The R&D business

Money matters

India has most of the advantages to conduct drug discovery studies. However, money is 'the concern', as investors are weary of taking the risk, coupled with a lax regulatory scenario, which has led to a sluggish growth. Arshia Khan tracks pipeline potential & business mantras of pharma companies to tackle this inadequacy.

Sample this: There has been a noted increase in the R&D spending capacity of pharma companies. The R&D expenditure of the top 25 drug companies has increased from ₹ 27.47 billion in 2007-08 to ₹ 32.1 billion during 2008-09, an increase of almost 17 per cent. Yet, the pharma industry in India reports a lower R&D spending, ie, about 1.9 per cent of the industry's turnover. This spending is low compared to the investment on R&D by foreign research-based pharma companies, which is about 10-16 per cent of their turnover.

Total R&D spending by drug makers reached $ 683 million in 2008-09 (or 7.75 per cent) of their sales. Among those that boosted R&D spending by more than 40 per cent in this period were Jubilant Organosys, Matrix, Sun Pharma Advanced Research Company Ltd (SPARC), Ind-Swift, Stride Arcolab and Piramal Healthcare. Besides these pharma/biotech companies, Dr Reddy's, Daiichi Ranbaxy Life Sciences Research, Glenmark Pharmaceuticals Ltd, Biocon, AstraZeneca Research India, Lupin, Torrent, etc, are also carrying out research studies.

Status quo

Despite companies pumping in money for R&D projects, new drug discovery & development has still not reached its full potential in India. As Hitesh Gajaria, Executive Director, KPMG, avers, "Indian companies still lack the financial strength to compete with MNCs." To tackle the financial crunch, the government is also infusing money to fasten drug discovery. As of now, India is reported to be spending about ₹ 20 billion every year on R&D. While the government contributes ₹ 5 billion, the remaining comes from the private sector. Hence, funding is the core issue that needs to be tackled. Gajaria further informs, "As of July 2010, the government had planned to set up ₹ 100 billion Venture Capital (VC) fund for financing new drug discovery projects in India."

More so, India's share of public healthcare R&D to total public R&D spending is mere two per cent, as compared to 23 per cent in the US. Hence, there is a need for policies that encourage more investment in healthcare, believes Gajaria. Striking a similar chord, V K Singh, CEO, Ethypharm Pvt Ltd, says, "R&D is a capital-intensive activity. Even though we are not in New Chemical Entities (NCE) research where sometimes more than science, serendipity plays a critical role & financing serendipity calls for a real appetite in R&D. Further, it demands immense patience & financial muscle." He explains, the complexion of Ethypharm's R&D is more of nature of incremental innovation. But, this type of R&D is iterative by nature. Creating value differentiators is expensive in this model as well. Ethypharm is globally positioned as a preferred partner for Life Cycle Management. The company ploughs back up to 25 per cent of sales revenues in R&D.

In the making of a blockbuster

Indian companies such as Dr Reddy's Laboratories (DRL) and Ranbaxy have a number of molecules in different phases of product development. A blockbuster drug is no small feat & the sheer financial commitment that could go into the research of one NCE with therapeutic efficacy & demand could stretch to more than $ 1 billion. As Glenn Saldanha, CEO & Managing Director, Glenmark Pharmaceuticals, informs, "We have eight molecules undergoing clinical trials. Each of our molecules is either best-in-class or first-in-class & is being developed for worldwide usage. If commercialised, each of them has peak sales potential of at least $ 1 billion." Saldanha underlines the strategy behind the R&D plan, "All our molecules are targeting unmet medical needs. And we have been able to conclude five out-licensing deals in discovery R&D collecting over $ 140 million (₹ 600 crore) in upfront & milestone payments so far." Glenmarks' total expenditure in R&D (discovery & generics) has been in the range of 3-5 per cent of is net sales, according to Saldanha.

"Pharma companies have always used the model of pursuing drug discovery & development by themselves, thus taking all the risks to reap the rewards solely. However, this model is proving to be increasingly unsustainable over time," underlines Gajaria.

He believes that one of the most effective business models used by companies like Pfizer, Eli Lilly, Roche, AstraZeneca & Merck is 'insourcing' to India for their research efforts. Also, these companies have set up their R&D centres in developing countries like India & China that offer many cost advantages along with technical skill & legal bandwidth. These centres focus little on *de novo* discovery, instead they target efforts on converting molecules to medicine or 'translation research'.

Mumbai-based Centaur Pharmaceuticals (with revenues of $ 40 million till March, 2010) is working on similar lines. The company has in-licensed the development & distribution rights for Sorivudine, a topical anti-viral drug from aRigen, a Japanese company, to market it in India & neighbouring countries, like Nepal, Sri Lanka and South Africa. Sorivudine is a drug for local application, for Herpes Zoster. Explaining the rationale S D Sawant, Managing Director, Centaur Pharmaceuticals, says, "The Phase I trials for the molecule have been completed in US, with Phase II & III in the pipeline. Therefore, we requested to in-license the molecule from aRigen for the Indian market. Centaur has already invested ₹ 1 crore through internal accruals, and will be investing ₹ 80-200 crore for phase II & III trials. Explaining the idea, Sawant says, "The idea is to take the promising molecules & work on them. This way we share the profits, though the risks rest with us." He quips, "For them (the partnering companies), Indian market is like peanuts, with low margins; therefore, we follow this strategy."

