

INDIA

global pharmaceutical R&D powerhouse – or contract research workshop?

In response to the ever-increasing costs of drug discovery and development, pharmaceutical industry leaders must constantly seek to increase productivity while 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 and research and development, and seeks to challenge the perception of India 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.

**By Dr Matthew
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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 the domestic industry which has thrived and grown on the manufacture of generics.

In principle, the patent reforms should create a significantly more favourable environment for Western-headquartered pharmaceutical companies to co-operate with their Indian counterparts. However 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 (discussed in **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 under way to improve matters, including setting up patent offices, personnel quality improvement and better use of digitisation, such as electronic filing¹.

The tax situation in India is also changing; many potentially 'pharmaceutical industry friendly' policies have been introduced². 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.

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 country-wide total of around 20,000. Around one-third of the country's bulk drugs are produced in and around Hyderabad in Andhra Pradesh.

Infrastructure, however, continues to be an issue. In 2005 India only invested 3.6% GDP (\$28 billion) on infrastructure (in contrast, China invested 9% GDP – \$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 an economic growth of 8-9%³.

Education and 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.

There is considerable life science research being undertaken in India (**Case Study 2**, looking at stem cell research, explores one example). Research from around 1,400 Indian institutions has been published in journals throughout the world. Among the more well-known institutions 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 from external agencies. The Government funding of the Indian Department of Biotechnology (DBT) has risen from \$15 million to more than \$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

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 crystallised form 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 by the original 1993 patent and not that filed in 1998. Since, under the revised regime Indian patent law only covers patents filed after 1 January 1995, this left 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 \$135 to \$2,700.

Novartis are challenging the Indian decision with a further court hearing now under way in Mumbai. Nevertheless, this situation puts into perspective several issues still outstanding in India's intellectual property regime and also highlights the different stakeholders involved – multinationals, domestic companies and NGOs.

Business



Figure 1
Map of India (used with permission)

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. Such partnering activity aids technology transfer 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 shows the 2004 graduate population). These numbers are comparable to China's, which had more than two million students graduating from its universities in 2003.

Despite the high number of graduates, there is a shortage of qualified clinical research professionals. Long term solutions are being sought, such as setting up new academic centres, institutes and clinical research studies in medical schools. The Mumbai-based Institute of Clinical Research India (ICRI) has recently entered an academic alliance with Cranfield Health, part of UK-based Cranfield University, in order to offer an accredited MSc in Clinical Research that also offers the top 50 students from ICRI the opportunity to travel to the UK as well as industrial placement opportunities. Students who successfully complete the MSc course will be awarded a degree from Cranfield University.

Drug discovery and development

There is a growing level of discovery and preclinical development research being conducted in India, by both domestic Indian pharmaceutical companies as well as 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 Organisations (CROs).

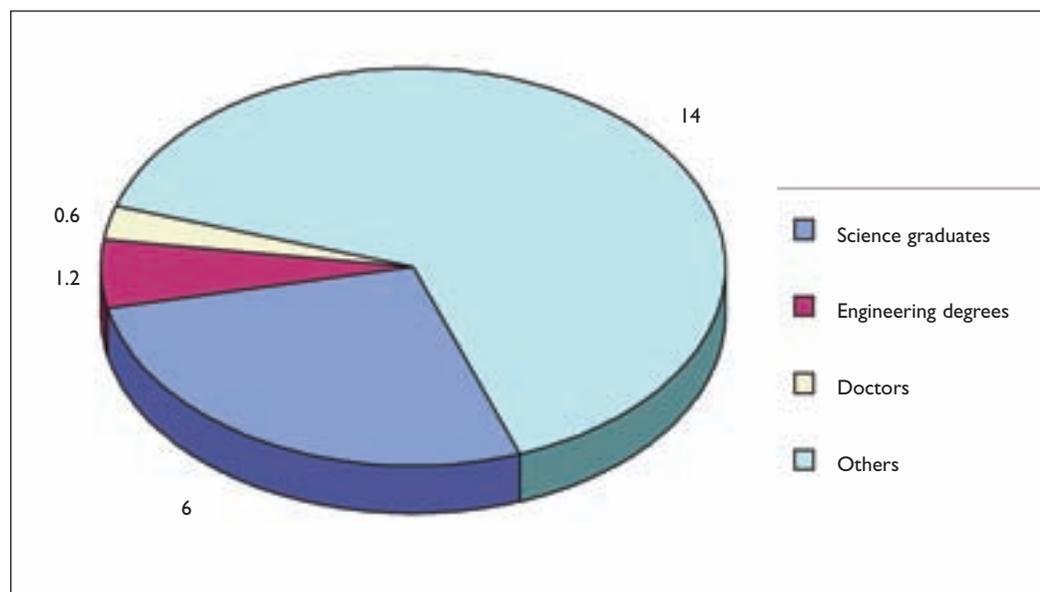
Research and development of novel drugs is an increasing area of interest for Indian pharmaceutical companies. R&D expenditure increased 40% from 2003/2004 to 2004/2005⁵. However, the absolute total, of \$402 million, is still low by Western standards, as is the average R&D investment for most Indian pharmaceutical companies,

