



Federation of Indian Chambers
of Commerce and Industry

DRUG DISCOVERY AND DEVELOPMENT

Business Opportunities in India





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By

Falguni Sen¹

Advisor, Observer Research Foundation, Delhi

Professor, Fordham University, Schools of Business, New York

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Foreword

The sustainability of traditional pharmaceutical Research & Development model is being questioned today with changing market dynamics, emerging markets and saturating growth rates in developed markets. New technological innovations in Research & Development in the past have been the source of competitive advantage. However today with complex and long development cycles and challenges in complying with regulatory and quality standards, different business models of Research & Development must be developed, tested and implemented.

In fact, a failure to do so may pose a threat to the future of the pharmaceutical industry. Despite such a challenge, advances in technology and innovation process do present the industry with opportunities to push forward and prosper. Exploring these future opportunities to leverage India advantages was at the center of the roundtable discussion organized jointly by FICCI and ORF on "Drug Discovery-The Business Opportunities in India" on March 19, 2009 in Mumbai with the support of Department of Pharmaceuticals, Government of India.

The full day meeting saw a frank and open discussion in all related issues between industry leaders hailing from pharma, biotech, diagnostic, CROs companies, Government institutions, hospitals and senior government officials from all concerned ministries - Department of Pharmaceuticals, Ministry of Health and Family Welfare, Department of Biotechnology. The issues discussed were acknowledged to be critical to maximize benefit from the business opportunity that Drug Discovery offers.

The interest shown by the concerned ministries was indeed heartening, and we are thankful to Shri Ashok Kumar, Secretary Department of Pharmaceuticals, Dr. MK Bhan, Secretary, Department of Biotechnology, Dr. K.K. Tripathi, Senior Advisor, Department of Biotechnology, Mr. Devendra Chaudhary, Joint Secretary, Department of Pharmaceuticals, Mr. Arun Jha, Joint Secretary, Department of Pharmaceuticals, Mr. Debasish Panda, Joint Secretary, Ministry of Health and Family Welfare and representation from office of DCGI for their presence and insightful comments during the deliberations.



We present this joint FICCI-ORF report based on discussions, to propose a roadmap for both Industry and Government to consider it as a way forward for the future and long term sustainability of the Drug Discovery Enterprise.

A handwritten signature in black ink, appearing to read "Falguni Sen".

Dr. Falguni Sen
Advisor,
Observer Research Foundation

A handwritten signature in black ink, appearing to read "Amit Mitra".

Dr. Amit Mitra
Secretary General,
FICCI

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1. PURPOSE OF THE REPORT

This report provides policy makers with a roadmap to the issues surrounding the "drug discovery enterprise" in India, which is edging towards becoming a booming industry. It is meant to provide perspective, so that future legislative, voluntary or other policy decisions strike an appropriate balance between two critical needs: the need for transparency and accountability of the bio-pharmaceutical research enterprise to advance public health, patient safety and public trust, and the need to ethically build capacity to enable the sponsors and investigators to remain active players in an innovative, sustainable health product industry and healthcare delivery system.

This report is based primarily on an interactive stakeholder workshop hosted in March 2009 as a joint enterprise of the Federation of Indian Chambers of Commerce and Industries (FICCI), the Department of Pharmaceuticals, Government of India and the Observer Research Foundation (ORF) Delhi². Participants representing a wide cross-section of stakeholders including industry, government, medical practice, ethics boards, clinical research organizations, and hospitals attended. The objective of all the workshops was to discuss and debate the existing provisions, gaps and the policy guidelines that need to be developed and the actions to be taken by the different stakeholders in the drug discovery and development industry to make it grow in an efficient and ethical way. A summary of the main issues and a set of recommendations are being included here. This will highlight concerns across the spectrum of stakeholders and will provide policy makers and other stakeholders with a roadmap of issues to consider in fashioning any future approach. The workshops did not vote on the recommendations. However, a number of issues did have broad agreement and are presented here as recommendations for further action.

A common objective guided the stakeholders. The drug discovery and development enterprise in India was seen to help the

- **Public:** *Get well and live longer and more fulfilling lives*
- **Firm:** *make good returns and sustain profitability to develop products which provide the public with its objective*
- **Government:** *to protect adverse effects and help define "acceptable" risk while acting as "watchdog" and "partner"*

² It also draws on two other reports: "Building and Managing Clinical Trial Capacity in India: Challenges in Ethics, Equity and Efficiency" (2006) by Falguni Sen and Vasantha Muthuswamy, and "US-India partnerships in Drug Discovery and Generics" (2008) by Falguni Sen





2. EXECUTIVE SUMMARY



Global transformation of the pharmaceutical industry has given rise to new business opportunities in drug discovery for India. India has become a preferred location for clinical trials. In the last few years there has been a growth in the number of pre-clinical research collaborations as well. Indian companies have transitioned effectively from providing a "cost and speed" based value proposition in the clinical trials part of the enterprise, and R&D support services to the drug discovery enterprise, into more value added areas. From fee for service models, firms have gone into risk sharing and partnerships. From licensing molecules developed in India at early stages they have gone into later stage licensing and are even looking into providing end-to-end solutions.

There are many stakeholders in the drug discovery and development industry such as the regulatory bodies, public research institutes, universities, hospitals, small biotech companies, specialized R&D firms, domestic pharmaceutical companies, the multinational firms, CROs, the doctors, the patients, NGOs and the media. Each stakeholder represents different interests and priorities. However, through it all they have some common objectives: they want the patients to lead better and fuller lives because of their innovations; they want the firms to make reasonable profits so that they can survive and continue to invest in innovations; and they want the government to set the right tone for the industry, act as a watchdog and protect public interest while providing the right incentives and partnering with the stakeholders in the industry.

This is a report of a workshop where multiple stakeholders discussed the issues underlying the drug discovery and development industry with a common goal of making it grow in an ethical way. The participants recognize the possibility that India can become a major player in the global drug discovery and development enterprise. In particular Indian firms could position themselves as "leaders" in the emerging bio-similar (follow-on biologics) market where India's expertise in innovations and in generics could be combined.

There is however, also the recognition of a number of constraints in achieving such a goal. The main constraint lies in a lack of resources. Sources of high risk funding are not easily accessible in India. Skills and trained personnel are also in short supply. Assets such as specialized equipment are, unavailable, inaccessible or underutilized and poorly maintained. Indian firms do not have a long history of being innovative in this industry and have not as yet been able to show results. Parts of the industry and the regulatory system are also seen to be working at odds with each other due to historical habits which need changing. There is limited cooperation between the public sphere and the private sphere.

The solution could lie in removing the irrationalities in the system and then leveraging limited skills and assets to generate higher efficiencies from synergies brought about through collaborations and partnerships. This needs to be complemented by generating a national inventory of skills and assets to assess shortfalls, and creating a multi-stakeholder governance system to optimally allocate resources to fill those gaps. The creation of a networked organization (consortiums, clusters etc.) with the appropriate culture of sharing may be the best course of action. New and innovative funding models, which could include the government acting as a private equity investor as an option, is necessary to implement the grand strategy. The presence of a strong vision for the drug discovery and development industry is deemed as essential in moving the solution along.

Vision, governance and operations can go far but "incentives" are essential to create successful partnerships and the culture of genuine sharing. Some incentives such as sharing of intellectual property are already in place but more tax incentives for companies and monetary incentives for individuals need to be put into place.

The government's proactive attitude in trying to energize this industry has been helpful and industry needs to put together a process and a structure that will facilitate a genuine public private partnership despite the sometimes, different objectives of its various stakeholders.

While finer distinctions exist, three broad types of activities may be discerned in the drug discovery and development enterprise-the pre-clinical (from lead generation and optimization to animal toxicological studies), the different stages of clinical trials (from proof of concept and Phase 1 to post market phase 4) and those related to regulatory and intellectual property concerns. This report addresses some of the key issues in each.

A summary of recommendations made in the following six areas in this report, is given below.

The vision needs to be articulated by the government in collaboration with key stakeholders to provide the big picture and guide the development of capabilities towards national objectives.

Resources need to be generated in innovative ways in order to be able to implement the mission. Creating **clusters and networks** is necessary to provide a system and structure for sharing and generating synergies in order to get the most returns from investments. **Preclinical** phase of the drug discovery process has its own needs and specific recommendations relevant to that stage as also the clinical trial stage are identified. Finally, a number of **regulatory** changes may be needed and are also summarized.

2.1 Vision

The vision needs to be led by the government using a consultative mechanism with the multiple stakeholders such that there is commitment from all and legitimacy to the process. Such a vision should:





1. Encourage industry to think big and focus on the first "Indigenously developed Molecule" that gives better therapeutic results in an established category,
2. Get the industry to focus on "synergies" and sharing of complementary skills rather than "self sufficiency" by each firm,
3. Provide "guidelines" for the development and structure of national and international partnerships and articulate elements of operating procedures to guarantee "shared learning",
4. Encourage "Industry-Academia" cooperation and provide "status" to industry focused research in academia,
5. Encourage industry to develop more trust and cooperation with each other for greater synergy,
6. Incentivize industry to develop an internal culture of "safety" by articulating a "zero tolerance" policy on drug safety and trial subject safety issues and encourage industry to continue a culture of efficiency,
7. Recognize and communicate to the public the necessary risks associated with molecule development and trials and articulate a vision for acceptable risk,
8. Establish a timeline for India to become a leader in "biosimilars" and articulate specifics on public investments in specialized assets to achieve this,
9. Declare willingness by the government to "partner" in key investments and create planning and advisory committees to direct a "complementary asset" focused investment where public funds are involved.

2.2 *Creating resources to implement vision*

The drug discovery and development enterprise may require multiple funding models to acquire the resources necessary to implement the vision. There is higher (and a different type of) risk in this enterprise and government and industry needs to be more entrepreneurial. While it is unfair to ask the government to absorb all the risks in this enterprise without any recourse to the returns, there may be ways of creating public-private partnerships that can achieve this. There is however, very little understanding of the ways of making such partnerships successful although opinions abound. There is a need to:

1. Establish structures and guidelines for public private partnerships where risks and returns can be appropriately shared,
2. Evaluate the different options suggested (private equity, de-merger, licensing, research collaboration, public private partnership, and market innovation), by matching each option with specific objectives. A committee needs to be formed to assess this,

3. Research the success stories of innovative ways of generating such financing/resources, and communicate these results through workshops, seminars etc.
4. Develop specific guidelines for public private partnerships in the drug discovery and development enterprise. This should include:
 - a. Structure of such partnerships
 - b. Risk-reward sharing mechanisms/guidelines
 - c. Governance structures such as (ownership of shared facilities, board structure, etc.)
 - d. Incentive mechanisms
 - e. Sequencing of work such as (public institutions focus on targets and private sector on lead optimization and thereafter)
 - f. Intellectual property
5. Work with other departments in the government to develop regulations in finance and other areas that will allow for the ideas suggested above. In particular, investigate the possibility of a government owned fund that can act as a private equity investment body in this enterprise,
6. Develop mechanisms within industry to articulate high quality projects for help in financing. Such high quality projects need to be consistent with the vision and national priorities set up.

2.3 Creating Networks and Clusters

Clusters need to be created where the entire value chain of the industry is represented. This will facilitate drug discovery. While elements of some clusters need to be physically proximal there is a way of creating "virtual" clusters to generate the same synergies for some projects. Formalizing "networks" which can act as these clusters can be implemented immediately if industry is willing to respond positively to the vision of sharing and complementarities.

Some of this can be achieved by:

1. A number of firms jointly sponsoring collaborative research with each other and with national institutes,
2. Seconding people from industry into government,
3. Government funds be made available for Industry R&D centres
4. Providing incentives for industry scientists to do some basic research and academic scientists to do some industry focused research





5. Conducting industry-academia workshops on research in specific therapeutic areas as well as technology platforms
6. Creating an apex body to facilitate industry government cooperation and help develop a number of key "communities of practice".

