



White Paper:

**India: Global pharmaceutical powerhouse –
or contract research workshop?**

Matthew Howard

Kinapse, August 2006

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In response to the ever-increasing costs of drug discovery & development, pharmaceutical industry leaders must constantly seek to increase productivity whilst simultaneously reducing costs and maintaining quality. Globalisation of drug discovery may provide such an opportunity, through the conduct of costly R&D activities in emergent economies at a fraction of the cost of the West.

This report provides an overview of the current environment for pharmaceutical R&D activities in India, including the intellectual property regime, infrastructure, education, research and development, and seeks to challenge the perception of India solely as a 'contract research workshop'.

Although there are considerable challenges that must be overcome, by describing both what is possible today and presenting what has already been achieved by various global pharmaceutical companies, we advocate that India actually has the potential to become a significant global R&D powerhouse of the 21st century.

IP & Infrastructure

In the past, entering the Indian pharmaceutical market was considered unviable by many global pharmaceutical companies for a number of reasons, including the lack of intellectual property protection, infrastructure hurdles and a restrictive regulatory environment. However, a recently strengthened Indian IP regime, initiation of regulatory and infrastructure reforms and a variety of fiscal incentives, indicate that the Indian environment is now moving in the right direction.

In 2005, Indian law became compliant with the World Trade Organisation (WTO) Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement. As a result, product patents are now possible on chemical molecules for new drugs introduced after 2005. This clearly represents a significant step forward for both novel drug discovery as well as the sale of therapeutics in the Indian market. However it will present challenges, as well as opportunities, to an industry which has thrived and grown on generics.

In principle, the patent reforms should create a more favourable environment for Western-headquartered pharmaceutical companies to co-operate with their Indian counterparts but only time, and outcomes, will convince Western pharmaceutical companies that the protection is sufficient. As demonstrated in the case of Novartis' Gleevec, where a patent recognised in the West still failed to be protected in India under the new regime (Case study 1), the situation is not yet completely straightforward.

A continuing criticism of the Indian patent regime is also the bureaucracy involved and long backlog of patent applications. Efforts are underway to improve matters, including setting up patent offices, personnel quality

improvement and better use of digitization, such as electronic filing.¹

The tax situation in India is also changing; many potentially pharmaceutical industry 'friendly' policies have been introduced.² A company conducting scientific R&D is now allowed a 100% tax deduction on profit for a period of 10 years. To promote direct investment in clinical development and data management, benefits such as exemption of import duty on clinical trial samples and exemption from service tax for a period of 10 years until 2015 have also been introduced.



Figure 1: States & Cities of India

Case study 1: Gleevec Setback for Novartis

In February 2006, the Office of the Indian Controller General of Patents, Designs and Trademarks refused to approve Novartis' 1998 patent claim for the crystallized form of imatinib mesylate, the active ingredient of Gleevec. The patent was refused on the grounds that the product is a derivative of a known substance, and as such the crystal modified form does not demonstrate improved efficacy. This is a key requirement of the Indian Patent Act and as a result the Office ruled that the key invention in the drug was protected only under the original 1993 patent. Under the revised regime Indian patent law only covers patents filed after 1 Jan 1995, leaving Gleevec without patent coverage in India.

In November 2003, Novartis had obtained exclusive marketing rights (EMRs) from the Patent Controller's Office for imatinib mesylate. Following this, Novartis managed to halt activities of six generic companies in the Madras High Court. A case brought by Natco Pharmaceuticals against the granting of EMRs for Gleevec to Novartis is currently pending in the Supreme Court and is likely to gain further momentum following the February 2006 patent ruling. The Cancer Patient Aid Association of India had also filed a petition against the granting of EMRs for imatinib mesylate as this would result in the monthly cost of this drug rising from US\$ 135 to US\$ 2700.

The setback marks the first such judgment under the new patent system and puts into perspective several issues still outstanding in India's intellectual property regime. It also highlights the different stakeholders involved - multinationals, domestic companies and NGOs.

Global companies looking to invest in India should also consider the inter-state variations within the country. The Indian pharmaceutical industry itself is predominantly clustered around Mumbai, Hyderabad, Delhi and Bangalore (Figure 1). The state of Maharashtra, where Mumbai is located, contributes about 40% of the total turnover in the pharmaceuticals sector in India. It has 4,100 registered pharmaceutical manufacturers out of a total of around 20,000. Around one-third of the country's bulk drugs are produced in and around Hyderabad in Andhra Pradesh. India also has several Special Economic Zones (SEZs) such as in Kandla, Madras and Cochin, where further tax incentives are available, and initiatives to create more SEZs are underway.