However, aRigen, the Japanese company with a drylab business model, has also partnered with companies in the US, EU and Korea. Dr Gensuke Tokoro, President & CEO, aRigen Pharmaceuticals Inc, explains the scenario in Japan, "Discovery research in Japan is only up to Phase I trials; therefore, we are always looking at partners after Phase I. Likewise, most pharma companies in Japan, EU and the US are looking for drug candidates that have concluded Phase I stage. So this is the missing link." aRigen raised $ 60 million from PE, VCs and High Networth Individuals (HNIs) to develop six molecules & has received milestone payments upto $ 25 million through its various out-licensed molecules, to companies from Switzerland, US, Japan & India.

Lundbeck followed a similar approach, which outsources entire projects to Contract Research Organisations (CROs) based out of Shanghai. However, the main challenge that these companies face, according to Gajaria, is integrating the in-house discovery work from its R&D laboratories with the collaborated work in developing countries.

Although another trend is to work with external entities including academia, CROs & other pharma service providers. The common driving factor that supports this model is playing by the strength of each involved entity, while, at the same time, optimising cost and time.

Therefore, according to Gajaria, the model that could work best in India includes expanding expertise to cover all areas of drug production. India enjoys various advantages, cost effectiveness being the key factor & the ease of establishing research centres. These factors should be leveraged in order to put a system in place that is capable of performing activities of the entire value chain that aid drug production.

Of course, the quality of research taking place cannot be overlooked and it is important that expensive research should yield efficacious products for the companies to continue their interest in NCEs & not simply depend on generics, a model that has always been adopted in India. As Nilesh Gupta, Group President & Executive Director, Lupin Ltd, says, "At the heart of Lupin's success is its R&D initiative. Lupin has developed sound capabilities in developing complex APIs to formulating value-added, difficult-to-make products to a highly evolved drug delivery & drug discovery programme."

Glenn Saldanha
CEO & Managing Director, Glenmark Pharmaceuticals

We believe that in the new world order, boundaries will blur and it is going to be one global market, one set of regulatory guidelines, with one talent pool.

K V Subramaniam
President & CEO, Reliance Life Sciences

The need of the hour is investment in R&D facilities & improving levels of basic research in universities by encouraging them to pursue top notch research. Public-private partnerships and industry-academia partnerships can help achieve this.

Nilesh Gupta
Group President & Executive Director, Lupin Ltd

The government is promoting pharma R&D by providing more Standing Operating Procedures (SOPs) and incentives & supporting investment for R&D through increased weighted deduction and the like. This makes India an attractive destination to a company looking to invest in innovation.

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Dr Gensuke Tokoro
President & CEO, aRigen Pharmaceuticals Inc

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He further informs that Lupin invested 7-9 per cent of its overall net sales into its R&D programmes over the past seven years. Lupin's strong growth, specifically in the advanced markets is a direct outcome of these investments. The expenditure on R&D during the last fiscal stood at ₹ 4,119 million, which was 8.7 per cent of the net sales, according to Gupta.

Explaining Glenmark's approach, Saldanha notes, "We believe that in the new world order, boundaries will blur and it is going to be one global market, one set of regulatory guidelines, with one talent pool." Therefore, the quality of products required across markets will need to be uniform because consumers & governments even in the least developed economies will demand the best for their own people. Saldanha further continues, "We have built Glenmark keeping this changing landscape in mind. And it is for this reason that we have always focussed on building significant presence in emerging markets, including India, and a fast-growing US generics business. Not only are we operating at both ends of the spectrum, ie, branded generics & pure generics, but are also running a successful drug discovery programme."

Explaining the business model at the company, Saldanha says, we plan to go to various places to attract the best talent in a particular area. For this, Glenmark has set up its discovery R&D centre for NCEs in India, the biopharmaceutical research centre for NBEs (Novel Biological Entities) in Switzerland and its clinical research facility in the UK. Glenmark has over 450 scientists working at its four R&D centres spread in these three countries.

India shining?

Though the competencies today are pretty much global, international companies are sourcing or even conducting R&D in India more for skill set & speed than for the lower cost. As Singh believes, "They gain much more in time value of molecule to market, than in terms of the cost of development. By compressing the development time by even 10 per cent they increase the effective marketable life of the product or the patent, & therefore the returns manifold."

Earlier, Indian companies, except the Indian MNCs like Ranbaxy & DRL, had good skills in chemistry and formulation. But for the softer skills like regulatory expertise & intellectual property they had to depend on overseas partners or local experts. In the last decade, there has been immense on-the-job learning & soft skills.