2.4. Preclinical

Shortage of skilled people and a shortage of animals are two areas in which some immediate relief may be needed. Streamlining of immigration laws in order to facilitate the acquisition of global talent will speed up the process of skill acquisition. Similarly laws governing the import of animals need to be relaxed to address shortages that may exist in the initial period. Ethics committees for sites conducting animal toxicological studies should facilitate preclinical animal studies to advance medicine and science when there are no non-animal alternatives, and when it is done in an ethical and humane way. Preclinical facilities should comply with GLP and other international standards for their data to be globally acceptable. Schedule Y mentions that "Toxicity studies should comply with the norms of Good Laboratory Practice (GLP)". However, the approvals today are many times granted to studies that have been carried out in laboratories that may not have GLP. Implementation therefore needs to be strengthened. In the infrastructure area more capable Phase I facilities are needed as are animal testing facilities. Such facilities need to be accredited for quality and safety. Ability to conduct toxicology analysis needs to be enhanced. Primate facilities must be expanded and those in the pipeline implemented expeditiously. Common services need to be created which will be shared on a fee for service basis. The advantage of ownership of such services by not-for-profit agencies should be investigated.

Indian firms need to develop the *technological* capabilities to select biological platforms and make more efficient use of bio-informatics. Eventually they must learn to work with less validated targets and develop their own "proof of concept" trials. They must learn to move from targets into working with platforms in order to reap the maximum benefits from the discovery process.

Indian firms need to do due diligence on companies conducting pre-clinical tests. Industry should develop an informal system (like a voting system) to help others identify those firms that conduct high quality pre-clinical tests and offer integrated services.

A number of *cultural* changes need to be made within the Indian firms if they are to succeed in the drug discovery process. A culture of discovery must be generated. This includes becoming less risk averse.

Good *leadership* is critical to the success of the drug discovery enterprise in India. Leaders have to provide the right vision and establish a culture and process where learning from the partners



will indeed take place. An enthusiastic leader with a good vision can be successful in attracting highly specialized expatriate talent into the firm.

The *organization* must move towards becoming an integrated drug discovery unit with proper documentation processes and functional and/or therapeutic expertise.

2.5 Clinical

Setting up a system of clear-cut *priorities* for clinical trials can help in providing a balance between benefits and risks/costs of the clinical trial enterprise. Such priorities can allocate public resources in a manner that meets national interests. For the private sector, priorities could mean speedier approvals with a possibility of closer monitoring. It could also mean private public partnership in high priority trials.

Ethics committees at different levels, ethical guidelines and norms, independent institutional review boards are all different ways of ensuring compliance with established ethical guidelines and good practices. Critical however, is the preparedness of the members of the ethics committees to take on this onerous task and actually implement some of the guidelines. Ethics committees cannot conduct their task responsibly unless they get the type of data needed to evaluate ethical behavior. Evaluating conflict of interest is an important task of ethics committees for which they may need special training and easy access to financial and other information. Cultural specificities in conducting informed consent may place some special burden in India. Vulnerable populations may need special consideration in the implementation of informed consent. The lack of punitive measures and/or legal liability may reduce the importance of the findings of the ethics committees.

Training of ethics committee members, accreditation of these committees and the development of more stringent guidelines with detailed operating procedures in response to the issues raised above needs to be undertaken. Funding for the ethics committee members, distinction between scientific and ethical reviews, operating procedures for implementation of informed consent and harmonization of the guidelines and rules between different parts of the regulatory process should be investigated. Vaccine trials may be treated differently in the approval process.

There has been some systematic and some ad-hoc growth in *capacity* in different parts of the clinical trial process. Much of this growth is taking place without any guidelines and is often uncoordinated. The lack of quality control in some of these capacity building measures has caused public concern. More regulatory capacity to evaluate NDAs and more trained principal investigators are needed. There is also a need for more GLP laboratories, an improved pharmacovigilance program and the ability to monitor GCP sites. The availability of insurance for subjects of trials is another matter that needs to be urgently addressed.





The creation of a working group to specify the needs for the urgent development of regulatory capacity in monitoring, oversight, enforcement and approval of trials will be helpful. An innovative structure with "consultants" is suggested. A definition of "conflict of interest" in the Indian context for these consultants is also recommended as a task for this working group. Curriculum changes in medical colleges to teach GCP, ethics, and research methodology is also recommended. A certification for Principal Investigators is also suggested.

Dispute resolution capacity in trials needs to be enhanced at various levels-between subjects and PIs, and between PIs and regulators. At the present time such resolution mechanisms are unclear and unknown.

The creation of a national database on clinical trial capacity in India will help in the planning and resource allocation process and in creating partnerships with synergies between firms. A database of prevalent diseases, therapies and large-scale epidemiological studies will also be helpful.

While growth in clinical trials is being fuelled by business opportunities there are several other outcomes. Development of world-class expertise in this area is one such outcome. However, care has to be taken to see that knowledge transfer from abroad and local expertise building takes place in a coordinated fashion. Quality control and joint-trials with reputed global players can give rise to building expertise in this area. Partnerships between public and private sector and with international organizations are a great way to increase expertise. It is recommended that guidelines be provided to ensure that learning does indeed occur through such partnerships. Human resource planning by both industry and regulator needs to be done carefully to deal with clinical trials of the future (such as molecular diagnostics and molecular epidemiology as well as latest social science techniques) to ensure that required expertise is available.

The trials registry in place needs to be integrated with the eGovernance sites being implemented by government. Simultaneously, there have been great strides in database management of clinical trials especially in the arena of multi site, multi country trials. Indian IT companies are trying to establish a leadership position in these technological platforms. The government should be proactive in working with ITeS companies to see how this could be stimulated.

Media has been criticized for sensationalizing a few cases without investigating systemic issues. Media on the other hand, have complained of lack of transparency on the drug discovery enterprise. What is the responsible role of the media in reporting issues related to clinical trials? It is felt that the media plays a very critical role in locating abuse of the system especially in identifying unethical trials and unreported serious adverse events (SAEs). Media should be seen as a partner in this enterprise and has to be provided training to better understand clinical

trials as well as more transparency to do more in depth reporting. It was felt that this would increase public trust in the enterprise that was fast eroding.

Public trust is a critical issue for survival and growth in this industry. A few transgressions can erode this trust considerably. Human subjects should be offered the same protections in all activities such as clinical trials, clinical research, devices, drugs and procedures and all these should get formally registered and approved. It is also recommended that a working group be formed to investigate different ways in which adequate post-trial care of subjects can be provided.

2.6. Regulatory

Regulatory process needs to be streamlined. They need to be holistic and long term focused. More capacity is needed for inspections especially of good clinical practices (GCP). Training of GCP inspectors needs to be completed expeditiously with some authority to punish offenders. Results of such inspections need to be made transparent and put on the CDSCO website. Outsourcing of the inspection process should be investigated. Creation of a "consultant" network will make the approval process for trials more expertise focused and more efficient. Regulations need to be harmonized with other departments in the country and with ICH and global practices. Trials accepted in India should meet all regulatory requirements of the major global markets and in addition should have uniquely Indian components based on safety.

Along with registration of CROs and the ability to monitor them, is the need for an accreditation system for clinical trial sites in general, and Phase I trials in particular. However, with all these regulations, India should follow the directives of "paper work reduction" which will also speed up the regulatory process.

Greater emphasis on developing the pharmacovigilance initiative as a priority is critical. Greater coordination is needed and regulation needs to be changed to include legally binding spontaneous reporting. The PSUR system needs more integration with ethics committees and others, and investment in coordination with global databases and developing data mining capabilities should be considered.

At the end of the report a number of specific recommendations are identified in nine areas.

1. **The vision**, it is hoped, will lead to energizing the industry to think big and work towards developing molecules, which will have superior therapeutic impact. It will also highlight the need for efficiencies and optimal allocation of resources, which need to be shared,
2. **Generating resources** will allow for collaborations to function efficiently especially in public private partnerships by creating synergies and a culture of sharing and will provide for financing of high-risk ventures,





3. **Creating networks and clusters** will create structures and governance mechanisms that will allow collaborative ventures to achieve the maximum synergies from their assets,
4. **Recruitment and training** will result in timely availability of skills and inculcate a culture of sharing and learning from others,
5. **The operations** will help in creating more efficiency, synergy and global regulatory compliance, and within individual firms it will create a culture of innovativeness coupled with a high regard for human safety,
6. **The capacity** gaps will specify investments which are urgently required even to create just a level playing field with a growing number of competitor countries in the region such as China, Singapore and South Korea,
7. **The pre-clinical** phase will club together key issues relating to that stage in the drug discovery process not covered by the earlier recommendations, and
8. **The clinical** phase will do the same for the clinical phase.
9. **The regulatory** arena will bring about a less contentious and more expertise driven system, which will have a holistic view and harmonize with requirements in the rest of the world, in a speedier and risk appropriate way

3. BACKGROUND SITUATION

The global pharmaceutical industry is changing rapidly. With downward pricing pressures in established markets on the one hand, and increasing costs due to regulations, competition and innovation on the other, the industry is being forced to look for new models of efficiency and impact. This coupled with a weak pipeline of new molecules capable of showing major improvements in therapy, is bringing the "blockbuster model" of the pharmaceutical industry into question. There are new risks, which exist not only in the development and market approval of drugs but can be found in its entire lifecycle. Further there is an increase in consumer activism, which is requiring an investment in tighter operating procedures, transparency and the maintenance of public trust.

The industry has responded in a number of different ways. There is a greater emphasis on life-cycle management of a molecule through delivery system innovations as well as approval for new indications and new market segments. Merger and acquisition activity in the industry has resulted in a consolidation of pipelines in some cases and greater market and distribution power in others. On the other hand, the industry has also fragmented further due to the growth of small R&D companies especially in the biotech sector, which have become new sources for innovations. Growth in established markets has slowed down considerably and non-traditional "pharmerging" markets (Brazil, Russia, India, China, South Korea, Mexico and Turkey) have become the new sources for growth. But this growth is not necessarily related to profitability as such growth is occurring in primary care sector where margins are low and competition is getting more intense and based on price. Profits still lie in specialty care where margins are healthy but volumes are relatively small and distribution is shifting to hospital and institutions with higher purchasing power than retail.

These changes have required the industry to restructure and adopt a more global outsourcing model to generate efficiencies. Manufacturing activities have been outsourced for some time; there is now an increase in the outsourcing of drug discovery and development as well. While this covers the entire discovery value chain from basic research till post market (Phase IV) trials the greatest portion of outsourcing happens in clinical trials. Pre-clinical work including lead optimization and target validation has also become a growing source of outsourcing in recent years and takes the form of fee for service and some risk sharing through partnerships.

It is in this context that the Indian drug discovery and development enterprise finds itself with unique sources of competitive advantage in order to become a major provider of innovations to the pharmaceutical industry for domestic and global markets. However, in order to succeed it





needs to create an innovation ecosystem consisting of not just the R&D enterprise but also the manufacturing, test and validation infrastructure, financing, delivery system (hospitals) and regulatory aspects. It needs to devise incentive schemes that will keep all the parts of the system working efficiently towards the goals of the discovery enterprise. The Indian drug discovery enterprise desires to move from fee for service transactions into more value added and risk taking business models, which will eventually allow them to introduce the first "Indian" molecule. This reputation is necessary if it is to compete effectively for global partnerships in the discovery process with competitors such as China, Singapore, South Korea and the like.

Capacity building is essential if India is to be perceived as a major player in the global drug discovery industry. Currently there is either a lack of high quality capacity or they are scattered in a way that economies of scale and synergies are not achievable. Indian firms strive to cover maximum ground on their own. There exists extensive opportunities for Indian companies to collaborate and create a network of complementary skills, which will offer both scale and specialization. For this however, an environment of mutual trust and cooperation is essential.

