



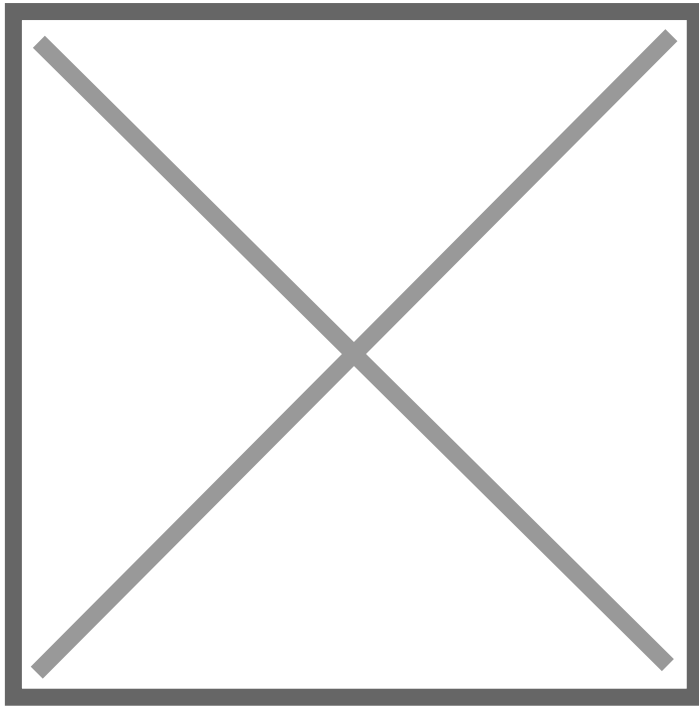
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Angling for Take Off

11 May 2004 | News



Clinical Trials

- Development times for drug discovery not speeding up.
- Fewer trials included in the dossiers.
- Number of subjects showing little variation in recent years.
- Fewer bigger trials take the same time as smaller trials.
- Getting more drugs in the market in a shorter period remains the challenge

These have been some burdens for big pharma companies globally. These companies are increasingly considering outsourcing and off shoring their drug discovery processes, R&D and clinical research. And Clinical Research Organizations (CRO) want to tap that opportunity. But with costs and speed being the key concerns, India is emerging as an important destination for obvious reasons like talent pool, facilities, large and diverse patient pool, qualified doctors, and many more. Today, global companies are not asking a question as to if they should consider off-shoring to India, but which phase of the drug delivery process in order to derive the maximum value.

The number of companies participating in clinical research and trials is going up. Recently, the Genetic Engineering Approval Committee has given green signal for a couple of companies like Novo Nordisk and Reliance Clinical Research Services to begin clinical research in India. If global big pharma are doing it, would the India pharma stay behind? Some Indian big pharmaceutical companies like Wockhardt, Lupin, and Sun Pharmaceuticals are working on new chemical entities and have established their own clinical research units to conduct trials for their new molecules. Slowly but steadily, clinical research and trials in India is getting ready for a big take off. Read on –

Narayan Kulkarni with Ch. Srinivas Rao

Full of promise

Indian market is still unorganized.

Compared with the global CRO market, the Indian CRO market is very small mainly because the companies are offering low-end services. Companies are doing bio equivalence studies, bioanalytical studies, and Phase-II and Phase-III trials. Dr Satish Bhatia, president, Wellquest, division of Nicholas Piramal India Ltd, observed that India's share is less than one percent of the global CRO market size of \$10 billion.

Global Trends

- Growth of offshore CROs (mainly India and South America)
- CROs rarely fail but some times they do e.g., Oread
- Still not a highly profitable business
- Looking to diversify out of drug development
- Now viewed as service stocks not growth stocks with resultant lower valuations and less orientation
- Little consolidation in CROs

Source: Technomark

The industry is divided when it comes to estimating the market size. But most of them believe that the present Indian CRO market is in the range of Rs 200-250 crore. Few say, it is in the range of Rs135-150 crore, while Dr Ajit Nair, senior manager strategic planning and clinical operations, SIRO Clinpharm, the first Indian CRO to commence trials in 1996, puts the figure at a much higher side of Rs 550- 600 crore. There are about 25 CROs working in India with many pharma companies having their own clinical research units conducting trials in 80 odd government and private owned hospitals.

