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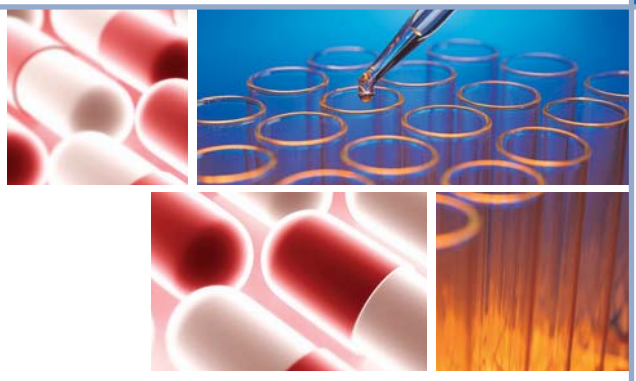

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PHARMACEUTICALS

Can India and China Cure the Global Pharmaceutical Market?

KAUFFMAN
The Foundation of Entrepreneurship

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Overview:
Globalization of innovation — industry by industry

Industries are often thought of in terms of the nations that have launched the greatest innovations. There is a perception of a U.S. automotive industry pitted against a Japanese industry, for example, or the U.S. pharmaceutical industry against the European industry. Globalization has, however, rapidly changed the underlying nature of these competitive relationships. As in the personal-computer industry, where components are designed and developed worldwide and manufacturing is largely performed in China, most knowledge-intensive industries have become modular.

Basic supply chains and distributor networks are today becoming increasingly fragmented. They are now characterized by a diversity of business models, a multitude of players, and a global footprint. Like a set of building blocks, these business components can be reconnected in different and sometimes surprising ways. Mass communication, low-cost computing, and global talent have enabled small- and mid-sized corporations to act in capacities impossible only a decade ago. Countries like India and China have been major beneficiaries of this trend. In certain industries, these nations are on the way to becoming hubs of research and development for the global market.

The Global Engineering and Entrepreneurship project at Duke University has been focused on the effect of globalization on the engineering profession and the sources of U.S. competitiveness. We have researched topics including engineering education in India, China, and the U.S.; the reasons engineering and technology companies are going offshore; the effect of immigrants on the U.S. economy; intellectual-property creation and entrepreneurial activity in the U.S. To better understand the globalization of innovation, we looked in-depth at several knowledge-intensive industries in India and China, the major countries undergoing the swiftest change.

We have researched the globalization of several industries by analyzing the shift of intellectual-property creation through global patent filings, economic data, global value-chain analysis, and extensive field research. The analysis of patent and economic data provided some useful insights, but we believe that our field research was the most effective method for understanding the globalization phenomenon.

We will present our field analysis in the context of the industry global value chains we defined. For this research, we made several trips to India and China and interviewed the executives of approximately 115 firms in the pharmaceutical, semiconductor, automotive, aerospace, cell-phone, and computer-networking industries. We toured their research labs, met heads of research and development (R&D) and local researchers, interviewed customers, and reviewed many of the technologies under development. We also interviewed academics at several universities and government officials in the local regions.

Here we present our analysis of the pharmaceutical industry, incorporating a value-chain analysis and company summaries of 16 Indian and Chinese pharmaceutical firms that highlight current business trends and transformations.

Summary of findings

Multinational corporations are searching for means to broaden their capacity for drug development while decreasing costs. Pharmaceutical firms in India and China are increasingly forging partnerships with these corporations to gain revenue and to develop their own expertise. These relationships largely appear to be symbiotic.

As a result of the movement of R&D to their countries, Indian and Chinese scientists are rapidly developing the ability to innovate and create their own intellectual property. Several firms in India and China are performing advanced research and development and are moving into the highest-value segments of the pharmaceutical global value chain.

What is noteworthy is that most of the advances in R&D in India and China happened over the last decade with the greatest momentum being built over the last five years.

Global pharmaceutical intellectual-property creation

In 2006, 5.5 percent of all global pharmaceutical patent applications (WIPO PCT applications) contained one inventor or more located in India, and 8.4 percent contained one or more located in China. This increased fourfold from 1995.

Business relationships

Despite issues with intellectual property, multinationals are finding greater scope for cooperation with several companies in India and China. They have developed a broad range of relationships, which generally seem to have been successful and to be expanding in magnitude and scope. These include:

1. **Original proprietary research**: Several Indian and Chinese firms are developing their own proprietary drug products targeting global or regional markets, but they lack the ability to advance a drug through the entire clinical-trial process and market them worldwide. These companies seek licensing agreements with, or make complete drug sales (i.e. inclusive of supportive clinical data) to, multinational pharmaceutical companies that have the necessary resources.
2. **Research partnership**: In these relationships, a multinational corporation supplies a research partner with an early- or mid-stage drug candidate and contracts the partner to develop it further. The domestic firm gains access to a novel compound(s) and potential assistance from its multinational partner, which in turn expands its own drug-development capabilities. A number of these deals involve cost and risk sharing in exchange for joint ownership of the intellectual property.
3. **Contract research organizations (CROs)**: These firms are typically contracted to perform specific stages of drug discovery, development, or testing, and receive a fixed payment upon reaching a predetermined milestone. Companies using this model do not assume any of the risk, positive or negative, associated with drug development. Several companies in India and China are specializing within specific disease types or within specific functional areas of the pharmaceutical value chain.
4. **Generics, APIs, and manufacturing**: India (and to a lesser extent, China) has a vibrant generics and active pharmaceutical ingredient (API) market. Companies that focus on this market carefully monitor the intellectual-property protection of major drug products. When a product comes off-patent, they explore means of mass-producing the drug using identical or similar chemical reactions.

Value-chain activity

1. Indian and Chinese companies are making strides in the highest-value segments of global value chains. In the lower-value segments, such as preclinical testing, animal experimentation, and manufacturing, however, Chinese firms appear to be more prevalent.

2. India is regarded as a more mature destination for chemistry and drug-discovery activities than China.
3. Domestic Indian and Chinese firms rarely have the capital and the regulatory expertise to develop a drug beyond phase II clinical trials. Their commercial development of new intellectual property therefore necessitates relationships with major multinational corporations.

Examples of Pharmaceutical Opportunities in India and China

1. Indian and Chinese firms, including Dr. Reddy's Laboratories, Glenmark, WuXi PharmaTech (NYSE:WX), and Hutchison MediPharma, are developing proprietary drug candidates, with the intent of forging marketing partnerships with pharmaceutical multinationals. Glenmark has already successfully completed several licensing agreements.
2. Dr. Reddy's Laboratories can conduct preclinical trials for 40 to 60 percent less than the cost of comparable activities in the U.S. Similarly, Aurigene can conduct chemistry work for a quarter of the cost.
3. After Eli Lilly was unable to collect a series of specific human tissue samples in the U.S., the firm contracted ShanghaiBio, which was able to collect 100 relevant samples in China in the course of three weeks.
4. In the U.S., tissue collection can cost as much as USD 2000 per sample. In China, this can be accomplished for around USD 300 per sample.
5. Pharmaceutical multinationals have begun partnering with Indian firms to conduct fixed-dose-eruption skin-reaction tests. Competition has now significantly reduced the cost of this work, from USD 80,000 to approximately USD 30,000.
6. In China, employees holding PhDs from top universities can be hired for salaries of around USD 15,000 per year.
7. By developing drugs and selling them in markets without product-patent enforcement, Cipla, an Indian pharmaceutical firm, has been able to provide anti-AIDS medication to India and Africa for around $300 per patient per year, one-fortieth to one-fiftieth the cost of competing treatments.

Other observations

1. Indian firms appear to be able to attract U.S.-educated and -trained scientists and engineers more readily than their Chinese counterparts.
2. In both India and China, a number of pharmaceutical firms competing for regional generics markets aspire to enter new-drug development in the next five years
3. Despite a leap in the number of clinical trials in India and China, the total numbers remain small compared with the U.S. and Europe. As of late May 2008, the National Institutes of Health's clinicaltrials.gov identifies more than 56,000 studies worldwide, including32,410 in the U.S., 750 in China, and 670 in India. These figures include current and completed clinical trials. When it comes to current clinical trials alone, the London-based Business Monitor International (BMI) in *Asia Pacific Pharma and Healthcare Insight* (May 2008) ranks Japan first in the Asia region with 406 studies, followed closely by China (389) and India (347). As recently as November 2007, BMI gave China a slender 274–260 lead over India in current clinical trials.
4. India's Planning Commission is claiming in 2008 that India is overtaking China in number of recent clinical trials, but the jury is still out.

Introduction: The pharmaceutical industry

The creation of a new drug requires significant capital investment. Pharmaceutical companies in search of novel drugs or means of treating documented symptoms must navigate pitfalls in early drug discovery and meet regulatory criteria for clinical trials. Food and Drug Administration (FDA) regulation of drug development makes the discovery cycle one of the longest of any industry: it is not unheard of for a decade to pass between an initial drug discovery and commercial availability.

To add to the industry's woes, a number of established blockbuster drugs held by major pharmaceutical companies will go off-patent in 2008 and 2009, leading to a sizable decrease in revenues amidst mounting competition from generics producers.

In 2005, the largest ten pharmaceutical companies by market share controlled more than 42 percent of the global pharmaceutical market, as opposed to a 30 percent share ten years earlier (Bertoncelj). This can be attributed mainly to consolidation through mergers and acquisitions. In 2007, their market share had fallen four points, to 38 percent. Table 1 lists the top ten sales leaders in 2007 according to the annual survey of *Pharmaceutical Executive* magazine (May 2008).

Table 1: Top ten global pharmaceutical firms — 2007 global sales

Rank	Company	Global sales	Global Market-share percentage
1	Pfizer (USA)	USD 45.1 bn	6.3%
2	GlaxoSmithKline (UK)	USD 39.2 bn	5.5%
3	Sanofi–Aventis (France)	USD 37.4 bn	5.3%
4	Novartis (Switzerland)	USD 29.5 bn	4.1%
5	AstraZeneca (UK)	USD 25.7 bn	3.6%
6	Johnson & Johnson (USA)	USD 23.3 bn	3.3%
7	Merck (USA)	USD 22.6 bn	3.2%
8	Roche (Switzerland)	USD 16.9 bn	2.4%
9	Wyeth (USA)	USD 15.7 bn	2.2%
10	Eli Lilly (USA)	USD 14.8 bn	2.1%

The contribution of emerging markets to global industry sales growth has increased from 13 percent in 2001 to 27 percent in 2006. Particularly strong growth occurred in China (by 15.9 percent), India (14.0 percent), South Korea (11.9 percent), and Brazil (10.9 percent) (Standard & Poor's, 2007). Though smaller than established western and European markets, emerging markets are becoming increasingly important. With these changing market dynamics, pharmaceutical multinationals are updating their strategies and business models to pursue new relationships with firms in emerging markets.

This paper will explore the role that India and China, the fastest-growing markets, play in the pharmaceutical industry. See Appendix A for definitions of some of the technical terms used.

Global value chains: an introduction

A value chain is the series of related activities that contribute to the production and delivery of a specific product or service. These activities include design, production, marketing, distribution, and support. Much of the contemporary value-chain literature has focused on mapping out global production and sourcing networks that link leading manufacturers, retailers,liter and marketers to their suppliers located around the world. However, the newest phase of globalization involves setting up and managing innovation and design networks across countries in different regions of the world. The value-chain framework helps us understand the structure and dynamics of these global innovation networks.

As companies' understandings of industry dynamics have matured along with their own core competencies, more complicated value-chain relationships have emerged. Today, value chains in many industries include various players in diverse countries. The effects of production facilities, design centers, and distribution channels on each other are tightly controlled and managed internationally. The rising complexity of these value chains has brought significant new opportunities and vast challenges. Global value chains have enabled corporations to take advantage of international talent, expand research and production capacity, and reduce development periods. But there are risks as well as rewards: through global diversification, control over specific tasks is diluted; loss of intellectual property becomes a greater concern; stage connectivity is threatened; and global trade regulations add new layers of restrictions. Relationships of power, control, and interdependence illustrated through global value chains are shaping the future of domestic and international business.

In recent years, the concepts of value-chain modularity and fragmentation have emerged as a way to explore the physical separation of interdependent value-chain stages. Though the uncoupling of value-chain stages is not a new phenomenon, its growing international focus represents a departure from previous industry trends (Arndt, 2001). Recent mass "offshoring" and "outsourcing" of specific functional groups within business units effectively demonstrate both value-chain modularity and international value-chain governance. In the global economy, this disintegration of production has led toward an integration of trade (Feenstra, 1998). Multinationals today employ modular value chains in an effort to take advantage of emerging markets, international talent pools, and global trade.

Research in the last decade has suggested that the geographic dispersion of multinational activities has acted as a source of knowledge creation. The decentralization of R&D and innovation activities is commonplace among large businesses today. Though a significant portion of innovation work remains tied to a corporate headquarters, the draw of human capital, and to a lesser extent market and technology access, are major drivers toward international fragmentation.

The internationalization of R&D and innovation activities requires a substantial commitment of resources. Though commonly used to eliminate or reduce the need for product localization, R&D internationalization has also increased the spillover of valuable technology competencies to local competitors. A critical factor in the success of a fragmented R&D network has been the efficiency of endogenous technology transfers between distant branches (Sanna–Radaccio and Veugelers, 2007).

Though value chains and supply networks are often represented as orderly progressions between distinct tasks or functions, these relationships are rarely one-dimensional. *Vertical movement* in traditional value chains is the progression of a product through its sequential development and production cycle. In contrast, through *horizontal movement*, companies explore opportunities to pursue relationships with outside firms in similar stages of the value chain. Horizontal movement could lead to new markets, cost-saving partnerships, or innovation opportunities. Finally, *diagonal movement* seizes integrative opportunities in other value chains and even in different segments. Diagonal connections may be used to mitigate risks or identify new applications (Pil and Holweg, 2006).

The pharmaceutical global value chain

A global value chain is the series of related activities carried out between and within firms that contribute to the production and delivery of a given product or service across national boundaries. The pharmaceutical value chain is characterized by *drug-discovery and drug-development* activity, to identify promising pharmacological candidates; *clinical trials*, to demonstrate the safety and functionality of these drugs in human subjects; and *manufacturing*, to mass-produce approved drugs through scalable high-yield chemical reactions. The sequences of these stages can be found in Figure 1.

Drug discovery and development

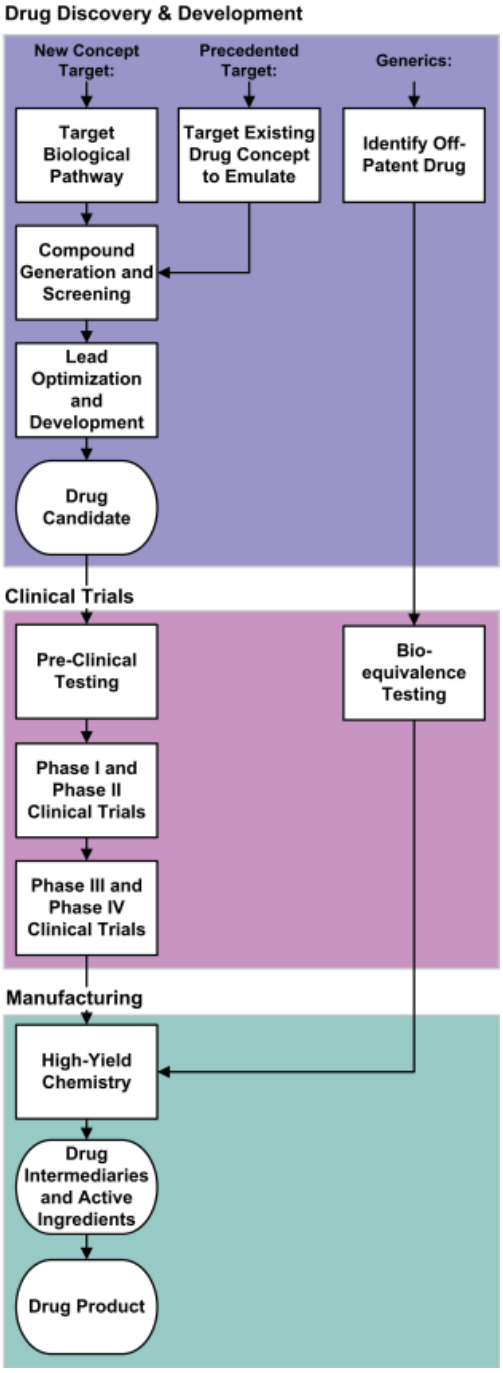
New pharmaceutical drugs largely fall into one of three distinct categories: *new-concept drugs*, *precedented drugs*, and *generics*. A *new-concept drug* is the *first* molecule designed to address a particular drug target. Drug targets are typically defined by a series of reactions leading to a disease or condition that can be affected through treatment. New-concept drugs are the most expensive to develop; in many cases, they depend on new research lines or biological-pathway models.

The majority of drugs actively in development can be classified as *precedented drugs*. These drugs rely on scientists' understanding of a documented drug target and the related functionality of existing drugs.

Finally, the manufacture of *generic* drugs uses the publicly available intellectual property documenting existing compounds that no longer qualify for patent protection. Generics markets vary significantly internationally, necessitating special efforts to abide by national laws that govern their distribution and sale.

Drug discovery and development for new-concept and precedented drugs is a complicated and iterative process. The first step is the identification of a drug target. This usually involves locating a specific series of biological events related to a disease

Figure 1: The global pharmaceutical or pharmaceutical global value chain



process. Identifying this series allows researchers to predict means of emulating, disrupting, limiting, or otherwise affecting that particular pathway. Researchers then engage in *compound generation and screening*, a process in which many biological compounds are collected and tested for any effect on the drug target. The compounds with the largest potential effects undergo *lead optimization and development*, a complicated non-linear cycle of chemical enhancement. Ultimately a *drug candidate* is produced.

Clinical trials

The FDA requires that a series of demanding clinical trials demonstrate a drug candidate's toxicology, efficacy, and specificity.

Preclinical testing monitors the effects of the drug when it is assimilated into a biological system, and is performed on animals and through laboratory tests.

Phase 0 clinical trials (not shown in Figure 1) are an optional first round of tests on human subjects and involve the delivery of very small drug quantities, called microdoses. These tests are designed to eliminate poorly performing drugs early and may obviate phase I.

Phase I clinical trials are generally conducted on a small body of healthy volunteers to test a drug candidate's safety and biological effects on humans.

These are followed by **phase II clinical trials**, designed to assess drug functionality and build upon safety findings obtained from phase I trials. Phase II trials are conducted on larger patient groups and gather information on the efficacy and safety of various dosages.

Phase III trials often represent a bottleneck in clinical trial development, as these are the most costly, time-intensive, and complex to run. They involve patient groups of hundreds or thousands of volunteers, depending on the target condition.

Phase IV clinical trials track a drug candidate for long-term safety effects after a drug has been approved for commercial sale.