There are a number of stakeholders involved in the capacity building process. The Ministry of Health has a regulatory role through its departments/directorates and councils. The newly formed department of pharmaceuticals can coordinate a number of disparate compliance issues and harmonize existing regulations. The department of biotechnology has been very innovative in fostering private public partnerships and laying its own infrastructure to facilitate the development of the biotech industry. The department of science and technology plays a critical role in creating the culture for research. The Indian Council for Medical Research (ICMR) has been actively supporting clinical research through its various initiatives and facilities for microbial containment, preclinical toxicology units and clinical pharmacology units, in addition to proposed animal facilities for transgenic and biomedical research. They have assisted in regulatory evaluation and compliance and on many occasions have had to take on the role of a national ethics committee, issuing guidelines for cutting edge research from time to time. The hospitals where trials are conducted must have systems in place including efficient and independent ethics committees that can best deliver the ethical and efficient conduct of trials. The doctors and nurses who are engaged in the trials are critical to this process and need to be properly trained in being principal investigators and study coordinators respectively. Site management organizations therefore play an important role here, and a need for a robust adverse event reporting system cannot be neglected. The Indian pharmaceutical companies need to have adequate databases to monitor and track the trials and must possess clinical research expertise in design and implementation. They need to be able to connect some of the recently spun-off R&D capabilities with the clinical trial enterprise. The investment community from private equity to venture funds and conventional lending agencies need to understand the nature of risk and return in this enterprise. The independent clinical research companies need

to develop systems to monitor the implementation of the trials. Good clinical practices need to be constantly reviewed for effectiveness in reaching the stated goals. Finally, the volunteers of the clinical trials need to trust the entire system and believe that its primary objective is protecting human subjects and improving healthcare in specific disease categories. Advocacy groups and responsible media are important stakeholders in ensuring that decision-makers hear volunteers' concerns and appropriate transparency is assured.

The stakeholders who are independent members of the drug discovery value chain are actively debating the benefits and costs of the enterprise. Their objectives and goals are different, and a dialogue between them will go a long way towards clarifying issues, debating priorities and creating the necessary trust. This is what the different workshops referred to in this report focused to achieve.

The regulatory regime in India has to strike a balance between the benefits and costs/risks of this enterprise. In the initial stages of evolution, an industry may not have the ability to self-regulate or implement decentralized decision making without some informed guidelines. Conversations such as those provided during these workshops help build a culture of common goals and priorities so that self-regulatory and decentralized systems can indeed evolve with growth in the industry. Till that happens however, there may be a need for a strong centralized regulatory regime which can guide high quality development of ethical capacity. And yet, there is a need for the government not to act as a mere "watchdog" but also to motivate as a "partner". This dual role is fraught with complexities and needs to be carefully managed. There is a need to professionalize the culture of this industry. Since this industry deals with the lives of people it has some unique norms. It cannot be viewed in purely commercial terms. It has to develop a culture of caring for human safety. Unlike many other industries however, risk is essential to the nature of experimentation in this industry but errors can kill the reputation of this enterprise or even that of this country. This industry is very sensitive to issues of ethics, morality and social justice since it deals with the lives of people. Thus extra vigilance is paramount if this industry is to succeed.

There has to be a system that quickly rectifies mistakes but understands the notion of acceptable risk and the importance of a scientific approach in mitigating a lot of risks. The regulatory system has a further responsibility of providing public assurance of safe guarding the rights and safety of the study subjects while ensuring the credibility of the data submitted for new drug applications. In some areas the distinction between devices, drugs and therapies is being obfuscated. Innovations in devices are happening very rapidly and clinical evaluations need to be done in a scientific manner to establish superiority over existing therapy. There is already a lot of awareness in India regarding clinical trials. Good Clinical Practices (GCPs) have been clearly spelled out and ethical guidelines have been articulated. A system to register and





approve clinical trials is in place. An "investigational new drug" and a "clinical trial" have been operationally defined.

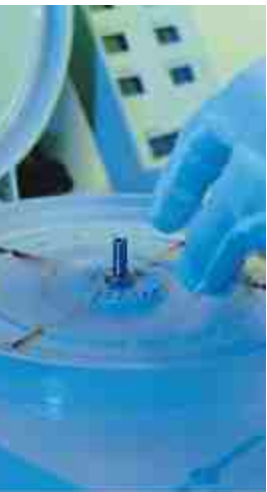
The national pharmacovigilance program, while in its infancy is likely to address some of the concerns related to drug launch. However, the regulatory system is already stretched in terms of its ability to monitor proper implementation. The expected fast growth in the industry is going to further stretch the capabilities of the system and highlight complexities and unintended consequences.

Outsourcing to Indian firms has happened for some time now. Indian firms started with functional outsourcing in areas such as process chemistry and the manufacture of intermediates. They moved to value added areas and began an emphasis on doing more biology. Pre-clinical development in the private sector (mostly rodents) was then established to match some of the work being done in governmental laboratories and universities. Soon thereafter some firms began to get intellectual property (IP) critical projects while the API and formulation businesses began to grow. This was followed by a growth in the synthesis business and lead optimization. Work on functional biology was started by the industry with toxicity and medicinal chemistry capabilities being developed. In the last two years or so licensing at pre-clinical stage and Phase I have occurred and we are beginning to see partnerships with developmental rights.

Although drug discovery in India is a relatively new phenomenon and thus far very few compounds have really been discovered in India, the potential for success is high. Cost and speed have been the primary value proposition provided by Indian firms. However, talent and specialized knowledge in new technologies may become the source of competitive advantage.

Reducing cost of drug discovery is critical to the long-term viability of global pharmaceutical industry. Building capabilities in India is critical to providing such a reduction in costs. By some estimates research costs, in India, for chemical entities are around 40% of the costs in developed countries and the costs for conducting clinical trials can be anywhere from 30-60% cheaper. Trials are also completed faster allowing for early entry in large markets. A three month entry advantage in a billion dollar market provides additional \$250 million revenue to the pharmaceutical company. Even universities in the US are looking for Phase I support from India in order to generate higher possible revenues from their discoveries.

Functional capabilities in chemistry, and growing abilities in biology, genetics and bio-informatics coupled with low cost clinical trial capacity is making India an attractive destination for drug discovery. This is especially true after January 2005 when India became WTO/TRIPS compliant in terms of intellectual property. During the period of 1994 to 2003, seven centers for New Drug Discovery were established. Since then a number of firms are engaged in different stages of the discovery process from lead generation and optimization, to target identification



and platform technology development right through toxicological and safety studies including large animal trials. While "faster and cheaper" is the value proposition offered by Indian firms in the drug discovery process, it is also likely to become the source of discovery of new molecules. The likelihood of this scenario will depend on how Indian firms develop new skills and capabilities and learn the complex processes of successfully launching a new drug into the market. Much of these capabilities are being acquired through partnerships with firms in the US and Europe.

Licensing out of new molecules after completion of either INDA filing, or early clinical trials has been the preferred mode by Indian companies due to lack of resources. However, the discovery phase has seen a number of projects being outsourced to them by foreign entities through fee for service contracts, build-operate-transfer (BOT) agreements, licensing agreements with royalty and milestone payments, marketing agreements or even broad-based strategic partnering without intellectual property issues clearly articulated. In general, partnership with global firms has been one of the quicker ways for Indian firms to gain needed capabilities.

Global partnerships have provided Indian firms with talent, equipment, international experience, and a culture favorable to the conduct of research in pharmaceuticals. In the short run, talent in the form of capabilities in biology, pharmacology, animal facilities, medicinal chemistry, clinical pharmacology and capacity in terms of sophisticated laboratory and diagnostics helps in getting a base set up. The possibility of being part of an integrated global site also has a lot of learning advantages.

However, India has to build expertise and capacity internally to move into drug discovery effectively. In particular, appropriate capacity needs to be built in the regulatory regime, infrastructure, training, and technology. The culture of the firm needs to orient itself towards efficient discovery by encouraging innovation, a desire for intellectual property and a prime emphasis on safety. There is a lot of uncertainty in this strategy and the leadership needs to be able to offer proper guidance and vision. It also needs to motivate local talent to learn and absorb the expertise and capabilities being brought in by global partners.

There is an increase in demand for clinical trials arising out of changes in the global competitive environment in the pharmaceutical industry, new technological possibilities and changes in the regulatory environment in some countries. Demand for clinical trials in India has skyrocketed in the recent years and is expected to grow exponentially in the next few years. A number of factors make India a very attractive location for clinical trials. There is optimism amongst a variety of stakeholders, about the potential for growth. There is a spurt of entrepreneurial and business activity in this area. Pharmaceutical companies have increased their number of trials, there has been a rapid growth of contract research organizations (CROs) and locations where clinical trials are being conducted have tripled. Secondary and tertiary organizations have also sprouted such as site managers, social workers and patient advocacy groups.





Along with the optimism for growth in this industry is the fear that vulnerable populations may be exploited. The benefits and costs anticipated in the fast growth of this enterprise may be summarized in the table below along with safeguards that can be built through a robust system:



**TABLE 1
BENEFITS AND COSTS OF CLINICAL TRIAL ENTERPRISE**

	BENEFITS	COSTS/RISKS	Proposed safeguards
1.	Access to experimental drugs	Possibility of exploitation of vulnerable populations	Strengthen ethical practices through training and robust regulations
2.	Doctors exposure to latest therapies	Indians used as guinea pigs (unscrupulous activities going unchecked and unpunished)	Strengthen ethical practices through training and robust regulations
3.	Overall quality improvement in clinical practice and diagnostics	Focus of healthcare shifting to income from trials at the cost of patient care	Informed consent and oversight audits etc can balance the shift in priority
4.	Availability of latest therapies	High risk new therapies not allowed in other countries being tried here	With informed consent process and compulsory registration of clinical trials, risk can be minimized
5.	Improvement in equipment and infrastructure	Creating expectations of cure and access to drugs we cannot meet	Make adequate preparations to meet the expectations
6.	Business opportunity and employment generation	Losing focus on locally prevalent diseases	Bringing greater convergence of business opportunities with local disease burdens
7.	Competitive advantage to Indian Pharmaceutical industry	Treatment facilities overwhelmed by clinical trial usage	Policies in multi-use sites to meet public health needs
8.	Stimulate FDI in pharmaceuticals	Loss of practicing doctors to clinical trials	The numbers are actually low and the anticipated growth in graduating new doctors should alleviate some of these problems
9.	Give India competitive advantage in biotechnology	A greater shift from rural into urban health care as research sites remain primarily located in urban areas	The emphasis in NRHM and other rural programmes is likely to counter this effect
10.	Give India competitive advantage in gene-based new drug discoveries	Lack of post-trial/post approval availability of tested drug; or availability of continued medical care for the subjects.	Government can make companies conducting trials liable for post trial therapy. This is already happening in a number of cases on a voluntary basis
11.	Access to healthcare in economically vulnerable populations		
12.	Ability to create sustainable new knowledge assets		

The stakeholders who are independent members of the clinical trials value chain are actively debating the benefits and costs of the enterprise. Their objectives and goals are different and a dialogue between them will go a long way towards clarifying issues, debating priorities and creating the necessary trust.

The advent of biotechnology in general and genomics and proteomics has created issues in assessing risk and safety that no regulatory system in the world has perfected. India is entering this industry at a time when no country can boast of adequate regulations to ensure safety. There is thus no other country to emulate. India has to come up with its own procedures unique to its realities and the technologies of its times. It is also an opportunity for India to be able to be at the forefront of this regulatory venture.





4. ISSUES AND VIEWS



4.1 Creating a "grand strategy" for drug discovery-need for a vision

A number of gaps in capacity building for drug discovery have been identified in Table 2. Filling these gaps will, in some ways, level the playing field between India and some of its competitors in the discovery arena, such as China and Singapore but it will not provide the competitive advantage needed to fully utilize the potentials that the country has to offer. There is need for a broader vision, which will move the "capacity building" locally towards "national needs" and globally towards "competitive advantage" making India the preferred destination for drug discovery.

Such a vision should allow for the most optimal allocation of our scarce resources. No matter how much India spends on the drug discovery enterprise it will not match the level of investments done in developed countries. Thus, the vision should be able to articulate priorities and create a culture of sharing of complementary skills and resources. Getting scale efficiencies is as critical as investing in the necessary skills and specializations.