Going with the industry, Surinder Kher, senior vice-president, iGATE Clinical Research International Pvt Ltd, said that the present CRO market size should be approximately Rs 200-250 crore. This includes the clinical trials conducted by the independent clinical research organizations, the clinical research outfits of multinationals like Eli Lilly, Pfizer, Novartis, and Aventis and some in-house clinical research is being done by Indian pharma majors. Kiran Mazumdar-Shaw, CMD, Biocon and president ABLE said, "Currently according to the Organization of Pharmaceutical Producers of India (OPPI) statistics, Indian CRO business is worth \$70 million growing at 30 percent annually. The Indian advantage in clinical development is clearly the speed of patient enrolment and thereby shorter time-lines for clinical trials." According to ABLE estimates, Indian clinical research and development business is expected to grow to \$1.5 billion by 2010.

What is heartening is that companies now are getting more focused. For example, Wellquest is focused on clinical research to support introduction of generic and NDDS products. Dr Bhatia informed, "Soon it would be followed by Phase I-III trials for NCEs." Wellquest that has got three accreditations and done 40 studies was able to garner revenues of Rs10 crore for the year 2003-04.

Spending Trail

Phase-I Rs 50-55 crore

Phase-II Rs 60-65 crore (\$15-20 million)

Phase-III Rs 130-135 crore (\$30-35 million)

Source: Ernst & Young 2002 report

Synchron Research Services, offering services in Phase-I, high throughput screening for rapid PK analysis, qualitative and

Â quantitative medical imaging, in silico drug metabolism studies, was able to garner Rs 5 crore for 2003-04. It has conducted 200 bioavailability and bioequivalence studies and six studies in Phase II-IV. Commenting on the focus areas of SIRO Clinpharm, Dr Ajit Nair said, "Clinical project management and data management are of immediate focus and will continue to be the mainstay, with innovative solutions for convenience and cost-efficiencies in these areas being the key differentiators in the future. The vision is to move from being only an outsourcing agent to being a partner who can contribute in minimizing the drug development risks while maximizing competitive advantage." This has brought in more revenue to the company and was able to add Rs 31 crore in 2002-03.

Lotus Labs in 2003-04 has been very aggressive. Recently it announced to set up a 50-bed facility in Chennai to conduct clinical trials, bio studies and the center is expected to be operational in six months. "Lotus is spending Rs 1 crore on this. Over the past 36 months, we have conducted over 300 biostudies. We plan to build a separate facility in St John's Hospital to conduct Phase-I trials in-house at an investment of Rs 2.5 crore," informed VV Raghavan, managing director, Lotus Labs, on his company's current developments. The company is talking to Shantha Biotech to conduct Phase-III studies of the latter's erythropoietin. Lotus Labs is also in the process of setting up training centers in good clinical practice and good laboratory practice. Lotus Labs expects to touch Rs 14 crore during 2003-04.

ClinInvent Research Pvt Ltd has adequate staff for monitoring, project management, and quality assurance and has the backing of The Chatterjee Group. Dr Arun Bhatt, president of the organization, ClinInvent Research, said "Our focus is on all phases of clinical trials mainly in the areas of oncology, neuro-psychiatry, cardiology and diabetes drugs."

Leading CROs in India

- Accutest Research Laboratories
- Apothecaries Clinical Research
- Asian Clinical Trials
- Biocon Clinigene International
- Clin World
- ClinInvent Research
- ClinTec International
- Â Diagno-search
- Eli Lilly
- GVK Bioscience
- ICON Clinical Research
- IGATE Clinical Research
- Lambda Therapeutic Research, Synchron Research Services
- Lotus Labs
- Novartis
- Pfizer
- Quintiles Spectral
- Reliance Clinical Research Services
- SIRO Clinpharm
- Therapeutic Drug Monitoring Lab
- Vimta Labs
- Wellquest

Pharma companies like Dr Reddy's Labs, Lupin, Panacea Biotec, Ranbaxy, Sun Pharmaceuticals, and Wockhardt are also working on clinical research sector.

Companies in Information Technologies Cognizant Technologies, Eassar

Vimta Labs, which operates in the areas of testing and validation, clinical research, clinical pathology, pre-clinical safety evaluations, environment assessment, and inspection and certification services, has seen 81 percent growth in its revenues over that in the previous fiscal. It ended March 2004 at Rs 35.11 crore in income.

Clinigene International, a Biocon subsidiary, offers clinical, bio analytical, bio statistical and data management services to its clients. Said AS Arvind, chief operating officer, Clinigene, "We concentrate on Phase-I&II&III&IV clinical trials, bioavailability/bioequivalence studies, and data management." The company has recently inaugurated a state-of-the-art human pharmacology unit at Sagar Apollo Hospital. This unit is spread over 3,000 sq. ft and can accommodate 26 volunteers at a time.

