Pharmaceutical R&D: India at the Crossroads

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In recent years the pharmaceutical industry worldwide has been criticized for the high cost of medicines and drug price increases that seem to have significantly outpaced general inflation rates. While the industry has contested the methods used to estimate pharmaceutical inflation and justified its pricing policies, it is clear that if pharmaceutical prices are to remain within a range acceptable to governments, payers, and consumers, something needs to be done to reset the economics of drug development.

Part of the reason for the high price of new prescription medicines is the increasing cost of drug development and falling productivity of the research and development effort. While the money spent on R&D by the industry worldwide is now estimated to be close to $ 60 billion, the number of new products coming out of the pipeline has steadily fallen since 1996. Research published in 2003 by the Tufts Center for the Study of Drug Development indicated that the fully loaded cost of bringing one new drug to the market was over 800 million dollars.

The solution, quite clearly, is to improve pharmaceutical research productivity. In other words, the number of marketable products emerging through the pipeline must increase at a rate greater than the rate of growth of research spending. And there are three major areas of focus in the endeavor to achieve this: 1) Attrition Management: the effort to identify unviable drug development candidates at an early stage, so that they can be abandoned before much money is spent on them; 2) Quantum improvements in research cost and efficiency; and 3) Finding ways to make major reductions in development time. The money saved by these measures can be used to undertake more development projects so that more drugs can emerge from the pipeline.
Can India be the tugboat for the world's pharmaceutical research endeavor? India has a clear advantage in costs. That the Purchasing Power Parity multiplier for India, at 5.43, is the highest across all countries of significance in this context indicates that, in general, one can get more than 5 times as much value for a dollar in India as one would in the US. Moreover, India leads by a margin of at least 20% over other low cost countries including China. However, one cannot expect research decisions to be made based on the sole basis of cost. Quality is extremely important because poor quality can be much more expensive in the long run than any savings accruing from cost arbitrage. Quality, in research, heavily depends on the quality of background and ongoing training that research workers have access to, and on the quality of environmental factors such as goods and services received from local vendors. The speed of execution is another critical factor in the choice of location for research, especially in the pharmaceutical industry, where effective, competition-free, patent life is extremely short, and extension in time-to-market by a day can translate to substantial loss of opportunity. Regulatory lead time when applicable, speed of patient recruitment in clinical research, and the availability of technology solutions such as high throughput instrumentation in the laboratory and remote data capture in clinical research, contribute significantly to execution speed.

Even when cost, quality, and speed can be delivered, capacity may be a limiting factor – the quantitative adequacy of facilities for research, including contract research facilities, third-party suppliers and vendors, quality healthcare institutions, a system of regulatory and ethical oversight of clinical research, and facilities for training and development. And availability of adequate numbers of trained personnel can be an important capacity constraint once volumes begin to grow apace.

Over the past few years entrepreneurs in India have developed capabilities across a wide spectrum of the pharmaceutical research and development value chain, from genomics, custom synthesis, physical and chemical characterization of molecules, *in vitro* studies and animal toxicology, to biopharmaceutics, execution of phase 2 and phase 3 studies, data operations and statistics. While considerable capacities are now available, by a global reckoning of scale these are still small. First-in-man studies are still restricted in India through regulation, while early discovery work is limited to a handful of local companies, a few contract research organizations (CROs), and some government laboratories. High throughput facilities are still rare, and facilities for animal testing are largely limited to routine tests in small animals. Facilities for human volunteer studies are limited largely to routine plasma-level testing of drug levels in male volunteers, although some sites are venturing into higher-end work. Most of the clinical trial capacity is tied up in operational execution of single studies, and experience with conception and execution of complete clinical development programs is limited. The appetite for fresh second-wave investments in asset-creation appears to be small.

Given these capabilities and constraints, what is the R&D turnover potential for India in the short to medium term? Based on the assumption that relevant global R&D spending is perhaps close to 60 billion dollars with a split of 33:66 in the non-clinical to clinical spend level, and current trends indicating that the fully-loaded cost of operations in India is 1/3rd and 1/5th of costs in the US and Western Europe for non-clinical and clinical operations respectively, the global R&D spend at Indian prices works out to approximately 15 billion dollars. A worthwhile target for India may be to begin to attract 10% of that spend – the equivalent of $1.5 billion.