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 (AIIMS) 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 most notably the USA, India stands to benefit from its permissive regime.

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Figure 2
Indian graduate population
2004 (figure in millions)⁴



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 companies¹, 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), a new R&D unit set up at Taloja near Mumbai, with an investment of \$3.9 million.

India is fast emerging as a hub for contract and 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 10 major multinationals as clients of its contract chemistry and biology services⁶. In an estimated \$40 million deal, GVK Biosciences is setting up a discovery research and development centre for Wyeth Pharmaceuticals with a dedicated workforce of 150 scientists⁷. Such India-based external resources, 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 countries⁸, and an

increasing number are 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 an increasing prevalence of Western, 'urban lifestyle' diseases including heart ailments, asthma, cancer and diabetes⁹. Patient recruitment into studies is rapid (although not without controversy, as discussed below); possibly a consequence of otherwise poor opportunities for healthcare¹⁰. 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 three key independent CRO players, accounting for 71% of the market share (some activities of Indian CROs are 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 (now Nycomed), 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 organisations.

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 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 of and adherence to GCP remains a substantial challenge. The central government, together with the WHO, has undertaken a 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 \$1.5 billion, around 10% of the predicted total world market¹¹.

The Indian pharmaceutical market

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

Globally, the Indian industry ranks fourth in terms of volume and 13th in terms of sales and it has been growing at 8-10% a year¹². The Indian pharmaceutical market has enormous growth potential with predictions of growth suggesting it may grow to about \$100 billion by 2025¹, driven by an increasingly large middle class population. This currently numbers around 300 million (of a population of more than one billion) and is estimated to be growing at 5% annually¹³.

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. 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). 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.

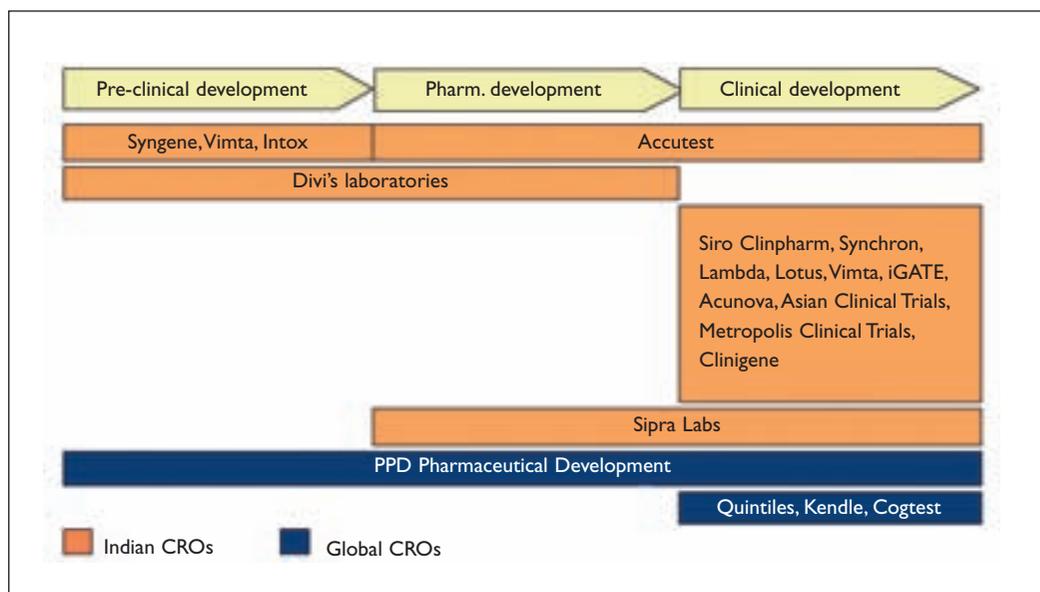
As a result, demand for quality healthcare services has increased and the changing lifestyle has led to changes in disease patterns, for example increased demand for new medicines to combat lifestyle-related diseases. As described previously, the recent regulatory and much awaited patent law

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: Example disease area research ongoing in India

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Figure 3
Example CRO coverage in India (Kinapse analysis 2006)



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 (now Nycomed) 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 approximately 50 personnel co-ordinating clinical development, biometrics and regulatory affairs. This is in contrast to ALTANA (now Nycomed, also see Case Study 4), Novartis and AstraZeneca, all of whom have invested more substantially in owned facilities.