In particular the following issues are identified where the vision could overcome barriers to the competitive development of the industry:

1. **Scale and Quality:** There is a need to substantially increase scale and quality of discovery innovation in India by focusing beyond limited disease areas or incremental improvements to develop true innovation in India with global potential. Indian firms are focusing on a limited number of therapeutic areas and with molecules that provide incremental benefits. They need to get more ambitious and target molecules that can deliver better therapies in more efficient ways. The overall vision needs to motivate the enterprise into thinking "big" and being proactive. Further, Indian companies can align their strategy to National priorities, which remain largely unaddressed by many developing nations.
2. **Skills Training:** There is a lack of personnel trained in state of the art research capabilities. To meet the demands of appropriate clinical research personnel in India, DBT has set up Clinical Research Training Centers (CRTC at AIIMS, New Delhi; MAMC, New Delhi; KEM Hospital, Mumbai; Amrita Institute, Cochin; NIMS, Hyderabad; Sughan Life Sciences, Tirupathi) to provide specialized training to clinical investigators (MBBS and MD). The purpose of the training is to make the clinical investigators understand the ethical and regulatory aspects involved in conducting clinical research/trials. Such training is anticipated to encourage young clinical investigators to initiate programs in clinical research

and translational medicine. Institutions such as NIPER continue to play an important role in filling this gap. However there is a need to create large for-profit institutions to better train India's biopharma talent. This can be done by industry itself (such as the Suven-Pfizer institute) but incentives need to be provided to overcome the industry's reluctance to enter this area. Partnerships with foundations, universities, and private equity need to be created. The overall vision needs to provide goals and directions for such partnerships while facilitating interaction between industry and academia and providing resource support for start-up where possible.

3. **Leveraging success in R&D support services:** There is a need to maximize use of India as a base for R&D support services by accessing global markets more aggressively and facilitating the improvement in the quality of service offered by these support services. India has become a very attractive location for clinical trials. And yet there are many impediments to becoming a major global player in this industry. There are problems with infrastructure, training, culture, operating procedures, public perception of the enterprise and regulatory cumbersomeness, which needs to be overcome. The vision for this enterprise needs to encourage knowledge transfer such that firms can go down the learning curve rapidly. It needs to encourage sharing of skills and capabilities and a consortium approach to getting value added business. Management of Clinical Trials supplies also needs to be improved, and infrastructure needs to be developed not only for evaluation of samples in Central Laboratories in India but also to store biological samples as per global norms to be able to retrieve if needed in the future.
4. **Building pharmaceutical capabilities in academia:** There is a need to increase pharmaceutical research at academic institutions that are guided toward product development. This can be achieved by providing more industry interaction as well as clearer policies on intellectual property sharing. The recent notification by the DSIR allowing Scientists to have equity stake in scientific enterprise while continuing in employment and facilitating mobility of researchers between industry and scientific establishment while in employment with their professional organizations may have a positive effect. However, guiding research towards product development needs more than just incentives. It is an issue of culture, of research training and of interactions with the entire ecosystem of drug discovery enterprise. A successful vision for this enterprise will encourage "industry focused" research in academia and will give it as much respect as "science for science's sake".
5. **Cost and Speed-building efficiencies in different phases:** There is a need to demonstrate that big pharmaceutical companies can develop new drugs in India at a substantially lower cost than current estimates. India needs to show a success story of a drug developed from target identification stage till regulatory approval for less than \$100 million. A vision that





emphasizes efficiency in every stage of the process while keeping safety and quality issues intact is necessary to create a culture that generates efficiency in an ethical way.

- 6. Preparing for leadership in biologics:** There is a need to develop biologics capability in India especially targeting the vaccine market and the bio-similar (follow on biologics) market. Indian biotech companies have a lot of strong technical capabilities but have not been able to position themselves as potential global players in the emerging bio-similar market. To do this they need to partner with investors and with pharmaceutical companies who have global distribution capabilities. Moreover, the regulations pertaining to biologics is nebulous in the country as is in most countries of the world. They need to be developed to complete a safe product development cycle. The Indian Government should work closely with other countries to evolve regulations for Biosimilars, with a purpose to ensure patient safety and help the Indian industry access markets across the world. There is also an Indian market that is still untapped and that could become the launching pad for molecules not yet in the market. There needs to be a vision that articulates this enterprise as a national priority. The type of vision articulated above needs to be generated in a way that is considered legitimate by the different stakeholders identified in this enterprise above. While a team approach may be used to articulate such a vision it appears that the government is at the present time best suited to deliver such a grand strategy. There are many departments within the government that are relevant to this enterprise and at the very least they need to come out with a joint vision that captures the essence of the arguments identified above.

4.2 Generating resources to implement the vision

Over the last five years Indian pharmaceutical companies have tried to capitalize on their strengths, which matched the needs of global transformation in the industry. In manufacturing, especially of generics, this was achieved through capacity building of cGMP facilities and demonstrating ability at stable and consistent production of high quality products. The growth of the local market and conventional funding along with access to global markets were sufficient to help such firms achieve the necessary scale and quality. The access to the global markets due to regulatory changes in the United States also helped generate economies of scale and other efficiencies.

The situation in the drug discovery part of the business is somewhat different. Clients are willing to pay "fee for service" for specific tests and support services rendered. These contracts allow Indian firms to build some of the capacities required for independent drug development. Clients today are considering engaging Indian firms in aspects of drug discovery but this trend has to accelerate. Conventional funding mechanisms are also not willing to take such risks or are unable to assess the nature of these risks.

Further, the risk-reward equation in this industry has changed. Risks of failure used to be the risk of a molecule going through the research stage successfully in the technical sense of the term. Today the definition of success is changing. Regulatory and more specifically reimbursement agencies (government and insurance companies) are expecting new molecules to demonstrate superiority in therapeutic capabilities to existing molecules. Such superiority is also being assessed in "cost of therapy" terms. Further, post market withdrawals of a number of potential blockbusters have increased the market risks. Consumer activism coupled with the ease of dissemination of information through new technologies such as the Internet coupled with demands for increased transparency in the process (note the clinical trial registry debate and outcome) has increased the post-market risks of the drug as well. This may change the calculations of the effective life of a drug during which time reasonable returns may be expected. All of this reduces the attractiveness of investment in early stage molecules and investments in the overall industry.

The bio-similar market is a different scenario where major opportunities may still be found. It is less crowded and because it is difficult to synthesize the follow-on (biosimilar) and the market is also not yet developed. Given Indian biotech firm's lead in some of these areas they should be able to aggressively compete in this industry if proper funding opportunities are available for them. It is heartening to note that the DBT BIPP program has in its recent announcements included Biosimilars for funding recognizing the risk associated with it and the technical and innovative content of development.

Indian firms have found some innovative ways to continue the high "cash burning" activities of the drug discovery enterprise through some unconventional funding.

The following funding models have been found to exist in the Indian drug development enterprise and were discussed at the workshop:

1. **Private Equity financing:** there is a lot of activity already in India but it is "under the radar" and specific to biotech and other niche pharmaceutical molecules. It has not really taken off in India since the innovation credentials of the industry are yet to be proven. Also, private equity usually has a 4-7 year return horizon whereas in the drug discovery enterprise you need a 7-10 year return horizon. Thus only late stage drugs or drugs with lower risk of failure are likely to be invested in. This is particularly true of venture funds where investments are made in companies already generating some source of revenue. Thus pure play drug discovery firms are not as attractive to them. The example of ICICI ventures withdrawing from Dr. Reddy's when the time horizon increased by 3 unexpected years is an example of this.
2. **De-merger:** or hived off R&D units are being used as mechanisms to generate higher risk funding and minimizing the risk of the shareholders of the overall company. While





examples exist such as Nicholas Piramal and Ranbaxy there is not much evidence as yet, of it creating value for increased funding of drug discovery.

3. **Licensing:** a number of Indian companies have licensed out their molecules. Typically this involves some upfront cash payment by the licensee and milestone payments along with royalty for specific markets. There are usually flow-back clauses in such licensing which allow the licensor to have access to process improvements made by the licensee and also access to specific material needed for manufacturing in markets where the licensee is not given explicit rights.

However, most licensing in India is between Indian firms and foreign entities. There is very little collaboration between Indian firms themselves who seem to be more in a competitive posture with each other. Whether it is an issue of trust or lack of complementary skills needs to be investigated.

4. **Research collaborations:** these are rapidly increasing. In many cases it starts as a "fee for service" situation and can develop into more risk sharing models. Such collaborations are happening mainly in the pre-clinical stages with Indian firms working primarily with validated targets.

Given the lack of collaboration between Indian companies in research due to issues of trust and lack of complementarities it may be possible to investigate a consortium approach to collaborations where complementary skills are planned into the asset structure of the specific consortia companies. However, this would require much planning and the mechanism for it does not exist. Public financial institutions could take a lead in creating such entities. Projects of national interest could provide an opportunity for such collaborations. Part of the reason for lack of collaboration may be the size of the total Indian market. Indian firms feel that there is not enough in it for everybody and thus the winner has to get all to survive. Once the mindset moves to looking at the global market and the Indian market also gets larger we may begin to see more naturally formed collaborations taking place.

A similar trajectory may be seen in the telecom sector in India where collaborations have indeed become the norm.

There is also an issue of "mindset". There is a lack of "competency based" trust in each other in the industry. And this is not just true of drug discovery but can be seen in the drug delivery part of the industry as well. There needs to be a shift in the mindset of the entire Indian pharmaceutical industry where there is more respect for each other's capabilities and thus possibilities of more cooperation and greater synergy.



There are exceptions where Indian pharmaceutical companies have indeed collaborated with other Indian companies for R&D. In those cases the same fears that the foreign firms have, need to be addressed such as leakage of intellectual property and marketing rights. An additional issue with Indian firms is that their history of success with generics which have high success rates and short term achievable goals and targets makes them even more risk averse in addressing collaboration issues.

Indian firms do not have a track record of success of bringing new molecules into the market. The idea of collaboration is that partners make use of complementary skills. Thus Indian firms who may have molecules would either invest in their own resources and assets to be able to take the molecule right up to the market or they would collaborate with a foreign firm that has those complementary assets. This is evidenced in the history of molecules coming out of Dr. Reddy's where they started with licensing after Phase I and now with more resources and capabilities in place will take their molecules to Phase III.

Funding is the main issue of taking molecules beyond Phase II. Public-Private Partnerships can help a lot in this regard. The models, proposed by the Department of Science and Technology, are worth looking into as examples of such partnerships. There are many new innovative models emerging. If one looks at the ICICI bank, CSIR, Reddy lab, they are undergoing a collaboration of very unique kind that is has shown some degree of success. Collaboration happens with complementary assets. The industry has not yet developed those levels of differentiated specialized skills. In the next few years as differentiation and specialization develops, more local collaboration is likely and the mindset issue will be addressed by sound business analysis. But business rationale is still not there for collaboration within Indian companies because the degree of specialization in a targeted way to create a cluster has not emerged.

5. **Public-Private Partnerships:** Most such partnerships are occurring where the government facilitates the relationship between industry and research institutes. There are questions such as sharing of intellectual property and the subsidies offered to industrial profits, which need to be resolved. It is worth noting that for certain projects under the DBT BIPP scheme, the industry has complete ownership of IP inspite of a grant in aid from the government. The possibility of creating a not for profit organization to facilitate public private partnerships was explored. The increasing popularity of open source drug discovery and the role of the government in encouraging/regulating it needs to be investigated further.

For partnerships there have to be high quality projects proposed by industry and other institutions. There appears to be a lack of high quality projects, which are likely to make an impact, that are waiting to be funded. For SMEs, there is funding available for clinical trials





as well. All vaccine trials can be funded by government money. There is also foundation money and global partnerships for high quality skills and capabilities that are available for vaccines. For bio drugs there is need for targeted development of appropriate skills and the ability to generate economies of scale in the utilization of such skills. There is a lack of a framework for governance of public private partnership, which is holding it back.

Government is ready to approve a number of projects but industry needs to first invest in long-term capabilities and not just short term profits. A useful area for partnership may be joint hiring by industry and government of highly skilled people in drug development.

