CONFERENCE ON CLINICAL RESEARCH: ROAD MAP FOR INDIA

24 – 25 September 2003, New Delhi

Background Paper

In an age of globalization, and of shared resources and benefits, the world is in an age of complementing and supportive competencies and capabilities; India's phenomenal resources in the realm of manufacturing, services, and human capital, stand at the threshold of this global transformation.

Global pharmaceutical industry is undergoing a paradigm shift. New technologies in R&D, pressure to manage spiraling healthcare costs, consumerism, and uniform IP laws are causing pharmaceutical companies to rethink and realign their strategies. There is a heightened focus on R&D productivity, increasing throughput of NCE's, reducing the development time and controlling overall R&D expenditure.

Global pharmaceutical industry is undergoing a paradigm shift

The Global Pharmaceutical Market is estimated at US $ 427 billion today. The current size of the Indian Pharmaceutical Industry is US $ 5.3 billion. R&D costs account for nearly US $ 60-65 Billion. Nearly 2/3rd of the R&D costs go towards drug development.

Clinical Trial Research, which constitutes approximately 70% of time and money spent on developing a new drug, is an area of extreme importance for all companies. Outsourcing pre clinical work & clinical research accounts for nearly US $ 13 billion.

There is an increased focus on reducing the costs of clinical development.

Contract Research Organisation's are fast gaining importance because of their global access to investigating sites, specialized local expertise and competitive pricing strategies.

In the present IPR regime, importance of timely Clinical Trials has become extremely important, as reflected by the steadily increasing number of Global studies.

There is an increased global trend towards collaboration and outsourcing

Pharmaceutical companies are increasingly adopting new and collaborative outsourcing strategies to be able to synergise efficiencies with increased innovation.

Outsourcing has indeed emerged as the new mechanism to optimize innovation; it is now beginning earlier in the process of drug development. With new approaches being broadened towards outsourcing, the opportunity for the Indian contract service organizations is increasing multifold. The market today is estimated at US $ 9 billion.

Today, more patients, infrastructure, and monetary requirements increase the time and economic pressure causing companies to look outwards and outsource these time critical functions. Companies are thus increasingly looking towards non-traditional geographies to have access to treatment naïve subjects and support functions for their global trials.

India has a rapidly- growing and vibrant Healthcare and Pharma sector

The Indian pharmaceutical industry is one of the fast growing sectors of the Indian economy and has made rapid strides over the years. From being an import dependent industry in the 1950s, the industry has achieved self-sufficiency and gained global recognition as a producer of low cost high quality bulk drugs and formulations. Leading Indian companies have developed infrastructure in over 60 countries including developed markets like USA and Europe. In the last few years, several pharmaceutical companies have demonstrated that they possess the ability to engage in commercially viable research and development activities and become significant players in the international market.

Recent trends in the Healthcare Market that have the capacity to fuel growth indicate that the segment is expecting to reach US$ 40-50 billion by 2012. In India, key drivers of this growth would be the increased per capita spending on Health Care due to an increase in the general standard of living and people's incomes. Further, an important consideration in this changing pattern is the increasing prevalence of a new realm of diseases in India; lifestyle diseases are now driving most of the outpatient spending, and cancer and heat diseases constitute most of the in-patient.

India must develop capacity in Clinical Research if it has to emerge as an innovation hub in Pharmaceuticals & Healthcare

Indian companies are increasingly becoming global in outlook. R&D focus has greatly increased. Companies are investing and concentrating on R&D; both New Drug Discovery Research as well as Novel Drug Delivery Systems (NDDS).

Development of internal capacity in this area is a must, and the scenario in India is indeed changing towards the same.

India needs to build greater capability and capacity; this would include a sound infrastructure system, facilitative regulatory structure, well trained doctors, investigators and researchers, and the highest degree of compliance with ICH-GCP standards viz ethics committees and investigators.

The expertise that India must develop would encompass the range of necessary requirements and ingredients that would be required for quality research to be conducted independently. For India to emerge as a global innovation hub and leader in the realm of R&D, it is imperative for these capacities to be nurtured and conducted in-house.

These factors will form the bases for propelling India into the global R&D movement that is sweeping the Pharmaceutical Sector today.

