its process development and manufacturing capabilities. The company itself did not directly gain from the policy push of the 1960s and 1970s for pharmaceutical companies, even if it did benefit from the scientists, engineers and doctors available. Biocon however demonstrated that a company could advance without direct policy inputs if it were to invest in its own in-house R&D to find non-infringing ways to the same goal and take advantage of certain elements of the selection environment, such as opportunities in generic drugs. However, in recent years it has also benefited from interaction with universities and with other companies in the biopharmaceutical arena (which have themselves benefited from public research institutes) such as Shanta Biotech.[31] Biocon has now taken on the mantle of public policy champion and is helping direct the biotechnology policies of the government of Karnataka and the national government.

[31] The two companies have entered in to an agreement to produce human insulin.

Table 6.4.1 Industrial entry points into biopharmaceuticals

Product type	Product names	Details
Fermentation-based therapeutics	Statins (Lovastatin, Simvastatin, Pravastatin, Atorvastatin)[1]	lipid-lowering agents
Synthetic Chemistry-based therapeutics	LOLA, L-Ornithine L-Asparate (LOLA)	treatment of acute and chronic liver diseases
	Etamsylate	prophylaxis and control of hemorrhage from small blood vessels
Biological extracts from the industrial food sectors applied to therapeutics	Hexpan -	facilitate digestion and assimilation in the intestinal tract.
	Biotag	replacement therapy in pathological conditions in which the concentration of bile acids in upper intestine is low
	Pepsin	digestive aid.
	Trypsin-Chymotrypsin	debriding agent, anti-inflammatory agent
	Papain	breaking down proteins.

Source: Adapted by the author directly from company reports.

Biocon, as other Indian biopharmaceutical firms, was omnivorous in sourcing technology until they developed the capability to make or develop it internally.

Table 6.4.2 Learning channels for Biocon

Entity name (date operations begun at Biocon)	Entity type	Source	Type of learning
Papain (1978)	Plant enzyme extract	Technology transfer from then co-founding company, Biocon Ireland	Manufacture
Isinglass (1978)	Marine hydrocolloid	Technology transfer from then co-founding company, Biocon Ireland	Manufacture
Koji fermentation products (1984)	Enzyme	In-house R&D	Methods and machinery needed for this enzyme's manufacture not known. Developed own small-scale manufacturing processes in less than 3 years through R&D, beginning with microbial strain selection, development, plant design and fabrication.
Proprietary "Plafractor" technology, US	Fermentation-based solid state surface	In-house R&D	

patent 2000	manufacturing technology		
	Fermentation-based submerged manufacturing technology	In-house R&D	

Source: adapted by author from company reports and interview materials

The table below shows the business evolution of the Biocon conglomerate, mirroring its technological learning path. It has evolved from enzyme and fermentation manufacture and marketing, to producing generics, which are developed through a proprietary process technology, thus giving them significant leverage in patenting and product differentiation through control of the generic drug's attributes. In addition, the company has an "easy" source of revenue through contract R&D and manufacturing on multiple domains" enzymes, fermentation and generic drugs manufacture, more recently. It has also embarked on clinical studies for in-house drug development and as a contracted service to other companies.

Business unit	Function
Biocon India	Fermentation, enzyme R&D and manufacture for food and pharmaceutical industry
	Contract pharmaceutical R&D
Syngene	Contract pharmaceutical R&D
Helix	Contract biopharmaceuticals
Clingene	Longitudinal and genomics-based patient studies in selected disease and population segments for clinical trials and drug certification (Both in-house and contract studies)

Source: adapted by author from company reports and interview

A form of "lateral" technological learning has taken place[32], with a clear pathway unique to the history of the firm. Biocon's learning has not followed the tiered path of many Indian pharmaceutical firms with an entry point in public health, in part because the company emerged from industrial, not health applications and did not face the same regulatory framework. In recent years, as the move has been to adapt in-house fermentation expertise to biopharmaceutical applications, Biocon has also begun to face such criterion, but the company's capabilities have allowed it to target Tier 3 countries directly.

Two technology sub-areas, Solid State Fermentation (SSF) and Submerged Fermentation (SMF), in the company's repertoire came together in a variety of lateral ways to create their solid-state

fermentation patented technology. Importantly, SSF was the entry technology into enzyme research for industrial applications as well as in therapeutics in an attempt to manufacture Lovastatin, while SMF led in three directions-Lovastatin, Pravastatin and rDNA products. The entry points into different product avenues also created new organizational entities and service functions such as Clingene and Syngene as the company learnt laterally. Syngene created to deal with recombinant products, also helped in the creation of Simvastatin, while Clinigene dealt with biomarkers of various types. In the process, clinical trial capabilities were built in the larger Biocon family as well.[33] Biocon underlines the importance of the manufacturing-driven route to bio-pharmaceutical entry. Although the company invested in its own R&D early in its growth, its strengths lay in its ability to develop the process and *scale-up and manufacture* the substance. This ability in turn, led to the development of in-house proprietary fermentation technologies and processes that have led to entry points in fermentation-based biopharmaceuticals.

6.4.6 Case 5 "Learn while you Earn": Contract Research, High-throughput search

> *"(We view) CROs as a statistical way to encounter large volumes of biological problems and obtain detailed domain knowledge which is lacking in molecular biology. Genomics patterns are not ABCD patterns. (We) need an eye and experience and domain knowledge, the bottleneck is not enough molecular biologists."* (Interview)

The previous examples of learning dealt primarily with in-house search and experimentation driven by the company's own research efforts. Interviews with Contract Research Organizations, (CROs), however, show complementary paths to knowledge acquisition of new technologies, new applications, new geographic markets and new alliances.[34]

Both pharmaceutical and biotech firms have chosen a common pathway to develop multidisciplinary detailed domain knowledge-CROs, in biopharmaceuticals. While Indian companies have shown superiority in multiple segments of the pharmaceutical world such as computation, manufacturing, contract R&D, they make attractive partners even with unresolved intellectual property regime changes.[35] Thus, companies that can do multiple such tasks combined are more likely to pull ahead in their learning process because the gains are multiplicative, not additive, it appears.

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[33] Source: Kiran Mazumdar, CEO Biocon, in interview.

[34] In the case of Biocon, we saw the ways in which contract research and clinical studies wings arose from lateral paths of technological exploration. Here we investigate the actual learning pathway within the CRO.

[35] Interviewed firms spend considerable time ironing out the IP aspects of their agreements with clients and use it as a means to build their own IP-base, as later discussed.

The intellectual property and proprietary technology aims are negotiated over a period of time. Both older pharmaceutical and younger biopharmaceutical firms have chosen this mechanism to attract large international firms to do business with them. To do this, the firms need to demonstrate that they are not simply good service partners. The irony is that despite the potential (but rarely realized) conflicts of intellectual property if the Indian firm has an in-house R&D division of its own, these firms are sought after as they have "signaled" to international firms their ability to conduct high-caliber R&D themselves. One interviewee highlighted a business strategy in terms of learning to consolidate their proprietary base over time: "*First three years, we plan a simple services model, assign IP to client, later we negotiate IP, and later, develop IP ourselves. 2005 makes no difference, its only perception.*"(Interview)

A host of Indian private and public firms and laboratories are now taking on the services function as part of the earning while learning process.

International alliances

Company/PRI	International alliance	Nature of alliance
Dr. Reddy's Laboratory	Novo Nodirsk (largest insulin manufacturer worldwide)	DRL's new molecule for insulin-resistant diabetes has been licensed to NN.
Ranbaxy	Pfizer	Licensed a new drug molecule for benign prostatitis
Indian Institute of Chemical Technology	SmithKline Beecham Cytomed	High throughput screening services for drug molecules Process development of a new molecule
National Chemical Lab	DuPont	Process development of a new molecule
Bangalore Genei	AstraZeneca	Endonuclease supply
Nicholas Piramal	Hoechst Marion Roussel	Contract research
Wockhardt	Sidmark Labs	Sourcing and global marketing
Cheminor Drugs	PRI Inc.	Contract manufacturing and global marketing
NATCO Pharma	Mallinkrodt	Contract research for drug development
Glaxo India	Affymax	Combinatorial chemistry for drug design

Source: Bowonder, 2003.

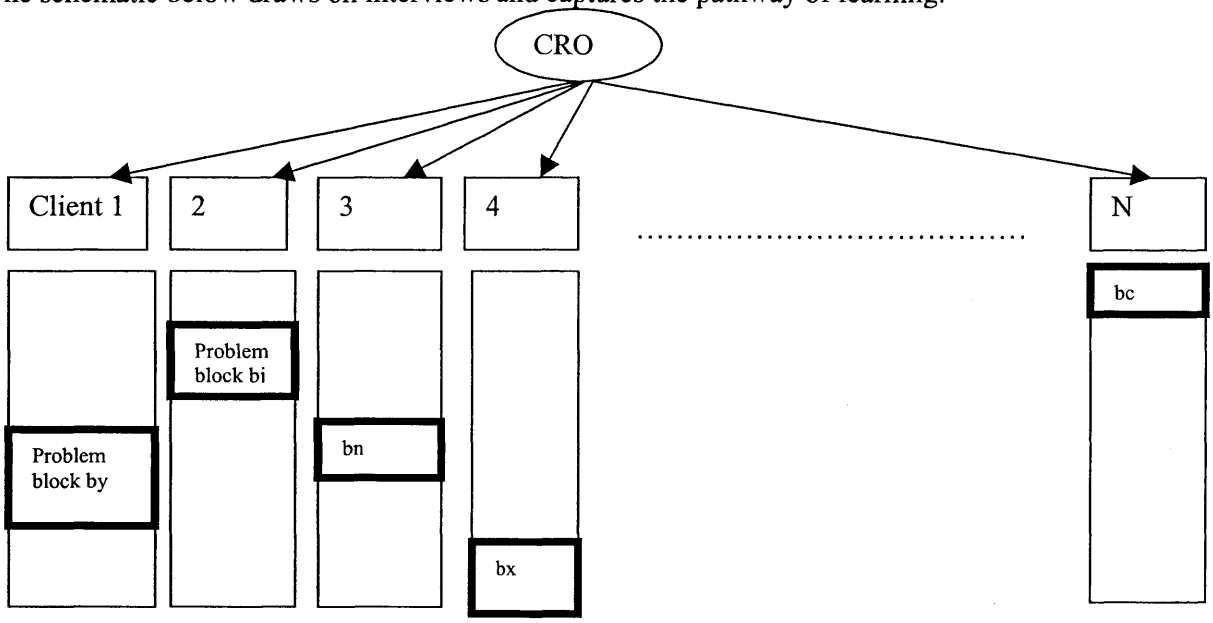
For such companies, the multi-pronged approach serves a variety of needs: First, the company gains a steady stream of revenues to grow. Second, the company is able to signal to both Indian and foreign companies alike that their in-house R&D function is of a certain quality.[36] Third, the company

[36] Some firms had limited in-house R&D functions and chose instead to be predominantly contract manufacturers, as opposed to contract researchers. While the manufacturing also required some R&D functions,

develops an array {N} of clients, each of which provides a distinctive block of problem solving {bi} in R&D to the CRO.