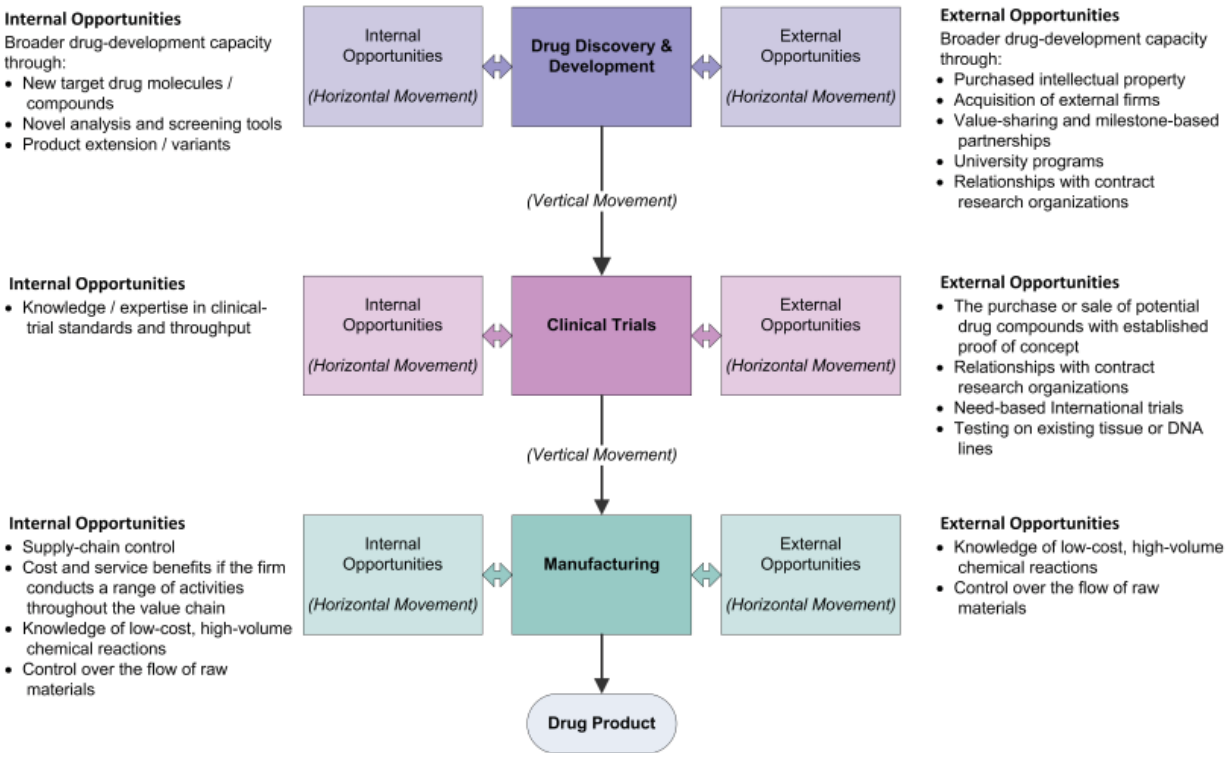
Manufacturing

To deliver a potential drug from a laboratory or small-scale testing environment to national or international patient populations requires reliable control of chemical reactions and manufacturing dynamics. In mass production, raw materials are combined in *high-yield chemistry*. Identifying scalable, simple, cost-effective chemical reactions by which to produce large quantities of a target drug is essential. These reactions produce *drug intermediates* and *active pharmaceutical ingredients* that are the building blocks of finalized drugs. Some pharmaceutical manufacturing companies mass-produce these intermediate components for consumption by other pharmaceutical entities. Through further processing and additional chemical reactions, a final *drug product* emerges for distribution.

Vertical opportunities in the pharmaceutical value chain

In the previous section, we outlined the stages involved in the pharmaceutical value chain, covering progression through *drug discovery and development*, *clinical trials*, and *manufacturing*. A drug candidate's development often proceeds linearly, but pharmaceutical corporations can extract maximum value from this chain by searching for vertical opportunities present in competing or partnering firms. These possibilities appear in Figure 2.

Figure 2: Vertical pharmaceutical opportunities



Within drug discovery and development, a number of internal and external opportunities exist for companies to enlarge their populations of candidate drugs. Internally, new-concept drugs or precedented drugs can be identified through novel and existing analytical and screening tools. Similarly, product extensions or variants can be created based on existing drug families with aging intellectual-property protection (patent evergreening). Drug candidates can also be acquired externally through corporate acquisitions; the purchase of promising intellectual property; or research programs with universities. Many large and multinational corporations have also begun engaging contract research organizations (CROs) to develop low- and mid-priority drug candidates. Finally, in an effort to minimize the increasing costs of discovery and development, large pharmaceutical companies are turning to value-sharing and milestone-based partnerships with trusted small- and mid-sized pharmaceutical companies in developing countries.

Internal and external opportunities also exist in time- and cost-intensive clinical trials. Pharmaceutical companies with prior experience in navigating FDA clinical trials and international regulatory agencies routinely use their staff's knowledge and expertise in clinical-trial standards to maximize efficiency in order to expedite drug

approval. The trials' high costs have encouraged the formation of new business relationships and external services designed to mitigate them. A business approach popular with small- and mid-sized pharmaceutical companies is to develop drug candidates through proof of concept, in an effort to maximize the candidate's value before selling its intellectual property to a larger corporation with the financial resources to navigate phase III clinical trials. CROs and need-based international clinical trials are also emerging as means to reduce the cost of the clinical-trial process.

Storm over intellectual property

Big Pharma has harbored a special fear of the intellectual-property practices of India's pharmaceutical industry, which long exhibited a mastery of the market for low-cost generics in the developing world. Deutsche Bank's senior pharma analyst, Barbara Ryan, refers to the "cannibalistic effect of generic substitution." Indian generics manufacturing hardly stands alone in facing such indictments. Highlighting the expiration in 2001 of Eli Lilly's patent of Prozac, she notes that the drug "lost 90 percent of its value in several weeks when generic fluoxetine was introduced" (Gray, 2006).

On the front lines of controversy is Yusuf Hamied, of the Indian firm Cipla, the world's largest manufacturer of retrovirals. Former Glaxo CEO and Chairman Richard Sykes labels him a "pirate." Hailed as a hero in the developing world for bringing an array of cheap generics to the poor and desperately ill, Hamied, a chemist, counter-attacks that Glaxo should have been regarded as "a global serial killer" for prices more than 30 times higher than Cipla's HIV medicines. Glaxo was hardly alone in his indictment. Hamied accuses many other global firms of charging 40 to 50 times more than Cipla's line of retrovirals. With a family heritage close to the Indian independence movement and Gandhi himself, Hamied rails against a restrictive British patent law of 1911 that left a legacy of expensive imported drugs lasting into the early postcolonial decades, with prices in India exceeding those found in pharmacies across Europe. He fought back and says he is proud of Cipla's scope: "We have more products than any [drug] company in the world. More than 1000 for humans, and 100 for animals." A founder of the Indian Drug Manufacturers' Association, he successfully lobbied for the passage of the patent law of 1972 that ushered in what the *Financial Times* calls "a golden era for the country's generic companies" (Jack, 2008).

Hamied stresses that he is not an opponent of patents, but rather fights monopoly. Indeed in an e-mail he recommends "a system similar to the Canadian Bill S-91 of 1969", which grants a "payment of four percent royalty to the originator". Under pressure to conform to the norms of the Washington Consensus and the World Trade Organization, the Indian Government has thus far spurned his counsel.

Significant change is under way, as India adopted a stricter regime of patent protection in 2005. The law did not allow for a transition period and peculiarly is backdated to 1995, which Hamied regards as a grave injustice. Within the pharmaceutical industry, India previously gave protection to patents on the manufacturing process only; now the nation extends this to the patenting of drug substances. Still Indian courts reject patent protection on mere "incremental innovation", the process by which a patent is "evergreened" well beyond its 16-year allotted span. Angry that Indian authorities and courts refused patent protection for the leukemia drug Gleevec, Novartis has suggested that it will shift much of its investment from India to China. (Houlton, 2007) This may seem ironic, as many corporate leaders, at least in non-pharma industries, regard India as a safer haven for intellectual property than China. Ranjit Shahani, president of the Novartis Group in India, implores the Indian government to find alternatives to lax intellectual-property regimes:

> Tiered pricing, donation programs, public–private partnerships, and differential pricing are amongst the ways to meet the access challenge that are more innovative than diluting patents. Such programs can work, provided the government ensures that discounted drugs are not re-exported to countries that can afford to pay. ("Novartis's Ranjit Shahani…", 2008)

Defenders of Indian cooperation with stricter patent regimes argue that enforcement should generate the long-term investment in R&D that will yield blockbuster drugs and future cures. They fear that devotion to generics is a short-term solution that will keep India starved of R&D investments, which remain below one percent of GDP for all industries. China invested 1.34 percent of GDP in R&D in 2005, but the government seeks to nearly double that by the year 2020. If R&D growth can be sustained, technocrats in India and China will look for many more enterprises to advance on the global value chain.

Our findings

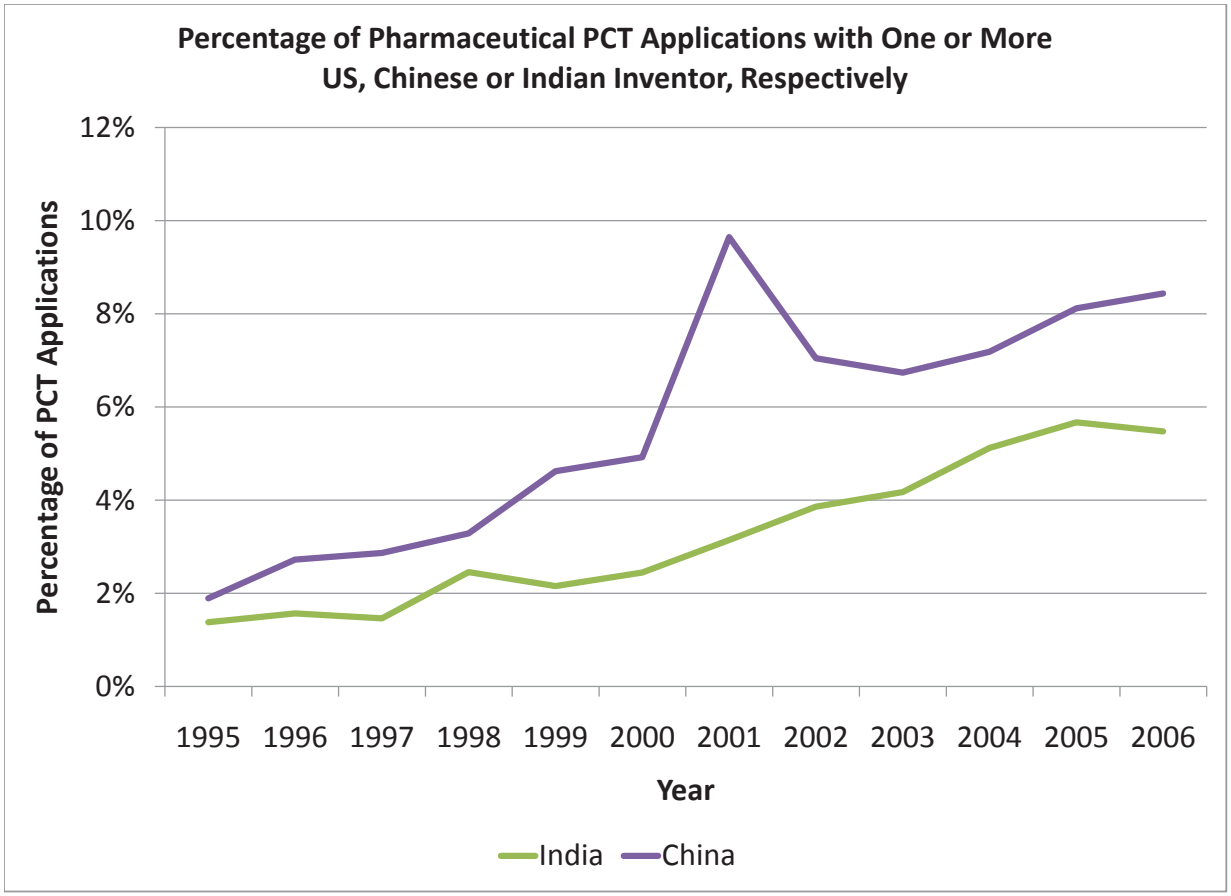
A series of 16 company summaries immediately following this paper's conclusion details the roles which a sample of companies in India and China are playing in the global pharmaceutical value chain. They also highlight the strategies and markets these firms are pursuing.

Our general observations are that multinational pharmaceutical companies, acting to broaden R&D activities without raising costs, are increasingly forging partnerships and research collaborations with companies in India and China. Business relationships vary significantly and include captives, partnerships, milestone systems, value-sharing, and direct buyouts. Some of these partnerships entail joint drug ownership and/or split-revenue arrangements rather than fixed milestone payments. The type of work assigned includes drug discovery, manufacturing, clinical trials, and generics production.

As a result of the movement of R&D to their countries, Indian and Chinese scientists are rapidly developing the ability to innovate and create their own intellectual property. This shift is evident in the increasing prevalence of Chinese and Indian inventors on global pharmaceutical patent applications. Their contributions increased fourfold from 1995 to 2006.

Figure 3 presents a time-dependent analysis of global patent applications filed through the World Intellectual Property Organization (WIPO PCT applications).

Figure 3: Global pharmaceutical WIPO PCT applications with one or more Indian or Chinese inventor



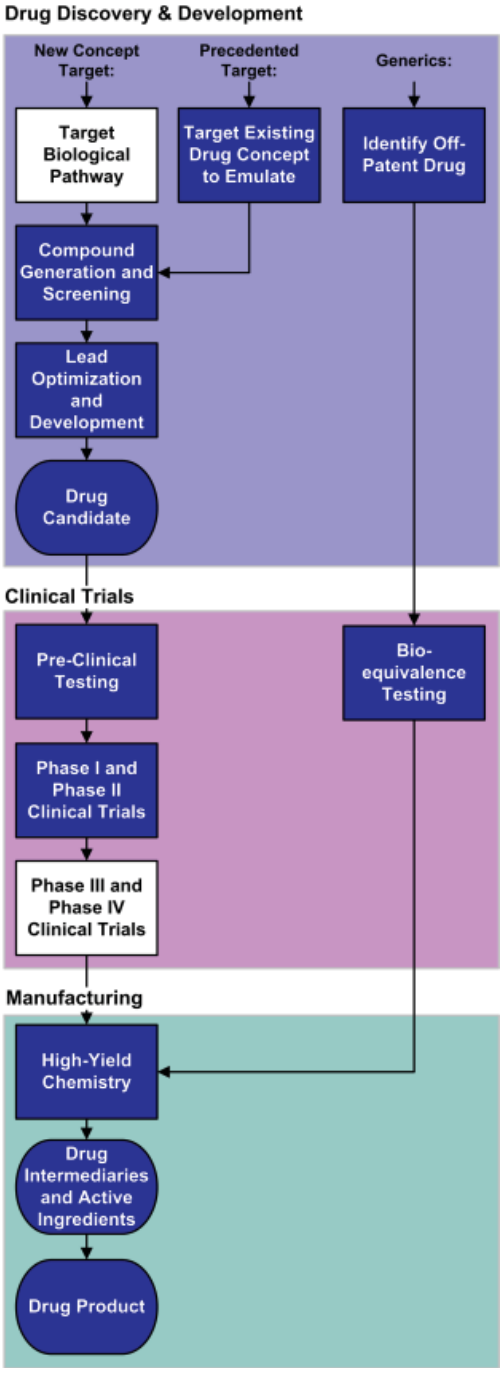
India and China in the global value chain

Indian and Chinese firms are increasingly occupying higher-value segments of the pharmaceutical value chain. Relatively few firms are engaged in the discovery and development of new-concept drugs, due both to the high initial capital investment such drugs require and to their high failure rate. Instead, many corporations are involved in the development of precedented drugs and generics. The large populations of India and China make both countries exceptional markets for low-cost generic drugs, and domestic companies that have succeeded in marketing them in volume are using the proceeds to fund drug research and development. These activities most often take the form of either internal development of precedented drugs or development of the drugs' intellectual property through partnership with a multinational.

Excluding multinational corporations' research divisions, we observed very few firms located in India and China with the personnel, capital, and expertise to successfully push a drug candidate through the entire clinical-trials segment of the pharmaceutical value chain. In virtually all cases, local firms required outside assistance to continue trials through phase III, which requires the largest patient pools, research periods, and capital investments.

Figure 4 indicates, using bold outlines, the stages of the pharmaceutical value chain in which domestic Indian and Chinese firms are most active. Value-chain boxes without bold outlines indicate no or little activity at this stage.

Figure 4: Pharmaceutical value-chain activity of Indian and Chinese firms



Business models and work complexity

The needs of multinational and emerging pharmaceutical businesses have created a symbiotic relationship in India and China. Multinational corporations are searching for means to broaden their capacity for drug-candidate development and decrease costs. Pharmaceutical firms in emerging countries realize that developing their own drugs or

partnering with multinational corporations will be their only means to gain access to the highest-value markets and technological expertise. This has led to a variety of novel pharmaceutical business models.

Original proprietary research: A number of Indian and Chinese firms are developing their own proprietary drug products for regional and global markets. These proprietary efforts are impressive for the range of capabilities and expertise they require throughout the pharmaceutical value chain. Drug target selection is based typically on a market or humanitarian need. They then navigate the complicated process of drug discovery and development, involving an array of chemistry, biology, and analytical skills. Often they advance a proprietary drug to proof-of-concept validation, which typically occurs at the end of phase II clinical trials. So validated, the candidate drug is more valuable, and often its owner seeks a licensing agreement with, or a complete drug sale (i.e. inclusive of supportive clinical data) to, a multinational pharmaceutical company with the resources necessary for completing its development and global marketing. Few companies in India or China have the financial capability or marketing skills to do this on their own.
In India, Dr. Reddy's Laboratories employed this strategy to internally develop a diabetes-inhibitor through phase II clinical trials. Similarly, the Chinese firm Hutchison MediPharma has developed a herbal-medicine extract to treat inflammatory bowel disease and a drug designed to be used in conjunction with radiation treatments for advanced head and neck cancer; both drugs are currently undergoing clinical trials. Ranbaxy is developing an anti-malaria drug, Arterolane (RBx 11160), which is undergoing phase IIB clinical trials.

Developing internal proprietary drug candidates is a costly, risk-prone venture. Many firms support this research by offering custom pharmaceutical services to outside companies or participating in the production of generics and APIs.

Research partners: A number of domestic Indian and Chinese pharmaceutical firms have emerged as research partners for multinational corporations. The most innovative of these relationships are based on value-sharing. Several firms have structured deals in which they receive royalty payments or partial ownership if a candidate drug reaches the marketplace. In these relationships, a multinational supplies a research partner with an early- or mid-stage drug candidate to develop further. The domestic Chinese or Indian firm gains access to a novel compound(s) and potential assistance from its multinational partner, which in turn expands its drug-development capabilities.

Examples of these value-sharing partnerships include collaborations between Ranbaxy and GlaxoSmithKline to develop a respiratory inflammation target, and between Advinus and Merck to develop a metabolic disease treatment.