Infrastructure, however, continues to be an issue. In 2005 India only invested 3.6% GDP (USD 28 billion) on infrastructure (in contrast, China invested 9% GDP—USD 201 billion).³ Measures have been taken to improve the availability and the quality of infrastructure, such as setting up independent regulators of the power and telecoms sectors, and the process of privatisation of Delhi and Mumbai airports has been initiated. Nevertheless, Montek Singh Ahluwalia, of India's Planning Commission, has stated that India must spend an additional 2.5-3% of GDP annually on infrastructure if it is to sustain economic growth of 8-9%.³

Education & Research

A successful academic network provides a steady stream of ideas, key opinion leaders, collaborative opportunities and potential recruits; lifeblood for developing a thriving pharmaceutical industry.

Considerable activity in areas such as biochemistry, molecular biology, biophysics, plant sciences, microbiology, genetics, immunology and biotechnology is being conducted in India. As shown in Case Study 2, looking at stem cell research, this activity is at the forefront of current medical and biotechnological developments. Research from around 1,400 Indian institutions has been published in journals throughout the world. Among the more well-known are the All-India Institute for Medical Sciences (AIIMS), The Indian

Institute of Science (IISc), The National Centre for Biological Sciences in Bangalore and National Centre for Biotechnology Education (NCBS).

There has been significant investment into Indian science from the Indian Government as well as external agencies. The Government funding of the Indian Department of Biotechnology (DBT) has risen from USD 15 million to more than USD 125 million a year. Funding has also come through from international sources such as the US National Institutes of Health, the Bill & Melinda Gates Foundation, the European Union and the Wellcome Trust. A particular focus has been to nurture industry-academia interaction. Nicholas Piramal, an Indian pharmaceutical company headquartered in Mumbai, has a fee-based agreement with the Institute of Genomics and Integrative Biology (IGIB) and this alliance has already resulted in two joint patents. Researchers at the Center for Biotechnology at Jawaharlal Nehru University in New Delhi, in collaboration with Panacea Biotech Ltd, have completed preclinical studies on a recombinant anthrax vaccine and will start Phase I trials shortly. The DBT earmarked 30% of its 2005–06 budget to sponsor such partnerships. In addition, such partnering activity aids technology transfer

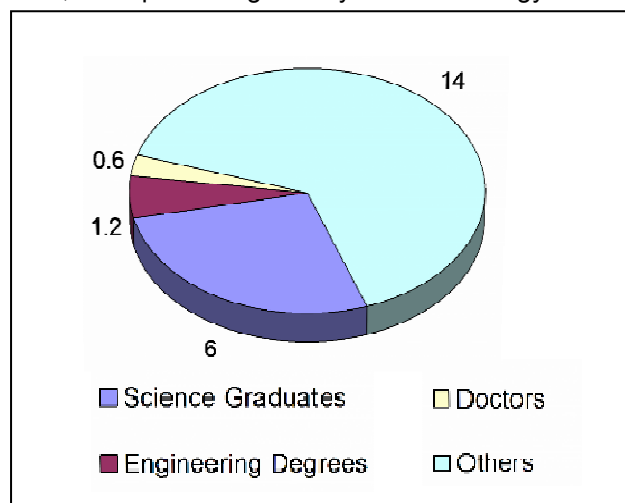


Figure 2: Analysis of graduate population of India.⁴ Figures are given in millions

Case study 2: Stem Cell Research

India currently has 'permissive' legislation regarding stem cell research, permitting the use of both adult and embryonic stem cells for medical research. Reliance Life Sciences (Mumbai), and the National Centre for Biological Sciences (Pune), have built facilities to preserve seven and three stem cell lines respectively. The All-India Institute for Medical Sciences is conducting therapeutic stem cell research work focusing on the treatment of muscular dystrophy, spinal cord injury, cerebral dysplasia, heart tissue damage, diabetes and motor neurone disease. Using bone marrow mononuclear cells, it has initiated clinical trials on about 40 patients. Given the controversy surrounding the use of stem cells in many Western countries, and mostly notably the USA, India stands to benefit from its permissive regime.

and, through practices such as internships, provides much-needed, hands on experience for young scientists.