> As one interviewee stated succinctly,
> "To build relationships, you can only do this as a services company. There is a lot of learning in each relationship" *(Interview, June 25th, 2002)*

The schematic below draws on interviews and captures the pathway of learning.



The firms first interact with each client on a purely individual basis with a well-defined set of IP restrictions in place. The client out-sources a specific problem block {bi}, which in many cases is poorly defined and/or has exploratory elements, the outcomes of which are obscure. In some cases the technological learning process coincides with repeated articulation and discussion with the client about how the block should be defined (the client is not always able to suggest the exact parameters to investigate). Next, the CRO takes on the block (or subset) after considerable investment of time on defining the boundaries of the problem where possible. Third, a search is conducted of all relevant materials in the public domain that can be used (including patent filings) for the problem at hand.[37] Fourth, laboratory-based and/or in silico (computational) problem solving occurs. Discussions go back

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the production tended to be relegated to certain well established and non-controversial (in terms of IP) areas such as generic drug manufacture or enzyme manufacture for the incumbent (and patent holder) itself.

[37] In some cases, this was done at the outset of problem definition/negotiation because the CRO had expertise in this area. Interviewees who had diabetes or oncology-related specializations often found they knew as much (if not more) in some problem segments, which has led to new niche areas being carved out as part of their business plan.

and forth with the client at all later stages until the outsourced problem is solved. Subsequently, with multiple clients, the process is repeated for different problem blocks {bi}.

However, where the greatest learning takes place relative to the firm's own R&D function is in dealing with multiple clients. First, with each client, the CRO has to estimate how important the problem is to the client to estimate how important its own capabilities in this sphere are on the world stage. It is predominantly in relation to its client that the CRO recognizes its true worth and what segments of expertise it should consider enlarging within its own in-house R&D effort. Second, the CRO must estimate and define the related problem blocks that it is not being invited to work on and which parameters of domain knowledge it is being excluded from. This requires not simply good business sense. To know what it is missing requires the CRO to be technologically fairly sophisticated to define the set of possibilities within which it is operating. Third, by combining multiple such interactions, while preserving IP integrity, the CRO also learns the dominant areas of opportunity, technological challenge and where its own in-house R&D function is lacking (or excelling).

An important industry-wise element to this individual learning trajectory is that CROs are gradually developing local clients, where many firms previously conducted all functions in-house.[38]
One company in cell-based therapies and with extensive links to large hospitals and clinicians searches for public domain knowledge opportunities and buys, rather than make at home. However, some level of expertise is still needed to recognize the opportunities and partner with hospitals for data analysis. Learning paths tend to be similar in some respects in the CRO model, and competition is increasing. The company stated, "*We give extension to the patent-mostly lots of trademarks. A progression of skills is happening. The only thing that brings in revenues is a good patent position. Buy rather than build, you can get cheap IP, good bargains. The biggest competition is local competition, our competitive advantage is the same as theirs*".

6.4.7 Case 6: Diversification: a company as a function of its environment

Firm 6 is a large company with a US and Indian base. It began in an entirely unrelated industry and then diversified successfully multiple times, growing in size, and has since moved into

[38] One interviewee stated "*Producing materials and contract research (is useful). It does help to do R&D yourself, VC money also keeps burn-rate lower and CROs keep this model healthy.*" Another stated: "*In combinatorial chemistry, India companies do not have the libraries of compounds like big pharmaceutical companies abroad. Thus, some smaller Indian companies are providing specialized chemistry, and especially combinatorial chemistry expertise to others. This service/CRO model allows rapid development time-lines. A network of like-minded companies in Bangalore is now emerging, where each needs the other and using local expertise is slowly becoming cheaper and more reliable to use than past foreign contacts.*" (Interview)

biopharmaceuticals. Their story is one of acquisition of capabilities from the local skill-base of chemistry and bioinformatics and they concentrate on services for process R&D, informatics and medicinal chemistry. More recently, they also provide services for various stages of pre-clinical and clinical trials. Company 6 has acquired both in silico capability and are constructing wet labs. Their competitive advantage is recognized by their executives and R&D personnel alike, as being within rapid scale-up and high levels of financial investments relative to the rest of the industry. *"Even Merck doesn't work on 5-10 targets simultaneously".*[39] They are able to do this because the diversified model allows them to channel money rapidly into promising areas. They are also extremely capable of accessing chemistry and life sciences knowledge rapidly from key contacts in the R&D laboratories of leading public research institutes.

Their knowledge-acquisition mode for services is built on a multiplicative factor of having multiple sources of capability in chemistry, biology, computing, combined with rapid scale-up of searches for drug discovery and development. In addition, their process R&D services comprise work on both intermediates and fine chemicals, catalyst design and development and process development for chiral drugs. Their learning process has been triggered by the search for appropriate skill resources. They have since employed a senior scientist formerly of a PRI, with a strong track record of accomplishments.

"*In a contract research organization, you don't know what contracts you will get....so you need breadth*".. "The technology bottlenecks are the identification of targets, validation of targets and number of hits. But this is hard, and one in India can do this." The increase in target protein patenting has limited the options of Indian firms and so joint ventures and licensing are the possible options. However, licensing can be prohibitively expensive and joint ventures can share their validated target proteins as part of the outsourced capability, making this a revenues plus IP sharing model, and thus attractive. They see their scale of operations as different from US CROs in two major respects. First, they depend on the scalability of skilled manpower, but who do need additional training, which they accomplish in-house in sophisticated laboratories. Second, they guarantee that their quality is the best, not just above average. For example, curation is a complex process with a number of reactions. One needs not just an informational database which many CROs can accomplish, but also the ability to put the date into an appropriate form i.e. Knowledge is critical. One needs at least four elements: (a)

[39] Whether this is true or not, the author cannot say, but it is sufficient information that Company D is deemed to be an attractive partner to a variety of major foreign firms.

ability to acquire data (b) create a simulation model (c) knowing the number of possible algorithms to try to hunt for possible candidates and (d) understanding the constraints and parameter of the search. In addition, they need to train manpower across degrees and in depth to conduct studies for lead generation and lead optimization. These workers need motivation and a level of innovation in their searches.

"*The problem is with biology screens, protein-based assays or cell-based assays. As yet, in vitro screens are a problem, but Indian scientists in the US have this capability, while we have in vivo capabilities*" Company 6 sees it "just as a matter of time" before it finds some promising drug molecules for its clients. They are strong enough just on the chemistry side to make investments in biological tools less urgent. Company 6 indicates that it is a function of its chemistry environment and past. *"We can't pick projects and future capability at random. A company sits in its environment. It can then expand into specific areas that complement these capabilities. The gaps between the US and us are increasing, not decreasing, in the biological sciences. However, in informatics and chemistry, this is not so steep. In informatics, India is pulling ahead or is already ahead. In chemistry, there is not much difference."*

It appears that the joint venture/shared IP model is attractive because the proof of concept is established and there are new targets in the public domain, which have not yet come to market. These present possibilities as do candidates that are in Phase III. Phase II drugs can sometimes show additional beneficial properties at that stage of testing.

6.5 Learning and innovation: where the search space is constrained

Firms have learnt "by doing" slightly differently (through mild product differentiation) each time. Furthermore, every time they speed up, scale up or manufacture for new customers, production parameters change and force firms to learn anew. Although the technologies are not necessarily at the vanguard of the field, they have stimulated considerable learning at firm level. As was the case in pharmaceuticals, here too, companies outside the leading few are distinctive. For example, Krebs Biochemicals, with approximately 650 employees, is ranked in the top 10 firms worldwide for the manufacture of Ephedrine and Pseudophedrine HCL/Sulphate using fermentation technology, partners with and supplies to other large companies such as Glaxo, Johnson and Johnson, Parke Davis, Pfizer, Ranbaxy, Lupin and Wockhardt, exports 50-60% of its total production to 30 countries, including Tier 3 countries such as Germany and the US. While its R&D investments as a percentage of sales are 1%.

It has now invested manufacturing efforts into the production of Pravastatin and is attempting to move into more complex drug segments .[40]

6.5.1 Technological and market uncertainties: Why learning by proving isn't as easy

In generics, biopharmaceuticals face some challenges that synthetic pharmaceuticals do not. The table below shows the primary differences between the two forms of manufacture. Bio-generics regulations are still being drafted in both the US and in Europe. Indian patent law is simultaneously witnessing reform in biological substances. Firms face manufacturing challenges scaling up active biopharmaceutical ingredients for bulk manufacture, uncertainties in the regulatory process, and large investments to show bio-equivalence.

Pharmaceutical Generic Drugs (Generics/Multi-Source Pharmaceuticals)	Biotechnologically Produced Generic Drugs ("Bio-Generics")
1. Essentially similar to original product whose patent has expired and contain the same active substance 2. Face a simplified approval process (ANDAs) 3. Face little advertising and use a generic as opposed to brand name 4. Compete with low prices/high volume (unless first to market or with exclusivity period) 5. Market size worldwide approx. US$380billion	1. Essentially similar to original product whose patent has expired and contain the same active substance 2. Face a simplified approval process (ANDAs) 3. Face little advertising and use a generic as opposed to brand name 4. Compete with low prices/high volume (unless first to market or with exclusivity period) 5. Market size worldwide approx. US$20 billion 6. Products potentially open to generic competition: erythropoietin, alpha interferon, hepatitis B vaccine, human growth hormone, insulin etc. 7. Large biogenerics firms outside India. Biggest obstacles: (a) ABPIs (Active biopharmaceutical ingredients) in bulk which do not violate patents (b) Lack of a clear regulatory framework (c) Expensive demonstration of bioequivalence, which is highly species-specific, among others. (d) Unclear product liability.

[40] Biospectrum, Vol 1, Issue 7, September 2003, p. 10, India,

6.5.2 Niche research: the legacy of secluded competition and local relevance

Niches do not have to be small in scope. The combination of local demand, and local skills, assure Indian companies significant markets in certain areas and arise from past investments in certain types of education, particular types of R&D infrastructure and the historical trajectory of pharmaceutical and other industrial firms.