Contract research organizations (CROs): CROs generally have a range of drug-discovery, drug-development, and clinical-trial capabilities and cater directly to the needs of their customers. Unlike a company developing an internal drug candidate or partnering with an outside firm, CROs have no vested interest in the research lines they are developing. A CRO is contracted to perform specific stages of drug discovery, development, or testing, and paid a fixed amount when a predetermined milestone is reached. It assumes none of the risk, positive or negative, associated with drug development. CROs typically become well-known for specializing within disease types or for their practical expertise in specific functional areas of the pharmaceutical value chain.

Generics, APIs, and manufacturing: India and, to a lesser extent, China have a vibrant market for generics and active pharmaceutical ingredients (APIs). Companies that focus on this market monitor the intellectual-property protection of major drug products. When a product moves off-patent, they explore means of mass-producing the drug using

chemical reactions identical or similar to those that produced the original. Bioequivalence testing is required in order to show the FDA that the generic form of the drug is functionally similar to the original.

These firms have a strong understanding of efficient, high-yield chemical reactions, as well as the ability to obtain necessary raw materials or to purchase outside active ingredients, drug intermediaries, or pharmaceutical products. Their manufacturing capabilities allow them to make high-volume sales to regulated and/or unregulated markets. Many pharmaceutical firms in emerging markets have generics businesses because of the relatively low barriers of entry associated with this work. Some have acquired the experience and expertise in generics chemistry and manufacturing to begin positioning themselves for drug discovery and development.

Depending on its size and complexity, a firm may leverage several of the above models. Table 2 below depicts the business models followed by the 16 pharmaceutical companies our research team interviewed for this study.

Table 2: Business models of interviewed firms

	High Value ←		→	Low Value
	Original Proprietary Research	**Research Partner**	**Contract Research Organization**	**Generics, APIs, and Manufacturing**
Advinus	X	X	X	
AstraZenca China	X			X
Aurigene		X	X	
Aurobindo				X
Biocon	X	X		X
Cipla				X
Dabur Pharma	X			X
Dr. Reddy's Laboratories	X		X	X
Hutchinson Medipharma	X	X		
Novartis China	X	X		X
Pfizer (China)	X	X		
Ranbaxy		X		X
ShanghaiBio			X	
Shanghai ChemPartner			X	
Sun Pharmaceutical				X
WuXi PharmaTech			X	

Though a number of domestic Indian and Chinese firms have emerged as partners in early and mid-term drug discovery and development, relatively few have the resources to develop their own drug candidates. Most firms specializing in drug discovery and development have expertise in advancing candidate drugs through phase II of clinical trials, after which a drug's proof of concept can be validated. Domestic Indian and Chinese pharmaceutical companies, largely lacking the financial capacity to advance a drug candidate through phase III clinical trials, often operate under a business model of original proprietary research, research partner, or contract research organization (CRO) (listed in Figure 4). A CRO that successfully advances a drug candidate to this level of development often receives a fixed milestone payment and then moves on to a new target. A research partner may receive royalty payments if the drug is successfully commercialized after clinical trials. Finally, a Chinese or Indian pharmaceutical firm engaged in original proprietary research would likely seek licensing agreements with or make complete drug sales (i.e. inclusive of supportive clinical data) to multinational pharmaceutical companies that have the resources necessary for completing development.

Glenmark, India, has completed several licensing agreements with Big Pharma. In 2006, it licensed GRC 8200, an experimental diabetes drug in phase II clinical trials, to Merck. Glenmark was paid USD 39 million up front, with a potential total payment of USD 296 million. The collaboration was abandoned when Merck elected to pursue treatments for diseases other than diabetes. In 2007, Glenmark completed a licensing agreement with Eli Lilly, involving a portfolio of TRPV1 receptors and a clinical compound named GRC 6211, undergoing phase II clinical trials. It was paid USD 45 million, with the potential to earn an additional USD 215 million based on milestone performance. Under the terms of the agreement, Glenmark will receive royalty payments if GRC 6211 is commercialized. In April 2008, the company received FDA approval to begin phase I testing of GBR 500, a monoclonal antibody under development for potential treatment of multiple sclerosis, chronic obstructive pulmonary disease, and inflammatory bowel disease.

Dr. Reddy's Laboratories is an example of an Indian firm that is pursuing parallel approaches to obtaining revenue at different stages in the pharmaceutical value chain. Dr. Reddy's has a strong generics- and bulk-manufacturing business that it uses to fund its own discovery and development of novel drugs. Four-fifths of Dr. Reddy's discovery work is on precedented drugs; about a fifth of its research effort focuses on unprecedented therapeutic areas (i.e. new-concept drugs). With a global staff of more than 9000 employees, Dr. Reddy's seeks to advance drug candidates through early phase II trials and then license or sell their intellectual property to major pharmaceutical players. Dr. Reddy's has already had some initial success using this strategy for a best-in-class diabetes-inhibitor molecule, which it licensed to a major diabetes company for an advance payment of approximately USD 3 million. In 1997, Dr. Reddy's licensed a drug candidate named Ragaglitazar, with the potential to moderate diabetic dyslipidaemia and blood-glucose levels, to Novo Nordisk. Although this drug candidate was very promising in phase I and II trials, in phase III it was identified as a carcinogen. The drug and its development had to be abandoned, but the drug's commercial potential had been significant: 1 mg was more than 40 times as powerful as the comparable USD 3 billion diabetes drug on the market. Dr. Reddy's continues to grow its drug-development capacity and to pursue novel research candidates.

Many firms are moving to value-sharing relationships. Examples are:

Aurigene — Forest; Novo Nordisk; Johnson & Johnson; MerckSerono
Hutchison MediPharma — Eli Lilly and Company; Merck; Procter & Gamble
Ranbaxy — GlaxoSmithKline, Merck; PPD
Advinus Therapeutics — Merck
Suven Life Sciences — Eli Lilly
Syngene — Bristol–Myers Squibb
Chembioteck — Forest
Jubilant Organosys — Eli Lilly and Company
GVK Biosciences — Wyeth
Nicholas Piramal — Eli Lilly and Company; Merck.

Aurigene, India, provides risk-sharing, milestone-based drug-discovery services to large pharmaceutical firms. Though a small player, employing just over 220 scientists, the company is engaged in more than ten running discovery programs. Its clients include Forest Labs, Johnson & Johnson, Orion, Novo Nordisk, MerckSerono, Debio, Elan Pharma, and RheoScience.

Hutchison MediPharma, China, is developing treatments for cancer and auto-immune diseases. It follows risk- and reward-sharing models to generate revenue by forming research partnerships and licensing its drug products that have reached the advanced stages of development (prior to phase III clinical trials). These revenues come primarily through milestone payments and drug-sale royalties. The company has partnerships with Eli Lilly, Merck KGaA (Germany), and Procter & Gamble.

Ranbaxy, India, prides itself on its drug-discovery and -development capabilities. Its 1400 scientists research new drug-discovery and drug-delivery systems. The company is collaborating with GlaxoSmithKline (GSK) and Merck on preclinical testing. Its partnership with GSK is risk/reward- and milestone-based, for pharmacokinetic, toxicity, and selectivity analysis on a GSK drug candidate.

Advinus Therapeutics, India, is developing drugs for inflammatory, metabolic, and neglected diseases through partnerships with Merck and the Drugs for Neglected Diseases Institute. The company receives milestone-based payments for developing drug candidates to proof of concept in phase II clinical trials.

Contract Research Organizations (CROs) provide research in drug discovery and development, pre-clinical testing, and early clinical trials. Firms such as ShanghaiBio and Wuxi PharmaTech follow this model. CROs rarely employ value-sharing relationships, instead relying on fixed-payment systems.

Many pharmaceutical firms in India and China have a strong understanding of efficient, high-yield chemical reactions, as well as the ability to obtain necessary raw materials or to purchase outside active ingredients, drug intermediates, or pharmaceutical products. Their generics businesses occupy only the shortened generics blocks of the drug-discovery and -development and clinical-trials value chains, which entail patent-monitoring and bioequivalence-testing. Their manufacturing capabilities allow them to profit from high-volume sales.

Local advantages

Most Indian and Chinese pharmaceutical firms are quick to extol the benefits of locating specific drug-development activities within their respective countries. They claim a cost advantage in terms of personnel costs, facilities, and land. Government tax incentives and development options are also available; nevertheless, some executives argue that additional programs are needed in order to properly promote the pharmaceutical industry.

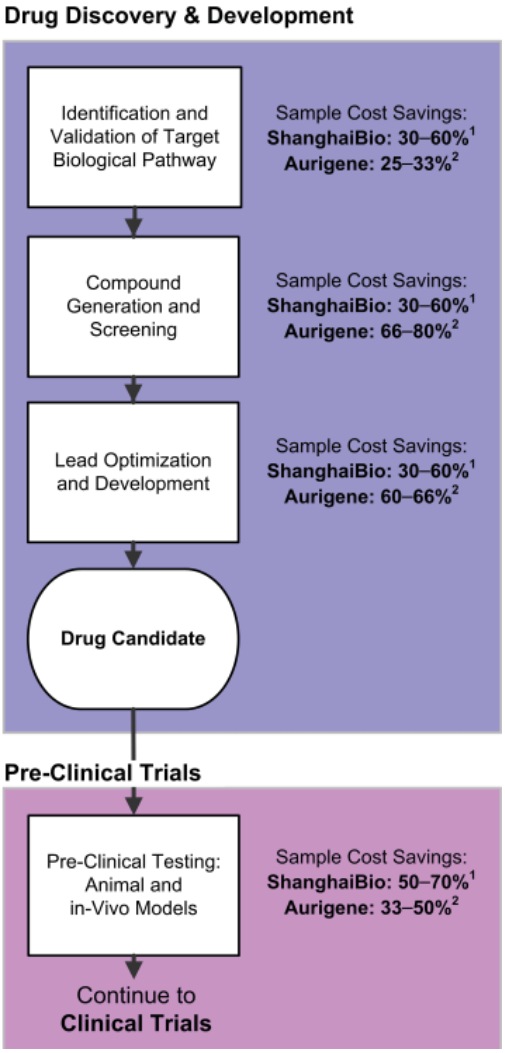
Development of human capital and an increase in Indian and Chinese returnees with U.S. education and/or business experience have also contributed to the rapid growth of these industries.

Cost savings

Cost arbitrage has been an enticement for multinational pharmaceutical firms to seek partnerships or contracted service relationships with Chinese and Indian firms. Figure 5 portrays the

magnitudes of cost savings that ShanghaiBio in China and Aurigene in India say that they can provide for their customers in the segments of the pharmaceutical value chain concerned with drug discovery and development and preclinical trials. These potential savings are relative to U.S. pricing and vary according to the type and complexity of the biological, chemical, or analytical work and quantity of biological samples required.

Figure 5: Sample pharmaceutical cost savings through partnerships with ShanghaiBio Corporation (China) and Aurigene (India) relative to U.S. pricing



1. Estimates provided by Dr. Jason Jin, President and CEO of ShanghaiBio Corporation
2. Estimates provided by Mr. C.S.N. Murthy, CEO of Aurigene Discovery Technologies Ltd.

Ethical issues and constraints on future growth

Although Indian and Chinese pharmaceutical companies have made substantial progress, there are significant constraints on future growth. Several domestic Indian companies were able to achieve early growth by relying on national patent laws that only recognized process patents. These companies were able to capitalize on internationally disclosed intellectual property and to fashion generic drugs based on the compounds described, for sale in markets unrestricted by product patents. The success of this strategy is subject, however, to national intellectual-property laws, which in some cases are being replaced by new regulations covering product patents.

International outsourcing can lead to backlashes and unforeseen risks. Illinois-based Baxter International came under a glaring spotlight for its blood thinner heparin, evidently contaminated through an active pharmaceutical ingredient manufactured by Changzhou SPL, located near Shanghai. Neither the FDA nor the Chinese regulators had previously inspected this plant, but reports of 20 deaths led to the descent of an FDA and media throng on the factory. Partisans of the FDA are demanding the hiring of more inspectors for this global work as well as a state-of-the-art data system to monitor drug imports. Democrat Bart Stupak, the chair of the U.S. House Subcommittee on Oversight and Investigations, is pondering legislation that could "prohibit the marketing of any drug from a plant that has not been properly inspected" (Wechsler, 2008).

There are other potential flare-ups of unrest. China is second in the world in experimentation on non-human primates. Though still well behind the U.S., which used 54,998 monkeys for research in 2004, "China is preparing to become the world's supplier of research primates", according to *Nature Medicine* (March 2006). Ambitious talk abounds of expanding primate colonies and research facilities, the sort of colossal testing regimes that could antagonize animal-rights activists worldwide. Efforts by the Beijing municipal government to initiate an animal-welfare law in 2004 encountered bitter public hostility when some opponents contrasted the acute poverty of the poorest 135 million Chinese, who subsist on less than one dollar per day, with the supply to monkeys of music, toys, and purified water. The purchase price for monkeys in China is estimated at one tenth that in the U.S., but scientists at the Kunming Primate Research Center (KPRC) and Beijing University's Institute of Molecular Medicine (Beida-IMM) admit that efforts to attain from the AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) accreditation for humane treatment have sent maintenance costs spiraling. Estimating the annual cost of maintaining monkeys at 25,000 Yuan per year (USD 3,500), biophysicist Zhou Zhuan, of Beida-IMM, exclaims that when meeting international standards, "Chinese monkeys are far more expensive than we ever imagined", ending up negating a substantial portion of the price differential between non-human primates held in China and those held in the U.S. (Hao, 2007; Mandavilli, 2006).

When it comes to medical experimentation on humans, China faced a human rights uproar when Deputy Health Minister Huang Jiefu conceded in 2005 that organs are taken from executed prisoners in order to carry out transplant surgeries. Amnesty International claims that China executes more prisoners than the rest of the world combined (Macartney, 2008). Both India and China remain vulnerable to accusations of abuses in testing protocols, especially because these nations are experiencing escalating shortages of trained inspection personnel. According to a report of India's Planning Commission, "There is a lack of world-class testing laboratory [sic] for validation of tests. Most importantly, there is a looming shortage of clinical-research personnel estimated at 30,000 to 50,000" ("No world-class lab…," 2008). Specifically, India needs trial investigators, auditors, and officials capable of serving on ethics and data-safety–management boards. The Office of the Drugs Controller in particular suffers from understaffing (Sinha, 2008).

Having executed the head of the State Food and Drug Administration (SFDA), Zheng Xiaoyu, in July 2007 on charges of corruption, China's government also confronts anxieties about severe long-term shortages of regulatory personnel for the torrid growth sector of clinical trials.

Partly due to its evaluation of regulatory conditions, A.T. Kearney's "Country Attractiveness Index for Clinical Trials" (*Pharmaceutical Executive*, May 2007) still rates the U.S. (at 6.68) significantly ahead of China (6.10) and India (5.58), though the latter two nations have big advantages in terms of (1) cost efficiencies and (2) enormous drug-naïve patient pools. Business Insights, a U.K. firm specializing in strategic market analysis, has forecast a tenfold leap in clinical trials in India from 2006 to 2011 (Mirasol, 2007). The total global market in clinical trials will reach USD 30 billion in 2008. The Planning Commission of India in April 2008 cites estimates that the value of the Indian clinical trials sector stands at USD 300 million, with projections of USD 1.5 to 2.0 billion by 2010. Elsewhere, there have been similarly ambitious predictions for growth in China. Though growth rates have been less spectacular so far in India and China, both nations are experiencing a significant surge in experimentation and clinical trials. In 2006 alone, India posted 65 percent growth in clinical trials, and in early 2008 the India Pharmaceutical Alliance reports that ten out of eleven of the world's largest global pharmaceutical firms have several clinical trials underway in India: GlaxoSmithKline (22 clinical trials), Johnson & Johnson (22), Eli Lilly (17), Bristol-Myers Squibb (17), Pfizer (16), Sanofi-Aventis (15), AstraZeneca (10), Novartis (9), Merck (8), and Roche (5) (Sinha, 2008). Though many analysts regard the growth of India and China in clinical trials as a juggernaut, a regulatory breakdown similar to the heparin scandal could mobilize key members of the U.S. Congress and turn public opinion against further offshoring of drug testing.

Though multinational companies are increasing the number and complexity of business relationships with external partners, they guard against accidental disclosure or loss of intellectual property by not actively assigning their most lucrative projects to them. This prevents Indian and Chinese partners from working on some of the most innovative and cutting-edge projects. The multinational firm Pfizer has not yet established any risk-sharing R&D partnerships with Asian companies, instead building a network of CRO partners to support its research projects.

Availability of talent and human capital continues to be a significant concern in both countries. Though Indian returnees, and to a lesser extent Chinese returnees, are available today in greater numbers than in years past, many pharmaceutical employees have limited experience with drug-discovery culture and the iterative, non-linear nature of important lead-optimization activities.

Conclusions

Cost pressures, the need to tap global talent, and growth opportunities in emerging markets have prompted western pharmaceutical companies to shift substantial manufacturing and clinical-trial work to India and China. Big pharmaceutical companies such as Merck, Eli Lilly, and Johnson & Johnson are now counting on these countries for research and development as well. Both nations have become major partners in preclinical and clinical testing. China, for example, has a very wide network of hospitals from which to draw human tissue samples and live patients. China is also a major supplier of non-human primates for testing.

At first, the aim of Big Pharma was to benefit from the lower labor and overhead costs of India and China. Increasingly these companies are turning to Asia to broaden the range of new drug candidates. Because Indian drug companies are those with the most experience in selling generic drugs in the U.S. that meet FDA standards, India is playing a more strategic role in early discovery. Companies such as Ranbaxy, Aurigene, Advinus, Nicholas Piramal, and Jubilant have negotiated long-term deals with western pharmaceutical companies to discover and develop new chemical entities. In a growing number of cases, the Indian companies share the financial risk in discovery as well as the potential financial rewards. One Chinese company, Hutchison MediPharma, has formed a similar partnership with Eli Lilly. Others are likely to follow suit as Chinese contract research organizations gain experience and western companies come to trust in China's ability to protect intellectual property.

It is too early to tell whether China and India will become important sources of new drugs. In contrast to industries such as software and electronics, in which there has been substantial growth in offshore R&D, the pharmaceutical industry takes many years for a new product to survive the process of clinical testing and regulatory approval. Most of the new risk-sharing arrangements date from 2005, so it could be another decade before there are concrete results.