India's graduate population of scientists and researchers is growing with nearly 2.5 million graduates added in 2004 alone (Figure 2). This includes 25,000 doctors and nearly 600,000 science graduates and post-graduates. These numbers are comparable to China's, which had more than 2 million students graduating from its universities in 2003 including 600,000 in engineering, 200,000 in science and 100,000 in medicine.

Despite the high number of graduates, there is a shortage of qualified clinical research professionals. Long term solutions are being sought, examples include setting up new academic centres, institutes and clinical research studies in medical schools.

Drug Discovery & Development

Significant and growing, discovery and preclinical development research is conducted in India by both domestic Indian pharmaceutical companies and by global companies using owned resources or through contract research organisations.

Research activities undertaken in India cut across all steps of drug discovery, from target identification and validation, lead identification and optimisation, through to candidate development (Case study 3 describes one example, the opportunity for toxicology studies). As shown by the examples in Table 1, early stage disease research activity is being conducted in India by both domestic and international pharmaceutical companies. In addition, a wide variety of services are being offered by Indian Contract Research Organizations (CROs).

Research and development of novel drugs is an increasing area of interest for Indian pharmaceutical companies. R&D expenditure increased 40% between 2003-4 and 2004-5.⁵ However, the absolute total of USD 402 million is still low by Western standards, as is the average R&D investment for most Indian pharmaceutical companies, at around 6% of net sales (A Western pharmaceutical company typically invests over 10%).

Even though in some cases Indian companies have out-licensed drug candidates to global pharmaceutical companies,¹ it seems probable that generic and contract work will remain the financial drivers of the Indian pharmaceutical industry for some time to come. To date, there has been a degree of collaboration between global pharmaceutical companies and those based in India. Merck India, for example, is active in early drug disease research through the Merck Development Centre (MDC). This is a brand-new R&D unit, set up at Taloja near Mumbai, with an investment of USD 3.9 million.

India is fast emerging as a hub for contract & clinical research, with several of the world's largest pharmaceutical companies conducting studies; however challenges remain that must be overcome to ensure that India consolidates its position and continues to grow in this key area.

Syngene, a subsidiary of Biocon India, serves six out of the top ten major multinationals as clients of its contract chemistry and biology services.⁶ In an estimated USD 40 million deal, GVK Biosciences is setting up a discovery research and development centre for Wyeth Pharmaceuticals with a dedicated workforce of 150 scientists.⁷ Such India-based external resources,

Company	Area of Research
AstraZeneca	Tuberculosis
Nicholas Piramal	Migraine, Tuberculosis, Psoriasis
Lupin Pharma	Type 2 diabetes, Obesity
Dr. Reddy's Labs	Arteriosclerosis, Restenosis, Dislipidemia.
Aventis Pharma	Anti-Infectives, Metabolism, Cardiology, CNS, Arthritis, Oncology, Respiratory
Novartis	Diabetes
Roche	Oncology, Virology, Transplantation.
FFIL, a 40% subsidiary of Schering-Plough (SP), US	Dermatology, anti-infective, anti-cancer, anti-histamine and corticosteroids

Table 1: Examples of disease area research in India

Case study 3: Preclinical Toxicology Studies in India

Pressure from animal rights groups in the West means that there is a growing opportunity to run preclinical studies requiring animals offshore. Currently the number of foreign organisations and companies sponsoring toxicity studies in India is limited, but examples do exist. They include Azaya Therapeutics, Connecticut Healthcare Systems, Interhealth Neutraceuticals and Yale University in the United States.

Several laboratories and National Institutes in India are now running preclinical development studies, ranging from animal efficacy to toxicology studies, including Clintox, Chembiotek, Rallis Research, the Institute of Toxicology Studies (INTOX) and the National Institute of Pharmaceutical Education & Research, INDIA (NIPER). The use of dogs, a key species used in long term toxicity studies, has recently also been allowed, although activity is currently limited in this area.

Regulation of animal experimentation in India is becoming more rigorous. The Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and independent Institutional Animal Ethics Committees are responsible for legislation in this area.

available for rapid deployment as appropriate, provide large pharmaceutical companies with development opportunities that may otherwise have been constrained by internal cost-issues.

