
Chazen Society Fellow Interest Paper

Drug Discovery Outsourcing: India Charges Ahead

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Cross-continental travel has become the norm for Rashmi Barbhaiya these days. “There is so much activity,” he enthuses as he steps off a red-eye flight from Bangalore to New York, his third trip of this kind in the past two months. His mission: to forge alliances with U.S. pharmaceutical companies eager to collaborate in the latest outsourcing trend to India—drug discovery and development research.

Barbhaiya is the cofounder and CEO of Advinus Therapeutics, a Bangalore-based drugmaker that began its life three years ago with the backing of India’s largest conglomerate, the Tata Group. After a 25-year stint as one of the lead researchers with Bristol-Myers Squibb in New Jersey and as president of R&D for Ranbaxy Laboratories Limited in New Delhi, Barbhaiya was eager to run his own drug discovery and development shop at the epicenter of the world’s outsourcing and emerging-innovation market. The result was Advinus, a company whose novel drug research is propelled by Indian scientists returning from abroad, domestic researchers and partnerships with global pharmaceuticals. Advinus is short for “Advantage India U.S.,” an appropriate catchall for the wave of drug discovery alliances and outsourcing that has resulted in hundreds of pharmaceutical companies and related research contractors popping up all over India. Why this sudden interest?

Based on the science alone, recent advances in two related evolving fields, genomics and proteomics, have identified a number of disease targets and created a ready market for outsourced drug discovery. Contemporary drug therapy has generally been based on a total of 500 biological targets, or key molecules, that are involved in a particular metabolic pathway specific to a disease or pathogen. In contrast, the human genome contains 35,000 to 120,000 genes, which code for at least 10 times as many proteins. Such progress has promised to generate a significant leap in usable drug targets.

However, pharmaceutical and biotech companies continue to face internal cost and labor constraints around the optimization and validation of new biological targets and molecular leads, especially in the face of downward economic activity. In fact, the sheer number of new drug targets produced is often too great for even the largest pharmaceutical companies to work on in-house. That, coupled with enormous domestic drug discovery and development costs, plus declines in R&D productivity, has induced the pharmaceutical industry to seek alternatives to meet its research needs.

The outsourcing of drug discovery services has become an increasingly vital part of today's pharmaceutical industry as companies seek to minimize inefficiencies around the existing "succeed or die" approach to drug discovery. As such, pharmaceutical companies have sought to supplement their internal drug discovery efforts as patents on blockbuster drugs expire. In some cases, the companies seek to utilize technologies that they are unable to rationalize in-house. According to a 2006 report by the consultancy Frost & Sullivan, the rapidly growing market for drug discovery outsourcing services on the demand side will increase to \$19.8 billion by 2011, fueled by advancing Asian markets, notably India and China. The largest outsourcers, now accounting for 25 percent of outsourced drug-discovery spending, are big pharmaceutical companies, such as Pfizer, Merck, Novartis, Bristol-Myers Squibb and Eli Lilly.

As in other industries, India has emerged as an attractive destination for drug discovery outsourcing due to the opportunity gains achieved in an industry where R&D failure rates are the norm and innovation is often begotten at exorbitant costs. Specifically, India provides advantages around ultraqualified and cheaper R&D personnel, a readily available, heterogeneous patient population and a less stringent regulatory environment that is still able to maintain international quality standards. A recent PricewaterhouseCoopers report indicates that India could well become one of the top 10 global pharmaceutical markets by 2020; the report also projects that industry revenues will reach \$3.3 billion by 2010.

In terms of intellectual-capital benefits, India's relatively inexpensive skilled-labor costs constitute an important driver in the growth of the country's outsourcing efforts. Salary, overhead and benefits for a drug chemist with a freshly minted PhD working in the United States is approximately \$300,000 a year, while an equally qualified scientist working in India costs less than a third of this rate. For years, Indian chemists were in demand by the country's pharmaceutical firms for their reverse-engineering skills, needed to produce low-cost, generic versions of popular patented drugs. The nature of their work changed when India signed the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights

(TRIPS) in the mid-1990s and became TRIPS-compliant earlier this decade, a shift that closed the legal loophole that allowed India to make generic versions of drugs still under Western patent protection. Now, quite a few of the Indian firms that produced generics, such as Dr. Reddy's Laboratories, are moving toward contract drug research through wholly owned subsidiaries.

The second-most populous country in the world, India has an enormous and ready market of available patients suffering from diseases of both the tropical and the industrialized worlds. And with few competing pharmaceutical-drug trials in India, many Indian clinical studies recruit patients 10 times faster than their counterparts in the United States. Furthermore, it takes, on average, only 14 weeks to set up trials, so even larger trials can be up and running extremely quickly. India also boasts 75 U.S. Food and Drug Administration-inspected facilities, more than any country other than the United States.