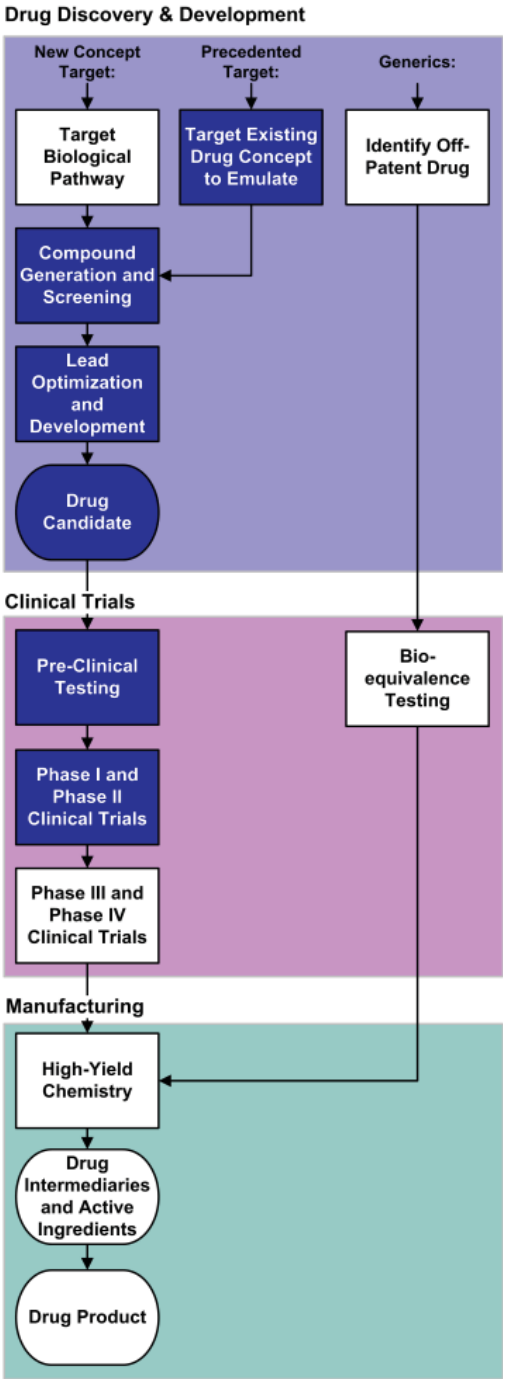
The early progress, however, is promising. Several companies, such as Ranbaxy, Advinus, Nicholas Piramal, and Aurigene, have achieved significant development milestones with new chemical entities. Several drugs from these partnerships are going into clinical testing. As a result, more work is likely to be outsourced, and the trend of R&D moving to these countries is likely to increase.

Company summaries

Here we present specific discussions of the types of pharmaceutical activities that various regional and international pharmaceutical corporations are engaged in. We conducted detailed interviews with 16 pharmaceutical firms in China and India to obtain information on their business models, value-chain activities, partnerships, and technology capabilities. Data presented in these summaries were obtained through a mix of interviews with company executives, company press releases, and site visits.

Advinus Therapeutics

Business model: contract research organization; drug-discovery collaborations; original discovery research
Active value-chain segments (highlighted in blue):



Company history

Advinus Therapeutics (Advinus) was founded in 2005 by the company's CEO, Dr. Rashmi Barbhaiya, who brought 21 years of experience at Bristol–Myers Squibb. Dr. Barbhaiya aimed to take advantage of the talent and resources available in India to cater to the growing demand for discovery and development of new drugs. He had worked with several of India's largest pharmaceutical companies and fostered several alliances between Ranbaxy and international companies, including GlaxoSmithKline.

The company is headquartered in Bangalore, India, and employs 600. Its Bangalore site provides preclinical and early-clinical R&D services. A second company facility, located in Pune, addresses metabolic diseases.

Tata, India's largest multinational conglomerate, recently invested $10 million in Advinus. Additionally, Rallis India, a primarily agrochemical Tata enterprise, sold its knowledge-services business, including drug discovery, to Advinus for USD 6 million.

Technology capabilities and value-chain position

Advinus is engaged in drug discovery and development and in clinical trials. The company's capabilities range from identifying precedent drug targets to conducting phase II clinical trials.

Advinus specializes in the discovery of molecules to target one of three biological areas: metabolic disorders (including obesity and asthma); inflammatory diseases (specifically respiratory conditions); and neglected diseases (including tuberculosis, dengue fever, and malaria). Advinus views its interest in these neglected diseases, which are mainly prevalent in third-world nations and not financially lucrative to address, as an act of strong corporate citizenship. The company views India as a unique environment in which to find solutions to the very diseases that affect its population.

Business model and partnerships

Advinus provides custom pharmaceutical services on specific projects and collaborates with outside firms on research partnerships. In the long term, the company seeks to build revenue through the development of original proprietary drug products. Dr. Barbhaiya believes that the current western model for drug discovery, in which budgets often exceed a billion dollars to convert a single molecule into a viable drug, is not sustainable. Observing that the probability of successfully completing clinical trials is greatly increased upon reaching phase III, Advinus has developed capabilities to advance drug molecules through phase IIB trials. The company believes that by retaining its molecules for longer and advancing their development through high-risk proof-of-concept clinical trials, it may be able to make higher profits on the sale of future internally developed drug candidates.

Advinus's most notable partnership is with Merck. The research for this partnership focuses on two programs to develop drug candidates for metabolic diseases. The partnership provides milestone payments of $74.5 million per target, with Advinus being eligible for royalties for any drug commercialized. Advinus will carry out research as far as phase II clinical trials, at which point Merck retains control through late-stage clinical trials. Advinus recently reached its third milestone in this arrangement. It is also conducting collaborative research with the DNDi (Drugs for Neglected Diseases initiative), a Geneva-based non-profit drug-development organization. The two are cooperating to formulate drugs to treat *kala azar* (visceral leishmaniasis), a disease common in India.

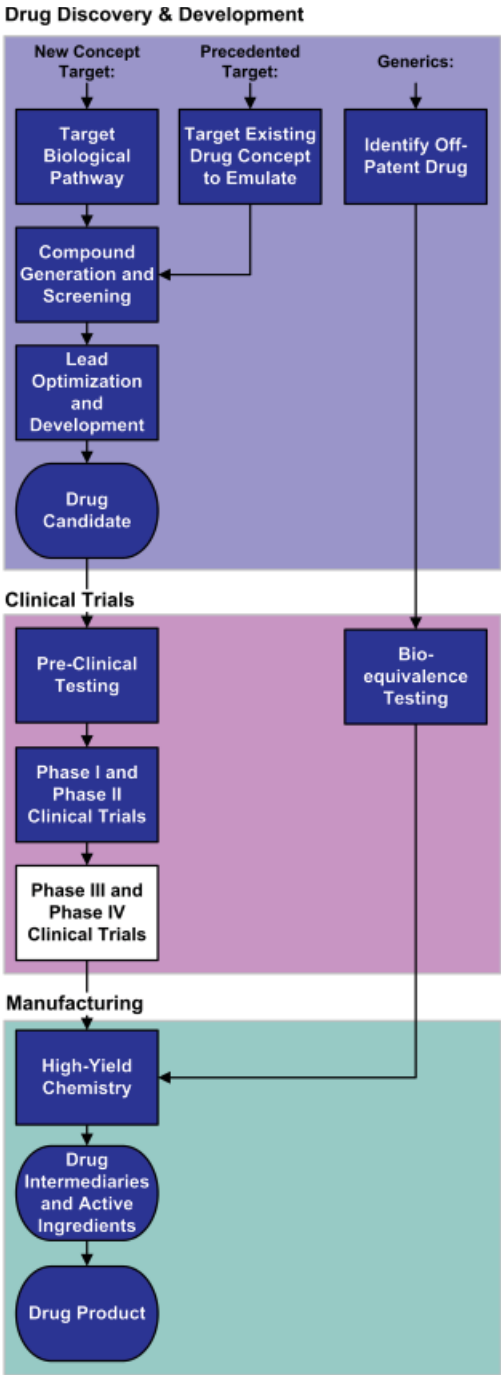
Strengths and limitations

Dr. Barbhaiya foresees several limits on pharmaceutical growth in India. Parts of the country lack substantive infrastructure to support large-scale industry, and the high attrition of talent in many pharmaceutical companies limits their capacities to expand or maintain projects. Advinus has been able to mitigate the latter by creating a series of innovative workforce training and development programs that have reduced its annual attrition percentages to single digits.

AstraZeneca China

Business model: original proprietary research; multinational division

Active value-chain segments (highlighted in blue):



Company history

AstraZeneca resulted from a merger between Astra AB of Sweden and Zeneca Group PLC in 1999. AstraZeneca is active in more than 100 countries and is increasing its presence in emerging economies such as India and China. The firm employs more than 65,000 individuals, just under 3000 of whom are located in China. In 2006, the company's sales totaled USD 26.5 billion, approximately USD 200 million dollars of which were made in China. AstraZeneca China is headquartered in Shanghai and has 25 branches in major cities. In 2007, the company established the Innovation Center China (ICC), to focus on translational science, through an investment of USD 100 million. Modeled on an existing R&D center in Boston, Massachusetts, this is a discovery center with cutting-edge technology.

Technology capabilities and value-chain position

AstraZeneca China is active throughout the pharmaceutical value chain but focuses on original proprietary research and drug manufacture. The firm has established large R&D centers and manufacturing facilities, including a USD 170 million manufacturing site in Wuxi and the ICC, in Shanghai.

AstraZeneca China focuses on discovering drugs for diseases prevalent in China rather than targeting global or western consumers. Dr. Zhang, Head of Innovation, ICC, states that AstraZeneca China is differentiated from its competitors through its guiding philosophy to be "in China, for China". A large proportion of its R&D spending is in six therapy areas: cancer, cardiovascular, gastrointestinal, infection, neuroscience, respiratory and inflammation. The ICC is currently focusing on cancer-related research.

Business model and partnerships

The creation of the ICC was a critical element in AstraZeneca's plan to expand its presence in China. According to Dr. Zhang, one of the key reasons for establishing the ICC was the discovery of differential response to drugs according to ethnicity. He also added that whereas R&D in the west primarily targets lung, breast, prostrate, and colorectal cancer, in China, liver and gastric/esophageal cancers are much more common.

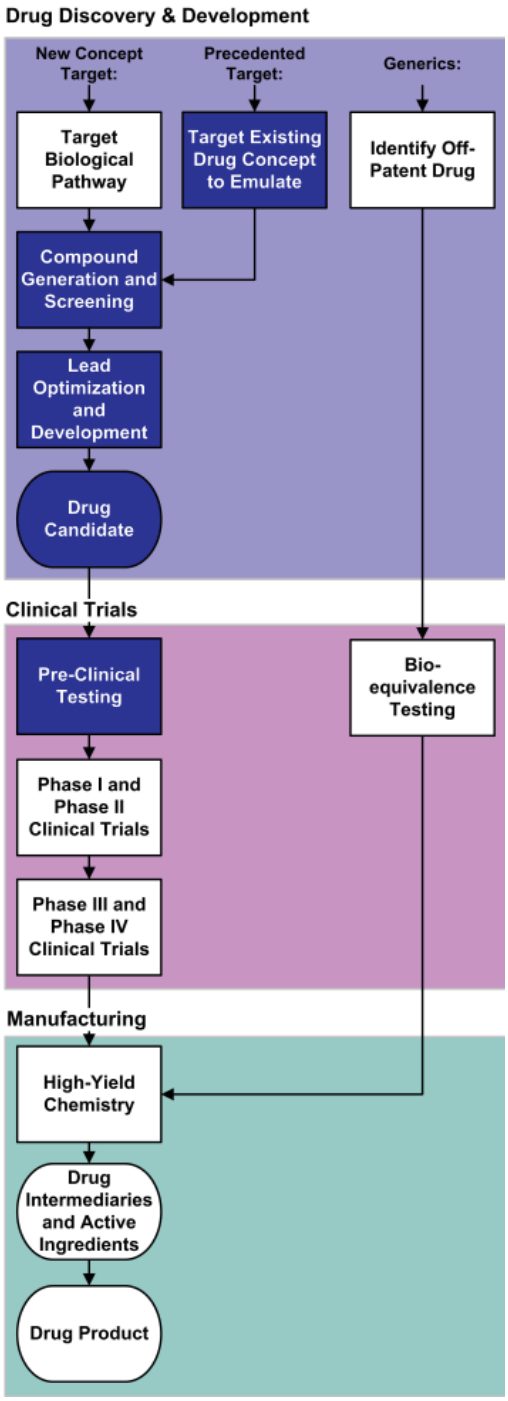
In dealing with diseases in which it has limited in-house expertise, the company has partnered with leading medical centers, research labs, and universities. It has collaborative programs and strategic partnerships with research institutions and hospitals in Beijing, Shanghai, and Guangzhou.

Strengths and limitations

AstraZeneca's biggest concern is hiring well-qualified and well-trained researchers. About a third of the ICC's researchers (PhDs and postdoctoral researchers) have a western education. The China-educated researchersoften lack practical training in drug discovery. Dr. Zhang added that though change in the regulatory environment in China could be faster than it is, it is moving in the right direction to attract major pharmaceutical companies' interest.

Aurigene Discovery Technologies

Business model: differentiated biotech company; early-stage drug-discovery collaborations
Active value-chain segments (highlighted in blue):



Company history

Aurigene Discovery Technologies (Aurigene), an independent subsidiary of Dr. Reddy's Laboratories, was founded in 2001. The company provides modular discovery services in chemistry and biology and describes itself as an *early-stage discovery-collaborations biotech*. It employs 220 scientists (110 of whom focus on biology) to perform drug-discovery research, and it plans to grow to include about 300 employees on 15 to 18 discovery programs. It has elected not to diversify into drug-development work, instead supplying early-discovery services only, to a multinational clientele.

Technology capabilities and value-chain position

Aurigene's services are in early discovery and refinement of novel drugs targeting metabolic disorders, cancer, and inflammation. Given a biological target, it specializes in hit design, hit-to-lead, lead optimization, and preclinical development. Often, it will evaluate 1000 molecules in this cycle. After completing Investigational New Drug Application paperwork, Aurigene passes drug-candidate development to its client. Aurigene is able to conduct many chemical analyses at about a quarter of the price of comparable work at a research facility in the U.S. This is due partly to the lower cost of employee salaries: only 50 percent of Aurigene's operating costs, in comparison with up to 90 percent of its comparable U.S. competitors' costs.

Business model and partnerships

Aurigene provides early-research services for major pharmaceutical players, including Forest Labs, Johnson & Johnson, Orion, Novo Nordisk, Debio, MerckSerono, Elan Corporation, and RheoScience. It does not push the boundaries of science, but instead provides cost-competitive means to broaden its clients' drug-discovery capacities. These relationships

are typically milestone based. Some of the company's relationships with smaller pharmaceutical firms are based decreasingly on cost arbitrage and increasingly on strategic value. In these, Aurigene's ownership in the intellectual property it develops increases with the amount of early-stage risk it assumes. The company does not control any of the intellectual property associated with its service work for leading pharmaceutical companies.

Aurigene's business structure is unique, in that it relies solely on service relationships to remain profitable. Few drug-discovery companies are able to meet their costs in this way, as its success depends heavily on the number, quality, and duration of client relationships.

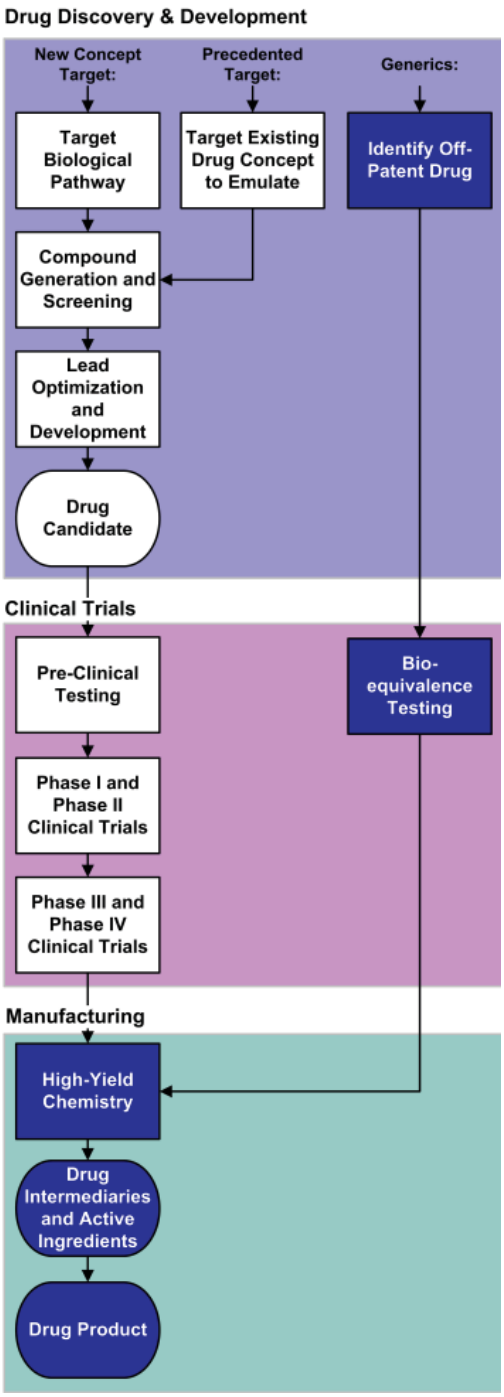
Strengths and limitations

Aurigene defines itself in terms of its business relationships, unique service role, and low discovery costs. A number of Indian pharmaceutical companies have built their businesses on cost-arbitrage strategies and are working hard to enter the drug-discovery market, but CEO CSN Murthy estimates that these companies are several years away from serious collaborative relationships with outside firms.

Mr. Murthy says it is very difficult to hire and retain senior-level talent in India. This problem has been partially alleviated, however, by the increasing number of returnees with U.S. training and expertise.

Aurobindo Pharma

Business model: generics, APIs, and manufacture
Active value-chain segments (highlighted in blue):



Company history

Founded in 1986, Aurobindo Pharma is a vertically integrated, R&D-driven company with a broad manufacturing portfolio and capabilities. The company's 2007 sales were USD 480 million and it employs 5000. In 2001, Aurobindo Pharma expanded its operations into the global generics market. The firms' products reach customers in more than 100 countries, including established markets such as the United States and Europe. Aurobindo is headquartered in Hyderabad, India.

Technology capabilities and value-chain position

Aurobindo is primarily involved in the creation of active pharmaceutical ingredients (APIs) and finished generic formulations. It derives forty percent of its revenue from the domestic Indian market. The export markets, providing the remaining sixty percent, include Asia, Africa, Europe, Latin America, and the U.S.

Aurobindo Pharma has commercialized more than 200 APIs and makes finished products from some of them. The company's cephalosporin antibiotics, antivirals, anti-HIV drugs, lifestyle-disease drugs, and semi-synthetic penicillin target global markets. The firm has more than 120 formulations, targeting global markets in seven different therapeutic areas: antibiotics (cephalosporins & penicillins); anti-retrovirals; drugs affecting the central nervous system; cardiovascular-system drugs; gastroenterologicals; anti-diabetics; and anti-allergics.

When Aurobindo's team identifies a promising drug alternative, it conducts an internal bioequivalence study. Aurobindo concentrates on research that makes sense to its customers, which are (the generics market aside) largely companies that buy APIs and intermediaries. It also offers chemical development and custom synthesis.