> *"India has a strong chemistry base, similar to that of Germany, as well as capabilities within public research institutes. Our skills are in organic chemistry and natural product chemistry (such as flavonoids etc from sandalwood oil, for example"*
> (Interview, June 12th 2002)

As in pharmaceutical research, the desire to apply older technologies to pressing local problems was expressed by one interviewee:

> *" We don't need tissue engineering or other more sophisticated technologies. We don't need many high-tech products to copy the US. We need basic things here. For example, water purification systems using rDNA technology, now that's what we need."*
> (Interview, June 12th 2002)

At the same time, the haziness of the regulatory options, the relative lack of locally patented tools, the cost of drug discovery and development work and the country's previous pharmaceutical history have led Indian firms to certain spaces of learning where, for instance, (a) proof of concept is well developed (b) where market opportunities have been created by the absence of big companies (c) traditional medicines and population-specific diseases present opportunities (see Jayaraman, 2003) (d) local applications are unavailable for existing products like diagnostic kits. A combination of constrained supply of certain skills and financial resources, and an immense identifiable demand in certain therapeutic areas has led to locally relevant and locally supplied niche technological foci.

Table 6.5.1 Local demand, local resources: niche research

AIDS diagnostic kits	Need locally usable, easily testable kits. Peptide-based kits now available.
Alternative cultures for rabies	Local research trajectories specific to resources available. Some scientists expressed concern that India had developed a nerve-tissue vaccine for rabies where the virus was isolated from the sheep's brain, while most other countries seem to use cell culture vaccines.
Antibiotics	Bacterial culture strains for antibiotics: Many existing strains such as streptomyces are developed from soil samples Other strains of bacteria are found more commonly and can be developed from less materials. Furthermore, many big pharmaceutical companies are pulling out because of alleged non-viability for resistant strains. Additionally, many pharmaceutical companies worldwide have been unable to meet the purity specifications of their USFDA-inspected plants.
Diagnostic kits for local needs, some of which have worldwide demand	Many existing kits worldwide are for diseases with little relevance to the tropics and to India. Some Indian firms have been able to make kits for neurosircosyrhossis (tapeworm induced), which are cerebro-spinal fluid based for antigens against this organism. Also PCR-based kits for shrimp virus.
Drugs for illnesses easily studied in large Indian populations	Diabetes type II, for example. Also, Indian population taxonomies for pancreatisis in Kerala, for example, allow linking of genetic features is closely-knit communities with large population samples.
New TB regimens	Search for non-DOTS strategies, i.e. less strict-regimens for administration of the drug.
Non-allopathic drugs (herbal, Ayurvedic traditional medicines)	A long tradition of Indian medicine is now being clinically investigated and taxonomies are being created with potential therapeutic values.[41]
Phage therapies	Antibiotics research and success crowded out this field from the 1940s onward Few other companies are pursuing this now. Tested in India in the 1800s, being re-visited. Being used for burns, where in India people often die of the infection, not the burns themselves.
Reagents of dual/triple track purity	Allows for different end-customers and price ranges, plus provide custom oligo-nucleotides, custom antibodies, sequencing services and PCR-based diagnostics for example, and provide a host of services to local companies, which foreign firms will not do. They also act as a test centre themselves, so viruses do not need to be transferred to other facilities.

[41] *"More than 70% of the population looks to traditional medicine, not allopathic drugs...Judging efficacy and validation by morn methods, standardization, fingerprinting could lead to an active formulation of a drug."* (Interview, June 14th 2002)

Over the past 5 years, the Technology Development Board of the Government has also created a reinforcing cycle by funding a variety of locally needed therapeutics and diagnostics, ranging from the production of amino Butanol as an intermediate for tuberculosis treatments (as an input for the production of Ethambutol Hydrochloride), production of antibiotics such as Cefixime, an orally active Cephalosporins, Hepatitis B vaccine development, and the development of the pediatric version of the recombinant Hepatitis B vaccine. The Board also funded cardiovascular drug development.[42]

It remains to be seen whether Indian firms will be able to consolidate positions over a broader set of technologies. They certainly lack the revenue streams and depth of public (and VC) funding available to US companies.[43] The primary constraint is not the ability to conduct search and experimentation in segments of the field that are being pursued in the US or other advanced, but the historical path that rewards firms (up to some point of saturation) to continue in past segments. The promise lies in the possibility that some of these "niches" are amenable to worldwide breakthrough such as diabetes studies, phage therapy or even systematically studied treatments originating from local traditions.

6.6 Stepping back into the process: The State and public domain innovation

"Government is now a driver again." (Interview)

A common critique of Indian pharmaceutical firms was that they have stagnated technologically, with only a few making substantial strides in innovative new products. Most had been seen as arising out of a "trading" and not "entrepreneurial" mentality, and with little appreciation for the science or technology behind the drug, mature or otherwise. This had been compounded by the unavoidable fact that drug discovery was an expensive, uncertain business, and most Indian companies simply lacked the resources to make substantial inroads into this process. Those that could appear to now be investing a rising percentages of sales revenues in R&D (with approximately 6-7% being the highest thus far in 2003).

Because of the shift in the life-science base of therapeutics, with the onset of molecular, cell biology and genetics, different learning strategies had been forced on Indian firms. Firstly, they now required a much greater appreciation of how to weave industrial and scientific interest more closely, a difficult undertaking for older firms built on a trading model. The requirement was to now straddle the interests

[42] "Technology board disburses Rs 30 crores for 20 projects", The Indian Express, April 20th 1998.

of multiple educational institutions, research institutes, and commercial entities such as firms, all supposedly with an interest in the same core technologies. Secondly, it required a learning situated around commercialization itself, no longer a process of trade, but of transfer of knowledge flowing across multiple institutions of learning. It also required the creation of new ones, such as intellectual property cells, licensing officers, legal knowledge, venture capital firms and policy mechanisms that encompass all of these.

As mentioned in Chapter 3, public research institutes such as the Central Drug research Institute (CDRI) and the Indian Institute for Chemical Technology (IICT) were known for significant advances in new drug routes, despite the pressures to privatize. CDRI has developed a one-a-week contraceptive pill (*Saheli*), the only non-steroidal contraceptive pill worldwide as well as its Memory Plus ™ and Vincristine (from Ayurvedic traditions). The Indian Institute of Science researchers have developed a male injectable contraceptive vaccine, which shows some promise. The National Institute of Immunology has made advances in contraception using extracts from the Neem tree and has created a second vaccine contraceptive, using HCG a human hormone, and is now undergoing clinical tests.

As previous sections highlighted, Indian public efforts in biotechnologies were initiated relatively quickly after the first commercialization of the industry in the US. However, its pharmaceutical industry trajectory was not easily replicated with the new role for biology-based models and the multi-disciplinary challenges facing scientists. Furthermore, the crisis facing Indian science and technology related in part to differing perceptions on the role of the public sector, specifically its research and commercialization functions. Some viewed the State as crowding out private research, while others viewed private companies as incapable of undertaking cutting-edge research. Yet others suggested that the R&D focus should be in areas with local relevance for the masses, not in treating "urban diseases of the West". However, where most public and private sector interviewees converge is in the interpretation of US biotech history and the under-appreciated role of public domain research and funding in propelling US companies forward.[44] One statement captured the challenges facing Indian companies in their self-assessments of skills and their acculturation (and awe) that Western private firms appear to be able to accomplish so much: "*US companies didn't have cutting edge research.*

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[43] One enthusiastic interviewee said: *"What you are seeing now in Bangalore is Genentech early on; with companies looking for new products to India, but also to the world.... We have the historical fortune of now having a corpus of like-minded people".*

[44] Only a small sub-segment of interviews suggested other views. Furthermore, even where the public role of the US was critiqued, it was in the context of inefficiencies with the public funding distribution and evaluation of returns of agencies such as the U.S. National Institutes of Health.

Human insulin work came from licensing through City of Hope research. We are made to believe that corporate scientists have done this." (Interview) "The entire knowledge base of this industry is public domain. The US story is one of slow development {of capabilities} and absorption capabilities of companies" (Interview, July 5th 2002). It also suggests that a re-reading of innovation history from western examples may be useful. As one scientist said, "*There is a lack of understanding (in industry) of US history and a lack of understanding of science itself and its applications*". (Interview, June 14th 2002).

Other examples of public sector undertaking (and less publicized) are companies like the National Dairy Development Board which is now working with Indian Immunologicals Limited (Hyderabad) for a foot and mouth vaccine in cattle and has since diversified into human biologicals, and the Indian Institute of microbial Technology (Chandigarh) which is working on live recombinant DNA vaccines for cholera and rabies. At the same time, the Centre for Diagnostic Fingerprinting (Hyderabad) has a worldwide distinction as one of the few to have developed a genetic process for overproducing plasmid DNA and the Indian Institute of Science also was able to bring down the cost and dependence on imports for plasmid DNA. Preliminary data suggests that firms have been seeking out public research collaborations, thus pointing to a possible avenue for research on policy options.[45] One potentially significant area of increased governmental activity is in funding exploratory work, which it already does in modest amounts. Companies spoke about how the search parameters in biopharmaceuticals are constrained by lack of funds.

[45] This is consistent with findings in Ramani (2002), which highlights that their number of collaborations with PRIs is greater in their sample. However, their sample implied that Indian firms initiated more collaboration with foreigners than with Indian research centres. This is consistent with my findings, since the export-push period has been formative in teaching Indian firms how to negotiate, and build intellectual property in-house as well as through collaborative work. However, Ramani (2002) suggests (but does not show significance) that R&D expenditure may be inversely related to size of the firm. Redwood (1994) and Lanjouw (1998) suggest that tacit knowledge in the engineering field may prevent companies publishing or patenting, particularly when considering the cumbersome patenting system in the country.

6.7 Science and business: new interactions for old players

Indian industry-wide advances have arisen in part from gains in diverse, but related skill segments.[46] The role of public information and knowledge and the ways in which they can be utilized to push an entire economy forward, is made richer by this section that describes tensions between science and business in India. While these tensions have always existed in the pharmaceutical industry, the fast-paced, science-based approach to biopharmaceuticals has made problems more visible.