The Indian arm of the American pharma giant Eli Lilly & Company is putting its concerted efforts in conducting clinical research by partnering with key thought leaders and experts in the therapeutic areas. Working with over 40 hospitals in India, including government and private hospitals, Eli Lilly (India) has 17 large and small clinical research projects running involving both phase II and III trials.

Quintiles Spectral (India), a subsidiary of Quintiles Transnational, leads the segment in India with turnover of more than Rs 38 crore for 2002-03. It is conducting clinical research involving more than 70 research sites and involved in over 40 research projects for 20 different pharmaceutical companies.

India is taking this opportunity seriously. And it has to as it has immense potential. "India due to lack of penetration of drugs has a huge patient population that has never been subjected to any drug and this gives a critical pool of naïve, uncontaminated patients which is important in conducting certain development work and clinical trials. Significant population biodiversity in India with its wide and varied gene pools can provide wealth of information for target identification, a key for the CROs," noted Alok Gupta, director, life sciences, Rabo India. "India will gain by researching diseases. The cost of clinical trials is 50 percent lower in Phase-I, 60 percent lower in Phase-II. Cost saving is not the only advantage. Ability to find and qualify the right patient pool is an appealing factor for Indian trials, and India also offers genetically and culturally diverse population where treatment-naïve patients are willing to participate in trials. For all this to happen, we have to be an ethical community," added Mazumdar-Shaw.

Nascent sector's woes

Issues confront this sector too.

The awareness about mega CROs opportunity is familiar topic these days. But this does not mean that the industry is not confronted with hurdles. Indian companies have their own share of woes while conducting the trials on human beings. This, the industry says, is mainly because there is no clear regulatory framework, which would support and encourage the companies to take up human trials in proper manner.

Dr Ajit Nair observed that the regulatory (DCGI) approval timelines in India are high as against the US. While it takes about 30 days in the US, here it is about 90-120 days. This puts a crimp in the project timelines. However, more often than not, this is made up by the enrollment timelines, as the enrollment rates in India are mostly higher than most developed nations. Expressing the same views, Dr Arun Bhatt of ClinInvent Research noted that lack of trained manpower, GCP culture, working of the independent ethics committees, regulatory uncertainties are coming in the way for the growth of the segment. According to Dr Shiv Prakash, managing director, Synchron, "The Indian CRO industry is still in an unorganized sector and regulatory approvals take long time. Maintaining confidentiality of data (data protection) is key issue before of the segment."

Key ICH Rules

- All clinical research data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. (ICH GCP 2.10, 4.9, 5.5, 5.14 and ICH E9 3.6 and 5.8)
- Systems with procedures that assure the quality of every aspect of the research should be implemented. (GCP 2.13)
- Quality assurance and quality control systems with written standard operating procedures should be implemented and maintained to ensure that research are conducted and data are generated, documented and recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirements. (GCP 5.1.1)
- If data is transformed during processing, it should always be possible to compare the original data and observations with the processed data (ICH GCP 5.5.4)
- Sponsor should use an unambiguous subject identification number or code that allows identification of all the data reported for each subject. (ICH GCP 5.5.5)
- Protocol amendments that necessitate a change in the design of the CRF, subject diaries, study worksheets, the research database and other key aspects of the CDM processes need to be controlled. (ICH E9 2.1.2)
- Common standards should be adopted for a number of features of the research such as dictionaries of medical terms, definition and timing of the main measurements, handling of protocol deviations. (ICH E9 2.1.1)

Dr Bhatia noted that the Indian companies are not able to conduct the phase I trials for foreign sponsors as these are not allowed at present. And the delays in getting approvals from the DCGI for starting clinical trials (phase I-III) have to be sorted out immediately. Further, "The challenges that are confronting the segment are the unstructured environment in hospitals and government institutions, lack of GCP awareness amongst the large institutions, and regulatory environment which is not well defined for all aspects of research," pointed Rajiv Gulati, managing director, Eli Lilly (India).

Dr Swati Piramal, director, strategic planning, Nicholas Piramal India Ltd said that the most worrying factor is outsourcing by Indian pharma companies for Phase-I clinical trials when Indian companies are capable of doing the same at a lesser cost are looking at MNCs to outsource their R&D work. She informed that this might be due to data protection, regulatory fear and delay in getting the approvals. Companies are working on how to protect the data. Dr Piramal said that Nicholas Piramal is discussing the issues like data protection, data security with Infosys Technologies.

Considering that CROs in India have a good potential and scope for attracting outsourced R&D, Ranjit Shahani, managing director, Novartis India Ltd, pointed, "The main hurdle will be the absence of data protection. Hopefully, there may be clarity and some positive policy framework that should be established by the end of 2004. Some of the other barriers include: absence of a clearly laid down time frame for permission of clinical trials and difficulties in custom clearance of clinical trial samples."