Aurobindo has gradually expanded its capabilities beyond API manufacturing. The company's in-house

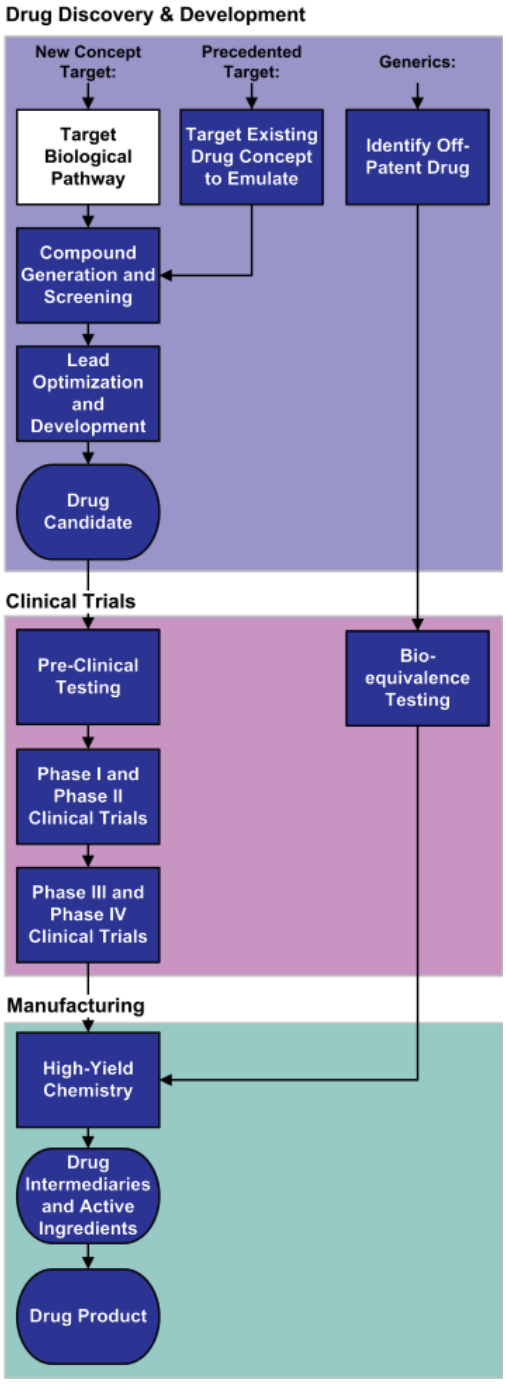
R&D team now has expertise in chiral synthesis, column technology, complex chemistry, fermentation, sterile manufacture, and other processes. Aurobindo states that it now produces its own intermediaries and formulations, after directly acquiring raw materials.

Business model and partnerships

Aurobindo's APIs are sold to customers who in turn use them in their own drug formulations and manufacture. In the four years prior to 2008, Aurobindo has made initial forays into the U.S. and European markets and is currently working to expand its distribution networks in these countries. Due to high entry barriers in regulated markets, Aurobindo first sold its APIs to companies in Latin America, Africa, and the Asia–Pacific. This allowed it to establish a network and gain a foothold in less-regulated markets.

Biocon

Business model: original proprietary research; research partner; generics, APIs, and manufacture
Active value-chain segments (highlighted in blue):



Company history

Biocon was founded in 1978 by its current chairman and managing director, Ms. Kiran Mazumdar-Shaw. Its headquarters are in Bangalore, India, and the company employs 3000. In 2007, its sales revenue was USD 219 million.

Technology capabilities and value-chain position

Biocon's products target diabetes, cancer, and inflammatory diseases. The company has three subsidiary companies: Syngene International Ltd, Clinigene International Ltd, and Biocon Biopharmaceuticals Private Ltd.

Syngene conducts custom drug-discovery research. It offers synthetic-chemistry and molecular-biology services for early-stage drug discovery and development. Its core strengths include chemistry and biology services.

Clinigene conducts preclinical development activities; clinical-data management and biostatistics for phase 0 clinical trials; and regulatory services for phase II and phase III clinical trials. The subsidiary undertakes this work using a human-pharmacology unit, bioanalytical-research laboratory, and central laboratory. These facilities are used to conduct in-vivo and in-vitro testing on both laboratory animals and human patients. Once a drug candidate has passed through phase III clinical trials, the project is passed to Biocon Pharmaceuticals.

Biocon Biopharmaceuticals focuses on product commercialization and manufacture. It is responsible for research collaboration, product development, manufacturing, regulatory filing, marketing, custom manufacturing, and licensing.

Biocon also actively produces generic molecules and active ingredients for sale to other pharmaceutical firms, as well as consumer drugs for sale in more than 70 countries. The firm's manufacturing capabilities have grown from enzyme production to recombinant protein assembly and antibody production. Its

drug portfolio includes Insugen, a brand of insulin; BIOMab EGFR, the first anticancer drug in India; and monoclonal antibodies and therapeutic proteins. Biocon also produces an extensive array of APIs, including anti-diabetic agents, anti-inflammatories, antioxidants, and nutraceuticals.

Business model and partnerships

In addition to its original proprietary research and manufacture of generics and APIs, Biocon offers custom manufacturing and research services. Its partners include Bristol–Myers Squibb, which has been a customer since 1998. Bristol–Myers Squibb increased the breadth of its relationship with Biocon in 2007 through a partnership with Syngene. As part of this relationship, Syngene will allocate more than 400 employees to focus on early drug development for Bristol–Myers Squibb.

The majority of Biocon's drug discovery and development; clinical trials; and manufacturing activities are internal, although the firm occasionally partners with other firms. The company also provides custom research services.

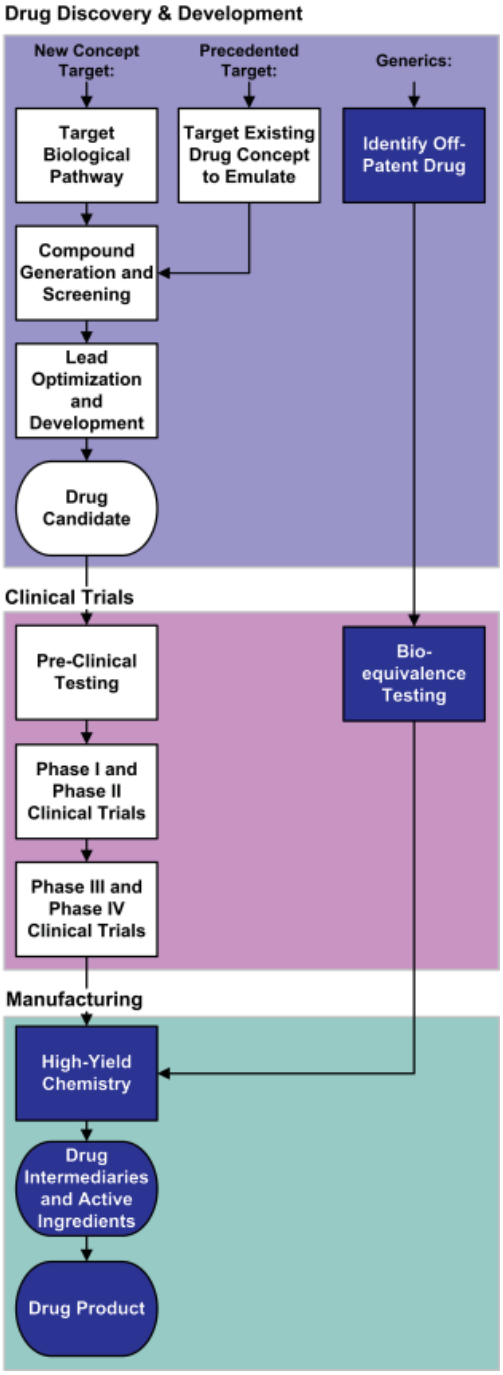
Syngene offers full-time–equivalent programs, in which the company provides its client with a project team for a specified period at a fixed rate. It also earns milestone payments and enters into risk-sharing ventures.

Strengths and limitations

According to Mr. Rakesh Bamzai, Biocon's Head of Marketing, the depreciating dollar is a major concern, as 65 percent of the firm's revenues come from sales in international markets. Biocon's range of capabilities, however, provides it with multiple revenue streams, allowing the company to balance risk and accelerate growth, he states. Competition within highly regulated markets is contributing additional pressures.

Cipla

Business model: generics, APIs, and manufacture
Active value-chain segments (highlighted in blue):



Company history

Cipla (Chemical, Industrial and Pharmaceutical Laboratories) was established in 1935 and has revenues of over USD 1 billion. Cipla is headquartered In Mumbai, India, and employs around 2200 individuals.

Prior to the 2005 amendment of the *Indian Patent Act of 1972*, the Indian government enforced patents on processes only. During this time, Cipla operated within these laws to develop and manufacture a range of generics and APIs for sale and distribution in markets not regulated by product patents. Cipla also contributed to humanitarian efforts in Africa by providing anti-AIDS medication for about USD 300 per patient per year, one-fortieth to one-fiftieth of the cost of MNCs' competing treatments. (Please consult the earlier discussion "Storm over intellectual property" for additional crucial background on Cipla, Yusuf Hamied, and the company's founding family).

Technology capabilities and value-chain position

Cipla operates within the generics, APIs, and manufacture segments of the pharmaceutical value chain. The company produces drugs to treat a variety of conditions, including AIDS, cardiovascular diseases, diabetes, and depression. These products are distributed to ~180 countries, including highly regulated U.S. and European markets. Cipla also manufactures pharmaceutical ingredients, drug intermediates, and generics that are consumed by international organizations and businesses, including

Big Pharma. The firm's manufacturing facilities have received regulatory approval in the U.S., the U.K, Australia, Africa, Hungary, Germany, Canada, and Brazil.

Business model and partnerships

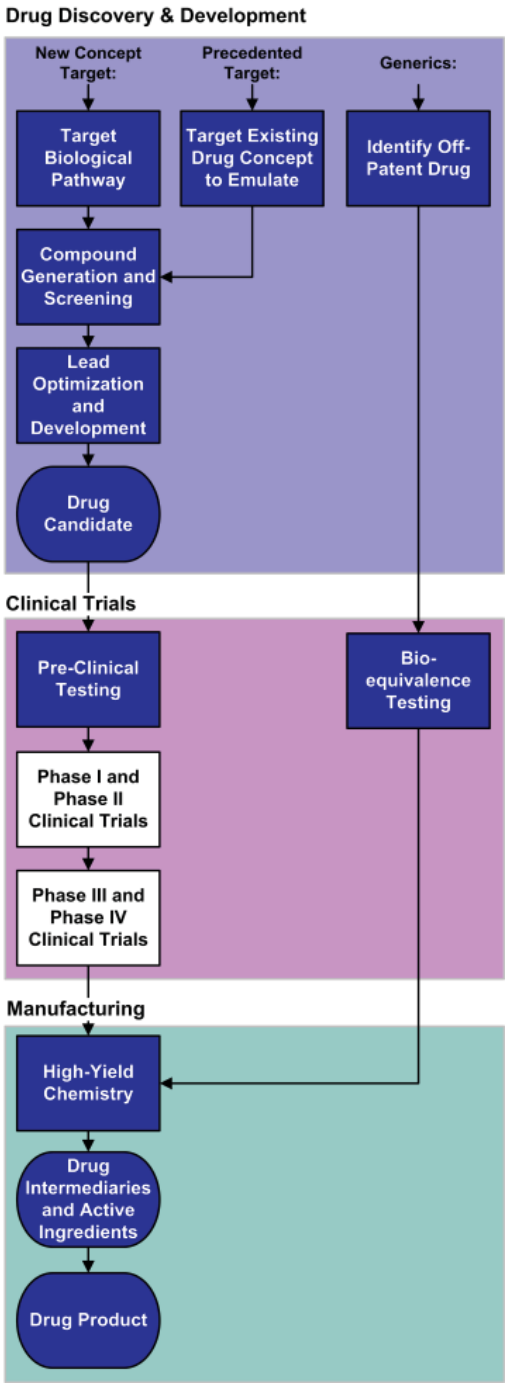
The company markets its own products world wide. It is able to offer its competitive generics pricing through international disclosure of drug data and its manufacture of its own drug intermediaries.

Strengths and limitations

Cipla's CEO, Dr. Yusuf Hamied, commented that competition within established drug markets is being hampered by drug "evergreening": extended patent protection on lucrative pharmaceutical drugs through incremental patent changes as expiration approaches. He explained that this is often accomplished by mixing drugs, changing delivery mechanisms, or altering the target condition a drug treats.

Dabur Pharma

Business model: original proprietary research; generics, APIs, and manufacture
Active value-chain segments (highlighted in blue):



Company history

Dabur Pharma, based in New Delhi, India, is an associate company of Dabur India limited, a healthcare corporation founded in 1884. Dabur Pharma was incorporated in 2003 and employs 1000 individuals, 200 of whom are directly engaged in R&D. In 2007, it produced sales of USD 77 million. In April 2008, the German healthcare company Fresenius Kabi acquired Dabur Pharma for USD 219 million, an unusually large pharmaceutical acquisition by a foreign company, in order to expand its drug portfolio and its API-production capabilities.

Technology capabilities and value-chain position

Dabur Pharma is involved in the development and manufacture of generics and APIs to treat oncology conditions, and to a lesser degree in the discovery and development of early-stage proprietary drugs. As a manufacturer of generic drugs, the company has seven Abbreviated New Drug Applications filed with the U.S. FDA. It manufactures drugs for commercial use through its facilities in India and the U.K. Its portfolio also includes more than 45 oncology-related APIs and finished-dosage forms. Its research occurs primarily through the Dabur Research Foundation, an independent research organization established in 1979. The foundation has filed more than 130 patent applications, of which 40 have been granted.

Until 2007, Dabur Pharma developed and marketed products in "less-regulated markets" such as India, the Asia–Pacific, the Middle East, and Africa. It entered the European and U.S. markets in 2007 and hopes to introduce 25 drugs in the U.S. in the next three to five years.

Dabur Pharma invests 10 to 12 percent of its R&D budget in new-concept drugs and drug-delivery systems. One of its successes is Nanoxel, the first nanoparticle drug-delivery system developed outside the U.S. The company released Nanoxel in India in 2007, after receiving approval from the Drug

Controller General of India (DCGI), India's drug-regulatory body.

Business model and partnerships

Dabur Pharma develops proprietary products until the preclinical testing phase. It then seeks to license its technology or form a partnership with a major multinational company in order to advance the compound through the risk- and cost-intensive clinical-trial phase. This business is complemented by Dabur Pharma's finished-dosage and API products, which are distributed to select Asian, European, African, and Latin American markets.

The company had an agreement with Abbott Labs in the U.S. to provide Abbott Labs's Hospital Products Division with finished-dosage forms of generic oncology products. The companies shared development, marketing costs, and profits. Dabur Pharma says itended this partnership in order to employ its subsidiary, Dabur Pharma U.S., for sales and distribution of its products in the United States.

Strengths and limitations

Dabur Pharma sees its vertical integration and specialization in oncology (unusual in Indian pharmaceutical firms) as a competitive advantage.

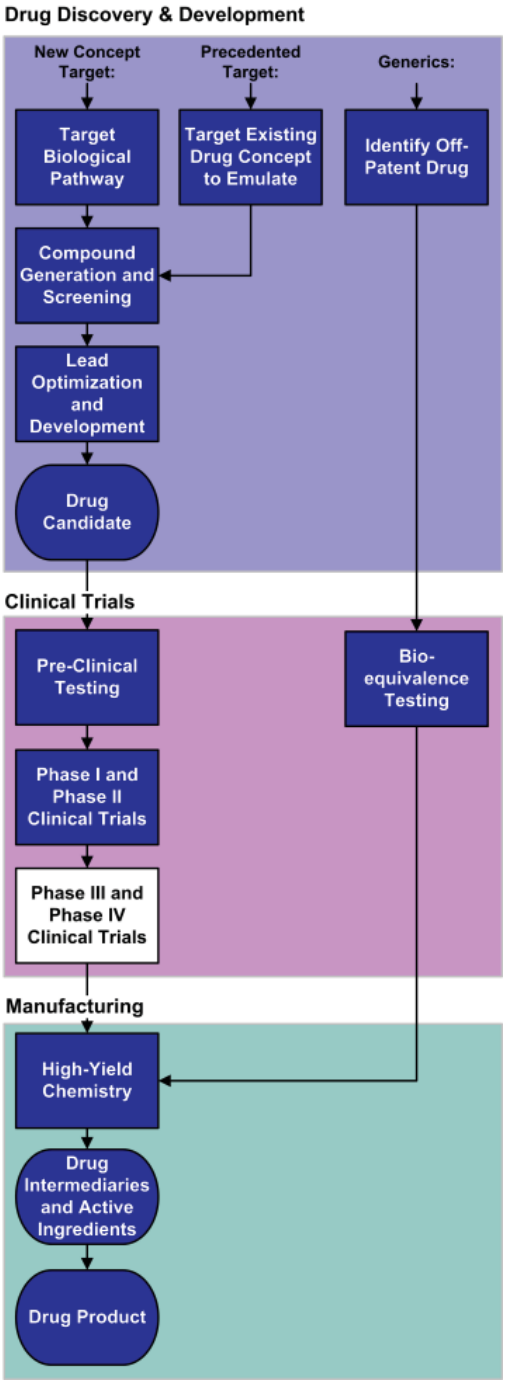
The high rate of attrition in the Indian pharmaceutical industry is a significant challenge to Dabur Pharma's ability to retain personnel who have received expensive in-house training.

With the number of global firms entering specialized fields such as oncology, price competition is another major challenge.

Dr. Reddy's Laboratories

Business model: original proprietary research; contract research organization; generics, APIs, and manufacture

Active value-chain segments (highlighted in blue):



Company history

Established in 1984, Dr. Reddy's Laboratories was an early entrant in and remains a significant player in India's pharmaceutical industry. In the late 1980s, the firm entered the bulk-generics market by reverse-engineering foreign drugs and devising new means of mass-manufacturing generic alternatives at costs attractive to the Indian market. In 1992, Dr. Reddy's began conducting drug-discovery research. Today the firm has ~9000 employees. In 2007, it generated sales of more than USD 1.44 billion.

Dr. Reddy's is listed on the New York Stock Exchange.

Technology capabilities and value-chain position

In addition to developing generic products, Dr. Reddy's is actively engaged in a variety of drug-discovery programs. Its short- and medium-term investments are in the creation of generics and APIs and the provision of custom pharmaceutical services for Big Pharma. Dr. Reddy's generics business markets more than 150 brands of finished dosages, and it releases 15 to 20 new products annually, including gastrointestinal, antimicrobial, cardiovascular, dental, dermatological, diabetes, pain-management, and urological drugs.

Dr. Reddy's API business includes commercialized products in 25 regulated markets and more than a hundred products in near-regulated markets. These APIs are produced using seven FDA-approved plants in India and Mexico and are distributed to more than 800 customers in 100 countries, including top-tier global and regional generics companies. Dr. Reddy's also offers custom pharmaceutical services to various customers, including emerging companies and more than five major pharmaceutical players. These services include drug-discovery and -development and manufacture, and often use Dr. Reddy's R&D facilities, organic-chemistry expertise, or analytical capabilities.

Medium- to long-term revenue comes from drug-discovery research, specialty pharmaceuticals, and biologics (also called bio-similars). Dr. Reddy's drug-discovery research involves the collective efforts of ~300 chemists and engineers and 21 organic-chemistry laboratories located in research centers in Hyderabad, India, and in Atlanta, Georgia. These groups focus on cardiovascular and metabolic disorders; oncology; and bacterial infections, and they develop potential drugs through in-house research and partnerships. Dr. Reddy's is also engaged in the development of special pharmaceuticals and biologics — innovation-based, differentiated product development focusing on the creation of new biological entities and second-generation variant biologics — targeting the North American and European markets.