The mixing of public domain and private research capabilities has brought a host of complications and anxieties to the fore. First, the concerns that low-cost work will drive the economy, second, the stagnation in commercialization capabilities has perhaps never become as evident and necessary as in biopharmaceuticals. One problem has been the difficulty in chemistry-trained scientists and engineers in the private sector from embracing "new" biology tools and models of therapeutics[47]. Another has been the difficulty in initiating and sustaining conversations between public and private sector researchers, particularly within whose responsibility the proof of concept lies. Universities such as the Indian Institute of Science have tried to innovate institutionally by allowing professors to spin off companies and creating industry research consortia on campus. However, problems have arisen since the 1980s of proof of concept, scaling up and compatibility to real-world conditions. *"When the diagnostic kit was sent to 4 Mumbai hospitals, they said, "it doesn't work". The capabilities within the hospital were bleak (but even so) we have a lab to end-use gap. We need to be able to move from "milliliters" to "drops", move from "distilled water" to "tap water": (Interview)*

As one statement typified the difficulties pharmaceutical firms had in embracing newer tools after the 1980s: *""In the 1990s there was a lot of pressure in parliament from international hype in the biomedical area, to push to develop diagnostics-antibody or DNA. About a dozen diagnostics came out, zero came to market. On the one hand, scientists did not know what makes it work in the field and on the other, companies had problems. Family-based pharma companies were only capable of putting a wrapper on a product and selling it. Towards the end of the 1990s, [there was] a sea change and*

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[46] *"With an analogy to computer science, we have speed of programmers, quality of programmers and number of contracts. India is good at all of these things more than all other countries and all of this is in one country. Therefore, even if they work with the US or other companies, they foster each other's capabilities because they need them. Thus, each epsilon improves and cumulatively combines to produce a big delta. So delta doesn't depend on only domain expertise in molecular biology, genetic etc, but also on domain expertise in other areas." (Interviewee)*

[47] Those companies begun by academic scientists trained in the life sciences have not faced this problem.

there is a learning period of working together. In the last 5 years a big change has occurred and a newer class of entrepreneurs in Hyderabad, engineers or scientists, including life sciences, working abroad, then came back and started companies."[48] There now appear to be more people in industry who grasp the fundamentals of science, and more scientists who choose to become entrepreneurial. A cultural change providing increased prestige for industry work, previously awarded to academics, is gradually taking place.

Although faced with considerable problem-solving challenges in the discovery and development phase (particularly the latter), a variety of companies highlighted the role as centres of excellence that public domain research bodies should strive for, not all of which are easily reconcilable. *"Basic research is vital for product development".... "We do too much in-house. CDRI*[49] *should be doing something cutting-edge and pass it on." Money should go into fundamental research and academia rather than a biotech fund; Science in PRIS should also look to scale up their own technologies..... ""Unless we have one academic centre of excellence and motivate professors to start companies, we won't find small dedicated biotech firms, because they are not parented well by big pharma". .... "Government should be funding pure science and global excellence, a laissez-faire model". "Basic science is needed."*

A critique of academic scientists that emerged from both academics and industrialists during interviews was the view that academia is a low risk profession and that Indian academia tends to do reconfirmation findings, or minor permutations on known problem areas. While industry forces a certain frequency of problem solving challenges, academics can avoid this by simply switching to another research area and may never have to actually solve a technical problem that creates a procedural bottleneck. The tensions are highlighted in the annoyance of the private sector that academics should be interested in money at all, and the perception by many scientists in public research that industrialists know nothing of science. *" We have the best biophysics people in the country, but they want money for what is given away almost free in the US. There is no accountability in Indian academia, no products out, no rigorous peer review and they are not forced to test ideas."* (Interview, July 11, 2002)

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[48] Another interviewee described the fundamental challenges to moving into drug discovery in biopharmaceuticals: *"It is hard to do drug discovery because (a) there is no synergy between academia and industry. Start-ups are very sparsely populated. (2) Capital intensive (3) Lack of high-quality academics in biology. Indian academia is good at hands on skills, but we are followers not leaders in conceptualizing areas and we have no management of science with connection to technology."*

[49] Central Drug Research Institute

What changed, however, were the nature of links between public and private sectors. Crisis-driven change here has meant that both have been forced closer together, the public because of resource constraints and a need to prove that demand exists, the private because they are not bastions of the science, or the infrastructure to discover. However, their conversation has been muffled, incoherent and frustrated at the best of times, and simply non-existent or furious, at the worst. Crisis-driven change has occurred not because of the Indian liberalization alone, but because Indian firms already established and export-driven, were facing challenges on new fronts, particularly the patent regime change and pressures of new regulatory markets. While the latter could mostly be dealt with in the company alone, the push to create new products, or greater product differentiation required dipping into the public research till again. PRIs faced new challenges since some were born and driven by chemistry-including biochemistry, while others were looking at whole-organism derived analysis. In addition, PRIs were pushed to find ways to create locally needed drugs. Furthermore, Hyderabad and other-manufacturing company sites were becoming centres of considerable riches made from mature product line manufacturing.

Another, more fundamental problem is arising on the continuing dependence on tools of analysis, many of which are now patented by US companies and must be licensed. This is exacerbated by curricular limitations in India, where inter-disciplinary work rarely exists or is rewarded and tools and products thus appear to be more difficult to generate.[50] [51] For instance, process technologies such as conjugation, reagents and micro arrays are all patented and act as input technologies for vaccine development.

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[50] There is limited interview data to resolve this latter issue. Certainly an interesting and relatively straightforward future area of research is the classification of innovations arising from India and other developing countries a function of disciplinary backgrounds of the team members and contrasting this with, say, the US.

[51] One interviewee described the process: *"The gap is widening. I see a technology lag to the US benchmark. Public domain knowledge is available from the US to India but there are no interdisciplinary programs here. We have computer science, but no biomedical engineering or tissue engineering. We need this! These are critical for 'black box technologies i.e. for transferring basic knowledge to commercialised products. For example, making a DNA sequence is a sealed box. Also, scientific and technological changes are causing a sea change in organic chemistry. Thus, in five years, our entire medical technology will depend on US products unless we begin basic engineering degrees and build to fields such as biomedical engineering. We also need national-level accreditation boards for good courses"* (Interview, June 12th 2002)

6.8 The changing selection environment

In the last several years several environmental factors have continued to change. The Drug Policy of 1978 was subsequently modified to the Drug Policy of 1986 and changed again in 1994 taking account of new Indian obligations under the WTO agreements, among others. Overall. Since complete economy-wide liberalization in 1991, industrial licensing for drug manufacture has been abolished except for those bulk drugs manufactured using recombinant DNA technologies, those bulk drugs requiring in-vivo use of nucleic acids, and formulations targeting specific cell and tissues. The same applies to Foreign Technology Agreements for recombinant DNA technology-produced bulk drugs.

Pressures on manufacturers of older segments has increased following the GOI approval for allowing free imports of 5 important bulk drugs such as those for Vitamin B1 and Tetracyclin.
There has also been a denial of permission for exporting new molecules (such as Viagra), which have not yet been clinically tested and cleared by the Drug Authority of India. This particularly affects Indian companies whose main business was to imitate new formulations. There has also been a transfer of some therapies to Over-the-Counter (OTC) status, which reduces their profitability.

Moreover, the remaining 5 drugs reserved for manufacture by the public sector was abolished in 1999, and almost simultaneously, in 2000, FDI through automatic approval was raised from 51% to 74% and eventually 100%. Public sector units are being privatized, including flagship enterprises such as Hindustan Antibiotics and IDPL. A new patents bill was introduced in parliament as well as further incentives for expenditure on in-house R&D. There have been revisions on price controls, with 4 price decontrol exercises in three months of 1999 alone by Pharmaceutical Pricing Authority. Finally, in sweeping changes to price control rules, a large number of drugs have been taken off the controlled categories and ceilings on profits raised in these and other segments of drugs.

An important additional institution, still being implemented, is that of health insurance. Over 80% of the Indian population remains without access to health insurance. Besides Central Government and some State schemes, the main providers of health insurance are relatively small non-governmental organization and co-operative insurance mechanisms, but which have a large potential for growth. The rapid growth of health insurance in the country is likely to have far-reaching effects on the pharmaceutical and biopharmaceutical industry and it is no surprise that some companies have been diversifying into this sector and stepping-up educational efforts on the principles of insurance.

The importance of public science to the evolution of the biotech sector in the US where the field has progressed the most is born out in numerous studies, but its particular dependence on public science relative to other industries is also important. (McMillan, Narin and Deeds, 2000). In the Indian case, the State has acted predominantly as customer, supplier and to a lesser extent, competitor. But broader, public domain research organizations (universities and public research institutes alike) have acted as a conduit for key technologies and as a negotiator at international level on behalf of its firms. In recent years, it has had an incubatory role, assisting small biotech firms[52]. Its primary strength (and weakness) has arisen in the domain of setting a socio-political vision of public health (even if only partially fulfilled), rules by which firms emerge, grow and encounter one another (including the policies of price regulation and licensing), and delineating the scope and scale of the marketplace (including intellectual property regimes and anti-monopolistic laws). In the export-phase, the role of the State has been relatively reticent compared to the first phase. Here, foreign determinants of health and safety regulations have largely shaped the innovation by Indian firms, and have been supplemented by international agencies acting as customers.

In all, findings suggest that in the key early phases of the industry growth, the source of innovation for manufacturing companies has been less in the interaction with suppliers (except when it was the State), not through downstream users (except in the case of exporting to tiered regulatory conditions or international public procurement). The central source of innovation has been the manufacturer itself combined with its links to public research institutes in the country. More recently, with biopharmaceuticals, companies and public domain research have been driven closer together, both in India and with foreign institutes. It remains to be tested whether Indian national publications and patents demonstrate a strong geographic self-similarity and dependence, i.e. cite national science (such as indicated by Narin and Olivastro, 1992 and others). However, it is clear that an attempt was made by the State apparatus-including departments of S&T, public research institutes and some universities-to develop locally-relevant technologies and products and modify existing mature instrumentation and analysis tools to be suitable for local R&D. In the case of Biocon and others such as Krebs, the products such as enzymes are intermediate goods and are used across sectors. Some innovation does indeed occur by interacting with the user, but the major breakthroughs appear to have driven by in-house R&D combined with PRIs. This story that demand conditions did not uniquely

[52] Examples of firms that have been assisted in the Bangalore-Hyderabad region are: Xcyton (National Institutes of Mental Health and Neurosciences, NIMHANS), Avesthagen (assisted by NCBS site facilities and the University of Agricultural Sciences), Shantha Biotech (Osmania University and CCMB), Genotypic Technology (IISc and University of Madhurai. Also equipment from the Centre for Biotechnology, Delhi),

determine the trajectory of firms as often described through users and through suppliers appears common to some other stories abroad in the industry. In particular, the role of search in a space of scarcity (the supply side) warrants future study.[53]

The two cities where most interviews were conducted have also competed with each other to develop bases for innovation and high technology. Nevertheless, as local capabilities develop, cross-city alliances are also being forged. There is some evidence of increased collaboration of companies and scientists across the boundaries. Some companies have more than one location in the two cities, others interact with scientists in the other city.[54]

6.9 Summary:

Biopharmaceuticals has shown a different trajectory of learning than that of synthetic pharmaceuticals. The advances worldwide are relatively new, yet certain categories of therapeutics are already mature, such as human insulin and erythropoietin. However, here, because the substance is biologic in nature, and not chemical, the variations by species are considerable, as are the conditions for holding a process stable. Bioprocess engineering faces considerable challenges in scale up and manufacture. In addition, the tacitness of the process is significant as are economic conditions for appropriation.