Currently 20-30% of the world's clinical trials are being run in developing countries.⁸ Of these, a growing proportion is now being conducted in India, by domestic Indian pharmaceutical companies, Indian CROs and multinationals. Several factors have contributed to this growth. India has a highly heterogeneous and largely drug naïve patient population with both indigenous as well as increasing prevalence of Western, 'urban lifestyle' diseases including heart ailments, asthma, cancer and diabetes.⁹ Another advantage has been rapid patient recruitment into studies; one consequence of otherwise poor opportunities for healthcare.¹⁰ Cost is also a major driver, in the development of a novel drug candidate clinical trials alone account for a third of the total costs. It is therefore unsurprising that Western-headquartered pharmaceutical companies have sought to source these activities in India where costs stand at 50-60% of those in Western countries. Most studies being conducted in India are currently in Phase III.

The Indian CRO market has grown from USD 1 billion in

1992 to more than USD 8 billion in 2002. Quintiles Spectral, SIRO-Clinpharm and Syngene are the 3 key independent CRO players, accounting for 71% of the market share (Example coverage of Indian CROs is shown in Figure 3). Approximately 60% of Western-headquartered pharmaceutical companies have outsourced some degree of clinical development to Indian CROs, However, to date only AstraZeneca, ALTANA, Eli Lilly, Novartis and Pfizer have actually set-up their own clinical research divisions in India (it should be noted that Roche and Pfizer have set up their own Regulatory Affairs organisations to gain approval for clinical trials in India.). The remaining companies utilise outsourcing relationships with independent clinical research organizations.

Concerns relating to the Indian healthcare system, quality adherence and the ethical situation in India persist. The Indian healthcare system is highly fragmented and there is no centralised insurance system in place. Barring the small network of specialised public trust and medical college hospitals, the overall system falls short in its ability to conduct trials that meet international standards. Criticisms include overlooking inclusion and exclusion criteria to achieve unattainable recruitment times, poor data archival systems and an

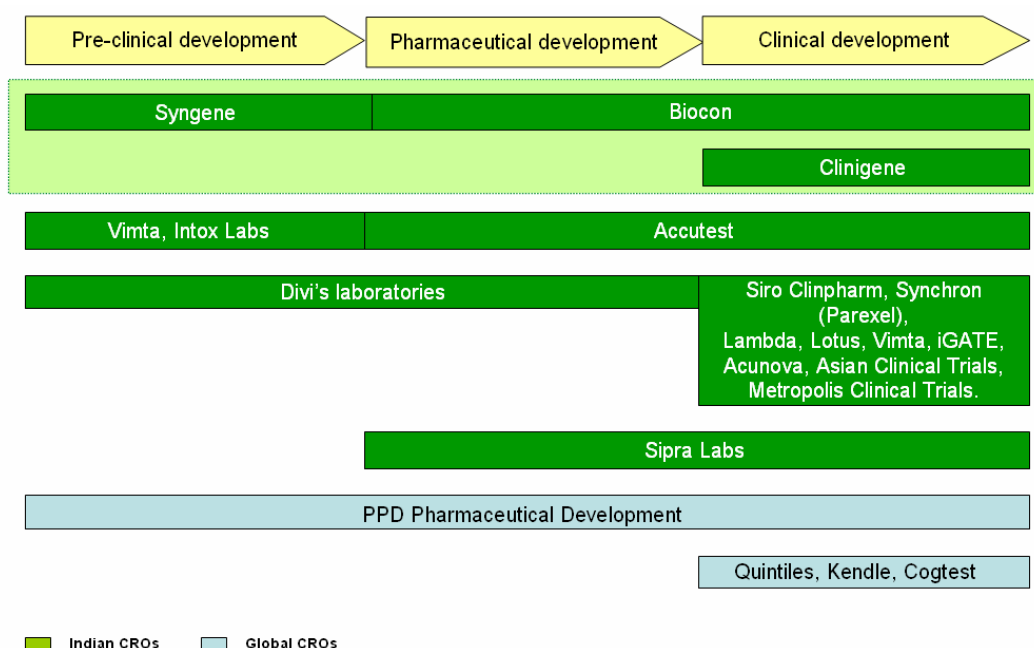


Figure 3: CRO services in India


















	Data processing	Pharmaceutical Development	Clinical Trials	Preclinical toxicology	Synthetic Chemistry / Medicinal Chemistry	Discovery Research
Outsourced			 		 	 
Directly Owned Investment	 		   		 	

Figure 4: Comparison of owned and outsourced pharmaceutical investment in India

impending shortage of clinical research associates and principal investigators. The most frequently cited concern regarding the administration of clinical trials in India relate to informed consent and monitoring mechanisms. A majority of the subjects undergoing trials in India are either illiterate or semi-literate and informed consent is often taken without complete understanding of the risks and benefits. Institutional Ethics Committees (IECs) need to be empowered and made to understand their roles and responsibilities to address this. This is happening, but will take time to take effect.