Business model and partnerships

Dr. Reddy's follows a variety of business models, including the manufacture and sale of generics, APIs, and branded finished dosages; partnerships and custom pharmaceutical services with major pharmaceutical players; and original drug-development programs. The company's goal is to take candidate drugs through phase IIa clinical trials and then seek licensing agreements, commercial partnerships, or customers for the drug's intellectual property.

Strengths and limitations

One of Dr. Reddy's strengths is control over its supply chain. Control over critical capabilities — process development, API-dossier submission, patent expertise, and manufacture — has allowed it to achieve cost-effective and high-speed development of bulk generics and APIs.

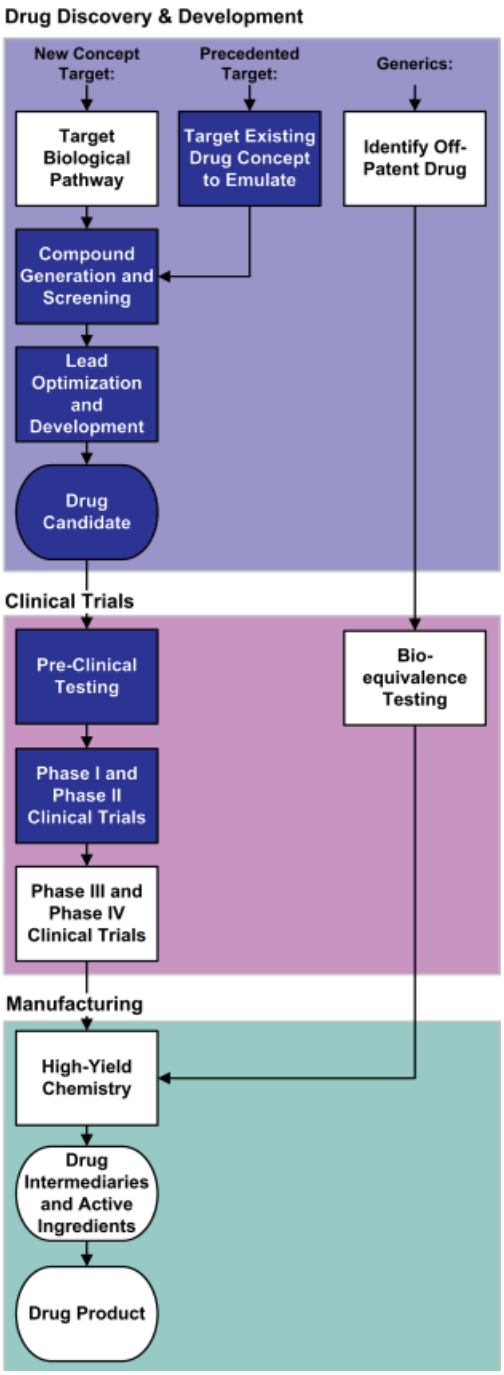
Dr. Reddy's has also achieved significant cost savings on certain drug-development activities. In some projects, the company says, preclinical trials can be completed for 40 to 60 percent less than the traditional research costs of a multinational corporation. These cost reductions result from in-place processes and lower cost bases. Conducting toxicology work in house has enabled cost savings of about 50 percent.

Dr. Reddy's states that its employee retention is well above industry average, and it has been able to grow its business through the acquisition of U.S.-trained talent. In the last few years, Dr. Reddy's has been very successful at acquiring personnel, most often Indian-born foreign nationals, from U.S. pharmaceutical R&D centers in the throes of closure. Individuals unwilling to relocate to India can sometimes be accommodated in Dr. Reddy's Atlanta facility.

Hutchison MediPharma

Business model: original proprietary research; research partner

Active value-chain segments (highlighted in blue):



Company history

Hutchison MediPharma, located in Shanghai, China was founded in 2002 as a pharmaceutical research and development firm. It is a wholly owned subsidiary of Hutchison China Meditech Ltd (Chi–Med), which is in turn 72 percent owned by Hutchison Whampoa Limited, an international corporation with diverse holdings that include a number of healthcare firms (Hutchison Baiyunshan; Shanghai Hutchison Pharmaceuticals; and Hutchison Healthcare). In 2007, Chi–Med provided USD 10 million in funding to cover the costs of discovery programs and clinical trials in the U.S. and China. The company has 200 employees.

Technology capabilities and value-chain position

Hutchison MediPharma focuses on precedented pharmaceutical targets and is active in all stages of drug discovery. Candidate drugs are developed through phase II clinical trials. The firm owns and operates a research and development facility in Shanghai's Zhang Jiang High-Tech Park and a Chinese-certified animal testing facility. Its discovery-chemistry strategy is based on new botanical drugs, semi-synthetic natural-product drugs, and synthetic compounds. It is currently performing clinical trials in the U.S. on several drugs with established proof of concept in China. Its two most promising, which have received FDA approval for phase I and phase II clinical trials in the U.S., are HMPL-002, a radiosensitiser for the treatment of head, neck, and non–small-cell lung cancers in combination with chemo and radiotherapy; and HMPL-004, a proinflammatory-cytokine inhibitor for the treatment of Crohn's disease and ulcerative colitis.

Business model and partnerships

Hutchison MediPharma focuses on the development of drugs to treat cancer and autoimmune diseases. Revenue for the company is generated via risk-and-

reward sharing in research (obtaining revenue from milestone payments as well as from royalties on drug sales) and by licensing its own drug products once they have reached the latter stages of development prior to phase III clinical trials.

The company has partnered with Eli Lilly, Merck KGaA (Germany), and Procter & Gamble. It also has several alliances with academic institutions, including the University of California at Los Angeles, Shanghai Institute of Materia Medica, the Genetic and Cell Biology Institute of North-Eastern Normal University, Hong Kong Chinese University, the University of Maryland, and Cambridge University. The firm engages these academic institutions in an effort to identify novel drug targets and build compound libraries.

Strengths and limitations

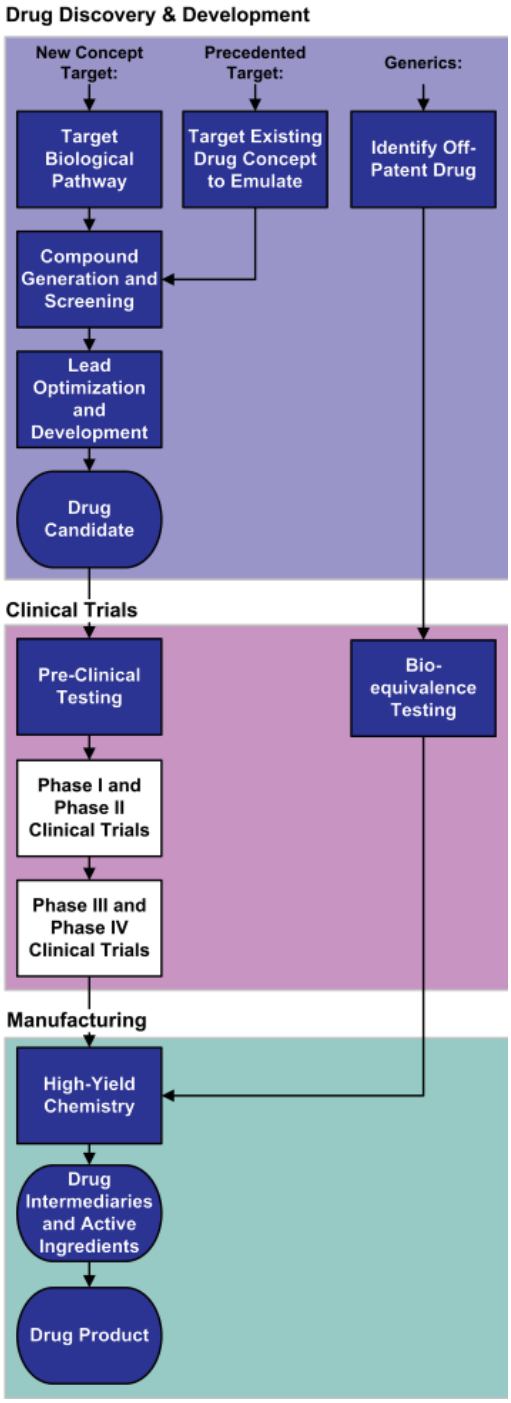
Hutchison MediPharma is one of the few domestic Chinese companies with a fully integrated drug-discovery and -development infrastructure. The firm believes it has an advantage in its ability to move drugs along the value chain quickly and efficiently by taking advantage of the Chinese clinical-trial regulatory environment for faster proof-of-concept studies, shorter patient-recruitment times, and lower patient costs than are possible in the U.S.

Most of Hutchison MediPharma's scientists are western-trained. The management team consists of former research executives of international pharmaceutical and biotechnology companies.

Hutchison MediPharma's CEO, Dr. Du, believes that improvements in the Chinese regulatory environment may provide her company with further advantages. China has only recently been exploited as a venue for global pharmaceutical-drug discovery and development, she says, and the laws and regulations have not yet adapted to this explosion of growth. She also believes that there is a bottleneck between research and development activities in China that modern regulations could alleviate, in terms both of the long approval time for the State Food and Drug Administration (SFDA) of China to allow for clinical trials and of the amount of preclinical data required in order to start clinical trials.

Novartis China

Business model: original Proprietary research; research partner; generics and manufacture
Active value-chain segments (highlighted in blue):



Company history

Novartis was founded in 1996 through the merger of prominent Swiss chemical and life-sciences companies Ciba–Geigy and Sandoz. In the twelve years since, Novartis has established itself as a prominent global pharmaceutical company with sales in more than 140 countries, annual revenue of USD 39 billion, and 98,000 employees world wide.

Novartis first established a Beijing office in 1997. Today, the company employs more than 2000 individuals in China. By 2007, China revenues had reached USD 342 million. With the Chinese market's projected growth, establishing a foothold in the country is a top priority for Novartis.

Technology capabilities and value-chain position

In China, Novartis is engaged in the discovery and development of proprietary-drug candidates and the manufacture and sale of generic drugs. It is building capabilities to pursue drug development through phase III clinical trials. Dr. Kevin Chen, Chief Operating Officer of Novartis Institutes for Biomedical Research in Shanghai, says that his company's focus has been on drugs for diseases that are prominent in the Chinese and Asian populations, such as infectious diseases and liver cancer. It is building a USD 100 million R&D center in Shanghai and an USD 83 million manufacturing and development center in Changshu to address these opportunities.

Business model and partnerships

Novartis China is actively pursuing projects aimed at the Chinese market. The company's internal R&D efforts are complemented by its collaborative efforts and partnerships with Fudan University, Shanghai Institute Materia Medica, and WuXi PharmaTech, amongst others. These collaborations are based

on knowledge sharing and information exchange to promote innovation, technology, and new-drug discovery.

Strengths and limitations

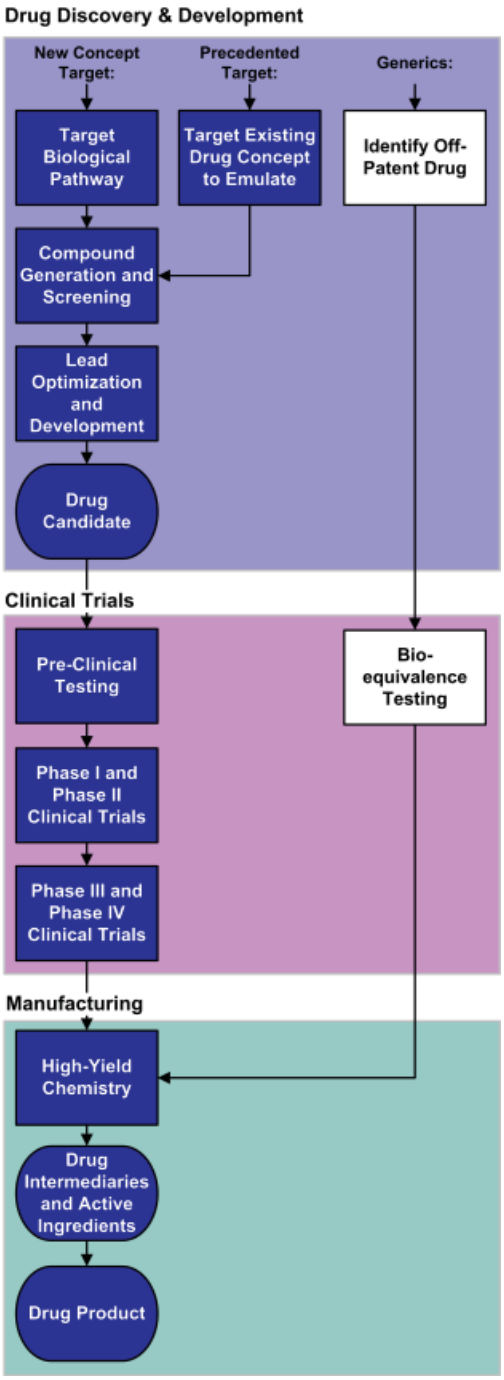
Having identified the immense growth potential in China, Novartis aspires to establish Novartis Institutes for Biomedical Research in Shanghai as a leading R&D center. According to Dr. Chen, some of the key challenges that Novartis faces in achieving its business goals are the ability to recruit and retain well-trained people and, as a global organization, to manage the cultural and geographic differences between East and West. Despite the availability of many Chinese graduates, there is still a shortage of highly skilled managers and experienced, well-trained researchers. Novartis is meeting the demand for skilled personnel by hiring western-educated Chinese returning to China in search of better opportunities. Seventy percent of managers and 30 to 40 percent of R&D staff members hold degrees awarded outside China.

Other key concerns include an English–Chinese language barrier; the timely availability of reagents; and regulatory constraints.

Pfizer (China)

Business model: original proprietary research; manufacturing

Active value-chain segments (highlighted in blue):



Company history

Founded in 1849 and headquartered in New York, U.S., Pfizer Inc. is the world's largest pharmaceutical firm by market share, controlling 6.3 percent of the global pharmaceutical market in 2007. The firm has 85,000 employees located in more than 150 countries, and its 2007 revenues were USD 48.4 billion. Its R&D spending in 2007 was USD 8.1 billion. Pfizer has grown significantly in the last two decades, largely through mergers and acquisitions; the firm was the 14th-largest pharmaceutical company in 1990.

Pfizer has been operating in China since the early 1980s. Pfizer (China) employs about 2500 individuals, of whom 200 focus on research and development (R&D). The company has invested more than USD 500 million in its China operation, which includes a presence in more than 160 cities and state-of-the-art pharmaceutical plants in Suzhou, Dalian, and Wuxi. Its R&D center in Shanghai is a part of Pfizer Global Research & Development.

Technology capabilities and value-chain position

Pfizer is actively involved in discovery, development, clinical trials, and manufacture. Its operation in China engages in sales and marketing; manufacturing; and R&D through partnerships with contract research organizations (CROs) and local academic research institutions. It also conducts clinical trials supporting its local and global drug development.

Business model and partnerships

Pfizer is increasingly relying on acquisitions and CROs to fill the company's drug-development requirements. About 50 percent of these needs are filled through acquisitions. Concerned for its intellectual property, Pfizer has built trusted relationships with only a few companies and has avoided collaborations involving its most sensitive intellectual property. It is now using its CRO partners

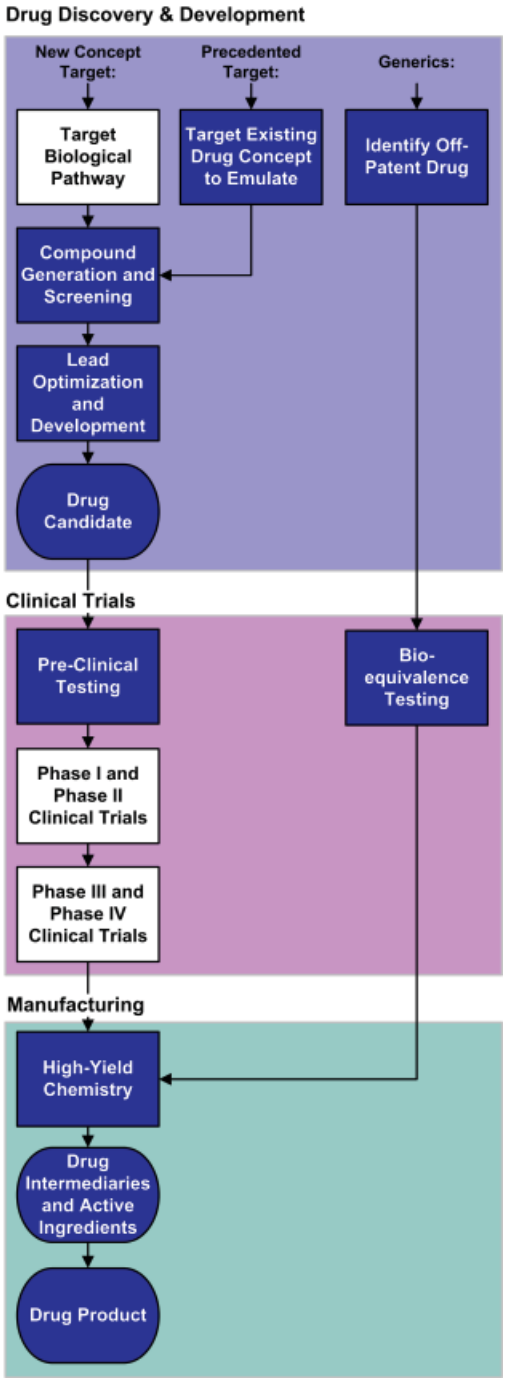
for more of the complex work, though. One such is WuXi PharmaTech, one of China's largest CROs, which Pfizer contracts to perform lab services and custom synthesis work.

Dr. Steve Yang, Vice-President and Head of Asia R&D, states that the majority of Chinese CROs offer R&D services that are functionally based (e.g. chemistry, biology, etc.) and that more Indian CROs offer integrated services. Despite this, Dr. Yang expects the majority of innovation in the near future to originate in the U.S. and Western Europe, given the substantial scientific-research ideas and expertise that both regions have accumulated in academia and industry in the past several decades.

In Asia, Pfizer has yet to negotiate any risk-sharing relationships with outside firms and continues to rely exclusively on acquisitions and CROs for drug-discovery. In addition, Pfizer's Shanghai R&D center, with about 200 employees, supports Pfizer's global clinical development. Pfizer plans significant expansion of R&D, especially in oncology and in types of disease common in Asia.

Ranbaxy Laboratories

Business model: original proprietary research; research partner; generics, APIs, and manufacture
Active value-chain segments (highlighted in blue):



Company history

India's largest pharmaceutical company, Ranbaxy Laboratories (Ranbaxy), is a sizable contributor to the global production of generic drugs. Incorporated in 1961, it employs more than 12,000 individuals, including more than 1400 are scientists engaged in research and development (R&D). Its revenue was USD 1.6 billion in 2007, of which USD 419 million came from North America and USD 365 from Europe. Approximately seven percent of the company's revenue was spent on R&D in 2007.