As for biopharmaceuticals, process expertise has become critical. The policy mix that assisted pharmaceutical firms (public health entry points, process development capability, patent regime, among others) has helped here too. However, a critical feature has been entry points of public health for vaccines and diagnostic kits which has allowed windows of learning to an otherwise emerging set of process technologies. The national and international procurement policies of WHO and UNICEF have been equally important. In both cases, the role of the State as initiator of technology transfer, creation and adaptation, has been systematic. In both the State and its public research apparatus has been important in "jump starting" private sector capabilities on a large scale, either through direct technology transfer and assisted commercialization, or indirectly, through infrastructure support or research services. India's leading biotech firms have obtained key technologies from the State and

[53] Novo Nordisk of Denmark), the world's largest producer of industrial enzymes and insulin, where innovation was driven in large part by scarcity of pancreas, from pigs, to manufacture insulin, rather than the obvious demand for insulin. Additionally, chemical companies also required pancreas since the trypsin enzyme used in industrial processes was also derived from pancreas. Further, theory had it that insulin and enzymes could not be obtained from the same pancreatic glands. Novo Nordisk, driven by pancreas scarcity, was forced to investigate this further and eventually proved the theory wrong. (See Laursen, Keld, 1996).

[54] Some older distinctions-that Bangalore was biology-based and Hyderabad chemistry-based, are slowly breaking down, although old competitive urges to differentiate cities, prompted one Bangalore scientist to state, *Bangalore supplies the brains, Hyderabad the manufacturing capability!"* (Interview, June 14th 2002)

have since invested in upgrading or deepening these technology lines. Contract research services have provided an additional window into cutting-edge research because they allow firms to encounter a much higher number of biological system problems than possible to launch projects with their own capital capabilities, and they allow in-house R&D activities and experimentation to complement external search. Lastly, private and public infrastructure in clinical medicine-hospitals, clinics- and a large domestic patient profile of distinct ethnic and disease profiles has allowed Indian biopharmaceuticals to straddle a much broader set of capabilities from drug discovery to taxonomy-building, clinical trials, drug development, manufacturing and sales.

However, there have been some important differences. While in pharmaceuticals, large firms have dominated the innovation profile, in biopharmaceuticals; smaller firms have also entered in vaccine development and in "bio-generics". The organizational forms have also varied with diversified business groups and dedicated drug discovery firms at the two ends of the specialization spectrum. State involvement has led the entry again, with Indian public research institutes initiating the indigenisation of the newer technologies and some transfers of technology into the private domain. Similar to pharmaceuticals again, private firms did not depend on the State alone. Some that had access to capital (externally through banks and venture capitalists, or internally through manufacturing revenues or service revenues) moved directly to drug discovery, or continue to work with a combination of public domain institutes in India and abroad (such as public sector research labs and universities).

From a technological standpoint, Indian biopharmaceutical firms face far greater market uncertainties in the US and elsewhere. Bio-generics are neither well defined, nor face clear regulations. This lack of market assurance has a large part to play in limiting Indian firms to niches with well-defined proof of concept such as vaccines (Shanta Biotech, Bharat Biotech International Limited, Wockhardt), antibiotics and exploratory potential therapies such as bacteriophages (Gangagen), again with public health implications.

In the biopharmaceutical realm, the implications of the product life cycle are less clear. Certainly, the prime innovations have arisen in the advanced industrialised countries and more mature segments are being investigated in India-diagnostic kits, vaccines etc. However, again, a point of considerable importance, that may lie closer to the suggestions of systems theories of innovation. What is being developed in India also corresponds to (a) niche areas that have either been mostly ignored or

jettisoned in the West, but have considerable import for the Indian population (bacteriophages, kits for diseases and population groups specific to the tropics etc.) or (b) industrial restructuring or convergence areas of expertise such as fermentation.

Overall, the number of total companies is small. An innovative segment is emerging which is attempting to compete on scientific capability as well as the low costs of R&D. Industrial biotech companies which have since entered drug production are also beginning to differentiate themselves into niche production areas drawing on their past enzyme and fermentation expertise. The sector is too young to draw any generalized conclusions about its future growth. However, the diversity in the technological learning paths of the various companies illustrate that in both mature segments and in emerging drug discovery and development opportunities, the existence of public domain technologies or off-patent techniques does not necessarily make a specific technology or set of tools easy to acquire, adapt or improve. It also suggests that certain niches develop because institutional competence (research profiles in universities and public research institutes) tends to preserve past trajectories, underlying the importance of tertiary educational investments and local relevance of therapeutics.

Chapter 7 Synthesis and Conclusions

> *"It has been assumed here that learning takes place only as a by-product of ordinary production. In fact, society has created institutions, education and research, whose purpose it is to enable learning to take place more rapidly. A fuller model would take account of these additional variables." (Arrow, 1962)*
>
> [It is desirable that we] *" do not treat learning as somehow an inevitable and uninfluenceable consequence of doing. Rather, learning is viewed more actively, and it is apparent that resources can be applied to learning." (Nelson and Winter, 1982, p.258)*

7.1 Introduction-Technological learning as shaped by selection environments

The analytical focus of this thesis was situated around two core areas: product maturity and the selection environment. This chapter returns to these two themes and related questions on innovation type and sequence. While the stages of population variation, selection and retention in the evolutionary process all provide insights into how learning occurs, the data has paid special attention to various selection pressures on firms and has shifted the focus away from intellectual property as the defining characteristic for the two sectors. Indian firms were able to advance despite their low R&D investments relative to their peers in industrialised countries and despite their "copying" and generic drug manufacture because a varied set of selection environments forced this learning on them. This dissertation showed first, that a changing selection environment laid out the elements of entry in building the industry; second, how innovation skills developed despite the fact that firms were primarily in mature product segments. Manufacturing skills were critical; they led to innovation through the ability to rapidly create slightly differentiated products, which presumably led to gradual shifts in the demand curve accompanied by simultaneous shifts in the supply curve due to lowered costs. The ability to scale up from lab to factory provided firms with an advantage due to proprietary process capabilities, manufacturing revenue streams and in-house flexibility and speed to reach market.

Early policy supports to build capabilities allowed some firms to move into subsequent environments, with culling of the population and honing of capabilities occurring at the cusp of each new phase. Thus, exclusively industry-level analyses and "new to world" markers for innovation mask the variety of firm-level learning strategies and innovative potential as they faced different selection pressures. Furthermore, policy can act to shape the selection environment, at the same time that it assists firms in recognising these pressures and offering incentives for building capabilities that can be selected for. Causal ambiguity and time lags accommodated in theories of selection, however, create special challenges. Cumulative pathways for capability-building matter, but may not show immediate results. Indian firms appear to have

benefited both from Phase I policies, and firm-level efforts in Phase II, but cannot securely extrapolate for later years in Phase III and beyond. Industrial policy acted to increase variation and create early selection mechanisms, while industry grapples today with issues of retention and adaptation. Variation among firms has been taken primarily as given during Phase I, and future research should study the specific traits that allow for increased diversity or homogeneity and positive selection of firms as they migrate to later phases. Firms have indeed been alternately assisted and pressured with patent regime changes. However, the interviews indicated an internal struggle for many firms to identify broader dynamics of selection and capabilities, but with a limited vocabulary structured around debates of intellectual property.

Indian nationalism was structured around core principles of socialism and equity in production and distribution. Notwithstanding this, leading firms by market share grew ever larger by production capacity, output volume, revenues and employment. If we situate Indian advance and that of other countries against a backdrop of learning- we can understand why innovation may arise even in mature products, and not driven by cost cutting alone, or why sequenced entry regulated markets may drive and sustain certain types of learning. Ownership also becomes one explanatory variable (and policy tool) to create indigenous capabilities. The vehicle of technological learning has been manufacturing and process capabilities. Thus, policies that rewarded (a) manufacturing and process innovation and (b) national ownership helped firms to advance. Technological learning was not neutral to firm ownership, confirming past studies.

Firms have emerged from a protected national context to an export-related set of opportunities. However, there was nothing automatic or "natural" about the progression of capabilities or of this transition. Indeed, the selection environment at the early stages structured the likelihood that some firms would be able to "graduate"', but the nature of the transition-to the export world, was varied. The move into developing countries could, perhaps, have been anticipated. However, the timing of the opening up of the US market through the Hatch-Waxman Act, to generic drugs was an unexpected opportunity for which prior preparation was imperative. Those that could make this transition were provided some technological and significant market advancement. The intellectual property regime in this framework was thus important less as a direct tool for companies to "copy and prosper" and more because it created a vast array of domestic product differentiation strategies and savings associated with multiple formulations and dosage types. More important than IP alone, were a series of policies designed to build capacity in the sector, and to force firms to back-integrate into bulk drugs so that national health security could be assured. Thus while profit margins declined due to price regulations on "essential" drugs, capacity increases and induced learning, resulted in some economies of scale. Patent laws also assisted firms to consolidate their

positions, hone reverse engineering and imitation skills to a fine art, and to increase competition for first-entry and speed of introduction to Indian markets of drugs on-patent elsewhere. However, the chronological analysis argued that the intellectual property regime alone couldn't explain India's advance to date, important though it was to acquisition of core technologies and market opportunities.

The limitations of views that over-specify a firm's agency and minimise the environment surrounding it, comes into stark relief in the biopharmaceutical sector, where institutional characteristics of firm-university-public research interaction and characteristics of the technology have served to make more complex the firm's interaction with its selection environment. Of some concern are the tensions between the perceived (and, in some cases, real) lags in biology skills in industry, contrasted with chemistry-based capabilities that vaulted the pharmaceutical industry to its present position. Also onerous is the burden of proof of concept-whether something is viable to commercially produce-requiring significant process capabilities and an understanding of science and market, a rare combination. Yet, despite these hurdles, biopharmaceuticals has benefited as a sectoral latecomer, from models for advance taken from the pharmaceutical industry, where industry associations and the socio-political ramifications of drug discovery and development have been well studied and adapted to a new technological imperative.