There is a tremendous potential for India in the realm of Clinical Research

In the present scenario, the global clinical trial outsourcing opportunity for India becomes vitally important. A McKinsey report projects that the potential opportunity from this segment of the pharmaceutical industry to be around US $1.5-2 billion by the year 2010.

A study by E&Y indicates that the total market value of clinical research performed in India between 1991 – 2001was an estimated US $ 70 –80 million. The study attributes this to a large subject pools in most major therapeutic areas, improved therapeutic infrastructure, increased awareness of the ICH Guidelines for Good Clinical Practice, and formulation of a specialized pool of research investigators.

India has much to offer – cost competitiveness, core capability and channelisation of time through expediency

India is today poised to emerge as a base for multi-centric clinical trials for new drug development by international companies. Indigenous companies are also increasingly building in-house capacities in this essential domain

An in-house Rabo India report pegs the expenses in India as less than 50% for Phase 1 studies and less than 60% for phase 2 and 3 studies as compared to the US. In the US, Phase 1 study costs US $ 20 million, Phase 2 costs US $ 60 million, and Phase 3 costs US $100 million.

An estimate of the cost of drug development by the Government Task Force for Pharmaceutical Research and Development indicated that IND can be undertaken at less than one-tenth of the cost in comparison to international cost of US $500-$800 million.

Clinical development of a new molecule constitutes one of the most vitally important steps that any pharmaceutical company has to take; it is the most complex and critical and cost intensive of all. International clinical development is an expensive, tedious, and prolonged process.

Clinical Research can be broadly divided into three phases, namely exposure to human subjects from phases I to IV. In-house research – Phase I, contract research, and research in universities/medical institutes are the main sources of conducting research. Phase1 forms the most decisive stage in the highly cost intensive process of drug discovery research and constitutes the most critically important for drug inventors and regulators; the total cost of drug development has an estimated cost of US $ 800 million.

India stands to gain tremendously from development of capacity in this area

The growth of the global clinical trial outsourcing opportunity in India is indeed very large. It has great benefits in store for the international companies that may choose India as a potential location for finding the right resource base. There will be several spin-offs on the Indian health care and services system. There are benefits to be expected from the kind of funding and investment that will come into the country globally. These advantages will help improve hospital infrastructure. It also allows for Indian physicians to participate in early phase global drug development programs

and, provide access to 'state of art therapy' to many deserving and Indian patients that otherwise may be deprived of therapeutic advances.

Most vitally, the ability to conduct quality research requires the highest level of expertise, and clinical trials are mechanism for knowledge transfer. Conduct of clinical trials in India allows for Indian population representation in the total population analyzed for the effect of the therapy and thus local experience of the drug is available to the health care community.

Given that clinical drug development costs make for over 2/3rds of total R&D spend, most companies find it more practical and cost effective to outsourced this specialized activity to other agencies. The availability of specialized service organizations for clinical research aim at reducing the commercial drug development costs.

India is increasingly being recognized as a quality player and preferred partner in global clinical village

International companies are looking for countries where they can meet a majority of the requirements for the most important trials. Recruitment of the right groups, comparative cost advantage, and the quality of the regulatory mechanism viz harmonization and compliance with international standards are key considerations.

There are vast economic and time pressures. Moreover, in identifying the correct country or resource base to conduct global studies, it becomes imperative to ensure that the key factors that can play a part to ensure reliability are well in place.

Amongst the important countries in Asia, India stands out with a great degree of prominence due to a variety of reasons that may best be summarized as India's strengths and the changing dynamics in the country regulatory infrastructure.

India is indeed strategically located in the arena of global clinical research & trials; there is an enormous opportunity to growth & development that lies ahead.

A large network of global companies are now looking at India as a potential center of knowledge, skill, and resource base, to synergies capabilities and create a scenario for global research & trials to be conducted in a country that is well equipped with the necessary requirements.

India has the medical expertise, legal & regulatory framework, and availability of a large & homogenous patient population that can be engaged for the benefit of both parties.