Industry does not partner well with government. They need to identify the gaps and make specific requests. Once the gaps are identified there is a need to assess whether the gaps exist because the specialized skills or assets are actually not in existence in the country or whether there is a lack of an organizational mechanism and incentive in place to utilize those assets appropriately. Incentive mechanism along with a non-profit organization could become the best vehicle for public private partnerships in drug discovery.

There is a need for interfaces to have successful partnerships. The industry also needs to harmonize the priorities across various groups.

One dimension of public private partnership is industry working with government research institutes. The mind-sets of the two groups of scientists are different even if they are collaborating. This can sometimes cause major bottlenecks. One-way of resolving this is for the research institutes to have very clear-cut strategic priorities during these partnerships. However, it is difficult to transform public institutions into translation facilities, which will no doubt be advantageous to industry. It is possible to look into the Institute of Life Sciences in Hyderabad model to see how the combination of a non-profit works with a focus on intellectual property of a university and an emphasis on commercialization and market success. The role and structure of their scientific advisory committee needs to be studied.

One structure for a government partnership could be the use of public research institutions to focus on target identification and allow the private sector then to take it forward. However, even for target identification some idea of industry's priorities would help the scientist make some implicit choices. Thus there may be a need to create "communities of practice" which would cut across individual silos and create fearless conversation in say one therapeutic area across multiple stakeholders in the industry. The problem lies in creating incentive schemes, which will bring diverse groups of people together. One way may be to create incentives for industrial scientists to work on basic research projects and research institute scientists to spend some part of their time in working on industrial research projects.

6. **Market Innovation:** There may be the possibility of creating an options market for molecules where there is information available at each stage of the process. In such a process investors may come in at different stages of the development cycle of a molecule and price it according to their perceived risks by taking options on their success. The key issue however, remains the lack of success stories of molecules being developed in India. There may be low risk areas such as phytochemicals where success is likely and end to end financing may be possible.

There should be a possibility for the government to act as a private equity partner and take some of the risks that traditional private equity does not take, and the recent BIPP program of the DBT has set this trend. There may be a need to change some income tax laws in order for government to do this but there is definitely a desire to implement this. This would allow India to acquire competencies that do not exist here and even acquire companies abroad in order to do so.

Firms are moving towards a portfolio approach to funding strategies for R&D. In other words multiple business models are being pursued. Thus private equity may be sought for late stage molecules (after phase IIA), while licensing brings some cash flow into the firm and fee for service adds to equipment and cash flow. Research collaborations can also exist simultaneously if the firm has established reputation in a particular therapeutic area or a particular technology platform. This multiple business model approach reduces the perceived risk for all players. However, organizationally it is a challenge to implement since each business model requires a different organizational culture for optimal effectiveness.

4.3 *Creating networks and clusters*

The Department of Biotechnology's Faridabad initiative is an attempt at creating a cluster for successful biotechnology research and commercialization. Its philosophy is to create a public private partnership to generate a community from different parts of the value chain. There is an application design center that acts as a pressure point for all the parts of the cluster to focus on application. There are in addition, service companies and platform technology companies. Land has been reserved for other companies interested in coming close to the cluster to locate their facilities there. Merck has already done so for its low cost vaccine facility. All the centralized equipment facilities are run by industry who are allowed to make money as long as the public interests are given due priority. Another approach is to find an institute of reputation and encourage them to start a cluster. The stem cell institute funded by the government to NCBS in Bangalore is another such example. The structure is such that the basic science institute and the translation science institute have the same governance structure.

A possible way of focusing research for commercial exploitation will be to allow scientists to share profits and to have equity in the company that will commercialize the molecule. Under





recent cabinet order scientists in India are now allowed to have an equity stake in a scientific enterprise / spin offs in professional employment with their research and academic organization. This option will also allow institutes to recruit scientists from abroad who require equity participation as part of their package. Creation of these communities of practice along with innovations in remuneration packages that include equity participation is likely to attract expatriate scientists to come back to India. There is a real shortage of high quality manpower that prevents us from the types of investments we ought to be making.

High quality experts are also in short supply for many regulatory approval and compliance issues in government as well as in the industry. This is sometimes the reason for delay in approval of critical but complex clinical trials. The ability to extend the notion of "community of practice" to scientific experts who can serve as consultants approved for a specified term to facilitate the regulatory process will be helpful.

4.4 Pre-clinical

Although regulatory aspects do not enter much of pre-clinical research it is important to factor these in. This may allow failures to be predicted early and increase success rates. There is the possibility of using technology to improve the success rates by following the US FDA approach of allowing biomarker guided drug development.

While training is critical it is the type of training that is at issue. There is a need for training in latest skills but also training in new culture of thinking and of doing science. Often collaborations in pre-clinical stage do not result in learning because the culture of learning and absorbing new ways of doing things has not been put into place. Learning from collaborators means learning not just how they did things but because of the mistakes they made how "not" to do things. There is a need to change the paradigm of work in the pre-clinical stage. Many drugs succeed through serendipity. The issue is how we increase our chance of going ahead with a molecule when luck provides us with one. A holistic approach to regulations applied on a case-by-case basis is needed. Regulations should be altered to facilitate the hiring of global talent to meet skill gaps. In particular, delays due to current immigration rules often result in loss of hiring opportunities.

Animal studies should only be permitted in facilities, which are accredited as being GLP compliant. Pre-human testing requires primate/large animal testing. However there are limited primate facilities available as yet. ICMR has proposals for transgenic animal facilities and a National center for non-human primate breeding center. Capacity in this area needs to be built and fast. There is a need to have licensed breeders who can maintain a supply of animals for various studies.

Reputation of companies that conduct world-class toxicological studies needs to be known by Indian firms. Companies in India are often unaware of the capabilities in the country and spend unnecessary sums of money to get these tests done abroad. There should be a mechanism to disseminate information on high quality capabilities available within the country. Many Indian pharmaceutical companies outsource safety, pharmacology and regulatory toxicity studies to other countries, due to lack of comprehensive facility existing in the country, which could carry out these studies in an integrated manner.

Preclinical infrastructure and training are needed. There is a need to share common services and a need to have the right people who can provide discussion on specific platforms. Every scientist does not require complete self-sufficiency in terms of in-house infrastructure. Pooling of resources for common facilities as a concept not only makes it less capital intensive, it also ensures capacity utilization. Not for profits should own the infrastructure and industry could use them on a fee payment basis for the services provided, the fees charged would be for sustenance of the facility. These two principles should guide the private public partnership in infrastructure at least for the pre-clinical phases. There is also a need to make an inventory of highly specialized assets available and their utilization so that the sharing theme can be made operational. This kind of mapping of capabilities and skills should be done as a priority. There is a need for key dedicated people with industry experience to want to come and work with the government to create such partnerships.

The existing Indian facilities' generation of preclinical data may not be accredited and the data generated by them therefore may not be accepted by Global regulatory agencies. Even though India has authority to grant GLP accreditation to CROs, this is not accepted globally mainly because of non-member status of India as OECD country. Recently a few CROs have been accredited with country specific OECD recognition but their services are limited and do not cater to the gamut of preclinical studies that are required.

There is no non-human primate facility existing in India except of CDRI and NIN. However, these facilities need to be improved to be able to meet and maintain GLP standards. Government run Institutes, Regulatory Authorities and Indian Pharma industry, couples the lack of infrastructure with limited understanding of different phases of discovery and development. Therefore, proposals to address the issues are not always effective.

Even though DST and DBT have floated various programs to encourage New Entities by encouraging Industry-Institute partnership the outcome has not been encouraging. The timelines are never adhered to. Industry is keen to upgrade infrastructure, taking advantage of duty free imports of costly chemicals and equipment, which could have dual use in research and operations. The research Institutes are often not keyed to the demands of the industry and their research is for academic purposes and not directed towards product development.





The following actions may also be taken:

1. Updating of Schedule Y to match global trends, possibly as a separate chapter and a rigorous implementation of GLP requirements.
2. Creation of National facilities to address industry need of performing tests on animals (Primates, large animals). There is no National facility within CSIR or CDRI, which can match the needs or standards for supply of Laboratory animals or participating in discovery/Development process. The government is known to have made several suggestions and initiatives, but they have not taken off.
3. Government should prioritize completion of the National Primate Center in the outskirts of Mumbai, initiated by ICMR and DST under the supervision of experts.
4. The National Center of Research in Reproduction can develop a Marmoset colony. Marmosets are small non-primates, easy to handle and very akin to human in PK and Metabolism aspects. This colony can be utilized for discovery as well as development purpose on a global scale. This can be undertaken as a project for implementation.
5. There is little awareness on setting up and maintenance of such facilities, making it difficult for any initiative, as they would run in to approvals and regulatory hurdles. The government should look into creating centers, which abide by global standards and are accessible to companies undertaking drug development in India. In addition, a group of experts should be available who can assist Indian companies in designing their preclinical studies and addressing other key issues in their preparation to IND application.
6. The government could therefore consider creating model national facility, which will offer complete package services to help companies till the INDA filing stage. This will imply a group of experts who can help in protocol design and other technical inputs, as well as experts who can propose IPR strategy.

4.5 Clinical

Regulatory processes for Phase I trials need to be improved. Definition of Phase I trials needs to be clarified and the regulations harmonized as per ICH guidelines. Today, regulatory requirements for *early drug development* in India are more restrictive than facilitative when compared to other global regulatory bodies. For example the draft ICH guidelines may require 1-month toxicology for the evaluation of new investigational drugs for the treatment of advanced cancer in Phase 1 clinical trials and 3-month toxicology package is needed to support Phase 3 registration studies. As per Schedule Y however, the current toxicology requirement for India is a 6-month toxicology package to initiate the first-in-man (Phase I) trial for all agents.

Phase I trials are permitted for molecules discovered in India. With increasing number of partnerships and co-development there is a need to have a uniform understanding and interpretation of "Indian" versus "Foreign" molecules. It is unclear what constitutes an Indian molecule. There are many variants including "discovered and developed in India", Discovered outside India but developed in India, Discovered in India and developed outside India, "discovered outside India but are partially or completely owned by Indian companies", "discovered outside India but handed over to an Indian company" which is charge of development. Existing regulations need to be overhauled to harmonize with international requirements without compromising on national priorities and interests.

There is a need for better **training** of personnel for Phase III trials. This includes CRAs, SMOs, PIs and ethics committee members. In particular, there is need for proper training of CRAs and project managers at the investigator sites.

Curriculum change is necessary where bio-ethics is taught to all medical personnel. ICMR has recognized a need and already developed a Bioethics curriculum, and is looking at training programs across India and working on its inclusion in the curriculum. Documentation training needs to be improved and started earlier in the education process. Physicians need to be trained from the very beginning in the area of research documentation. This will facilitate their acting as principal investigators.

There is a great variability in the conduct of *ethics committees* in different institutions. Informed consent rules need to be properly administered and ethics committees need to develop better operating procedures to ensure GCP compliance. Greater transparency in the drug approval process and better enforcement of guidelines is needed. The following actions should also be taken:

1. SOPs for ethics committee need to be spelt out and some centers of excellence need to be showcased and replicated.
2. There is a need to register or accredit ethics committees as well.
3. There is very little incentive to be part of an ethics committee. Thus competent persons often do not participate. There is a need to develop some required incentives for ethics committees.
4. Frequency of meeting of ethics committees needs to be standardized.

The *approval process* especially for biotech products needs to be streamlined. There are multiple departments from which approvals are needed. There is a need to create a single window from which all approvals may be obtained based on one application. Facilitating the movement through the regulatory process will be very beneficial.





Principal investigators are overwhelmed by paperwork especially during Phase III trials. There is a shortage of trained principal investigators on one hand and they are overworked with non-technical and compliance issues on the other. This limits the number of trials they can reasonably handle. The incentive for PIs in government hospitals is also not high enough to justify the amount of work. Paper work reduction for regulatory compliance is a worldwide phenomenon. India should make sure that it is in the forefront of such changes. There is a need to keep in touch with the partnership between USFDA and Duke University called the Clinical Trials Strengths for Nation Initiative whose objective is twofold:

- a) Revive a sluggish pharmaceutical environment in the USA and
- b) Have a think tank that would devise methodologies for clinical trials, which would minimize delays without compromising on safety and efficacy.