What do the outsiders think? Dr William A Haseltine, founder and former chief executive officer, Human Genome Sciences, who was there recently in India, told the biotech forums, "India can partner early with companies, take the products through clinical trials and develop them. But there are issues of ban on Phase-I clinical trials of outside drugs and pharma companies face problems in getting animals for testing. Both of these issues should be solved politically. Also for clinical trials, hospitals records need to be automated and the general infrastructure needs to be improved. India is an attractive destination for outsourcing because of the trust that the western countries have in it."

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Dribbling the tribulations

Dribbling the tribulations

Industry gets proactive.

For every problem there is a solution and problems cannot go all alone. The industry has come up with several suggestions to address the matters. The suggestions include formation of professional and independent ethics committees, which can speedily provide reviews of protocols and informed consent forms. Formation of a bank of volunteers (female and male). Sticking to the ICH-GCP guidelines, which is the preferred guideline. Last point is the one, which every CRO echoes vehemently. "The role of a CRO is to monitor and see that investigators are complying to ICH-GCP practices," informed Shamiq Hussain, general manager, ClinTec (India). He felt that the industry should now collectively promote the awareness on the internally practices as this will help the industry to win many projects.

Dr Ajit Nair too feels the same. "If all clinical trials were to be conducted as per ICH-GCP, then we should not foresee any controversies. But what we need to make people understand is that, all humanly possible precautions are taken by the sponsorer, regulatory agencies, CRO independent ethics committee and other clinical trials-related bodies to minimize the risk to a patient during the trials. Hence media education about trials and the ethics is must. Future is great if the correct purpose and intent of trials is passed on to the media and regulators."

Dr SP Vasireddi, chairman and managing director, Vimta Labs has his share of suggestions, which would help the segment to grow vertically. "Organizing campaigns like AIDS/HIV awareness programs to educate the people about the benefits of becoming the part of the clinical trials, establishing strong relations with academia and industry (both pharmaceuticals and IT) to get the trained manpower through tailor made courses that are accepted and recognized by industry. These measures will definitely bring in some relief to the segment."

Ranjit Shahani of Novartis India has come out strongly in support of key policy incentives that can strengthen the role and contribution of CROs. His recommendations being:

- Incorporation of a five-year "Data Protection" clause, as is done all over the world, preferably in Schedule "Y" of the Drugs Act;
- A regulatory framework harmonized with international regulatory practices.
- Incentives for setting up CROs through tax reliefs and infrastructural facilities at concessional rates;
- Government to fund and set up a campus (park with common facilities), which can be leased to CROs (Singapore Model);
- Institutionalize linkages between universities, research laboratories and industry;
- Inbuilt incentives to hospitals for participating in clinical research;
- Weightage for experience in "clinical research" in promotion of Medical Teachers;
- Facilitating Venture Capital;
- Incentivizing introduction of new advanced technologies to be used by CROs like Gene microarray expression profile analyses, computer-aided validation systems, direct connect web portals, in-house laboratory information system, and interactive voice response systems.

For the growth of any industry, besides the efforts of the companies, government support in the form of incentives, duty reduction/exemption will make difference. What does the CRO segment expect from the government? The industry is looking at reduction in import duty on research equipment, make import of requisite equipment duty free, financial assistance to the entrepreneurs who are entering into CRO industry in form of funds or subsidy, tax benefits in the initial growing stage, make the earnings from R&D tax free, issuance and strict enforcement of guidelines, good audit system and single window clearance.

Swaminathan Subramaniam, chief executive officer, Sanmar Speciality Chemicals and ABLE Special Interest Group member, brought out some more dynamics associated with the contract research services. "Since research services is about delivery and life services are related to IP intensive industry, the government has a very responsible role to play in facilitating the industry. India needs to be promoted as a research services destination rather than research product destination; there is no mechanism or standard for contract sharing; the IP environment is confusing; the industry needs to collaborate with the academia. There has to be a code of conduct for biotech members (especially research services)."

Meanwhile Dr Shiv Prakash pointed out that self-regulated CROs with commitment to quality and ethics are not foreseeing any problems of growth despite certain controversial issues. Besides there are many investigators who are not GCP trained but are highly inclined to get involved in conducting clinical trials and such enthusiastic investigators, if trained for GCP will create an ocean of good investigators for almost all indications.