India – Strengths, Capabilities, Potential

India's sterling strengths and ability to do provide a resource pool of international reckoning may be best summarized as follows;

- Enormous pool of treatment naïve patients; India possesses a rich biodiversity and gene pool
- Large geographical coverage; India has the potential for multi patient recruitment at major cities across the country
- English as the medium of communication; A majority of Indian doctors and investigators are western educated and thus greater harmonization in methodology of working and communication can be depended upon
- Pool of Highly skilled and well trained doctors, investigators, and medical personnel
- Large pharmaceutical presence; India has a thriving pharmaceutical market that has grown largely due to a prominence of generics
- Economic advantage; One of the most important strengths that India has to offer is markedly lower costs and increased benefits at a lowered price. This reduction on expenditure eases the pressure on the total R&D spend and acts as a potential boon to the company that has just invested millions in drug development
- Compliance with International regulatory standards; India today has a rich resource pool of GCP compliant ethics committee's & GCP compliant investigators, moreover the effort towards greater harmonization is ongoing
- Strength of Indian infrastructure; Indian infrastructure has grown multifold and today has the capacity to manage global trials and studies with precision. This includes functions of data management, mining, and the use of specialized functions in the realm of IT and telecom
- Central laboratories that are certified by international organizations are available. They cannot only service studies conducted in India, but also, in due course of time act as central laboratory for all countries in Asia where global clinical trials are conducted.

India, a country of vast magnitudes & proportions, is also a country of multifarious diseases. There is an opportunity to understand and explore these better and find solutions that will have world side implications and bring the benefit of quality treatment in the long run.

India has a population base that exceeds one billion; this allows the country to lay claim to every sixth subject in the world. Presently, over 80 government & privately owned Indian hospitals are engaged in global clinical trials. It is estimated that this figure will grow exponentially by 2005; this time will also herald the beginning of an era where product patens will come into play, generating a time of greater harmony with global norms.

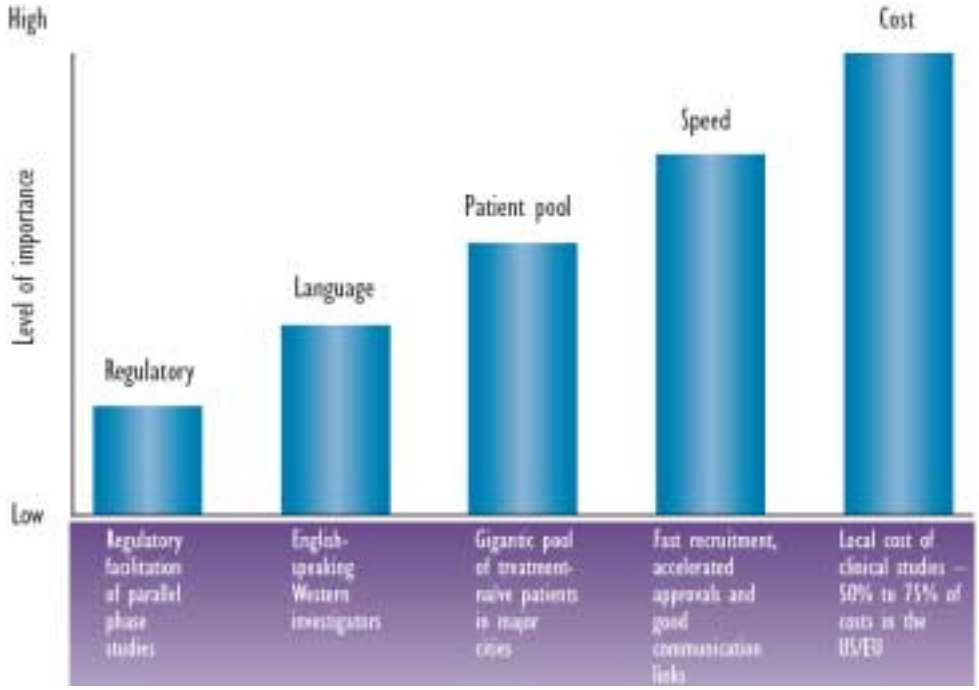
Perception is vitally important here. There are indeed greater implications for India to be recognised as a centre for quality research than simply a land of potential. The idea is not to market India as a potential destination for global clinical studies to be conducted, rather a resource rich centre that has the key strengths and ingredients that make for high quality and content clinical research that can compliant with international norms.