Institutions such as NIPER play a critical role. They need to balance their approach towards academics and teaching and increase interaction with industry for inputs to their research projects. Their emphasis on training is needed, but they have to be matched with the Industry need. Institutes like NIPER will require assistance to interface with industry. FICCI is actively assisting NIPER in industry consultations for their courses on clinical trials, and hopefully this will lead to creating the requisite skill sets for the industry.

The DBT has also started courses in order to provide training and research in product evaluation, dossier preparation, patient recruitment, data management, ethical, consent form etc. to make the Clinical Investigators understand the ethical and regulatory aspects involved in conducting clinical research and trials. It is being implemented in Clinical Research Training Centers at AIIMS, New Delhi; MAMC, New Delhi; KEM Hospital, Mumbai; Amrita Institute, Cochin; NIMS, Hyderabad; Sugan Life Sciences, Tirupathi.

Good Clinical Practices (GCPs) have been clearly spelt out and ethical guidelines have been articulated, but the experience with implementation is relatively short. The regulatory system is already stretched in terms of its ability to monitor proper implementation. The expected fast growth in the clinical trial part of the industry is going to further stretch the capabilities of the system and highlight complexities and unintended consequences.

The following actions may also be taken:

4.5.1 Prioritization

1. India should have a system of prioritizing clinical trials based on national interests. National interests for the purposes of clinical trials may be defined as:
 - a. Drugs, whose approval will provide benefits to a substantial segment of the Indian population

- b. Drugs, for diseases relevant to Indian populations which may or may not have a high priority in other countries including orphan drugs,
 - c. Clinical trials, which will give Indian manufacturers/researchers a competitive advantage in the global pharmaceutical market and knowledge,
 - d. Trials that leverage private and public resources (partnership trials such as those private sector trials which allow "piggy-backing" of public interest hypotheses testing).
2. A list of criteria for trials that will not be allowed in India should be publicized. Such criteria may include, banned drugs in other countries, Phase I for drugs developed outside India unless justified etc.

4.5.2 Ethical review Mechanisms

1. Training of ethics committee members needs to be vigorously implemented. Such training should include international and local concerns and programs should clarify "equivalent" protections - i.e., what India considers equivalent to those internationally adopted.
2. Accreditation of ethics committees will help in improving the quality of such committee's operations and continuously reviewing their performance. An accreditation system should be set up in a stepwise manner.
3. In general SOPs for all ethics committee need to be spelt out and some centers of excellence need to be showcased and replicated.
4. There is very little incentive to be part of an ethics committee. Such incentives need to be developed.
5. Frequency of meeting of ethics committees needs to be standardized.
6. While the tasks and decisions of the ethics committees have been developed there is a need to develop more detailed guidelines on the specifics of the operating procedures to implement these tasks and decisions. Such operating procedures must include types of information and infrastructural facilities and access that must be accorded to committee members and their deliberations. Guidelines for funding of such committees need to be developed to ensure effectiveness without conflict of interest.
7. The operating procedures should distinguish between scientific review of trials and ethical review and simultaneously have a system in place that allows a combined review as well wherever needed. The expertise needed for scientific and ethical reviews are different and the operating procedures should account for that.
8. Preventive trials (vaccine) need special considerations. Community involvement should be mandated in such trials. The experience with community advisory boards should be





investigated to see the appropriateness of mandating such structures for preventive trials or research in life-threatening settings where commonly accepted ethical principles (such as obtaining informed consent prior to enrolling research participants) may not exist.

9. While elements of informed consent forms are well laid out, the operating procedures for implementing these forms need to be standardized. Guidelines need to be issued and approval should be conditional to following these guidelines. Ethics committees may be given the added responsibility to monitor the informed consent process.
10. Harmonization of guidelines and rules between different parts of the regulatory process needs to be done. At the present time there is some confusion regarding the role of departments outside the jurisdiction of MoHFW in the trial approval process. The criteria and timing of referrals and intervention of such departments need to be formalized and publicized.

4.5.3 Ethical Capacity Building

1. There is need for the urgent development of regulatory capacity regarding clinical trials. Capacity in monitoring, oversight, enforcement and approvals is needed in that order of priority. A working group needs to be urgently formed to specify these resource needs.
2. In order to achieve the above, innovative structures may have to be created. Specialists in disease categories as well as disciplines need to be identified who will act as paid regular consultants to the regulatory body for a period of five years. A sub-committee of the above working group should be formed to develop the details of this "virtual matrix structure". Replicating the USFDA structure may be too ambitious given the number of trials conducted in India. An India specific regulatory structure with appropriate capacity is urgently required. Indian definitions of when "conflict of interest" for consultants/experts exists need to be developed.
3. For need-based trials the creation of a public sector CRO should be investigated. Priority trials with public and private participation can be coordinated through such an organization. Such a CRO will act as an example of good clinical practices and will help train professionals for such work. Such a public sector CRO should have multi-departmental relevance (in particular be relevant to the work of DBT, DST, CDSCO, ICMR).
4. Teaching and training of Principal Investigators should be introduced in medical colleges. GCP, together with research methodology and ethics, should be taught as part of the regular curriculum of medical programs.
5. Certification of Principal Investigators will add to the capacity for trained investigators. A system for such certification should be developed.

6. A database for capacity available in India for Phase I, II and III trials may be created. This should be part of a GCP certification process for clinical trial sites.
7. Phase I trial capacity is particularly limited and of high risk. There is need to monitor this carefully. Demand for Phase I through IIa in India is likely to be high. Caution should be used in the approval process for Phase I and special rules may need to be written into the Indian GCP to ensure that Phase I sites are capable of handling the risks involved.
8. A committee should be formed to investigate the possibilities /develop the modalities of insurance for clinical trial and research subjects.
9. Dispute resolution capacity in trials needs to be enhanced. A committee should investigate the ways in which disputes could be best resolved in the interests of the subjects as well as that of good science.
10. Standardization of laboratories and a list of labs approved to conduct clinical trials tests should be identified. More labs to be GLP certified.
11. Data needed to prioritize effectively has to be generated. Currently there is a lack of data on diseases prevalent, therapies recommended and results of large-scale epidemiological studies. A system to generate and disseminate such data needs to be established.
12. Training in the use of statistical sampling techniques with small sample sizes should be introduced to monitors to ensure compliance with GCP. United States FDA best practices in this regard may be evaluated.

4.5.4 Clinical Trial Expertise Building

1. Global trials should be used to transfer knowledge locally. Ways in which to do this need to be investigated.
2. Training should be given to building expertise for the next generation of clinical trials that will be based heavily on genomics and proteomics routes to drug discovery and will need new skills.
3. Expertise needs to be built in the area of molecular diagnostics and molecular epidemiology as well as the social sciences geared towards the conduct of clinical trials.
4. Incentives need to be provided to develop capacity in research design, data management and analytics aspects of clinical trials. Trends in outsourcing these tasks as well as India's skills in these areas can provide competitive advantage to Indian firms.
5. Public health expertise needs to be urgently enhanced. This may require the setting up of more public health education capacity.





4.6 Regulatory issues

There have been some recent positive changes in the regulatory processes. USFDA is helping the Indian government in clinical trials on how to carry out regulatory inspections and in the appropriate training of inspectors. Industry needs to create one apex body which would identify and communicate the changes they feel are necessary in the regulatory process. The government welcomes a consultative process for regulatory streamlining in the drug discovery enterprise but would like industry to speak with a uniform voice.

There has been an issue of quality of CROs as many have been mushrooming in India. Registration of the CROs will be made mandatory. Process for implementation and review of this, needs to be developed and communicated to the industry. Guidelines for the conduct of clinical trials are going to be put on the website for comments before finalization. Industry should take a proactive stand and make suggestions.

Regulatory inspections of the clinical trials have been initiated and the US FDA is helping in conducting workshops to train inspectors. There are a series of workshops, training programs organized at national and regional levels as well and international exposure is also being provided to auditors. On-site inspection is a part of their training process, and the industry is offering their facilities for mock trials. However, co-auditing with US FDA inspectors might provide them with more relevant training in a meaningful way. Human resources are being augmented to ameliorate current shortages. Until this regulatory capacity is up and running, the government does not intend to open up Phase 1 trials for all molecules.

The regulator in its process of training and mock audits should define an audit process and share it with the industry. Inspection findings need to be transparent and posted on the CDSCO website. More often there is no closure to investigations and the rumors fuelled in the media about a particular drug or a company adds to the apprehensions of the industry and sends a negative message to the world.

The possibility of a market based mechanism needs to be explored to establish a self-regulatory regime to achieve the same results as "inspections". On the one hand it may be possible for the government not to be involved and get third party inspections done. Additionally, there may be a need to change the perception of inspectors into "valuators" with an oversight system in which major defaulters are identified and punished.

Harmonization with international standards is an objective of the government keeping in mind the special needs of India and the Indian political, economic and cultural system. Time for approval is coming close to international standards. However, industry applications are often incomplete which delays approval. There are times when it is not industry's fault but bureaucratic inability to discern the information from what has been provided. The



eGovernance system to be introduced should improve the efficiency of the approval process and bring in greater transparency.

A longer-term perspective on regulatory change is needed. A holistic approach to regulation is needed to make sure that one set of regulation not contradicts another. While speed and capacity have been taken care of there is a need to pay attention to the development of proper expertise. Each therapeutic area needs specialists to review protocols and a network of consultants/advisors need to be formed with proper incentives and controls for conflict of interest to ensure that due diligence is done carefully and expeditiously. There needs to be a science driven approach to regulatory approvals.

There is also legislation pending on medical devices and their testing and approval. This will allow for actions to be taken for non-compliance. Changes in the regulations are being brought about keeping in mind the latest requirements. Guidance documents and SOPs are being framed. Conduct of dossier review is being imparted by Health Canada, WHO, and US FDA.

A National Pharmacovigilance program has already been set up and is being scaled up to involve all the 280 medical colleges in the network. Industry partnership in this program is essential and a system needs to be put in place to achieve this. The system of periodic safety update reports (PSUR) has yet to be clearly defined and adhered to for clinical research, and the ethics committees have a role to play in an efficient alert system to prevent mistakes being repeated in multi-location trials. The necessary partnership system of regulatory, pharmaceutical manufacturers and academic/non-profit/NGOs needed for a proper vigilance system is not in place. What exists is not as yet properly coordinated. Legally mandated spontaneous reporting may be necessary and resources invested for collection of data, coordination with WHO and other drug databases and the application of modern data mining techniques in order to establish a proper pharmacovigilance program in India.

A number of regulatory initiatives are already in process. In particular the following are noteworthy although their implementation needs to be accelerated:

- a) Registrations of the Clinical trials have been made mandatory.
- b) Guidelines are being framed for registration of CROs. Guidelines for oversight audit of clinical trials are going to be put on the website for comments before finalization. Industry is encouraged to take a proactive stand and make suggestions.
- c) Benchmarks are being developed to assess the quality of clinical trial sites.
- d) Accrediting agency is being explored to certify trial sites.
- e) The eGovernance system introduced should improve the efficiency of the approval process and bring in greater transparency.





- f) A National Pharmacovigilance program has already been set up and is being scaled up to involve all the 280 medical colleges in the network. Industry partnership in this program is essential and a system needs to be put in place to achieve this.