7.2 Learning pathways:

Indian industry saw at least 3 distinct types of selection environments, only the first of which was strongly policy driven and where most analyses remain. The remaining two were driven by regulatory and technological changes in the industry, which required new institutional configurations in the two sectors. Instead of an environment driven by intellectual property rules alone, 3 types of learning emerged depending on the selection environment of the time and amid resource constraints: Induced (phase I, 1950s-1970s), Tiered (phase II, 1980s-1990s), -Uncertain (phase III, 1980s-2000s).[1] The table below summarises the learning pathways, the era in which they occurred and the nature of the sub-phases of

LEARNING	S.E.	YEARS (APPROX.)	SUB-PHASE
Induced	Phase I-Policy Phase	1950-1970s	Public effort Private effort
Tiered	Phase II-Regulatory	1980s-1990s	Tiered worldwide cGMP regulations International vaccine procurement Generic drugs
Uncertain	Phase III- Regulatory and technological	1980s-2000s	Biopharmaceuticals and diversity of 6 example pathways studied

[1] As highlighted in the chapters, Phases 2 and 3 were overlapping in time period and tiered learning continues today for an increasing number of firms in the two sectors.

learning that they involved. Resource constraints seem to have dogged firms in their approach to drug discovery through many sub-phases.

This dissertation analysed India's performance in two sectors with substantially different constraints and opportunities. The advance occurred under two technological paradigms of synthetic and natural product chemistry on the one hand and subsequent biological advances on the other. The findings indicate the importance of understanding the broader environment in which firms are situated and the capabilities that arise within this environment. In such a view, there is no "automatic" capability pathway, but selection criteria, devised in some cases by national policies and social concerns, or by international agencies, constrain and shape the path of firms. In particular, innovations through process capabilities appear not to be driven by cost-cutting concerns alone, but are honed by forces of the environment. Firms have weathered pressures ranging from low profit margins in some segments, impending changes in the intellectual property regime, variations within the export markets and more recently, the pressures of adapting to new technological imperatives. Yet, a few firms have shown some tenacity in adding to their repertoire of technologies with some novel products and processes. Relative to their counterparts in some advanced industrialised countries such as the US, UK or Switzerland, these leading firms have a limited range of new products (New Chemical Entities, NCEs), but this number is slowly rising, showing that a move from "imitation" to "innovation" is indeed possible. But the data suggests more: that in the development of skills to counter problems of financial and material resource constraints, uncertainty, information disruptions and regulatory changes, firms have also been forced to find new paths to older problems, raising the question of what characterises novelty and innovation. These findings suggest that more research is needed on the dynamics of innovation and on the characteristics that distinguish firms from each other within the same environment. This dissertation demonstrates that the story of the rise of pharmaceutical and biopharmaceutical capabilities in India is both more complex and fraught with difficulties, on the one hand, but also offers more possibilities for building capabilities in developing countries and other sectors within India, than current debates anticipate if process capabilities are seen as a goal in themselves and not simply the means to new products.

In addition to the 3 distinct types of learning in 3 chronological phases, there were also other types of sequential learning occurring at industry level (but not necessarily for every firm). The table shows a stylized progression of technological and market learning and advance through 3 steps along three dimensions for entry, capture and upgrading path for pharmaceuticals. Further tests could be put in place to see if such a progression is a valid representation for developing countries and if their implications for public health drug manufacture can be coherently translated into policy design.

Type of learning	Step 1	Step 2	Step 3
Market entry	Public health drugs	Other essential and non-essential drugs	Other "non-essentials" high value-added drugs (cardiovascular, "lifestyle",
Market capture	Domestic market	Unregulated and consolidation of domestic market	Regulated tiered markets and further consolidation of domestic market
Upgrading	Importing bulk drugs and manufacture	Manufacture of bulk drugs from local raw materials	Generic drug manufacture and a few NCEs

The sequence of market entry was not coincidental. Firms were able to build abroad on what they had built locally. Once the domestic market was mostly consolidated, the move began into overseas-unregulated markets and firms then systematically "graduated" into more stringent regulated markets. Home markets were thus experimental grounds for technological advance combined with building up of complementary assets of distribution, marketing and building brand names. Government policies thus assisted firms in technology acquisition, adaptation and the building of these assets. Unregulated overseas markets helped consolidate gains on these fronts and brought in "easy" revenues, since often the regulations were of lesser intensity than in India. The first tier of regulated markets in the transition economies also proved a learning challenge.

(A) **Induced learning**: a State-constructed selection environment based on an interplay of core beliefs of technological self-reliance (of which intellectual property is only one tool) and an economically, politically and technologically defensible and strategic choice of public health drugs as an entry point (for which MNCs were one source of technological sophistication). This also created a capture of the domestic market, a step with considerable learning value. Multinational firms were sidelined, but kept within the industry (and not nationalised) because no Indian firm as yet had significant technological capacity. From a technological standpoint, policies created market incentives (large domestic market size and public procurements) and a psychological boost for technological investments. Policies thus allowed firms a chance to strategically enter an otherwise inexorable product life cycle. All policies were not without fault. Supply in many areas fell short of targets, and price regulations arguably lowered costs and created further incentives for process innovation, but acted unwittingly as an export-push strategy. It is impossible to know whether more firms could have "graduated" to a higher level of capabilities had they had a better constructed export policy supporting them, Some companies have suggested that the level of intervention by the State at all levels was excessive. Yet, the evidence indicates that many supports-such

as the patent regime, preferential licenses and procurement, were critical when firms were faced with the technological assets (and revenues, perhaps most importantly) of foreign firms.

(B) **Learning-by-proving:** Emerging from this State-led selection environment, some Indian manufacturing firms were able to quickly take advantage of far-reaching changes in the international drug markets, including policy changes to enhance competition in the US. Thus, if public health acted as a market entry and market capture point, then regulatory conditions in tiered markets served to provide continuous technological and quality variations that enhanced firm-level learning. The evidence demonstrates that Indian firms advanced technologically and in business acumen through tiered markets which served two functions: First, they allowed Indian firms to interrupt the continuous progression of the product life-cycle and capture new markets without necessarily producing more sophisticated technologies. Second, regulatory sequencing allowed for "consolidation plateaus", where technological and business learning imbibed in one tier could be further absorbed into the company's organisational and technological framework before the creation of strategies appropriate for the next tier or set of countries within the same tier. At each plateau, multiple country markets presented themselves for lateral expansion and increased revenue streams without the need for significant leaps in technology. Firms were allowed the opportunity to build complementary assets alongside, such as patent capabilities and rapid filing with the appropriate regulatory authorities. In addition, international agency procurement was decisive for vaccine (and some diagnostic kit) providers, serving to reduce demand and regulatory uncertainties and providing a stepping stone into foreign markets in the way that tiered regulatory markets had done for pharmaceutical firms in other segments.

(c) **Learning under uncertainty:** However, in the case of bio-pharmaceuticals, regulatory environments and institutional models are poorly defined (except those imported directly from the pharmaceutical sector) and tiered markets do not exist. Technological changes have been rapid and the number of commercialised therapeutics very small. Thus Indian firms must learn to cope with a spectrum of uncertainties, technological and regulatory alike. Information on new technologies and non-infringing processes is unavailable and firms now invest energies heavily to be part of more international networks of knowledge. As a shift in the underlying technologies took hold in the post-1970s era of the explosion in molecular biology, Indian firms have also ventured back to national laboratories and local universities to tease out State-led capabilities from an earlier era to develop a nationally and geographically specific set of niche markets, while continuing to forge alliances abroad. Many innovative firms have emerged from manufacturing histories and the same policies that rewarded process capabilities, but faced with a change in technological paradigms, a new set of firms is emerging alongside primarily focused on drug discovery and development.

In all cases, those firms with in-house R&D capabilities were best positioned to learn quickly and absorb and modify new knowledge (new to them, if not to the world). However, this sector is still young and learning patterns are yet to emerge.

7.3 Process capabilities: the goal, not just the means

Manufacturing is not the only innovation path in Indian pharmaceuticals/biotech. However, almost entire Indian technological advance has occurred in firms with manufacturing histories. The Indian evidence from secondary sources and interviews suggests that cost continues to play an important role in all Indian pharmaceutical and biopharmaceutical segments. Even in innovative firms, it is closely tied to low R&D costs, particularly the availability of cheap but highly skilled personnel. However, the Indian case, while consistent with the wage advantage story, suggests that cost-cutting measures alone were not the prime drivers of innovation in scale-up and manufacturing. Firms attempted their own search efforts. Secondly, low wages cannot explain the clearly differentiated two broad (and evolving) segments of the pharmaceutical industry, and the high-end contract researchers (and manufacturers) of the Indian biopharmaceutical sub-sectors.

While it was indeed true that the ability to scale up and manufacture was critical to many of the success stories, the specific tiered regulatory learning environment and the uncertainties and rapid technological changes occurring in biopharmaceuticals significantly shaped them. Indeed, in the case of biopharmaceuticals, a "pure process" set of technologies, the absence of such a structured learning sequence has precluded the obvious opportunities for Indian firms, no matter how well honed their process abilities. Overall, the move of Indian firms into process capabilities was considered an affordable expertise; firms were not making a choice from an open-ended set of alternatives ("product versus "process") but from a specific historical path.

Process development is a non-linear, unpredictable process since many chemical and biological processes are sensitive to scale and many second-order perturbative effects come into play when the operational volumes and temperatures are increased. An interesting feature is the way scale-up and process improvements can be adapted to existing technologies. For instance, a few firms have emerged from strengths in the fermentation and brewing industries with enzyme R&D and have since moved into biopharmaceutical manufacturing, and then into R&D to create bio-generic drugs. Although the product is now relatively mature on the world market, a significant learning process has taken place within these firms. Their breakthroughs can be said to come less from a "science-push", and far more from directed technological problem solving associated with environment control and scale-up for mass manufacture of

enzymes. In the Indian case, process capabilities led to the ability to find 1. New ways to known ends and as a by-product, to find new ends themselves while searching for new pathways.2. New ways to use existing processes because of resource constraints, and new ways to link promising properties of compounds across projects (sometimes looking for very different applications) due to resource constraints.3. New ways to link in-house R&D with contract R&D services and enhance search and experimentation through both, so that the universe of known ends is ever expanding. Process developments then should be considered both the goal itself to product improvement and cost reductions, not the means alone.

7.3.1 Innovation type and sequence:

In the Indian case, process innovations abounded relative to products, due in large part to the supply-side incentive of process patents and lack of product patents. Price controls in particular, appears to have eventually acted as a disincentive to invest in early-stage R&D, but did increase process investments to find new ways to (a) reduce manufacturing costs further (b) speed up entry into patent-expired drug segments (c) speed up entry into drug segments where new therapeutic effects can be demonstrated. There has been a distinct incentive for innovations arising from a "manufacturing-push" resulting in sophisticated process engineering and manufacturing experience in these firms' ability to develop path-breaking R&D and product capabilities. Furthermore, resource-constraints, both financial and skill-based, have channelled energies further into process development.