Ranbaxy sells products in 125 nations, in 11 of which it has manufacturing facilities. With significant experience in the manufacture and distribution of generics, the company is now actively engaged in expanding its high-value capabilities.

Technology capabilities and value-chain position

Ranbaxy designs and manufactures generic drugs, APIs, and pharmaceutical intermediaries; conducts internal research on new drug-discovery and drug-delivery systems; and is collaborating with GlaxoSmithKline and Merck on preclinical testing.

The company's generic drugs target infectious, cardiovascular, central nervous system, respiratory, dermatological, orthopedic, nutritional, and urological conditions. Ranbaxy is also developing ten new chemical entities for use in infectious diseases, urology, metabolic disease, oncology, and inflammatory and respiratory illness. The company innovates in its generics business through an understanding of high-yield generics chemistry and the creation of fixed-dose drug combinations, combining multiple treatments in a single pill.

Business model and partnerships

Ranbaxy's business strategies include the internal development, manufacture, and distribution of generic drugs; partnerships with outside firms; and corporate acquisitions. It enhanced its portfolio of

products by establishing joint ventures and acquiring companies in Europe, Africa, and the U.S..

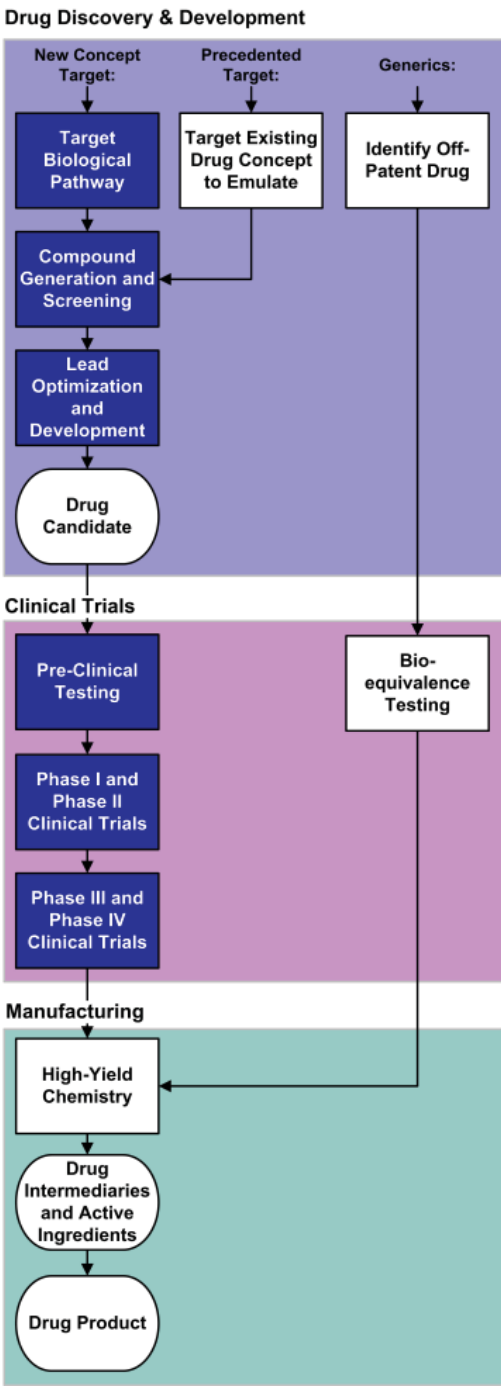
It is collaborating with GlaxoSmithKline (GSK) to investigate a range of therapeutics of interest to GSK, including anti-infectives and metabolic, respiratory, and oncology products. A joint Ranbaxy–GSK team recently approved the candidate selection of a respiratory-inflammation target, and in February 2007 Ranbaxy signed an agreement with GSK enlarging its development responsibilities. GSK presented Ranbaxy with a series of target compounds prescreened for suitability in high-volume manufacture. Ranbaxy's role is to perform toxicity, selectivity, enzyme-regulation, and inhibition studies on these targets. A recently signed agreement with Merck gives Ranbaxy responsibility for discovery and development through phase IIa clinical trials of several potential antimicrobials. Milestone payments for each collaboration may total more than USD 100 million, and Ranbaxy will be eligible for royalties from both. Alliance and partnership have enabled the company to enter new specialty therapeutic segments, including bisimilars, peptides, and limuses (anti-arteriosclerotic drugs).

Strengths and limitations

Ranbaxy's Executive Director, Ramesh Adige, believes that the strength of India's bench chemists combines with labor-cost efficiency to create a unique environment. Moving up the value chain into activities that are more lucrative requires greater investment in R&D, which his company is now making. Senior Vice-President (New Drug Discovery Research), Pradip Bhatnagar, acknowledges that foreign companies are often hesitant to hand over proprietary manufacturing processes or disease-related biomarkers, as these core pieces of intellectual property are instrumental in defining manufacturing practices and early-stage research respectively. He believes this caution is now changing.

ShanghaiBio

Business model: contract research organization
Active value-chain segments (highlighted in blue):



Company history

ShanghaiBio is the CRO subsidiary of Shanghai Biochip Co., Ltd, which was established in 2001 through funding from seed investors and the Chinese government. The company is located in Shanghai's Zhangjiang Medicine Valley and has a global business office in New Jersey, U.S. It employs 300.

In addition to performing contract research, ShanghaiBio has engaged in various academic biology-research endeavors. The firm also contributed to one percent of the human genome sequencing project and in ten percent of the Human Genome HapMap project.

Technology capabilities and value-chain position

ShanghaiBio has positioned itself as a provider of biological, preclinical, and clinical-trial services throughout the value chain. It offers a range of systems-biology tools and resources to enable its clients to target and analyze biological pathways and preclinical and clinical biomarkers. These include genomics, proteomics (study of the proteins that an organism produces), pharmacogenomics (study of the influence of genetic variation on drug response), target-validation techniques, bioinformatics, global logistics of clinical samples, and tissue banks. Shangahi Bio was the first Chinese service provider authorized to use Affymetrix GeneChips, a leading microarray technology widely employed in microarray studies, which analyze gene expression from many genes simultaneously, and it has analyzed tens of thousands of these gene chips in performing data analysis and sample processing for its clients.

The company has a tissue bank containing more than 10,000 samples with detailed clinical information. It provides preclinical trial services and support in phase I to phase IV clinical trials. The company has access to hospitals and to small and large laboratory animals and the neighboring service partners from which to obtain them. It conducts

drug-efficacy testing, pharmacokinetic analyses, and biomarker validations.

Business model and partnerships

ShanghaiBio receives fixed payments for its biology and research services, according to the type and complexity. In 2007, ShanghaiBio's work portfolio included 22 international projects with major pharmaceutical firms. Example clients include Merck, GlaxoSmithKline, Johnson & Johnson, and Lilly. Merck contracted ShanghaiBio for a long-term collaboration on a clinical oncology study. ShanghaiBio collected tissue samples indicative of four types of oncology for use in clinical trials; used its microarray expertise to analyze gene expression; and presented the final gene panels, unanalyzed, to Merck, allowing Merck to maintain exclusive control over the intellectual property arising from its research. For Johnson & Johnson, ShanghaiBio provided a genotyping SNP analysis of metabolism genes obtained from clinical samples in many countries.

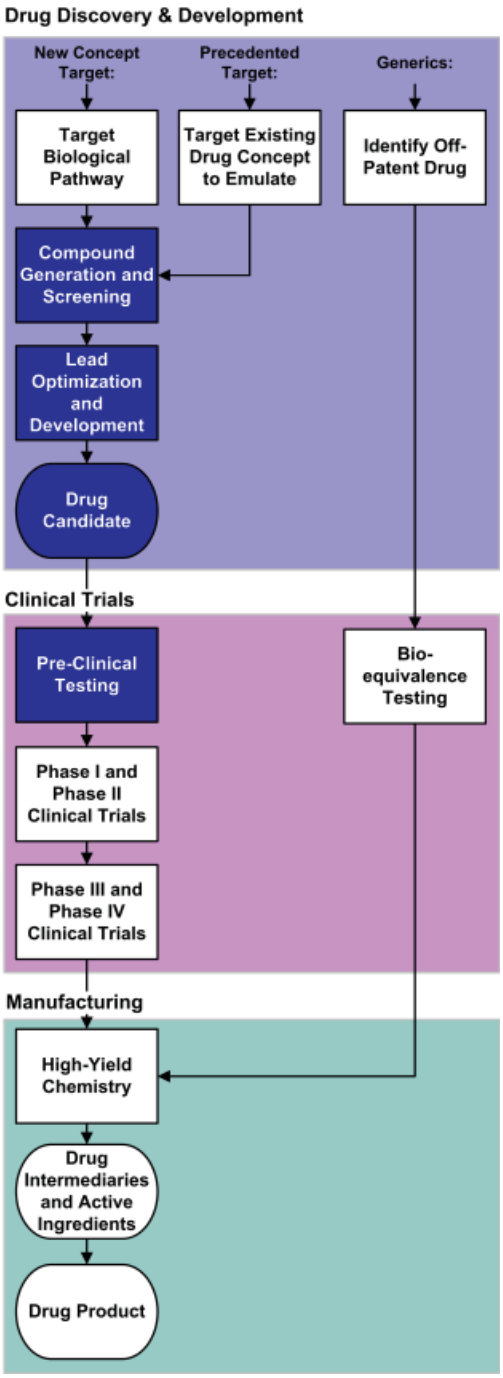
ShanghaiBio states that it was able to collect 100 specialty biosamples for Lilly during a three-week period in China that were nearly impossible to obtain in the U.S.

Strengths and limitations

ShanghaiBio says it is able to provide its clients with timely and cost-effective services, achieving these savings through its possession of a significant proprietary tissue and blood bank; the relative ease of new-tissue acquisition in China; strong internal technology capabilities; dedicated project management; and quality control. On many projects, it is able to offer prices 30 to 60 percent lower than U.S. pricing, and sample-collection costs can be discounted by as much as 90 percent.

Shanghai ChemPartner

Business model: contract research organization
Active value-chain segments (highlighted in blue):



Company history

Shanghai ChemPartner, a contract research organization (CRO), was founded in 2003 as the flagship subsidiary of ShangPharma, China's second-largest pharmaceutical and biotechnology CRO. As of 2008, it has about 1200 employees, 15% of whom hold PhD degrees.

In November 2007, the company received a strategic investment from Texas Pacific Group, a private investment partner, to integrate drug-discovery and -development processes.

Technology capabilities and value-chain position

Shanghai ChemPartner provides project-specific R&D capabilities in the fields of pharmaceuticals, biotechnology, agrochemistry, and chemistry. It operates a state-of-the-art R&D laboratory, including 800 synthetic workstations, in Shanghai's Zhang Jiang Hi-Tech Park. It is active in all stages of drug discovery and development, beginning with compound generation. The firm is often engaged to perform biological-target validation, assay development, hit-to-lead optimization, and preclinical development. The company performs no clinical trials but is involved in preclinical development, and its services include discovery chemistry; library generation; analytical chemistry; medicinal chemistry; process chemistry; absorption, distribution, metabolism, and excretion (ADME) studies; natural-product chemistry; computational chemistry; and drug design. As a CRO, Shanghai ChemPartner does not specialize in any disease area but tailors its services to customer requirements.

Business model and partnerships

Shanghai ChemPartner performs custom research services within the drug discovery and pre-clinical trials portions of the pharmaceutical value chain. Its clients include Curis Inc. and LEAD Therapeutics.

Strengths and limitations

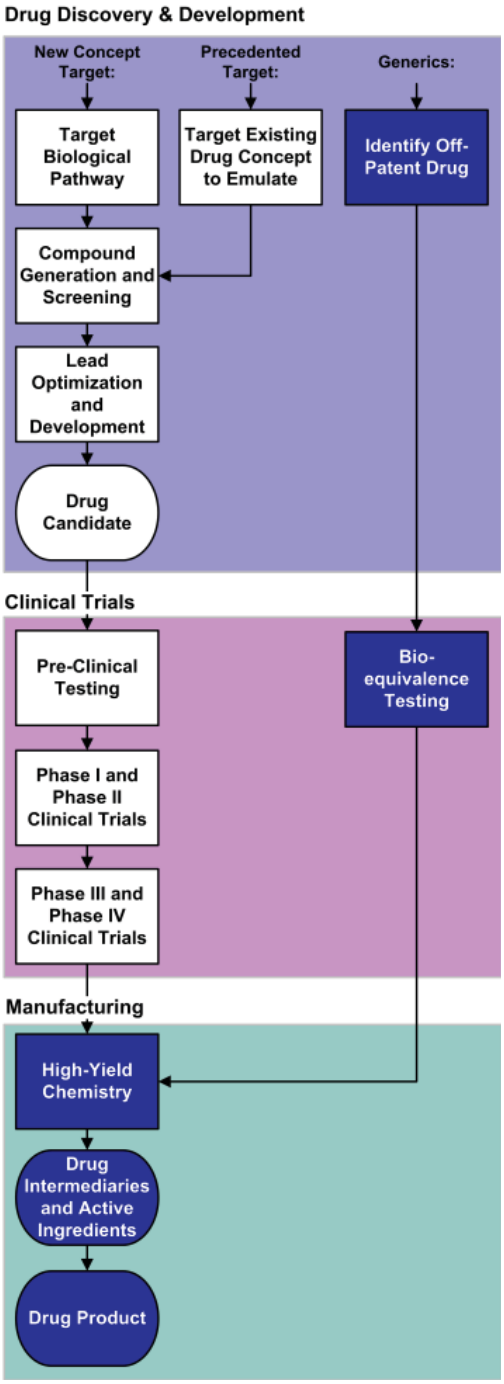
Shanghai ChemPartner's Vice-President of Biology, Dr. Xu, believes that three factors give the company a competitive advantage over its American CRO counterparts: speed, quality, and cost. The management staff is western-educated, and the majority received U.S. degrees. About 50 management and scientific leaders have western degrees or work experience.

Dr. Xu sees several hurdles to future growth of the pharmaceutical industry. First, the cost of labor is rising, and competition for top talent is becoming fiercer. Second, the company is finding difficulty in the import and export of biological samples and reagents to and from China. Finally, regulatory restraints limiting the acceptance of new-drug applications and the creation of new clinical trials remain to be overcome.

Dr. Xu also believes that westernizing the Chinese pharmaceutical industry will be necessary to attract western multinational business. The industry is in a state of rapid change, vigorously broadening its product range and abbreviating the cost and time of drug discovery and development.

Sun Pharmaceutical

Business model: generics, APIs, and manufacture
Active value-chain segments (highlighted in blue):



Company history

Sun Pharmaceutical Industries Limited, located in Mumbai, India, was founded in 1983. It began with five products that treated psychiatric ailments, and these were sold in only two states in India. As of 2008, Sun Pharmaceutical employs more than 7000 , on three continents, and has 17 manufacturing units and two research sites. Its revenues in the year to March 2008 were USD 800 million, of which 43 percent came from finished dosages sold in India and 41 percent came from generics sold in the U.S.

Technology capabilities and value-chain position

Sun Pharmaceutical develops specialty APIs and formulations targeting niche segments of the Indian pharmaceutical market, including drugs to treat cardiovascular, gastroenterological, psychiatric, and neurological disorders. The firm has two R&D centers, which house more than 550 scientists, and its facilities include stability-testing labs, nanotechnology labs, liposome labs, and an aerosol area. Ten percent of the company's net sales is spent on generic-drug research and development. The company has been awarded 70 patents on technology developed through its research endeavors.

Sun Pharmaceutical also has 17 manufacturing facilities, seven of which (six in India and one in Hungary) are devoted to the production of APIs and are ISO 14001– and ISO 9002–approved. The company offers more than 150 APIs, the majority of which have been approved for distribution in regulated markets, including Europe and the U.S.

Sun Pharmaceutical has a number of subsidiaries, most of which it acquired. Caraco is its U.S. generics subsidiary. Sun Pharmaceutical's acquisition of M.J. Pharmaceuticals, whose plants are approved for the

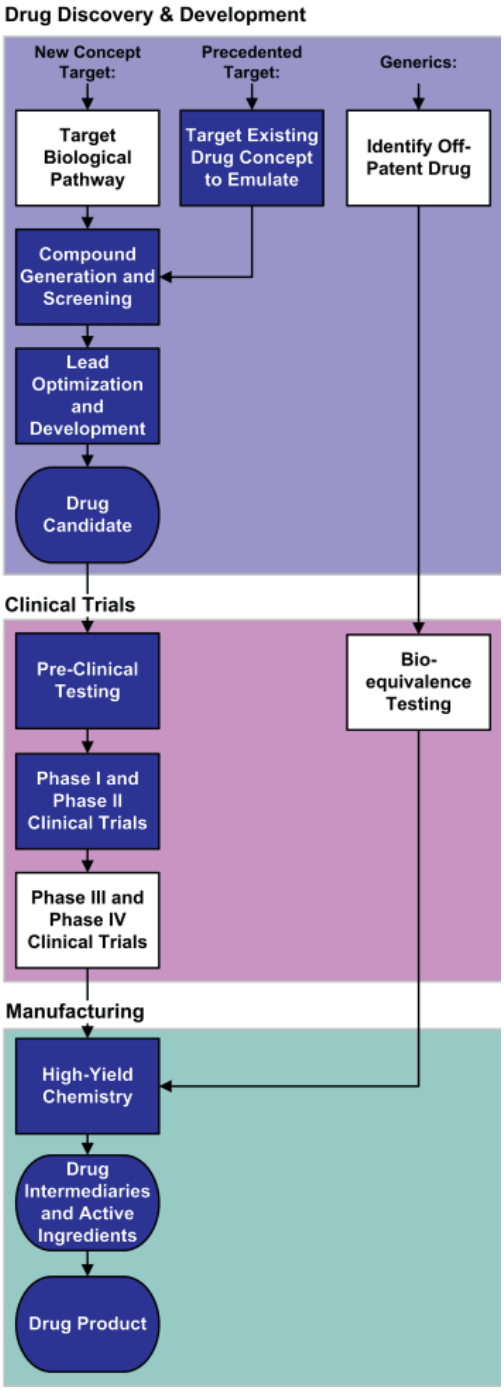
manufacture of products in South Africa, Brazil, and Columbia, enabled it to progress in international markets. Acquisition of ICN Hungary in 2005 enabled it to enter the controlled-substance API-manufacturing market. A merger with Tamil Nadu Dadha Pharmaceuticals provided capabilities in fertility, cancer, anesthesiology, gynecology, and pain management.

Business model and partnerships

Sun Pharmaceutical has relationships with several Indian, Chinese, and European companies that supply it with pharmaceutical ingredients. Within the U.S., it distributes products through Wal-Mart, Walgreens, CVS, Cardinal, and others.

WuXi PharmaTech

Business model: contract research organization
Active value-chain segments (highlighted in blue):



Company history

WuXi PharmaTech was founded in 2000 as a pharmaceutical and biotechnology contract research organization (CRO). It currently has 3300 scientific staff members, including 2550 scientists, and provides integrated services in drug research and development (R&D), clinical trials, and manufacture. The company has more than 700 customers, including major pharmaceutical, biotechnology, and medical-device companies in the U.S., Europe, and Japan. In 2007, WuXi PharmaTech earned USD 33.9 million on revenues of USD135.2 million. In January 2008, it acquired AppTec Laboratory Services, a U.S.-based company. Company officials state that they expect this acquisition to help double revenues in 2008.