Key growth drivers for success of the Contract Service Organisations (CSO) market include:

- Steadily increasing growth of R&D spending
- Need for speed to market
- Discovery challenge created by patent expirations
- Need to capitalize on advancement in the realm of biotech, genomics and other discovery research
- Cost containment

Key success drivers for the CSO market include:

- Consistent high quality
- Global presence
- Breadth of services
- Broad or focused therapeutic expertise
- Strong and flexible data systems
- Diversified customer care
- Reliability
- Timeliness
- GLOCAL (Global Reach Local Expertise)



Source: BUSINESS BRIEFING: PHARMATECH 2003; "Global Clinical Trials in India – Challenges & Opportunities" by Dr Dhananjay Bakhle, *Director Medical Research & Regulatory Affairs, Aventis Pharma Ltd*.

Road Map for India: The way forward

Lack of an IPR regime; India is a signatory to the Trade Related Intellectual Property Rights agreement as a part of the WTO regulations; this will guarantee intellectual property rights and patent protection to companies holding the patent from 2005. Presently, due to a lack of protection, innovator companies have been losing money be virtue of not being able to introduce their new and cutting edge research in the Indian market due to the presence of generic brands of innovator compounds.

Companies have had a feeling of mistrust in the past and are doubtful if their data will remain in safe hands.

Perceptions are changing. The Indian market and government is now gearing up to the fact that India will have to comply with these product and process patent norms come 2005; this is just under 18 months away and the scenario in India is undergoing a slow but steady transformation.

There have been concerns regarding Compliance with ICH GCP norms.

Once again, the scenario is changing. Solutions are simpler; employ the services of well trained investigators who are well versed with International Conference on

Harmonisation (ICH) Good Clinical practice (GCP)/ ensuring that clinical research associate and study monitors are trained in GCP and supported by standard operating procedures that are compliant with GCP & GLP (Good Laboratory Practices).

Today the guidelines in India do follow the newly prepared guideless on GCP. These are based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), FDA, and European and World Health Organisation recommendations, and covers most of the important aspects of GCP.

For over a decade, companies have been conducting global research in India and have not faced problems on account of GCP non-compliance. There is a two way mechanisms at play here with companies adding to the level of compliance and it growing along side the increased research that is being conducted here now.

Issue of submissions to the FDA; in earlier times, India was not a well-accepted destination for clinical studies. Since the late 80's, clinical trails have been made mandatory in India as a regulatory requirement for getting NCE' approval. These were considered bridging studies to generate data from Indian patients and GCP was not a mandatory requirement for the same.

An important concern for international companies has been that of data quality and acceptability by FDA and EMEA, as it is of paramount importance for drug developers considering a non- traditional country for clinical trials.

Today, GCP compliance is an imperative that is followed with every study; all studies require stringent control wit monitoring and audits from the sponsors.

The new GCP standards that have been given by the Health Ministry are in some ways even more stringent than the ICH guidelines. Today, all sponsors and, investigators in India follow these norms, and there is indeed an increased awareness of there being a flux of GCP compliant investigators and GCP compliant ethics committees in the country to monitor these important global trials.

Today, many MNC's and International companies are now conducting their global studies in India.

Regulatory mechanisms: pitfalls, changes, dynamics, & developments

It is very interesting to trace the historical development of the regulatory reforms that have impacted and guided the growth of capabilities and global studies in India

In 1988, the government legislated a new law stating the requirements for the approval of new drugs for import of manufacture. This was inserted as a new schedule to the Drugs and Cosmetics Rules known as Schedule Y.

This was the same year in which Clinical Trials were made mandatory for all new drug introductions/ as a regulatory requirement for getting NCE's approved.

Schedule Y stipulates that the first applicant for any new drug should generate data in local clinical trails conducted in approximately 100 patients at 4-5 centres. This schedule also indicates that permission for such clinical trials would be given for one phase behind the development status in the rest of the world. However, for a second and subsequent applicant for the same compound, no clinical trial would need required since they could show bio-equivalence to the first product approved and introduce their brand of the generic in the market.