Advances in Indian companies, have been small, but noticeable improvements in processes and products, quality control, preparation for clinical trials and more recently, learning to file for approvals abroad, and litigate, if necessary. Furthermore, they have attempted to hold on to older public health niches (antibiotics, vaccines, diagnostic kits) with newer technologies and sustained compliance with US FDA standards, while other MNCs have failed to hold on to. Their stresses on capabilities that are difficult to imitate: finding multiple paths to the same end drug, finding multiple lateral uses for the same compounds, finding multiple small, but valuable add-on features to existing drugs etc., have all built on certain historical constructions of opportunity and later windows of opportunity.

In biopharmaceuticals, the characterisation of some of the originating breakthroughs do indeed come from a scientific discovery, but the evidence of learning paths shows that it is dependent a great deal on adaptation to existing technologies. Process development sophistication often arose from related, but technologically "old" fields in latecomers, such as brewing and fermentation in liquor, food and pharmaceutical sectors, which were then the basis for product advancement in biotech and pharmaceuticals. Thus maturity of process from one sub-area is translated to rapid advance of both

process and products in another. Furthermore, companies compete on speed, ability to litigate as well as change processes in-house, thus awarding bonus points for agility to vertically integrated companies, where constancy of supply, purity of samples and problem-solving can all be coordinated more comprehensively.

The NCEs of these companies may not be categorized as "true" novelties in the sense that they arise where their competitive advantage is greatest: process modifications to existing entities that bring out novel properties for example it may minimize side effects or eliminate them, or improve efficiency of uptake. Since some of the companies such as Ranbaxy and Cipla also specialize in Novel Drug Delivery Systems and new platform technologies, the novel properties may be revised dosage or dosage form, which demonstrates, increased therapeutic efficiency. While novelty has been demonstrated, the evidence from Indian pharmaceuticals suggests that even supposed "radical" breakthroughs (the category of NCEs used to show innovation) are often incremental improvements. They derive from a long history of experimentation, in this case in manufacturing and process engineering and process chemistry.

The data reveals that early technological capabilities in the Indian pharmaceuticals and biopharmaceutical sectors was more due to the State structuring a nurturing selection environment, than it was due to some price-driven market selection leading to "spontaneous" capabilities in firms. Later capabilities were honed by international export opportunities seized by a sub-set of innovative firms who also built up in-house R&D capabilities. However, the selection environment was not simply a culling mechanism. It was used strategically to build process capabilities and induce firms to learn and upgrade their capabilities. Thus, this dissertation argues that process capabilities should be seen as a *skill set* central to Indian (and indeed, other national) innovation, not merely as an intellectual property unit of analysis, set against products. The first, processes, have given rise to the latter, products, against the conventional view that process innovations arise after product innovations and predominantly to push down costs.

In case of sequencing, there appears to be no simple rule, running counter to that suggested by Kim et al. "imitation" does lead to innovation in many cases, but often imitation and innovation exist alongside and in most cases, innovators are imitators some of the time, and imitators are also innovators some of the time. Specifically, the study of Indian pharmaceuticals shows that (a) process innovations did not always come after mature product innovations but to search for new ways to create new products (b) that process innovations themselves often led to product innovation opportunities and (c) Process innovation also provided accelerated time to market since competitors could not as easily copy a process as they did with

products. This allowed companies that were quick to patent or file for exclusive rights to drugs going off patent, to establish a significant head start on competitors.[2]

The evidence suggests that more research is necessary to determine if a clear sequence is visible. Industry-wide, imitation to innovation has some value as a metaphor, but hides firm-level capabilities where innovation and "imitation" exist side-by-side. Furthermore, "innovation" is a context-dependent description, and appears to rely in part on the specific selection environment and regulatory standards applied to novelty. Firms have been differentially "innovative" at different times even in their path to create "me-too" drugs, or in their search for new processes to old drugs. Indeed, consistent with the NIE evidence from East Asia, multiple learning strategies have been used.

7.3.2 Responding to demand while grappling with supply

Should local market demand alone been sufficient to propel the industry forward, then we should have seen Indian firms meeting the immense needs for local tuberculosis, AIDS, malaria and other local diseases. Indeed, demand had been created and sustained by the State and international procurement agencies at various times. It had not been market driven until India's export push, largely driven by falling profit margins at home under a strict price control regime and coinciding with an increase in overseas opportunity. The main challenge was access to key technologies to jump start the local industry, strictures on acquisition of knowledge (such as product patents), problems in technology transfer to upgrade existing processes and finally, the lack of raw materials or pure input materials. In short, in-house innovations emerged under resource-constraints at the outset, not merely well articulated consumer or other demand. Companies were forced to vertically integrate (more on grounds of induced efficiency from uncertain inputs) rather than some magical convergence to efficient scale and forced to delve into existing stores of past competencies to find new areas of endeavour, deliberately turning their backs on potentially new areas of work that would have required new investments and skills.

The findings point to the fact that fundamental capabilities built in Indian firms were not indigenous alone at every phase, but a variation over time. The richness of the story also lies in the multiple strategies within one industry. S. Korean technological advance for instance, while clearly heavily dependent on State intervention across industries, was also dependent on exports to the US. The rise of other countries, including Japan (and many of today's developed countries) also occurred at a time when patent laws were less stringently monitored. Indeed, the importance of the East Asian cases as guides to development

[2] Less publicised endeavours in public health and vaccines, also showed innovations for local applications. In many cases firms appear to have innovated because of a hard-budget constraint or because of a scarcity of appropriate materials. This "resource-constrained" innovation needs mention since the economics field tends to associate an abundance (or at least deliberate investment) of resources as a pre-requisite for innovation

seems to lie more in the variation in paths across the cases rather than their similarities as various authors have recently suggested. However, there has been not enough attention paid to the conditions that are often seen as exceptional, but perhaps more correctly are the rule: i.e. changing international dimensions of technology, trade and current events that proscribe the path of many developing countries, such as bi-lateral trade opportunities, WTO rules, specific national events such as legal battles with foreign firms, or technological choices gone bad. In the desire to show clear-cut causality between event and outcome, models run the risk of minimising the role of other changes in the environment.

7.4 Bringing the State back into the Process: new imperatives for old actors

While the Indian story indeed shows that State intervention was a crucial determinant of early capability, it also demonstrates that international changes, particularly export markets through regulatory and procurement-driven upgrading, have since shaped the path of leading firms and their innovation effort. The pharmaceutical industry and biopharmaceuticals have witnessed dramatic shifts in market structure and technologies. While it is certainly true that national policy measures do matter, the Indian case shows that at different times, past the traditional 'infant protection' phase, international policies-such as the Wax-Hatchman Act in the US, arisen as a US-based national policy measure, or international public health procurement, have been equally important in structuring environments for selection and learning, and not just as 'shocks' to the learning system. But the findings of external environmental influence and selection, does not weaken the importance of national policy, far from it. Indeed, the data demonstrates that early skill-building and capture of the large domestic market, driven in large part by Indian industrial and health policies, were critical to the eventual growth and export-push of Indian firms.

The story of building technological capabilities in the private sector has been neither a simple dichotomy between import-substitution and export-orientation, nor one of the public versus the private sector. In particular, economy-wide liberalisation has spurred both greater exposure to foreign markets, regulations and competition, but also created new needs for old relationships with the State R&D apparatus, and for new roles for the State itself to build legitimacy with the private sector. In the early years, firms sought the State's expertise for sourcing technology, upgrading and for procurement. Public health policies and public labs provided the initial means for technological advance through formulations and key public health drugs. Public labs were sources of highly trained workers and tertiary education policies augmented this. Government policies structured competition to aid latecomer firms and create roadblocks for MNCs in the local market. The Indian government's process patent regime was a deliberate attempt to move nationally owned firms into technological innovation. However, patent law, although usually seen as such, was not the only driver, since almost all countries had the same patent regime for some or most of this century.

In later years, the role of the State diminished in pharmaceuticals and the early technological learning led to Indian firms moving in sequenced stages abroad and then seizing generic drug opportunities in the highly lucrative, but competitive US market. With the advent of biopharmaceutical opportunities, early investments in State research laboratories and universities paid off in part by creating a pool of skilled labour available to work on recent biotechnologies. Relatively reticent in the intermediate export phase, the State has re-emerged in the genomics and post-liberalisation era as a partner for firms seeking to upgrade and re-defining itself as a supplier of technologies, skills (scientists), managers and infrastructure in the presence of a better articulated demand from Indian companies and facing pressures of its own. Overall, for both synthetic and biological pharmaceuticals, public domain and industrial research have been driven closer together.

However, with uncertainties in regulation, with rapidly changing tools and applications, biopharmaceuticals in India is largely relegated to niches such as vaccines, some diagnostics and "bio generics" (possibly the most uncertain of them all). Thus, while the State has not always been necessary, its role in innovation has been to create a base for R&D in the public sector and attempt (not always successfully) technology transfer to private firms. While the US market has led the demand and created the ultimate market, the State and local firms have been pushed together to find ways to retain the domestic market at the same time that they strive to become more competitive globally.

Corresponding to the learning taxonomy, there have been three diffuse phases of State response to the state of technological capabilities within the private sector. First, State involvement structured the initial entry and foray into a vast array of essential drugs. This period of *induced* technological upgrading in public health as an entry point was a necessary component of transferring domestic market dominance into Indian-owned hands and induced large firms as the leading innovators. Second, growing private firms did not build capabilities pushed by the State alone. They themselves were agnostic about the most appropriate path, choosing a combination of in-house R&D for reverse engineering as well as novelty, joint ventures and inward licensing. In fact, just as the pressures to stand on their own were mounting, the State apparatus for transferring technologies and the private sector's capacities to absorb or commercialise them were severely mismatched. Since the focus (and pressure) at all times was to move into more highly value-added segments, this required product differentiation capacity, which arose from *necessary* technology investments in process development. Again, while Indian-based foreign firms had access to the same skilled people and superior sets of technologies, Indian patent and production laws and price controls acted to create indigenous capability for Indian-owned firms. In particular, they unwittingly

created immense incentives for process development and export. Thus, while export-led learning was desirable in itself, it does not appear to have arisen due to any concerted policy push. Third, export markets have been a constant allure, but Indian companies initially lacked the capabilities to enter the most regulated of them. The State was able to structure the initial capabilities, but not the outward push. Here, both firm-initiated strategies (US generic drug market), and international procurement policies (from WHO and UNICEF) created regulatory sequencing in tiered markets and created appropriate conditions for voluntary technological upgrading. While some Indian-based foreign firms have been able to use these public health procurement opportunities, most did not export from India to the US for the generic market. In recent years, more foreign firms have adopted similar strategies for local production. Thus, in the long term, Indian-owned firms will have to differentiate themselves from these other contenders.