Technology capabilities and value-chain position

WuXi PharmaTech specializes in laboratory services, preclinical development, and manufacture. Its laboratory services include lead generation; lead optimization; synthetic chemistry; assay development; drug metabolism and pharmacokinetics; absorption, distribution, and excretion; metabolite identification; animal-disease modeling; and toxicology services. Its pharmaceutical-development services consist of preformulation studies, analytical development, stability evaluation, and regulatory-submission–preparation services. It is one of the few originally Chinese companies with these laboratory and developmental capabilities that also manufacture drugs.

WuXi PharmaTech operates a large research facility in Shanghai Waigaoqiao Free Trade Zone; a cGMP-quality manufacturing plant in Jinshan District, Shanghai; and a new Tianjin research facility. It is constructing in Suzhou what is routinely called China's largest preclinical drug-safety center, a building 323,000 square feet (30,000 square metres) in floor area.

Business model and partnerships

WuXi PharmaTech says it plans to remain a service company. It has a passion for researching possible compounds for new-concept drugs, but no interest in the financial risks associated with the low success rate of candidate drugs.

WuXi PharmaTech does not specialize in any disease area, but instead tailors its service to its customers' requirements. Similarly, using the CRO model, it assumes none of the financial risks, positive or negative, involved in pharmaceutical R&D, and disowns all interest in the intellectual property created in the collaboration. About 80 percent of its revenue comes from relationships with American companies; 15 percent from European; and five percent from Japanese. Its partners include Merck, Pfizer, and others. When it was first established, most of its customer relationships were transactional and tactical, but the company says its relationships with partnering firms are becoming strategic and long-term. In the majority of drug-development relationships, WuXi PharmaTech is contracted to create molecules and to prepare them for clinical trials.

Works Cited

Arndt, S.; and **Kierzkowski**, H. (2001), "Introduction", in *Fragmentation: New Production Patterns in the World Economy*, Oxford: Oxford University Press, pp 1–16.

Bertonelj, Andrej; and **Kesic**, Dragan (2007), "Strategic Aspects of Global Pharmaceutical Industry", *Oeconomica* 2007:1.

Freenstra, R (1998), "Integration of Trade and Disintegration of Production in the Global Economy", *Journal of Economic Perspectives* 12(4):31–50.

Gray, Nicole (2006), "Keeping Pace with the Evolving Pharmaceutical Business Model", *Pharmaceutical Executive* May 2006:92–101 (quotation on p. 94).

Hao, Xin (2007), "Monkey Research in China: Developing a Natural Resource", *Cell* June 15, 2007;129:1033–1036.

Houlton, Sarah (2007), "Novartis Pulls Out of India: The drugmaker heads to China after patent request is denied by the courts", *Pharmaceutical Executive* October 2007:26.

Jack, Andrew (2008), "The man who took on Big Pharma: Yusuf Hamied makes cut-price generic versions of the world's most successful drugs. Is he a crusading champion of the poor, or just a profiteering 'pirate'?" *Financial Times*, March 29–30, 2008, Life & Arts supplement:1–2.

Kripalani, Manjeet (2008), "In India, Death to Global Business", *BusinessWeek*, May 19, 2008:44–47.

Macartney, Jane (2005), "China to 'tidy up' trade in executed prisoners' organs", *The Times* (London) December 3, 2005:48.

Mandavilli, Apoorva (2006), "Monkey business: China is preparing to become the world's supplier of research primates. But are Western scientists ready to buy?" *Nature Medicine* 2006;12(3):266–267.

Mirasol, Feliza (2007), "Drug discovery hits India", *ICIS Chemical Business*, 23 July 2007 at http://www.icis.com/Articles/2007/07/23/9046295/india-drug-discovery-thrives-in-competitive-r.html

"**No world-class lab for clinical trials in India: Plan panel**" (2008), *India Express* April 11, 2008.

"**Novartis's Ranjit Shahani: Patenting Innovation 'Is the Best Protection for Patients'**" (2008), India Knowledge @Wharton online, May 15, 2008 at http://knowledge.wharton.upenn.edu /india/article.cfm?articleid=4286

Pil, F. and **Holweg**, M. (2006), "Evolving from Value Chain to Value Grid", *MIT Sloan Management Review* 47(4).

Sanna-Randaccio, F.; and **Veugelers**, R. (2007), "Multinational Knowledge Spillover with Decentralized R&D: A Game-Theoretic Approach", *Journal of International Business Studies* 38:47–63.

Sinha, Kounteya (2008), "Clinical Trials: India pips China, is popular destination", *Times of India* (Bangalore) April 5, 2008:13.

Saftlas, H.; and **Diller**, W. (2007), "Industry Surveys — Healthcare: Pharmaceuticals", Standard and Poor's November 29, 2007:13

Wechsler, Jill (2008), "Supply Chains Without Borders: International Outsourcing Carries Risks for Marketers and Regulatory Challenges for FDA", *Pharmaceutical Executive* April 2008:28–30.

Appendix A: Glossary

Active Pharmaceutical Ingredients (APIs): the intermediate chemicals and compounds used in the manufacture of final drug products.

Biological pathway: the set of linked biological components and their mutual interactions over time that generate a particular biological effect.

Bioequivalence: pharmacokinetic similarity (of drugs) as established statistically.

Compound: a chemical structure comprising identical molecules each of two or more elements.

Drug target: an enzyme, receptor, channel, or other kind of molecule participating in a biological pathway.

Efficacy: capacity to produce a desired effect.

Enzyme: a protein that acts as a catalyst in chemical or biological reactions.

Precedented drug: a drug that seeks to affect a well-documented drug target.

Generic drug: a drug manufactured under license to its patent's owner or after expiry of patent rights on its manufacture.

Hit-to-lead: a series of screens imposed during drug discovery that identify the most promising "lead" compounds from a larger pool of high-potential "hit" compounds.

Innovation system: the infrastructure, team-building methods, or corporate culture used to facilitate innovation.

In vitro: in the laboratory.

In vivo: in the body.

Lead optimization: widely considered the most challenging stage in the drug development process. In lead optimization, promising "lead" compounds identified through screening are enhanced through multistage refinements of their chemical structure to maximize specificity within a target drug pathway. This process is highly iterative and nonlinear.

Microdose: a dose (administered during clinical efficacy trials) sufficient to enable monitoring of pharmacokinetics but not drug toxicity or safety.

New-concept drug: a drug that is the first to be designed to take advantage of a drug target.

Parenteral: piercing or bypassing the skin or mucous membrane.

Pharmacokinetics: absorption, distribution, metabolism, and excretion (of a drug).

GLOSSARY

Phase IIA Clinical Trials: Clinical trials assessing drug efficacy on a small population of human subjects.

Phase IIB Clinical Trials: Clinical trials assessing efficacy and dose ranging on large populations of human subjects.

Value chain: the interrelated series of activities that contribute to the production and delivery of a given product or service.

Value-chain governance: the series of power and coordination relationships between a firm and its suppliers, characterized by supplier capabilities, codifiability of information, and transaction complexity.

Appendix B: Methodology

Company summaries: Here we use a case-based analysis of pharmaceutical companies located in India and China to ascertain how new business strategies and value-sharing relations are allowing firms in both countries to contribute to international drug-discovery and drug-development projects. We conducted on-site interviews in Shanghai and Beijing, in China; and in Bangalore, Delhi, Pune, and Hyderabad, in India. These were supplemented by phone interviews. We sought out staff with intimate details of a company's strategic activities, research and development projects, and future vision. In most cases we interviewed Chief Executive Officers, Chairmen, and Vice Presidents. During our interviews, we sought to extract data on each company's business model and relationship with partners; research and development activities; personnel training; and recruitment.

Value chains: We analyzed value-chain constraints on the type and complexity of drug discovery and drug development, clinical trials, and manufacturing work being assigned to India and China. Based on established academic literature; reports; and our team's site visits, we structured the breakdown by stages of these value chains to most accurately depict the key steps involved in this increasingly fragmented industry.

Intellectual property: In order to track the global locations of recent innovation, our team made use of the World Intellectual Property Organization's (WIPO) Patent Cooperation Treaty (PCT) database. PCT applications are a means of seeking intellectual-property protection in multiple countries simultaneously. Currently recognized by 184 member countries, WIPO allows an individual or entity to file a single international application to begin the patenting process rather than submit individual national or regional patent applications.

Each piece of intellectual property described in a PCT application is accompanied by a group of International Patent Classification (IPC) codes. These codes allow intellectual property to be grouped independent of technology areas. Our team conducted a detailed analysis of IPC codes that classify biological and chemical reactions relevant to the pharmaceutical industry; medical equipment; and diagnostic procedures. By analyzing the codes most often filed under by the highest-earning pharmaceutical companies, we were able to identify a listing of 379 codes that encompass a representative sample of pharmaceutical filings (see Appendix D). We used these to estimate the change in pharmaceutical PCT application filing activity from 1995 to 2006.

Appendix C: Detailed pharmaceutical value chain

Here we present a more detailed version of the pharmaceutical value chain (see Figure 6), including more-detailed discussions of the activities characterizing drug discovery & development, clinical trials, and manufacturing activities.

Drug discovery and development is the process employed to identify new biological compounds and then refine and develop them into a drug candidate. The *clinical trials* process is the series of tests required by most developed markets to demonstrate a drug candidate's safety, efficacy, and manufacturability. Finally, the *manufacturing* process depicts the high-yield, scalable chemical reactions required to mass-produce a drug. Boxes in this value chain are representative of a stage in the process. Bold text, such as "**Drug Candidate**", inside a rounded box indicates a product. A detailed explanation of the interactions between the stages follows.

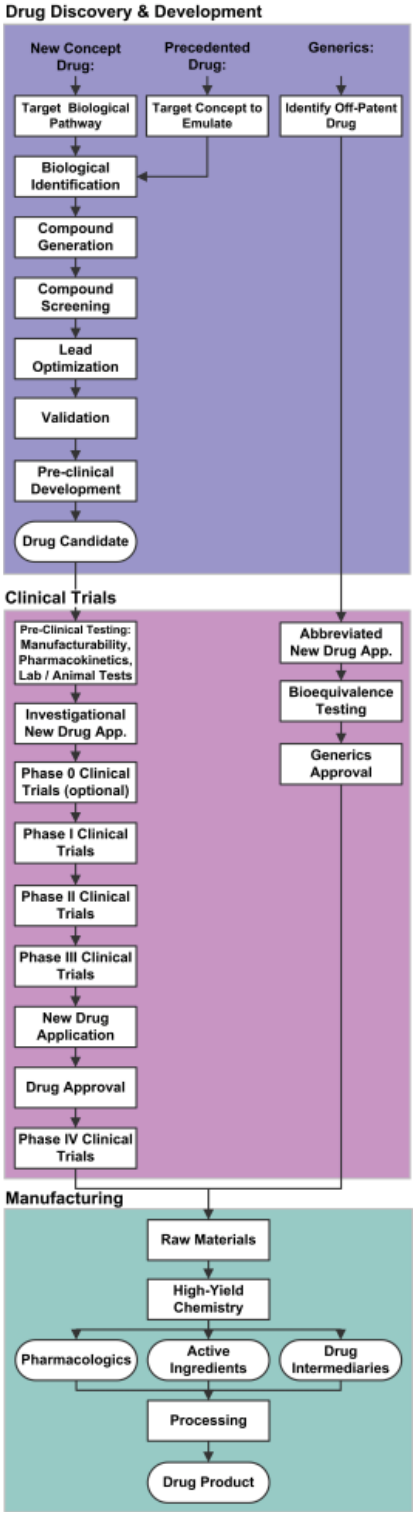
Drug discovery and development: New pharmaceutical drugs largely fall into one of three distinct categories: *new-concept drugs*, *precedented drugs*, and *generics*.

A *new-concept drug* is the first drug product designed to take advantage of a particular drug target. These are the most expensive drugs to develop; in many cases, they rely on new lines of research or biological-pathway models. New-concept drugs represent a minority of all drugs in development and are usually developed by large international pharmaceutical corporations with substantial R&D experiences and resources and technically proficient personnel.

The majority of drugs actively in development can be classified as potential *precedented drugs*. These potential drugs rely on scientists' knowledge of a documented drug target and the related functionality of existing drugs. Precedented drugs often compete with a preexisting drug on the market or are intended to provide incremental improvements or differentiation.

Drug discovery and development for new-concept and precedented drugs is a complicated and iterative process. The first step is the identification of a drug target. This usually involves locating a specific

Figure 6:
The detailed pharmaceutical value chain



biological process related to a disease. Identifying this series allows researchers to predict means of emulating, disrupting, limiting, or otherwise affecting the drug target. In the *biological identification* stage, researchers identify a specific molecule, generally a large protein or enzyme that plays a role critical to disease progression.

Future drug-development efforts will aim to minimize, redirect, nullify, or reproduce the effects of this molecule in order to alter the expression of the disease, invoke immune responses, or counter the results of another biological process. To accomplish this, researchers engage in *compound generation*, a process in which a multitude of biological compounds is collected from amongst natural products, genetically produced compounds, chemically synthesized compounds, and the contents of compound libraries.

Through a detailed *compound-screening* process, the most promising compounds are identified: those that have the largest effect on the drug target. Multiple, increasingly scrupulous screens ("hits-to-leads") highlight the compounds with strongest potential effect.

This stage is followed by *lead optimization*, widely considered the most challenging in the development process. In lead optimization, promising "lead" compounds identified through screening are enhanced through multistage refinements of their chemical structure to maximize specificity to a drug target. This process is highly iterative and nonlinear.

Optimized compounds are *validated* through a series of chemical and laboratory tests to confirm that their refinements have not reduced their desired effect on the drug target .

Before clinical trials can begin, the FDA requires evidence that a drug meets basic safety standards. *Preclinical development*, in the form of successful in-vitro laboratory or animal studies, can be used to validate a drug's toxicity and pharmacological effects to satisfy these requirements. Ultimately a *drug candidate* is produced that, accompanied by a Chemistry, Manufacturing, and Controls (CMC) documentation package, can enter clinical trials.

Finally, the manufacture of *generic* drugs relies on publicly available intellectual property documenting existing biological compounds that no longer qualify for patent protection. Generics markets vary significantly internationally, entailing specialized efforts to abide by national laws that govern generics' distribution and sale.

Clinical trials: The FDA requires that a series of demanding clinical trials demonstrate a drug candidate's toxicology, efficacy, and specificity in order to test its conformity to standards of safety and effectiveness. Before clinical trials begin, three parallel streams of preclinical testing must occur.

Laboratory and animal testing is completed to determine whether the candidate drug appears to meet basic safety and efficacy requirements.

Pharmacokinetic analysis is conducted to gauge a drug candidate's *absorption, distribution, metabolism, and excretion*. *Absorption and distribution* testing determines the amount of compound that is actually assimilated into and incorporated by the biological system. The biological pathway and the results of absorption and distribution testing determine whether a substance will be administered orally, topically, or parenterally. *Metabolism and excretion* testing ascertains how a drug candidate is functionally processed or modified by the biological system it is introduced to. Blood, urine, and feces are analyzed at regular intervals in order to gauge drug metabolism. Finally, preclinical *manufacturing and chemistry* tests determine whether a drug candidate can be produced in large quantities in a time- and cost-effective manner.

The completion of preclinical testing is accompanied by the filing of an Investigational New Drug (IND) Application with the FDA. This application, which documents the compound's chemical structure, findings of prior testing, and manufacturability, is approved by default unless the FDA finds fault with the documentation within thirty days of filing.

Following IND approval, a rigorous series of clinical trials begins. Throughout this process, status reports are regularly sent to the FDA. Recently created, *phase*

0 clinical trials are brief exploratory trials limited in duration to seven days or less, in which microdoses of a drug candidate are delivered to human test subjects in order to monitor its pharmacokinetics. The trials' main purpose is to exclude poorly performing drugs from the time- and cost-intensive clinical trials that would otherwise follow.

As noted earlier, *phase I clinical trials* are generally conducted on a small body of healthy volunteers to test a drug candidate's safety and pharmacokinetics in human test subjects. They are followed by *phase II clinical trials*, designed to assess drug functionality and build upon safety findings obtained from phase I trials. Phase II trials are conducted on larger patient groups and gather information on the efficacy and safety of various dosages. *Phase III trials* often represent a bottleneck in clinical-trial development, being the most costly, time-intensive, and complex. They involve large patient groups, consisting of hundreds or thousands of volunteers, depending on the target condition. The trials must be carefully designed and expertly executed if they are to effectively demonstrate drug safety and efficacy and ultimately obtain regulatory approval.

Upon completion of phase III clinical trials, a *New Drug Application* (NDA) is filed. NDA documentation must contain all of the scientific information collected in a drug's development: all safety, efficacy, toxicology, and pharmacokinetic analysis; results from clinical and preclinical analysis; documentation of the drug's chemical structure; and all patent information. In some cases, NDAs can run to more than one hundred thousand pages in length. Following NDA submission, *drug approval* for commercial distribution is granted by the FDA. *Phase IV clinical trials* track a drug for long-term safety effects after FDA approval has been granted for the drug's commercial sale. This safety monitoring is in place to identify any potential long-term safety or toxicology concerns that did not arise during the previous trials.

The approval of generic drugs is far less time-intensive and clinically rigorous. Approval of an identified off-patent drug or compound requires filing of an *Abbreviated New Drug Application* (ANDA). ANDAs generally do not require a demonstration of safety, toxicology, or pharmacokinetics. Nor do they require the completion of the aforementioned clinical-trial procedures; these requirements are deemed to have been documented in prior NDAs when the target extant drug or compound was originally conceived. Instead, ANDAs require the documentation of bioequivalence. The documentation of their *bioequivalence testing* must show that a generic drug's performance is similar to that of its original drug predecessor. Given an acceptable bioequivalence profile, a generic drug will be approved for mass production.

Manufacturing: To deliver a potential drug from a laboratory or small-scale testing environment to national or international patient populations requires reliable control of chemical reactions and manufacturing dynamics. To mass-produce a drug, *raw materials* are combined through *high-yield drug-production reactions*. Identifying scalable, simple, cost-effective chemical reactions by which to produce large quantities of a target drug is essential. These reactions produce *drug intermediates*, *active pharmaceutical ingredients*, and *pharmacological products* that are the building blocks of finalized drugs. Some pharmaceutical manufacturing companies mass-produce these intermediate components for consumption by other pharmaceutical entities. Through further *processing* and additional chemical reactions, a final *drug product* emerges for distribution.

Appendix D: International Patent Classification (IPC) codes used in our WIPO PCT analysis

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C12P 39/
C12P 9/
C12P 13/
C12P 17/
C12P 19/
C12P 21/
C12P 41/
C12P 7/
C12Q 1/
C12R 1/
C40B 60/
G01F 1/
G01F 11/
G01F 25/
G01N 24/
G01N 1/
G01N 15/
G01N 21/
G01N 27/
G01N 30/
G01N 31/
G01N 33/
G01N 35/
H01J 49/
H04R 29/