

PHARMA R&D IN INDIA: THE PROMISE OF SUSTAINABLE INNOVATION

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It is indeed a pleasure to be with you today. One of the first things that occurred to me when I received the invitation to participate in the Global Portfolio Manger's Forum is that we have several things in common. We need to demonstrate returns on our portfolios, allocate resources and take decisions under conditions of significant uncertainty. I must thank Sukumar Rajah to giving me this opportunity to be with you - my fellow risk takers.

I

Growth in the pharma industry is driven by the introduction of new products and all of us are painfully aware of the rising costs of developing a new drug and fall in productivity. Many equity analysts have put out remarkably detailed and perceptive analyses of the problem.

Bad news travels fast and this concern seems to be widespread. The issue is being widely debated in various forums – not just among scientists and analysts. A couple of days ago, I typed in four words into google – pharma R&D productivity crisis – and got over 4000 hits in 0.2 seconds! I thought pharma R&D provided remedies, but it also seems to be triggering depression.

My goal today is therefore not to spend too much time on describing the problem, which all of you know, but brainstorm with you on the opportunities particularly for Indian companies, that arise from some specific aspects of the problem.

Around the time I started my career about thirty years ago, we were struggling to make the most basic drugs. At that time few would have thought that India would emerge as the leading manufacturer of low cost active pharmaceutical ingredients and generics for the world.

Today, India has the largest number of FDA approved manufacturing facilities outside of the US, so much so that the US FDA is planning to open an office in Delhi for its inspectors. Over the last several years, India has consistently made the largest number of drug master file submissions for bulk actives for generics and over a third of the submissions are now from India. Last year, close to 20% of the total filings of abbreviated new drug applications for finished dosage forms in the US was from India.

From generics to new drugs, from imitation to innovation, is a big leap. Unlike the generics business, R&D is the lifeblood of big pharma in the US and Europe and so far it has virtually been its exclusive preserve. Indian pharma R&D cannot hope to break easily into this exclusive club for many obvious reasons. But for reasons that may not be obvious, but to me appear compelling, there is growing optimism that Indian companies have an opportunity in the R&D space.

A little before I received the invitation to be with you today, a headline in an issue of Scrip magazine caught my eye. The headline was “India will deliver on innovation” and the person who asserted this was Brian Tempest, the CEO of Ranbaxy, who was speaking at the FT Global Pharmaceutical Conference in London some weeks ago. To support his thesis, he quoted from an analysis that demonstrated that the average Indian chemistry researcher was better educated, put in 40% more working hours every week and cost the company less than 7% of his US counterpart. And who did this analysis? None other than Pfizer.

So lets look at some of the other reasons that suggest that there is an opportunity for Indian pharma R&D.

II

The first point I want to make is that the 20th century model of drug discovery and development is unsustainable.

If you look at some of the annual surveys of members of the PHRMA and the studies quoted by them you will find that by the end of the 20th century, the cost of development of drugs has become unsustainable.

The PHRMA companies alone are spending over 30 billion dollars every year on R&D, up from 2 billion dollars in 1980. On the other hand, there has been a decline in the total number of drug approvals by the FDA in recent years with just about 20 drugs approved annually, significantly lower than the number in the ‘90s.

The often quoted Tufts study estimates the pre tax cost of development of a new drug, including phase IV studies to be 800 million dollars – a 6-fold increase in 25 years. And the PHRMA quotes a study that only about 3 out of 10 new drugs recoup the post-tax R&D spend of close to 500 million dollars.

So who is paying for all of this? Clearly, the consumer and the economy have borne the brunt of this decline in productivity as big pharma, which has historically accounted for much of his spend, has more often than not posted double digit growth in the bottom line. Clearly, the party cannot go on forever.

There is a growing sense of outrage at this state of affairs. Firstly, the diseases of the poor go unnoticed. The Global Forum for Health Research has highlighted the 10/90 rule: 10% of global research expenditure is devoted to conditions that account for 90% of the

global disease burden. There are a number of initiatives which are seeking to create a sustainable model to address this issue.

Large populations in the developing world, who had access to affordable medicine because of the lack of patent protection, or lax implementation, will soon find they are unable to afford the cost of new drugs.

Probably the greatest and most effective pressure will be exerted in the US itself. Senior citizens in the US account for about half the prescription drug expenditure and most often they do not have effective insurance.

Public expenditures on health care have soared, particularly for new therapies. Policy makers have tried to contain this problem by recourse to price controls, but this will have limited impact for all the usual reasons.

The fundamental issue is one of containing cost of development of new drugs. The 20th century model for drug development will not work. This realization at diverse levels, from countries to corporates, will provide the impetus to search and adopt new models of sustainable innovation.

And as always, every problem is an opportunity, if one is prepared to think differently.

III

Before I urge you to come up with out-of-the box thinking, let me first deal with some of the approaches that have been widely discussed, which have a bearing on the opportunity for India and Indian companies.

The first is a question of size. Bringing a drug to market is very expensive and very risky. No Indian company has the size as yet to bear this risk on its own. But, as is commonly known, we were the first of several Indian companies that have sought to get over this problem by outlicensing new molecules for development.

This opportunity is perhaps larger than one might think. Of the 30 billion dollars or so spent on R&D by the PHRMA companies, a third of the expenditure, 10 billion dollars, is spent in discovery and preclinical. 40% of R&D personnel, over 30000 scientists, are working on this phase in the PHRMA companies alone.