"Instead of creating the perception of controversies, we need to focus on how best can we contribute to this science? Individuals and organizations involved in this science need to work together to overcome the challenges that we face in this area to become globally recognized. We need to recognize that every new industry takes time to develop and mature. This industry is just in infancy and challenges will be there. We know that there are certain areas where we need improvement but we need to be a part of the solution rather than being part of the problem and get away from unnecessary controversies," noted Surinder Kher.

India getting noticed

The world is watching India quietly.

There has been a concerted effort to make things work. In fact, "International bodies like NIH are taking notice of the potential. Universities like John Hopkins are looking at India," DA Prasanna, executive chairman, Manipal Education and Medical Group India Pvt Ltd, pointed out. He added that one or two variables are not successful clinical research, but consistency is what matters.

Increasingly, there has been a trend towards forming alliances, educational institute-industry collaborations, and hospital-CRO alliances. Take for example Manipal. It has a very strong medical research activity. It wants to use the CRO opportunity to fund its research activity. Recently, it tied up with Quintiles Research, whereby the Manipal Group will be the preferred research partner for

Quintiles in India, Nepal, and South East Asia for clinical trials. Quintiles will have access to Manipal's integrated platform of clinical material across its six campuses. "This agreement provides the platform for accelerated clinical research supporting effective drug discovery and launch," said Sachin Rajan, vice president, diagnostic services & clinical trials, Manipal Hospital, Bangalore. Further, there will be Quintiles certification for those involved in the clinical trials.

Another trend has been that hospitals, which have huge space, are letting the CROs build labs too. For example Lotus Labs has tied up with St John's Hospital in Bangalore for building the facility. Similarly, Sagar Apollo has given a floor in its Hospital to Clinigene.

A lot of information technology companies and referral labs are showing keen interest to expand their activities by taking up clinical research and data management projects. Novartis India, an MNC is investing \$1 million in setting up IT development center in Mumbai with a headcount of 60 to co-ordinate its drug discovery and development process. Iso Moshfegh, global head of development IT, Novartis Pharma AG informed that this center will help reduce the drug development cost by \$42 million. This is the opportunity one has to look at. The opportunities are also there in data management, report writing, animal toxicology which are part of the clinical research.

One should not be totally carried away. While making a presentation on the global CRO trend in Mumbai Dr Graham Hughes, scientific director, Technomark Consulting Services, UK, observed that the pharma industry in the US and Europe is under unprecedented pressure and it may not be in position to keep up its promises. But they are reluctant to change to different types of outsourcing—tactical subcontracting and strategic outsourcing. So the CROs are feeling the knock on pressures. They should look at options that should come from top—down.

Also small companies have started forming alliances to tap the opportunity collectively. Life Sciences Alliance is an example of Shasun Chemicals and Drugs, Suven Life Sciences Innovasynth Technologies and Austin Chemical Company of the US coming together to get the contracts. The alliance members say it will be easy to convince the source if we are in group to meet their requirements. Also several educational institutes are actively looking at offering clinical trials courses.

With a concerted and cohesive efforts, the industry is working towards seizing the opportunity.

Mumbai to be the CRO hub of India

Government of Maharashtra is proactive in leveraging its strengths—hospitals and trained people in medicine. It is looking at developing Mumbai, the financial capital of India, as a hub for Clinical Research Organizations. Its proximity to the western countries like the US, European Union and the International airport provide strong base for the government of Maharashtra to establish CRO hub at Mumbai. It has hired the services of McKinsey and Company to put down the strengths and loopholes to fill in.

Dr Swati Piramal, member of the biotech council of government of Maharashtra, said that Confederation of Indian Industries' MahaBioYatra, state government, hospitals and academia are working together in this regard.

Dr Piramal informed that 10 km radius around Parel in Mumbai has 6000 hospital beds. Reputed hospitals such as Jaslok, Hinduja, Bombay, JJ, KEM are located in and round Parel. And these hospitals are attached to academic institutions. The faculty at these have been practicing and doing the clinical trails for last 20 years but they are not aware of the opportunity and how to do it in professional manner. They need some training on issues like ethics, ICH GCP guidelines and working within the purview of the independent ethics committees. The biotechnology council of Maharashtra has taken steps to train the people in this sector.

"We don't want to take any chances. Before commencing we want to assure that everything is on the track, including the trained people in CRO sector, " said Dr Piramal.

University of Pune, located just 180 km from Mumbai, which has been offering courses in bioinformatics and biotechnology will shortly start offering courses in clinical data management. The process in this regard has already commenced. Prof. AS Kolaskar, vice chancellor of University of Pune who is eager and anxious to start a course in clinical data management, has conducted a program late last year to understand the opportunities in the industry and to get the feed back from the industry people.