The following actions may also be taken:

1. Existing regulations need to be overhauled to harmonize with international requirements. The rationale for deviation from international norms, such as for reproductive toxicological testing, needs to be clearly communicated to industry participants.
2. The approval process needs to be streamlined. This is particularly important for biotech products where multiple departmental approvals are needed. The possibility for creating a "single window" approval process should be investigated in an expeditious manner.
3. A longer-term perspective on regulatory change is needed. A holistic approach to regulation is needed to make sure that one set of regulation not contradicts another.
4. The possibility of a market based mechanism needs to be explored to achieve the same results as "inspections".
5. Improved capacity for GCP inspections with ability to punish defaulters. Inspection findings need to be transparent and posted on the CDSCO website.
6. There is a need to pay attention to the development of proper expertise through the creation of a network of "consultants" who are experts in specific areas and can therefore review protocols more effectively.
7. Implementation of GLP in preclinical study centres and GCP in trial sites should be strengthened.
8. Paper work reduction for regulatory compliance is a worldwide phenomenon. India should make sure that it is in the forefront of such changes.
9. Develop capacity for accreditation/licensing of clinical trial sites especially Phase I sites as a priority.
10. Improve pharmacovigilance with mandated reporting and better coordination.



5. Key Recommendations

(Based on the presentations, discussions and other background material at the workshops, the following recommendations are offered)

5.1. Vision

1.1 The government and its various departments need to take the lead in developing a vision for the drug discovery enterprise which will encourage it to think "big" and be proactive in targeting molecules that can deliver better therapies. Such a vision will encourage industry to get more synergies by sharing complementary skills and strategically investing in assets that build such skills.

1.2 Formal partnerships between industry and academia need to grow. Goals and directions for such partnerships must emerge from the vision. Such a vision should also encourage knowledge transfer and learning between firms and also lay out the guidelines for learning from collaborations - domestic and international. The guidelines for a consortium approach to generating value added business should be provided.

1.3 In particular, interaction between industry and academia needs to grow. A successful vision for this enterprise will encourage "industry focused" research in academia and will give it as much respect as "science for science's" sake.

1.4 Recognizing the potential for Indian firms to take the lead in the emerging bio-similar industry, the vision must make the discovery ecosystem, which is likely to achieve this result a "national priority" where projects are approved faster and there is a constant review of the progress at the highest levels.

1.5 This vision needs to help create a shift in the mindset of the entire Indian pharmaceutical industry where there is more respect for each other's capabilities and thus possibilities of more cooperation and greater synergy.

1.6 This vision needs to help create a shift in the mindset of firms and individuals from "self-sufficiency" in possessing all necessary assets and skills to sharing with trust.

1.7 A culture focusing on efficiency needs to be created with an emphasis on cost, speed and quality. Cost and speed in the drug discovery enterprise remain India's prime source of competitive advantage in the initial stages and needs to be leveraged.

1.8 A culture focusing on safety needs to be fostered. The vision should articulate a zero tolerance policy on drug safety and trial subject safety issues.





1.9 The vision should make clear the willingness of the government to partner in key investments even as a private equity investor.

5.2. Generating Resources to Implement Vision

2.1 "Consortiums" need to be initiated through tax incentives and public financing. Planning and scientific advisory committees need to be formed to ensure that investment in assets is happening in a manner to provide "complementarities".

2.2 Incentive mechanism that encourage sharing along with a non-profit organization, which acts as the common interface between the private and the public could become the best vehicle for public private partnerships in drug discovery. This needs to be investigated further.

2.3 The possibility of creating an "options market" or a NASDAQ like exchange for trading of molecules should be investigated further. This can provide necessary risk financing as well as become a vehicle for collaborations, consortia and cluster formations.

2.4 In order to synergize the private public partnership, public research institutions may be encouraged to focus on target identification and validation and allow the private sector to take it forward to lead optimization and testing.

2.5 Incentives for Intellectual Property sharing by scientists and their institutions are now in place but their impact needs to be continuously evaluated. Similarly, the ability for scientists to take equity positions in firms where their innovation may be implemented or create their own firms, are steps in the right direction. The complexity of such systems acting as incentives for public private sharing makes the continuous assessment of such systems critical.

2.6 Establish structures and guidelines for public private partnerships where risks and returns can be appropriately shared.

2.7 Evaluate the different options suggested (private equity, de-merger, licensing, research collaboration, public private partnership, and market innovation), by matching each option with specific objectives. A committee needs to be formed to assess this.

2.8 Research the success stories of innovative ways of generating such financing/resources, and communicate these results through workshops, seminars etc.

2.9 Work with other departments in the government to develop regulations in finance and other areas that will allow for the ideas suggested above. In particular, investigate the possibility of a government owned fund that can act as a private equity investment body in this enterprise.

2.10 Develop mechanisms within industry to articulate high quality projects for public financing. Such high quality projects need to be consistent with the vision and national priorities set up.



2.11 Develop specific guidelines for public private partnerships in the drug discovery and development enterprise. This should include:

- a. Structure of such partnerships
- b. Risk-reward sharing mechanisms/guidelines
- c. Governance structures such as (ownership of shared facilities, board structure, etc.)
- d. Incentive mechanisms
- e. Sequencing of work such as (public institutions focus on targets and private sector on lead optimization and thereafter)
- f. Intellectual property

5.3. Creating Networks and Clusters

3.1 Coordinate recommendations for "vision" and "generating resources" to aid in the development of networks and clusters.

3.2 Create "communities of practice" which would cut across individual silos and develop conversation in one therapeutic area across multiple stakeholders in the industry.

3.3 Create an apex body to facilitate industry government cooperation and help develop a number of key "communities of practice".

3.4 Devise incentive schemes, which will bring diverse groups of people together. The option for providing incentives for industrial scientists to work on basic research projects and research institute scientists to spend some part of their time in working on industrial research projects should be evaluated.

3.5 Develop incentives for

- a. Firms, to jointly sponsor collaborative research with each other and with national institutes, and to send people from industry into government
- b. Industrial scientists, to do some basic research and academic scientists to do some industry focused research

3.6 Conduct industry-academia workshops on research in specific therapeutic areas as well as technology platforms.

5.4. Recruitment and Training

4.1 Begin a targeted development of appropriate skills and the ability to generate economies of scale in the utilization of such skills. A task force should look into the precise nature of skills gap in the pre-clinical and clinical phases. Such a task force should include an assessment of public and private sector institutions.





4.2 Develop a system to meet the shortage of really high quality manpower that has hindered the implementation of a number of worthwhile schemes. The system should allow joint hiring by industry and government of highly skilled people in drug development.

4.3 Increase the number of large for-profit institutions to better train India's biopharma talent should be assessed. The example of the Suvem-Pfizer institute could act as an example of such an enterprise.

4.4 Create training programs on "learning from collaborations". Learning from a collaborator's history of successes and errors is an art that needs to be imparted to the scientists.

4.5 Scientists need to learn how to change their ways of work and create a new culture of learning and research. Pre-clinical research requires a combination of enthusiasm for ideas, creativity and hard discipline requiring detailed documentation. It requires self-confident individuals who can work alone and work in teams at the same time. It requires individuals who can learn from their mistakes and the mistakes of others. Methods need to be devised to impart this kind of training.

4.6 Fill the shortages in high quality personnel in chemistry, biology, molecular biology, pharmacology, toxicology and medicinal chemistry to generate higher speed and efficiency in pre-clinical work. Increase number of training sites and revamp existing centres (including universities) in terms of curriculum to meet this need.

4.7 There is a need for scientists with "business sense" who have capabilities for conducting technology assessment studies and due diligence on global companies offering services. Short programs need to be offered to develop these capabilities.

4.8 Improve and increase capacity for training of personnel for Phase III trials. This includes CRAs, SMOs, PIs and ethics committee members. Although effort is already ongoing in these directions there is a need for greater training capacity, speedier diffusion of new ideas and standardization of curriculum. In particular,

- a. There is need for proper training of CRAs and project managers at the investigator sites.
- b. Curriculum change is necessary where bio-ethics is taught to all medical personnel.
- c. Documentation training needs to be improved and started earlier in the education process. Physicians need to be trained from the very beginning in the area of research documentation. This will facilitate their acting as principal investigators.
- d. Principal Investigator (PI) training in medical colleges and hospitals should be increased.
- e. Ethics committee training

5.5. Operations

5.1 Develop methods to create and share common services with the right mix of expertise and stakeholder representation that can provide advice on specific platforms. Evaluate the

Department of Biotechnology implementation of such structures in terms of their wider applicability and on a larger scale. In their model:

- a) Major core equipment management is in the hands of non-profit companies and not with the institutions.
- b) Not for profits own the infrastructure and industry provides guidance based on the degree of satisfaction with services provided. These two principles guide the private public partnership in infrastructure for the pre-clinical phases at DBT.

5.2 Develop an inventory of highly specialized assets available and their utilization rates so that the sharing theme can be made operational. This kind of mapping of capabilities and skills should be done as a priority. Appoint a multi-stakeholder task force to implement this.

5.3 There should be a mechanism to disseminate information on high quality capabilities available within the country.

5.6. Capacity Building Gaps

Specifically, the following gaps in capacity for drug discovery were identified and resource investments need to be made to reduce their negative impact.

Table 2: Gaps in Drug Discovery Capacity

6.1	Infrastructure	Primates and animal testing, certified lab and imaging diagnostics, clinical research training, strategic investments, adequate phase I capacity, accessible BSL 3 and 4;
6.2	Training	PI training; increase number of sites and quality in chemistry, biology, molecular biology, pharmacology, toxicology and medicinal chemistry
6.3	Regulatory	Coordination between departments, approval capacity, transparency, priority review, harmonization, therapeutic nano-particles, GCP trained auditors, Phase I auditors, Phase I clarity, informed consent SOP, import of animals, funds for PPP, immigration laws for hiring expatriate talent,
6.4	Technology	Selection of biological platforms, efficient use of bio-informatics; learn to work with less validated targets and develop own proof of concept trials; move from targets to working with platforms
6.5	Culture	Culture of discovery, excitement about research, sense of discipline and an inner desire to create intellectual property; more risk taking
6.6	Leadership	Attract good talent--expatriate talent, create a sense of having fun; show enthusiasm for research
6.7	Organizational	Documentation, specialization (therapeutic); culture of multiple revenue streams and multiple funding models in the same organization
6.8	Eco-System	Interaction between different functional units; manage synergies; use work on biosimilars (antibody) to help create drug discovery capability





The key issue is to conduct a proper skills and assets inventory in the country with utilization rates. There is a suspicion that good quality capacity exists underutilized and a system needs to be put in place to properly share and generate the required synergies from existing capacity before investing in new ones. The concept of clusters, consortia and commonly owned facilities are ways of implementing this.

5.7. Pre-clinical

A number of recommendations relevant to the pre-clinical phase have already been offered above. A few additional recommendations specifically relevant to this stage follow.

7.1 Implement Schedule Y provisions to match global trends, especially for regulations related to animal toxicological studies and regulatory toxicological studies as mentioned in the section on regulations.

7.2 Create a National facility to address industry need for performing tests on animals (Primates, large animals).

7.3 Prioritize completion of the National Primate Center, initiated by ICMR and DST.

7.4 Create a marmoset facility. Evaluate the possibility of locating it at The National Center of Research in Reproduction.

7.5 Create a group of experts to assist Indian companies in designing their preclinical studies and addressing other key issues in their preparation to IND application.

7.6 Create a national facility to offer complete package services to help companies till the INDA filing stage. This will imply a group of experts who can help in protocol design and other technical inputs, as well as experts who can propose IPR strategy.

5.8. Clinical

A number of recommendations relevant to the clinical phase have already been offered above. A few additional recommendations specifically relevant to this stage follow.

8.1 Publish a list of criteria for trials that will not be allowed in India.

8.2 Create a system for accreditation of ethics committees to be set up in a stepwise manner. Spelling out SOPs and showcasing some centers of excellence. Clear incentives need to be developed for participating in ethics committees.

8.3 Operating procedures for implementing informed consent forms need to be standardized. Guidelines need to be issued and approval should be conditional to following these guidelines. Ethics committees may be given the added responsibility to monitor the informed consent process.

8.4 Harmonization of guidelines and rules between different parts of the regulatory process needs to be done. At the present time there is some confusion regarding the role of departments outside the jurisdiction of MoHFW in the trial approval process. The criteria and timing of referrals and intervention of such departments need to be formalized and publicized.