I think this represents a major opportunity for Indian companies. Let me draw from my own experience. Of our first 8 molecules in the preclinical stage, three were licensed to big pharma and we are developing one of them ourselves. Two of the molecules that we licensed successfully completed phase II. Its true they did not make it to the market, but the point I am making here is that the quality of the preclinical drug candidates we developed are not in question. And how much did it cost us? 57 million dollars.

Let me also say that this is no flash in the pan. I am optimistic that we will continue to deliver cost effective candidates for development in the near future.

Dwell for a minute on the costs incurred by big pharma at the preclinical stage, make any assumption you like about the actual costs, and you will still find that we are hugely productive and cost-effective in comparison.

It is likely that the significantly lower costs incurred in bringing a drug into phase I, whether by inlicensing or contract research will not only make eminent sense to big pharma, but also contribute to mitigating the larger problem of an unviable cost model for bringing a drug to market.

But I feel that it is not enough to merely leverage the lower cost structure in India. One must also have an arguable case that the root cause of the current problem – R&D productivity will also be addressed with an India advantage.

IV

There is a widespread notion that size and scale are necessary for R&D productivity is quite prevalent. I'm talking of productivity here as distinct from the feasibility, which I have dealt with earlier.

There inclination to believe that size and scale would enable the R&D engine to gain momentum has atleast in part been the driver of mergers and acquisitions, and you know all about this. This has definitely demonstrated some immediate – and sometimes dramatic – results on the bottom line.

Lets spend a few minutes on this proposition.

Some of you may have met Ed Scolnick who is something of a living legend. He was the Chief Scientific Officer with Merck and later the President of Merck Research Labs when it was at the pinnacle of its scientific leadership. He retired last year after 17 years with Merck and was responsible for bringing 29 drugs and vaccines to the market, some of which fundamentally changed the way in which diseases are treated. He is now a Professor of Biology at MIT, a Research Associate at Mclean Hospital, and a Senior Lecturer in the Department of Genetics at Harvard.

In 2000, two of Merck's biggest rivals had sealed mergers. As you well know, Glaxo was combining with SmithKline and Pfizer had gobbled up Warner Lambert. Their research budgets became much larger than Merck's and the sheer scale of operations was thought to be a guarantee of success in innovation. Scolnick thought about the implications and studied the research output of Merck's own sites across the world. And let me quote what he had to say: "The thing that's really most striking was that the size of the site has nothing to do with its productivity, absolutely nothing. There's no correlation. None."

Scolnick's scepticism continues till today. A Financial Times survey of heads of research and senior R&D decision makers from the world's 200 largest pharma companies was reported in Scrip earlier this month. Only one of the 33 respondents said that mergers contributed to R&D productivity, while 23 said that mergers were bad news because of the uncertainty it creates. Only 3% thought that big pharma had the most innovative companies and 67% believed that small to medium companies were the most innovative, along with spin offs from universities. Significantly, there was notable interest in investing in R&D in Asia, particularly India and Singapore.

V

Fundamentally, a global solution has to be found to reverse the trend of rising costs and declining productivity of pharma R&D.

Some have vigorously advocated a science and technology solution. This holds a lot of promise from the scientific viewpoint. Technology approaches have focused on improving efficiency in discovery, improving success rates in validating targets and clinical trials, shortening timelines and hastening identification of attrition. Biology, chemistry and clinical development have all received attention. Among the approaches that hold promise include pharmacogenomics, proteomics, computational chemistry, in silico and combinatorial chemistry as well as high throughput screening.

An extensive study by the Boston Consulting Group some years ago argued that drug development costs could be halved from the estimated 800 million dollars if some of the new approaches were aggressively adopted. At the same time, they recognized the problems: the risks that accompanied the newer technologies, the complexities of their management as also the likelihood of increased costs in the short term. We took a hard look at some of these approaches and I think it will still be a while before we can bank on these technologies for fixing the productivity and cost problem.

If one believes that smaller companies have higher productivity and lower costs, the fundamental problem to be cracked is how to bring this advantage to bear on more, if not all, stages of development.

That's the challenge we face in DRL and indeed in India. Outlicensing is a part solution; it does not exploit the advantage of productivity and low cost over a large part of the development process.

I am not convinced that big pharma will necessarily be the most cost-efficient in development, just as it is clear that they are not necessarily the most cost-effective in discovery.

There is also the "NIH" – Not Invented Here – syndrome, which has quite often increased costs, delayed or even killed development projects, for reasons other than science. The higher resource allocation is necessarily to molecules which have the higher potential for

commercial success. But as everybody knows, commercial estimates in early stages of development have sometimes been awfully wrong.

It makes instinctive sense to me that that a small company ought to develop its own drugs to a later stage for greater value and lower costs. A single child in a family gets more attention than when there are a dozen children.

But no small company can afford to take the risk of development, even if it can find the money. We have a 150 million dollars sitting in the bank, but we dare not take the risk of development with it.

The risk – and the costs have to be shared. In the process there will be the additional advantage of the rigour of review by two parties. Which again instinctively appeals to me. A two-parent household is usually better for children than a single parent one!

I am sure that entrepreneurial solutions to the problem will emerge. The problem is too large to remain without solutions. And it occurred to me that I cannot leave this problem with better people than you.

Thank you for your attention.