A testament to the success of the outsourcing model, in late 2007 Advinus achieved the first milestone in its drug discovery collaboration with Merck that focuses on target programs for metabolic disorders. Since November 2006, these companies have been working closely together to develop clinically validated drug candidates, with Merck retaining the right to advance the most promising of these candidates into late-stage clinical trials. "This milestone was achieved three months ahead of schedule, largely due to the exceptional working relationship between the two partners," Barbhैया says. "The achievement validates the company's business model and is a testimony that novel drug discovery is the wave of the future for India."

However, despite this seemingly rosy outlook, intellectual-property protection, trust, honesty and transparency in India persist as concerns for Big Pharma. In fact, Ernst & Young recently estimated that almost two-thirds of pharmaceutical executives are worried about the threats to intellectual property in India. While the Indian government has deliberately taken measures to alleviate these concerns, legal and regulatory loopholes around patent protection and market authorization still abound.

In fact, until a few years ago, the Indian pharmaceutical market was primarily involved in the production of generic drugs. Several factors contributed to the industry's focus on generics: an absence of product-patent protection until 2005; the low average disposable incomes of Indian drug purchasers, many of whom were unable to afford branded medicines; and the huge R&D investments of time, effort and expense required to introduce newly patented drugs to the market.

To better protect intellectual property, in 2005 India enacted an amendment to the TRIPS agreement, the Patent Protection Act, which for the first time provided patent protection in India

for pharmaceutical products that are classified as “new chemical entities” (NCEs). The earlier law provided patent protection only for the process of making drugs, not for the drugs themselves. However, it remains unclear how long it will take for the benefits of the new law to take effect. Furthermore, many multinational companies are not completely satisfied with either the scope of patentability or the market-authorization standards and are therefore continuing to work closely with the government to address ongoing concerns. The latest data indicate that there are 40 times as many patent applications awaiting approval in India as there are in the queue in the United States. This may be due to ambiguity in the language of the amendment concerning the technical requirements for what constitutes an NCE or a “technical advance,” among other broad phrases used to define the requirements for patent protection.

India has additional fundamental gaps in its drug discovery and development offerings. While the country has a strong talent pool of general chemists, there is a dearth of Indian technical workers specially trained to perform certain drug-related biological analyses. The perception by the pharmaceutical industry is that medical chemistry is still rather weak in India, that preclinical research is still engaged in ongoing development and that phase I studies, which provide for the initial introduction of a new investigational drug into voluntary human subjects, are just beginning to gain traction. Additionally, for more advanced biochemical projects, timelines are sometimes longer in India than they are in-house for many pharmaceutical companies, often because deliveries from chemical suppliers are slower due to India’s lagging infrastructure and assorted business delays.

Additionally, India may soon find itself in the middle of a controversy between Big Pharma and public-health activists if it decides to flout patent protection on certain cancer and AIDS therapies developed by such corporations as Pfizer and Roche and to develop generic versions for distribution to the neediest patients in developing countries; India should be making its decision in the next few months. Drugmakers say tight patent laws stimulate vital research; activists say the ensuing price monopolies prevent the drugs from reaching the neediest people in developing countries.

The TRIPS agreement does permit governments to override drug patents to allow the production of generic copies of drugs deemed critical to public health in poor countries. In October 2007, Canada became the first country to allow one of its companies to export a generic copy of a patented AIDS drug to Rwanda. Last year, Thailand was the first to override patents for non-AIDS drugs, issuing licenses for patented cancer drugs despite intense industry resistance and criticism from the United States for flouting patents. Thus, while India would not

be an iconoclast if it were to proceed with a generic strategy, it could potentially impact the pricing structure for multinational pharmaceuticals, which may have to consider reducing rates for drugs in developing nations as a means to combat patent evasion.

As a result of these challenges, a portion of drug discovery outsourcing work by global pharmaceuticals is still directed toward such specialty drug discovery companies or biotech firms in the United States as Millennium Pharmaceuticals, Pharmacoepia and Albany Molecular Research, the first two of which also develop their own drugs. Meanwhile, as the Indian drug discovery industry continues to evolve, gaining an edge with the production of a continual pipeline of drugs, faster approval cycles than in the West, proactive government policies and improved legislation for clinical trials, it is well positioned to quickly outstrip any near-term competition. For this to happen, however, the Indian government must continue to make a proactive effort to remain a steady and vigilant watchdog of fair patent protection and international trade practices going forward.

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