On the contrary, K V Subramaniam, President & CEO, Reliance Life Sciences says, barring a few examples of innovative R&D efforts towards new product development, this is still at a nascent stage in India. He remarks, "The need of the hour is investment in R&D facilities & improving levels of basic research in universities by encouraging them to pursue top notch research. Public-private partnerships & industry-academia partnerships can help achieve this." Gupta adds to this, "The Indian government is promoting pharma R&D by providing more Standing Operating Procedures (SOPs) and incentives & supporting investment for R&D through increased weighted deduction and the like. This makes India an attractive destination to a company looking to invest in innovation."

Thorns in the way

While protection of IP in India does not seem to have any direct relation with the placement of research projects in the country, the poor sentiment resulting from a failure to fully recognise & protect intellectual property is sufficient to negatively influence MNCs to conduct research in India. There is divided opinion on this as well. And Singh believes this to be true. He justifies the reason, "There is a negative perception about India in this regard, which may have in some measure hampered Foreign Direct Investment (FDI) in R&D in the country. Novartis overlooking India and going to China for R&D can be an example of this." He also stresses on the need for a public-private-partnership (PPP) initiative.

Counting on the hurdles in the way, Gajaria enumerates such as limited funding from FIs, VCs & the government are likely to decelerate the expansion of R&D efforts in India. Collaborations between the big drug companies in the Indian market to control the cost benefit & large reserve sources will further intensify competition.

Although Indian companies complain of the lax regulatory scenario, Dr Tokoro, remarks, "It cannot be worse than Japan. We are good in discovery projects other than making formulations. He stresses on alliances to be the next in thing, and cites an example. "GSK & Pfizer alone do not have the capability to bring out a blockbuster molecule, as each stage requires critical assessment. Therefore, new drugs will only come out through alliances and never from 'a company' alone." He explains drug discovery success in Japan. All Japanese companies put together have 14 blockbuster molecules, 10 of which can be attributed/identified with some scientist/individual. The distressing part is that only three of them have been promoted within the organisation, while others had unsuccessful careers."

Pointing towards the lack of sense to focus on important areas, Dr Tokoro reminds that, globally, companies are working on cancer drugs, diabetes and other lifestyle-related drugs. He stresses on the need for Indian companies to focus on these areas.

Also many of India's regulations relating to pre-clinical & clinical trials are conservative, for instance, the prevention of first-in-man testing for drugs developed outside India. India needs to make some harmonising effort in this respect to reduce ambiguity & simplify the process of compliance. Likewise, there is a need to sort out the large number of patent applications that are pending and also make arrangements for data protection. Indian patent law should also define 'incremental innovation', which is still an ambiguous subject & leads to misunderstandings between global pharma firms & authorities, says Gajaria.

Success strategies

R&D collaborations are an upcoming trend in the pharma industry. A recent example is the collaboration between the Indian Council of Medical Research (ICMR) and Federal Ministry of Education and Research (BMBF), Germany, to initiate joint R&D projects in areas of oncology, regenerative medicine, neurosciences and infectious diseases. Going ahead, companies will focus on Advance drug delivery and Novel Drug Delivery System (NDDS).

Singh highlights the future trends, "In the post-genomic era, target-specific therapy & personalised medicine will open a whole new realm for application and innovation. A lot of the traditional medicines of Indian and Chinese systems will also be finding their way back to consumers through the multinationals." On companies rolling out blockbuster molecules, Singh avers, "There are limits to Cartesian reductionism but never to innovation. There may be a perceived stagnation in New Drug Discovery Research (NDDR) but there is still immense scope for innovation in NDDS. I see good potential for some of our platform technologies like Flashtab, Locktab, Organogel and Lipid Nanocapsules (LNC). Highlights Gupta, "Having identified Advanced Drug Delivery Systems (ADDS) as a future growth driver, Lupin has made significant investments in the drug delivery systems space over the last four years."

Now nevertheless using PE or VC funds to invest in R&D is not a new concept and has been in practice since long. The difference will come in for deal structuring, which depends on company profile, as the target companies are not in distress. As Abhinav Mehra, Senior Consultant, Healthcare Consulting, Datamonitor India, says, "The most popular way of obtaining funding is to spin off some of the research into a new outfit. While the company owns a minority stake, the majority is owned by investors."

He further highlights, the competition for fund-raising is also becoming tough. Overall, there are 78 India-focussed funds on the road looking to raise $ 24 billion, according to data compiled by Prequin, a UK-based fund tracker. There are about 117 pan-Asia private equity funds - which have India as one of their geographies - currently targeting to raise aggregate capital of $ 59.2 billion.

With the high cost of drug development, there is always a pressure to reduce the R&D time and cost without compromising on clinical success rate. Therefore most leading drug makers have recently undertaken or are in the process of implementing broad cost reduction programmes, notes Mehra.

Also, companies are likely to undergo broad cost initiatives to maintain sustainability, along with adoption of right technology & science. Drug development alliances will gain momentum to leverage resources & cut R&D costs, and deal values are expected to increase over the next few years.

Mehra hints, "India can aspire to become an innovation hub by 2020. However, this will require globally competitive research infrastructure, world-class talent, funding, PPP." Significant research can also come from industry academic partnerships.

V K Singh
CEO, Ethypharm Pvt Ltd

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S D Sawant
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