This has historically discouraged MNC's from carrying out global clinical studies by their local subsidiaries which preferred to wait for their innovator brands to be approved in source countries and then carry out limited bridging studies for local approvals. This created a gap between the introduction of new products in India with the rest of the markets worldwide.

There are of course ethical considerations that must be taken into account. So far, Schedule Y of the Drugs & Cosmetics Act 1940, had been created with the intent to safeguard Indian subjects. It needs to be emphasized here that, for all drugs that the Indian population is currently using and benefiting from, the 'guinea pigs' have been western populations. The paradigm shift that needs to occur amongst the regulators, the scientific community, the media, and most importantly the people, is that this form of research does not constitute exploitation of 3rd world countries; rather, it enables 1/6th of the world's population to access the benefit of biomedical innovation.

The government has recently notified the amended Schedule Y of the Drugs and Cosmetics Act. At present, any IND of foreign origin has to be subjected to the phase prior to the phase it has reached in a foreign country, as a means of extra caution. This is of critical concern to regulators and companies. However, India would now be partaking in multi centric global trials concurrently for new drugs of foreign origin for Phase 2 and 3 trials.

However, while the Phase 1 trials are not been permitted, there is potential for making certain exceptions to this rule. Permission for these trials might be considered on the basis of the criterion of need based trials; trials thus might be permitted if the target disease of the drug is found to be prevalent in India in a

manner that requires special consideration. It also attempts to lay down detailed norms for clinical trials conduct and protocols as well as approval for new drug manufacturing/marketing and imports.

The government has also recently relaxed the duties that are levied on clinical trials samples. Now, clinical trial samples may be imported without having to pay custom duties. This has reduced the economic cost barriers on the local partners, thus attracting more studies and work from abroad.

The recent steps taken by the apex bodies in the government that look after this areas are indicative of the governments commitment to building India's capacity in this direction further, moreover a testament to the commitment of the government to aid the creation of a sound and facilitative regulatory infrastructure.

Admittedly so, there are still regulations that need to be put in place; correct implementation of these guidelines could help propel India into the global league for clinical research and trials.

Investigator capability has also built over the years. One of the key attributes that India has to offer is indeed the presence of a large and well-qualified pool of investigators. Most of them are English speaking and western educated and are well tuned into conducting studies for local regulatory needs. A range of training programmes have been conducted by different agencies across the country to help further specialize and train these skilled personnel and familiarise them with ICH guidelines.

From the regulatory point of view, a license for importing clinical supplies is granted with clinical trial permission. Most Indian companies today have, or are well on their way to developing Good Manufacturing Practice audited facilities for their supplies.

Today, there are several International CSO's operating out of India and many local CSO's that have now acquired a standing of their own independent stature after many years of consider performance. There is also complete outsourcing.

Back Office services support, data base development and management, data mining, data management etc; a host of infrastructure requirements can be fulfilled by moving these operations to India.

Shifting these operations to India is estimated to reduce at least half the costs.

India has come far on many counts that are vitally important to the growth of a quality clinical research & trials infrastructure in the country. This includes a large and diverse patient population, networks of academic and medical centers, well-

preserved genetically distinct population groups, and a well qualified pool of doctors, scientists, and technicians.

India does need to rebuild and channelise its focus on up gradation of hospital infrastructure to meet GCP standards, regulatory guidelines, and establishment of GCP compliant ethics committees; these are some areas that remain bottlenecks and require immediate action if India has to develop as a hub for clinical research & trials.

The year 2005 should herald the beginning of vast changes in the Indian Pharmaceutical Industry; these will be directly linked to the changes and developments in the global markets.

There are several small steps to be taken before we can make this giant leap to raise the global awareness and acceptance of India as a quality resource base; the path ahead is not to transform India, for we believe that India is well on the path of improvisation where it is needed, rather the challenge is to rise to meet the global need of the hour and change perceptions to heighten awareness of the benefits and plethora of advantages that lie therein a country with so vibrant and rich a resource base.

The gains from this would be a giant leap forward for India as a nation, and the pharmaceutical industry as a whole.

Thank You
to the Scientific Committee for their input towards the Background Paper.

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