The general prospects for business process sourcing from India continue to be bright at this time. This is reflected by the AT Kearney Offshore Attractiveness Index where India scores head and shoulders above the closest competitors, including China, Malaysia and Philippines in the neighborhood and the countries of central and Eastern Europe and Latin America farther afield. However, the competition from these very countries gets much tougher when we analyse the prospects for the flow of pharmaceutical research dollars into India. Factors that detract from the country's ability to attract global pharmaceutical investments include the growing perception that intellectual property protection afforded to pharmaceutical products is at best incomplete, with restrictions on patentability, delays due to pre-grant opposition to patents, the threat of litigation and compulsory licensing, and the lack of data exclusivity. While protection of intellectual property in India does not seem to have anything to do directly with the placement of research projects in the country, the poor sentiment resulting from a failure to fully recognize and protect intellectual property is sufficient to negatively influence placement decisions.

Another detractor is the small size of the Indian pharmaceutical market. Indian domestic sales for pharmaceuticals accounts for merely 1.5% of global pharmaceutical revenues. Even if some of

the issues with intellectual property get sorted out over time, India is expected to remain a weak market well into the next decade due to low spending by the government on healthcare, lack of effective health insurance, and existence of a cost-plus system of price controls. This will make it difficult for the top management of global pharmaceutical companies to justify major investment in a country that provides so little in terms of revenue. For clinical research, in particular, the possibility of including top researchers and academicians as clinical investigators provides a legitimate early means of familiarizing medical opinion leaders with new therapies. Since this can have an impact on the commercial fate of the product, this opportunity has traditionally been reserved for large and potentially large markets.

Furthermore, capacity constraints are likely to emerge if the scale of research operations in the country becomes moderately large, with competition for a limited number of facilities and a relatively small pool of trained and experienced personnel driving up costs and eroding competitive advantage. Indeed, competitive advantage is already being undermined by a growing number of markets providing generous incentives and offering aggressive welcome packages to attract research investment and spending. Top among countries aggressively pursuing research dollars are Canada and Ireland. Others include Italy, Spain, Portugal, and New Zealand, and several individual states in the USA. Closer home, Malaysia has put in place an aggressive program to attract research. The nature of incentives offered by these companies ranges from major corporate and personal income tax exemptions and credits to direct and indirect subsidies, real estate concessions, and direct, no-strings-attached public funding of private research.

So, can India beat the competition and emerge as a global hub for pharmaceutical research in the next 4-5 years, attracting annual research spending to the tune of 1.5 billion dollars, growing its share of pharmaceutical research spending to perhaps 15% of global volumes by 2012-15, and then holding on to that share as the absolute volumes of global pharmaceutical R&D grow in the next decade and the cost advantage over other locations erodes with the rising Rupee? The answer, to my mind, is a simple ‘No’. Not without decisively eliminating some of the detracting factors listed above, and not without major incentives to attract global research spending that will compensate for those of the detracting factors that cannot be eliminated.

A straightforward system that may be easily implemented would, for example, use additional revenue generated by the scheme to provide a coveted relief for commercial operations. This could take the shape of import duty waiver on commercial pharmaceutical imports equivalent, in the beginning, to half the value of the additional tax revenue generated by inflow of foreign funds into pharmaceutical research and development in India. As an illustration, for every dollar of foreign currency inflow into research, the central government would be expected to earn revenue through direct and indirect taxes worth an average of 25 cents. In the subsequent year the government would allow for 12.5 cents in duty exemption for commercial pharmaceutical imports.

The possibility of duty exemption on patented imported products would be a very strong fiscal incentive for large pharmaceutical companies to consider major growth in research spending in India. The current effective duty rates inclusive of all surcharges works out to about 42% on the landed cost of goods. This substantially increases the burden on patients and impinges on the affordability of imported goods. Limiting duty waivers to patented products would ensure that

domestic industry is not adversely affected by this measure while still serving as an incentive to attract research investments as well as lowering costs of high-end imported medicines for the Indian consumer.