In India, AstraZeneca has three divisions. The first, AstraZeneca Discovery Bangalore is part of the AstraZeneca R&D network mainly focused on tuberculosis research with an overall current and planned investment of more than \$40 million. More than 100 scientists are presently employed at the site. The AstraZeneca Research Foundation supports education and technological innovation by organising seminars and symposia in India. Finally, AstraZeneca Pharma India Limited is the Marketing division of AstraZeneca India. It has interests in six therapeutic areas: cardiovascular, respiratory, maternal health care, oncology, infection and neuroscience, all supported by a cGMP compliant manufacturing unit.

In addition to the outsourcing and off-shoring opportunities, collaborative R&D with Indian pharmaceutical companies and research institutions should be considered.

As has been discussed, there is considerable ongoing medical research in India and numerous examples of collaboration between Indian pharmaceutical companies and academic institutions. Western pharmaceutical companies should actively expand the

Figure 4
Example Western-headquartered pharmaceutical company investments in India (Kinapse analysis 2006)

	Data processing	Pharmaceutical development	Clinical trials	Preclinical toxicology	Synthetic chemistry/ Medical chemistry	Discovery research
Outsourced	Pfizer		Pfizer		AstraZeneca, Novartis	AstraZeneca, Novartis
Directly-owned investment	Novartis		AstraZeneca, Pfizer		AstraZeneca	AstraZeneca

Case study 4: ALTANA in India

ALTANA, the German pharmaceuticals and chemicals company (now owned by Nycomed) has demonstrated an aggressive approach to the Indian opportunity. In 1998 ALTANA entered into a joint venture with Zydus-Cadila Healthcare to set-up a manufacturing and marketing subsidiary to serve India, directly citing the future potential of the Indian market for branded as well as generic pharmaceuticals. In early 2005 ALTANA announced the construction of an R&D centre in Mumbai with an investment of around \$75 million, which will be responsible for managing clinical development, including phase I-III studies as well as preclinical research activity. The focus will initially be on synthetic chemistry but is expected to broaden to include molecular biology and other upstream research activities.

ALTANA currently has two large phase III studies running in India, one investigating the efficacy and safety of Ciclesonide in preschool children with asthma and a second examining the effect of Roflumilast on exacerbation rates in patients with COPD.

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scope of their partnering activity to not only look at Indian pharmaceutical companies, but also to the Indian institutional network for licensing and co-development opportunities. A case in point is Evolva Biotech (Switzerland), which is setting up its own discovery programme at the Indian Institute of Chemical Technology (IICT), Hyderabad.

Deal activity between Western-headquartered and Indian pharmaceutical companies is increasing. Approximately 50 deals have been struck, the majority from 2000-2005. Of these, only about a third have been with top 30 (by R&D spend) Western pharmaceutical companies. However, the larger Indian companies, such as Ranbaxy Ltd, have made several significant deals with major Western companies. Indian-Western partnering activity to date has focused on oncology, anti-infective, metabolism, inflammation and cardiovascular disease areas.

In the future, drug discovery will be an integrated global activity with each step conducted where the value proposition is the strongest.

As this paper has discussed, India now presents opportunities throughout the pharmaceutical value chain. However, Western-headquartered pharmaceutical companies frequently use this resource in a piecemeal fashion – 'dipping-in' to countries such as India at certain points in the drug discovery and development process when required. In some cases this is more in response to acute capacity issues rather than as part of a cohesive strategic approach. For example, Indian resources may be called upon when additional derivatives of a lead compound are needed and onshore chemistry

resources are unavailable. While this is a perfectly valid activity, it is more in keeping with the view of India as a 'workshop' than as a partner.

In the future, drug discovery and development will be a truly global process, with activities conducted where they make the most strategic and economic sense, co-ordinated within international company frameworks. This should improve efficiency and productivity and, crucially, deliver future therapeutics to patients in Western and developing markets more effectively – and we believe India has the potential to have a major role.

About Kinapse

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

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

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