Implementation and adherence of GCP (the ICMR Code) remains a substantial challenge. The central government, together with the WHO has undertaken a large campaign to train regulatory personnel, as well as private clinical investigators, the details of good clinical practices (GCP).

Despite these concerns, and in light of reforms such as the adoption of strengthened patent laws, and the allowance of parallel multi-centric trials in India following an amendment to the Drugs and Cosmetics Act, some estimates suggest that by 2010 the Indian clinical trial market may be worth USD 1.5 billion, around 10% of the predicted total world market.¹¹

The Indian Pharmaceutical Market

The value of the Indian pharmaceutical market is projected to grow from \$10b in 2005 to \$100b by 2025

Globally, the Indian industry ranks 4th in terms of volume and 13th in terms of sales and has been growing at 8-10 percent a year.¹² The Indian pharmaceutical market has enormous growth potential with predictions of growth suggesting it may grow to about \$100 billion by 2025,¹ driven by an increasingly large middle class population. This currently numbers around 300 million (of a population of over one billion) and is estimated to be growing at 5 percent annually.¹³

As a result, demand for quality healthcare services has increased and the changing lifestyle has led to changes in disease patterns, for example increased demand for

new medicines to combat lifestyle-related diseases. As described previously, the recent regulatory and much awaited patent law changes will also contribute towards the growth of the market.

Seizing the Opportunity

Western pharmaceutical companies have taken a variety of approaches towards investing in India, these can serve as guides for other companies.

Of the top 30 western-headquartered pharmaceutical companies, 18 are currently active in India. However, the approach differs between companies.

Figure 4 examines the investment taken by some example companies (in this case Pfizer, AstraZeneca, Novartis and ALTANA) in terms of increasing complexity- from data processing to discovery research. Pfizer has invested in limited directly-owned facilities in India (within the R&D space) with the exception of the clinical trial area, with investment in a clinical research unit of approx 50 personnel co-ordinating clinical development, biometrics and regulatory affairs. This is in contrast to ALTANA, Novartis and AstraZeneca, all of whom have invested more substantially in owned facilities.

AstraZeneca has ventured into a variety of activities in India, including early disease research and drug discovery. In India, AstraZeneca has three divisions. AstraZeneca Discovery Bangalore is an integrated part of the AstraZeneca R&D network mainly focused on tuberculosis research with an overall current and planned investment of over USD 40 million. More than 100 scientists, working closely with AstraZeneca's global network of R&D centres, especially the genomics and infection research centres in Boston, USA, and in Cheshire, UK, are presently employed at the site.

The AstraZeneca Research Foundation supports education and technological innovation by organizing seminars and symposia. AstraZeneca Pharma India Limited is the Marketing division of AstraZeneca India. It has interests in six therapeutic areas: cardiovascular,

Although key stages of drug discovery are not yet possible entirely in India, or at present not widely available, (such as GLP toxicology, or Phase I studies of compounds not developed within India), substantial components of the drug discovery process can still be conducted in India in combination with the West in a highly cost-effective manner.

Figure 5 shows a model for such a global drug discovery process. In this case, activities are conducted where the value proposition is strongest. Note that this is not simply a case of conducting activities where they are cheapest, but where the combination of knowledge, price, speed and expertise is the most compelling.

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Summary of Kinapse services

Kinapse provides specialist services to life sciences R&D organisations, with specific expertise in:

- R&D process and organisation design
- Resource planning and management
- Performance management including performance scorecards and benchmarking
- Change and programme management
- Product, Market and Company research and analysis.



Our business consulting professionals blend extensive consulting experience with senior R&D management experience.

Our onshore-offshore operating model allows us to bring together the very best people in virtual teams, who are passionately committed to the success of their clients. Our lean operations in Europe, and staff located in the Kinapse Offshore Delivery Centre in Delhi enable us to deliver highest value services at unbeatable blended fee rates for R&D consulting.

In addition, Kinapse provides a suite of specialist information processing services including, clinical trial publishing, clinical data analysis, regulatory licence maintenance and scientific communications.

The Kinapse team has worked for the following major Pharmaceutical R&D Companies and related organisations: Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, CMR International, EMEA, Genentech, GlaxoWellcome, GlaxoSmithKline, Johnson & Johnson, MHRA, Novartis, Pfizer, Roche, Schering AG, SmithKline Beecham and Wyeth.

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