Will such an incentive scheme get the country to the target 10-15% of global pharmaceutical R&D volumes by 2012? If we assume that the current flow of external funds into pharmaceutical R&D adds up to about $ 150 million, and the growth trend is 40-50% inclusive of inflation, we may expect to cross the $ 300 million mark by 2010. At a billion dollars worth of pharmaceutical imports, companies pay over 400 million dollars in import duties and under this R&D incentive scheme it would take $ 3.2 billion worth of pharmaceutical R&D to eliminate the duty paid, so there would be sufficient room for companies to bring in research dollars worth 1.5 billion in the short-to-medium term. If they did, the government would earn 112.5 million worth of incremental revenue over what it would have earned at an R&D spend level of $ 300 million without a duty exemption scheme. In the process, about 25,000 new high-value jobs would be created, and patients would pay less for patented imported medicines, and the additional revenue earned by the government could be used to improve healthcare services to the poorest sections of society – all of which would be in line with the government's public interest objectives.

Any economic incentives would have to go hand in hand with regulatory initiatives and capacity building measures. The office of the Drugs Controller General of India has already taken major initiatives that will go a long way in facilitating the growth of clinical research in the country while safeguarding the safety and interests of patients, encouraging the ethical conduct of high quality research, and ensuring the quality of pharmaceutical products. These include mechanisms to monitor quality of imported products, enforcement of Good Manufacturing Practices (GMP) across all sections of the industry, and harmonization and upgrading of rules and regulations governing pharmaceutical research through revisions to the Drugs and Cosmetics Rules. However, further alignment of regulation will be required going forward. Restriction on the conduct of first-in-man and early microdosing studies, formal and informal restrictions on animal testing and irrational pre-clinical testing requirements that go beyond what is required in Europe and America, slow regulatory approval for investigational drug approvals that take months when in other markets such approval is automatic and time-bound in the absence of a specific clinical hold, unnecessary duplication in the need to conduct Phase IIIB studies in India when the international data package already contains data generated in India, and so on.

Other second generation regulatory changes sorely required include provisions for regulatory pre-approval and accreditation of human research facilities; setting up of a national system of oversight of ethics committees; adverse event monitoring regulations that would make it mandatory for every company authorized to develop or market pharmaceutical products to have a validated and functional system of adverse event monitoring for investigational and marketed products; harmonization of rules pertaining to pharmaceuticals across states; amendment of the 4-year limit in the definition of a new drug that currently absolves manufacturers of generic products from having to submit any data to federal regulators; and comprehensive plans to enhance regulatory capacity and expertise within the Central Drug Standards Control Organization.

The need for capacity-building is not unique to the pharmaceutical regulatory agencies. Capacities need to be built into all other sectors within the R&D continuum if we wish to bridge the gap between the current volume of research conducted in the country and the aspirational target of a global R&D hub requiring investments to be made in R&D facilities such as drug discovery laboratories, toxicology centers, and contract formulation and packaging development units, but also in building electronic documentation systems in our hospitals, training and funding hospital ethics committees, training physician-investigators, site staff, and monitors, data operators, statisticians, and medical writers. In addition, support service capacities will need to be built – such as internationally accredited pathology laboratories that are geared to clinical research requirements, contract pharmacy and safety monitoring services for clinical research, and medical research oriented divisions or cells within courier services and translation agencies that cater to the special requirements of biomedical research. Of these, the need for accredited training facilities and services is perhaps the most urgent. Access to a gamut of operational training courses is needed spanning clinical research monitoring, clinical project management, clinical research methodology, genomics and bioinformatics, drug regulatory affairs, pharmacovigilance, research ethics, pharmaceutical medicine, pharmaceutical research management, and pharmaceutical industry and research orientation for journalists and media professionals.

In conclusion, a global need for enhanced research productivity and trends in globalization of the pharmaceutical industry have come together to throw open a unique opportunity for the growth of pharmaceutical research in India and other countries that, in the 50-year history of modern drug discovery and development, have never before participated in the process in any significant way. In order to capitalize on its competitive advantages and remain ahead of competing markets, India must take active steps to attract pharmaceutical research investment, including the introduction of self-financing and revenue-generating fiscal incentives, encouragement of capacity building measures, continuing regulatory reform, and initiatives in specific research-oriented education and training. Implementation of these measures at this time will be critical to building this country into a global hub for pharmaceutical research and development.

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