While its record at technology transfer from PRIs to firms was relatively dismal, and its ability to meet its production targets for certain categories, or reward innovations-by assistance to commercialise- when they arose were even worse, overall, it managed to increase domestic competition (even in the relative absence of foreign firms), increase technological levels of capability, secure key technologies (through the process patent regime) and keep costs down. In particular, process capabilities in chemistry and engineering are now firmly established, making some sub-segment of Indian firms innovative, many attractive contract research and contract manufacturing partners worldwide and creating considerable opportunity in explaining laterally along the pharmaceutical value chain, linking in clinical actors- hospitals, laboratories etc and bio informatics/computational biology experts.

However, in the biopharmaceutical and broader biotech realm, this form of success came less easily. Firms had neither clearly defined technologies, the time to learn (technologies were changing too rapidly in the West), nor the need for close ties between science and commercialised technology suddenly came to the fore. The weaknesses of the State infrastructure in supplying relevant technologies to firms, and the limited abilities of the latter to receive absorb, adapt and improve them were suddenly visible. However, the timing of the molecular biology revolution corresponded well with India's own opening of the economy and considerable realignment of priorities of its public research apparatus. Nevertheless, viewing economic advance as driven by policy goals alone hides the adaptations by firms (and the individuals who comprise them) to changes, expected and unexpected, in the environment.

7.4.1 Revisiting the Infant-Industry: protection and competition

The early selection environment, which governmental policies certainly influenced, has been discussed most often in the developing country literature in terms of biased weighting in favour of indigenous firms and infant industry protections that were undeserved. While the record of state protections to young industries is mixed, the Indian pharmaceutical history suggests that variants of traditional protections may be helpful in understanding how government policies can assist a young industry. The demand that the State-and international agencies- can generate through technology procurement programs particularly those linked to public health in this industry, may be a powerful stabilising factor that diminishes uncertainty and provides legitimacy to firm-level search efforts. These however can only assist long-term learning if they are closely linked to upgrading requirements and strict standards.

Could Indian firms have been induced to even greater technological levels of mastery and higher orders of competition? Quite likely. In some cases such as price regulation, export planning and technology transfer between public research institutes and private firms, Indian State attempts were clumsy at the best, and undermined future technology absorption at worst. However, the end result is that despite the problems of commercialization of key technologies and in under-supply of certain drug segments because of price controls, the Indian industry is robust, the Indian market is highly competitive and leading Indian firms are becoming global firms in market reach. In particular, the entry points of public health drugs and the deliberate exclusion of foreign firms from the Indian market appear critical in the history of Indian pharmaceutical capabilities. In the case of biopharmaceuticals, many companies arose from similar histories, or drew on similar sets of talent and infrastructure in the public research institutes and from other private firms. While Indian tertiary education policies were de-linked from this capture process, they were nevertheless central to galvanizing an entire industry on cheap, but highly skilled labour.

The reason Indian firms may have escaped stagnation during protectionism, is perhaps because a healthy prior level of competition existed in the industry, and the profit margin increases promised abroad lured such firms to each different 'level' of selection. In particular, access to the highly regulated US market through a hierarchy of less regulated markets has encouraged Indian firms to innovate, speed up, increase quality, and scale up operations and exports. An important lesson from this story is that export opportunities for developing countries will continue to be an important source of learning. The extent to which these markets remain open to exports from these countries is a contested area, however.

7.5 The importance of technology-specific prescriptions

Characteristics of the technology need far greater attention. Past economic studies, even from the institutional school, have tended to treat policy prescriptions, and the role of the State, relatively independent of how the technology varies. Despite the industry's gains and the learning by firms, there are some limitations to how broadly this path can be generalised. First, pharmaceutical and biopharmaceutical regulations are highly specific to the industry. The multi-tiered "stages of growth" that so characterise the pharmaceutical story of this thesis is difficult to replicate. Yet, the lessons to be drawn from this research for developing economies are broader than this. Entry/capture points, tiered learning and supports to indigenous firms in both mature and emerging technologies can be internalised into other industries, as can the role of public supports for developing process capabilities industry-wide. Technology-led variation in policy prescriptions should be clear. In the case of antibiotics, for example, Indian firms have continued to manufacture, albeit with limited innovation, but are now in a position to make gains from the exit of many global firms from this segment. Furthermore, niche areas, such as studies relevant to the Indian sub-continent (or other developing countries), require different types of promotional policies than do those competing in the world market against large multinational firms. Even in biopharmaceuticals, the extent of supports needed for small, innovative firms, requires different forms of agility and responsiveness from public research efforts than does pharmaceuticals as a whole.

In biopharmaceuticals, the path was different: From reagents to fermentors, quality control raised serious problems and the cost of demonstrating bio-equivalence, combined with a hazy regulation climate, created learning problems for firms. In addition, the field of biological research and emergent tools forced industry to look closer to the scientific originators in universities and PRIs. Problems of coordination between science and industry became pronounced. While learning by doing was done through repeated process innovation in natural and synthetic pharmaceuticals, biopharmaceuticals was in essence a process and nothing else. Species specificity, manufacturing environment and quality problems were severe. The regulatory uncertainties were exacerbated by closer time horizons. Thus tiered export markets dependent on clear regulations and capture of the home market, were simply not existent in the same fashion. Similarly, multidisciplinary challenges are significant.

Variations across technology in the paths of learning can be partly attributed to uncertainty, which arises because of new technologies, difficulties of technology transfer and new regulations and information constraints. Secondly, assured market access linked to technological upgrading such as the procurement policies for vaccines, for example, becomes a critical component of this learning for some firms. It minimised uncertainty and boosted firm-level investments in in-house R&D. Yet, this is not simple

protectionism. This sequential challenge allowed significant learning and sustained lessons from one market to the next more highly regulated one. Firms straddled multiple tiers at once and did not necessarily have to move out of one before they entered the next.

In the age of TRIPs, the policy challenge becomes noticeable. Once product patents are introduced, the demarcation may become evident, between innovative process capable firms and all the rest. However, policy makers still have a few cards up their sleeve. If the growth of indigenous firms is indeed a national goal, then protections from foreign competition at the early stages of firm growth can only occur under rules of relatively high domestic competition where firms are kept from technological stagnation.[3] The interview and archival data indicates that the rules of the competitive selection mechanism can be structured to favor technology upgrading. First, the government should be particularly focused on making market opportunities available and attractive to Indian firms. International and national public procurement is one path, where high-quality output and R&D investments are rewarded, as are creating other export markets. Second, public research institutes could be far greater assets to indigenous firms than they have been, with difficulties on both the public and private side. A "Mission mode" goal for scientific and technological challenges in the health sectors is another means to galvanize public support, private investments and interest and State funding, expertise and infrastructure. Thirdly, "demand" pull through public funding (successful in the US case) could fashion innovation even in mature segments where large MNCs are pulling away, and where explicit exclusion of foreign firms may not be necessary (and difficult under WTO rules). Finally, although far more challenging from an international foreign policy perspective is to fashion educational, R&D and other institutional supports to develop process skills despite TRIPs. Indeed, although many have written TRIPS off as a completed chapter, this dissertation raises questions of the appropriateness of such homogenization policies given the diverse industrial and learning pathways in the single country case and two sectors. The research emphasises the inappropriateness of trying to "catch up" or treat developing countries as perpetual 'latecomers'. External regulatory triggers to upgrade cannot have much value unless the developing country has some level of indigenous institutional structure to propel firms to be competitive.

[3] Even acknowledging that leading firms still had some monopoly power in their respective sub-segments, the vast majority of manufacturers still appear to have been faced with considerable price competition.

Conclusions

Despite the evidence that Indian companies had a historically low rate of R&D investments, started by "copying" on-patent drugs (legal in India) and moved on to generic drugs, many faced high competition, at home and abroad, low cost but high quality requirements and high speed needs.

Current debates, which either analyse the technological advancement of developing countries primarily in terms of intellectual property regimes, suggest that the only vehicles of innovative technology are foreign (Western) firms, or that only long histories of high R&D spending by firms result in innovative industries, entirely miss the significance of India's trajectory of technological upgrading. Those that argue that the main opportunity for developing countries is merely through cost cutting in mature segments miss the evidence of Indian innovation even in mature product lines. The selection environment in which these technological capabilities were acquired cannot be divorced from national visions of socio-political and economic advance, nor can they be uniform over time and countries. Various environments selected for and honed process capabilities further. Details of the technology need to be brought back into economic discussions of markets, States and technological learning since roles and structures of any institution are difficult to generalise across technological challenges. The research findings imply that industrial development can emerge from a variety of technological entry points and these can be strategically structured by supporting public policies, particularly in procurement. Indeed, at least three broad types of learning for process development capabilities have taken place, reflecting the selection environment of the time.

India's introduction of product patent laws in 2005 has also created pressures on firms to build in-house R&D capabilities and search locally for profitable alliances with public-domain research institutes. Current weaknesses are the relative numbers of innovative firms to those that compete on cost alone. Furthermore, India's low-cost advantage for the innovators is predominantly in R&D (costs of scientists/engineers) and this will erode when more MNCs enter the market and woo this low-cost high-skilled labour. The strengths of the industry besides the innovative capabilities, are the sheer number of manufacturers, increasing numbers of internationally certified facilities, contract manufacturers, contract R&D service providers and public health suppliers to international agencies and foreign governments.

Imitation by itself with no parallel in-house process or product innovation is unlikely to be as successful a strategy. Companies that are truly innovative in processes are always on the lookout for product

innovations. There is no clear dichotomy between companies that are product developers/ "true" innovators, supposedly, and those that are process developers. I.e. imitators eventually do become innovators, but even imitators are innovators some of the time. Importantly, a strong historical component of innovators' work has been imitative themselves of others. Furthermore, "older" technological capabilities often gave rise to rapid advances in areas with new technological product opportunities.

There are continuing weak links in the innovation chain. In particular, both industries suffer from small numbers of firms with significant potential for high quality discovery or development and manufacture. The pharmaceutical industry is particularly skewed in terms of the numbers of innovative firms to the huge number of drug manufacturers predominantly following well-beaten paths. The extent to which the numbers of innovative firms and high quality manufacturers rise, the more likely that Indian industry can continue to adapt and overcome challenges posed by their future selection environments. Indeed, it will also dictate the extent to which they shape these environments as well.

The research indicates that process capabilities should be seen as a vital set of skills integral to advances in both processes and products in the industry, and not analysed primarily as a unit of intellectual property protection. Secondly, "catch-up" frameworks appear not to be wholly useful in studying technological advance. In this industry, many niche areas of expertise were historically driven and have created specific strategies for learning that are dependent on local skills and past policy choices. Finally, public health access debates should be broadened to address firm-level learning opportunities and procurement policies for developing countries. Indian history shows that these debates are intertwined.

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