8.5 A working group should be urgently formed to specify resource needs for approval and monitoring. Capacity in monitoring, oversight, enforcement and approvals is needed in that order of priority.

8.6 Create innovative network structures of consultants for expertise based speedier approval.

8.7 Create a public sector CRO for need-based trials. Priority trials with public and private participation can be coordinated through such an organization.

8.8 Create a certification of Principal Investigators to add to the capacity for trained investigators.

8.9 Create a database for capacity available in India for Phase I, II and III trials. This should be part of a GCP certification process for clinical trial sites.

8.10 A committee should be formed to investigate the possibilities /develop the modalities of insurance for clinical trial and research subjects.

8.11 Dispute resolution capacity in trials needs to be enhanced. A committee should investigate the ways in which disputes could be best resolved in the interests of the subjects as well as that of good science.

8.12 Standardization of laboratories and a list of labs approved to conduct clinical trials tests should be identified. More labs to be GLP certified with globally acceptable certifications.

8.13 Build expertise for the next generation of clinical trials through training in genomics and proteomics routes to drug discovery. Expertise needs to be built in the area of molecular diagnostics and molecular epidemiology as well as the social sciences geared towards the conduct of clinical trials.

8.14 Incentives need to be provided to develop capacity in research design, data management and analytics aspects of clinical trials. Newly developed public health expertise needs to be integrated into drug discovery activities.

5.9. Regulatory

A number of recommendations relevant to regulations have already been offered above. A few additional recommendations specifically relevant to this stage follow.





9.1 Overhaul existing regulations to harmonize with international requirements. The rationale for deviation from international norms, such as for reproductive toxicological testing, needs to be clearly communicated to industry participants.

9.2 Streamline the approval process especially for biotech products where multiple departmental approvals are needed. The possibility for creating a "single window" approval process should be investigated in an expeditious manner.

9.3 Evaluate the possibility of a market based mechanism to achieve the same results as "inspections".

9.4 Improve capacity for GCP inspections with ability to punish defaulters. Inspection findings need to be transparent and posted on the CDSCO website.

9.5 Updating of Schedule Y may be needed to match global trends, possibly as a separate chapter and monitoring capability for implementation of GLP requirements.

9.6 Paper work reduction for regulatory compliance is a worldwide phenomenon. India should make sure that it is in the forefront of such changes.

9.7 Develop capacity for accreditation/licensing of clinical trial sites especially Phase I sites as a priority.

9.8 Create a system for prioritization of clinical trials based on risk assessment and national needs.

9.9 Improve pharmacovigilance with mandated reporting and better coordination.

9.10 Coordinate with other departments to develop a system for the government to act as a private equity partner.

6. ACTION ITEMS

Table 3-Action Items

	ITEMS	RESPONSIBILITY
1.	Develop a vision	Multi-stakeholder with government taking lead
2.	Planning and scientific advisory committee to create incentives, structures, governance, and intellectual property, for clusters, consortiums, networks	Government with the help of Industry Academia group
3.	Public-Private Partnerships <ul style="list-style-type: none"> ● Task force to recommend guidelines for public-private partnerships in drug discovery and development ● Task force to evaluate current systems of public-private partnerships and shared resource 	Multi-stakeholder Multi-stakeholder
4.	Committee to identify key research areas of high quality for public financing	Industry with help from national research institutes
5.	Organize Industry academia workshops on key therapeutic areas	Industry and international cooperation
6.	Conduct a skills and capability gap analysis for drug discovery and development enterprise	Multi-stakeholder
7.	Create inventory of highly specialized assets and utilization rates	Industry
8.	Curriculum Development <ul style="list-style-type: none"> ● Medical curriculum development ● University curriculum development 	Government Government
9.	Develop new training programs (including business analysis and pharmaco-economics)	Industry, NIPER, ICMR, Research institutes
10.	Focus groups on innovation, culture of safety, efficiency and sharing	Industry (firm level)





Table 3 continued...

	ITEMS	RESPONSIBILITY
11.	Develop accreditation systems: trial sites, PI, Ethics committees	Government, ICMR, with industry panels
12.	Update Schedule Y for animal and reproductive toxicology	Government
13.	Create animal facilities	Government
14.	Create facility to offer complete package of services for INDA to Indian firms	Government-Industry
15.	Guidelines harmonization for trial approval including a "single window" option	Government
16.	Create expert network for trial approval	Government/ICMR/DBT
17.	Task force for "insurance" and post trial maintenance of trial subjects	Multi-stakeholder
18.	Address need for "dispute resolution" principles in clinical trials	ICMR with legal department
19.	Create database of clinical trial capacity including GLP approved laboratories	Industry
20.	Develop rating system of sites conducting toxicological and other pre-clinical tests available to Indian companies	Industry
21.	Streamline clinical trial approval system	Government led multi stakeholder task force
22.	Increase regulatory inspection capacity-consider outsourcing	Government
23.	Inspection results posted on CDSCO website	Government
24.	Paper work reduction in regulatory approval	Consultant and US experience
25.	Expand pharmacovigilance capacity	Multi-stakeholder

7. APPENDIX 1

Agenda of the workshop and speakers

"Drug Discovery- The Business Opportunities in India"

March 19, 2009, Hotel Taj Lands End, Mumbai

Programme

Moderators: Prof. Falguni Sen, Mr. D G Shah and Mr. V K Topa

Opening Statement: Prof. Falguni Sen

Presentations by:

- Dr. Ajay Dhankhar, Partner, McKinsey & Company Inc - **Drug Discovery in India- Opportunities**
- Mr. Ranjan Kumar, Director-India Operations & Head - Pharma Life Sciences Practice, RocSearch - **Funding of Drug Discovery**

Q & A

- **Panel:** Pre-Clinical Capacity Issues (Training and Skill alignment, laboratory materials, diagnostics, primates, BSL3 and 4 level capacity available to private sector)

Lead Discussant: Dr. Govind Rajan, Vice President, Jubilant Organosys Ltd.

- **Panel:** Phase-1 Regulatory and Other Capacity Issues (toxicology, critical care and public private partnership)

Lead Discussant: Dr. Rashmi H Barbhैया, CEO & MD, Advinus Therapeutics Pvt. Ltd

- **Panel:** Phase-2-3 (GCP Inspections, Regulatory Approval - speed and transparency, principal investigator, training, ethics committees, public perceptions and training of the media)

Lead Discussant: Dr. Surinder Kher, Sr. Vice President-Clinical & Regulatory operations, Vanthys Pharmaceuticals Development



Comments by:

- Mr. Glenn Saldanha, CEO & MD, Glenmark Pharmaceuticals Ltd.
- Mr. Debasish Panda, Joint Secretary, Ministry of Health & Family Welfare, Government of India
- Mr. Arun Jha, Joint Secretary, Department of Pharmaceuticals, Government of India
- Mr. Devendra Chaudhary, Joint Secretary, Department of Pharmaceuticals, Government of India

Lunch

Summary of Recommendations by: Prof. Falguni Sen

The Way Forward-

- **Address by:** Mr. Ashok Kumar, Secretary, Department of Pharmaceuticals, Government of India
- **Address by:** Dr. M K Bhan, Secretary, Department of Biotechnology, Government of India

Press Briefing

8. APPENDIX 2

List of participants

Government

1. Mr. Ashok Kumar, Secretary, Department of Pharmaceuticals
2. Dr. MK Bhan, Secretary, Department of Biotechnology
3. Mr. Devendra Chaudhary, Joint Secretary, Department of Pharmaceuticals
4. Dr. KK Tripathi, Senior Advisor, Department of Biotechnology
5. Mr. Arun Jha, Joint Secretary, Department of Pharmaceuticals
6. Mr. Debasish Panda, Joint Secretary, Ministry of Health and Family Welfare

Lead Discussant

1. Dr. Govind Rajan, Vice-President, Jubilant Organosys Ltd.
2. Dr. Rashmi H Barbhaiya, CEO & MD, Advinus Therapeutics Pvt. Ltd
3. Dr. Surinder Kher, Senior Vice President- Clinical & Regulatory Operations - Vanthys Pharmaceuticals Development

Industry

1. Mr. Sanjeev Saxena, Chairman & CEO, Actis Biologics
2. Dr. Smita Singhania, Head Regulatory, Actis Biologics
3. Dr. Aftab Lakhdawala, Avaant Pharmaceuticals, Mumbai
4. Mr. Tom Sopwith, Chairman & MD, Biocommercialisation India
5. Dr. Arun Nanivadekar, Consultant, Clinical Research & Communication
6. Dr. Arun Bhatt, President, ClinInvent Research Pvt Ltd
7. R R Hirwani, Head, CSIR Unit for Research and Development of Information products.
8. Dr. Vasudeo Ginde, President & MD, DiagnoSearch Life Sciences (P) Ltd.



9. Dr. Sanjeev Ahuja, CEO, Joint venture Eli Lilly Inc USA & Jubilant
10. Mr. Glenn Saldanha, CEO & MD, Glenmark Pharmaceuticals Ltd.
11. TR Grover, Sr Vice President – Corporate Relation, Glenmark
12. Dr, Sanjay Mittal, Chief Cardiologist, Global Health Pvt Ltd
13. Dr. Dhananjay Bakhle, Senior Vice President & General Manager - India Reliance Clinical Research Services
14. Dr. Neelima Kshirsagar, Director & professor, Infectious Diseases & UDIRT - Maharashtra University Health Sciences
15. Mr. Shamnad Basheer, Professor in IP Law National University of Juridical Sciences
16. Dr. Amarjit Singh, President, Johnson & Johnson Ltd, Mumbai
17. Dr. Ashok Vaidya, Research Director, Kasturba Health Society, Medical Research Centre
18. Ms. Leena Menghaney Project Manager Campaign for Access to Essential Medicines, Medicins Sans Frontieres (MSF)
19. Dr. Sanjiv Shah, Consultant Diabetologist, Mediheights Healthcare Pvt Ltd
20. Dr. Amar Bhat, PhRMA USA
21. Dr. Narges Mahaluxmivala, Co-Chair - FICCI Clinical Research Committee and Senior Advisor - Clinical Development Services, Quintiles India
22. Ms Suneela Thatte, Executive Director, Quintile Technologies Private Ltd
23. Ms Pratibha Pilgaonkar, CEO, Rubicon Research Private Limited
24. Dr. Muruga Vadivale, Senior Director- Medical & Regulatory Affairs, Sanofi- Aventis, Mumbai.
25. Dr. Urmila Thatte, Professor and Head, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital
26. Mr. Vinod Topa, CEO, Sidmak Laboratories Ltd.

About FICCI

Established in 1927, FICCI is the largest and oldest apex business organization in India. Its history is closely interwoven with India's struggle for independence and its subsequent emergence as one of the most rapidly growing economies globally. FICCI plays a leading role in policy debates that are at the forefront of social, economic and political change. Through its 400 professionals, FICCI is active in 38 sectors of the economy. FICCI's stand on policy issues is sought out by think tanks, governments and academia. Its publications are widely read for their in-depth research and policy prescriptions. FICCI has joint business councils with 79 countries around the world.

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Contact:

Federation House, Tansen Marg, New Delhi - 110 001
Phone: +9111 23357081/ +9111 23738760-70
email: clinicalresearch@ficci.com

About ORF

ORF Vision:

India, in the next 25 years, will join the ranks of the world's great economic powers and transform significantly the quality of life of its one billion people.

ORF Objectives:

- Aid and impact formulation of policies and evolve policy alternatives.
- Create a climate conducive to effective implementation of these policies. Strengthen India's democratic institutions to enable coherent, reasoned and consistent policy-making.
- Provide reasoned and consensual inputs representing a broad section of opinion to improve governance, accelerate economic development, and ensure a better quality of life for all Indians.
- Monitor strategic environment.
- Work towards achieving international peace, harmony, and co-operation.
- Give direction to India's long-range foreign policy objectives.

Observer Research Foundation

20, Rouse Avenue Institutional Area,
New Delhi - 110 002, INDIA
Phone: +91-11-43520020
Fax: +91-11-43520003
E-mail: contactus@orfonline.org