

DEBT ACCOUNTING BLUES

STAY AHEAD.
EVERY WEEK

IDFC: BEYOND LENDING

19 June 2006

www.businessworldindia.com

Businessworld

Rs 10

The Race to create INDIA'S FIRST NEW DRUG

Dr. Reddy's diabetes drug is entering the final phase of clinical trials. Three other Indian companies have molecules in advanced phases of testing. They aim to hit the market as early as 2009

INDIA'S LARGEST SELLING
BUSINESS MAGAZINE



K. Anji Reddy, Dr. Reddy's

Molecule: **DRF 2593 (Balaglitazone)**
Treatment area: **Diabetes**

The drug promises to be better than two other glitazones already in the market. It has already proved in phase II clinical trials that it works and has few side effects. It is now going in for phase III trials. There is a good chance of this drug hitting the market.



TREBUNIAN SHARMA

Malvinder Mohan Singh, Ranbaxy

Molecule: **RBX 11160, a synthetic variant of the natural product artemisinin**
Treatment area: **Malaria**

The natural product works but is prohibitively expensive. This first synthetic version has been developed in collaboration with the Medicine for Malaria Venture. The product has been tested on small groups, and so far, seems to be working.

INDIA learns how to DISCOVER DRUGS

The industry matures as a dozen-odd companies get into the new drug research game. **By Gina S. Krishnan**



Glenn Saldanha, Glenmark

Molecule: **GRC 3886 (Oglemilast)**
 Treatment area: **Asthma, coronary obstructive pulmonary disease**

Oglemilast belongs to a category of drugs called PDE4 inhibitors that represent a new way of treating asthma. So far, the early PDE4 inhibitors have shown terrible side effects. However, the drug is only now entering phase II clinical trials.

A COUPLE of months from now, the compound codenamed DRF 2593 by Dr. Reddy's Laboratories will start being administered to a few thousand diabetes patients across the world. DRF 2593 has already undergone several rounds of stringent testing on smaller groups of volunteers. The tests so far suggest that it is well tolerated by patients, reasonably effective as a treatment for diabetes, does not have any serious side effects, and does not cause cancer, cell mutations or any harm to the foetus.

Now, DRF 2593 will have to clear its final test — a test that drug makers and regulators call phase III clinical trials. This will check out just how well it really works when tested on a sufficiently large number of patients — thousands as opposed to the hundreds tested in phase II. Side effects that may have been previously overlooked will also be monitored.

Phase III could take up to four years to complete, estimates Dr. Reddy's. But the company is reasonably sure that its compound will clear this round as well. It is betting on phase III trial statistics — over 75 per cent of compounds that make it to this stage also clear it. Dr. Reddy's is confident that its compound will be one of the successful ones.

If it does clear phase III, DRF 2593 could well become the first 'new' drug developed by an Indian company. So far, every



Habil Khorakiwala, Wockhardt

Molecule: **WCK 771 (Quinalone)**
 Category: **Broad spectrum antibiotic**

This is a relatively safe bet as it belongs to a well researched category of antibiotic drugs. It has already crossed phase II (A) and is moving into phase II (B). The big question is whether it will show any significant advantage over the other new antibiotics.

drug that has been created by the Indian pharmaceutical industry has been a reverse engineered generic — a copy of a drug that was already discovered by a multinational.

Of course, there is a chance that DRF 2593 will fall at this final hurdle. There is also a chance that one of the three other Indian companies — Ranbaxy, Glenmark and Wockhardt — that have compounds in advanced stages of clinical testing, will pip Dr. Reddy's to the goal post. Ranbaxy is testing its anti-malarial, Glenmark has a potential new asthma cure and Wockhardt has a new generation broad-spectrum antibiotic in the works. Finally, there is also the chance that all the four companies will see their molecules fall at the final hurdle. This story is not just about who will be the first Indian company to actually win the honour of having created the first new drug out of India. It is about how the Indian pharmaceutical industry is evolving from being mere copycats to discoverers of original drugs. And how it is developing the necessary skills for original research despite the resource constraints.

At the moment, there are at least 12 Indian pharma companies that are working on developing new drugs. An estimated 60 new compounds are in various phases of development and testing. These are not large numbers by world standards — GlaxoSmithKline has 143 new compounds under development while Pfizer has 140. But then, the first

efforts by an Indian company to develop a new drug started barely 12 years ago...

The First, Unsteady Steps

In 1994, K. Anji Reddy set up the first new drug development laboratory as a distinct facility, separate from his company's generic drug development lab. The timing was fortuitous: the multinational Hoechst was closing down its own Indian drug discovery lab and many of its scientists naturally gravitated to Indian laboratories. The original brief of the lab was to work on cancer drugs and antibiotics. As it happened, the scientists at Dr. Reddy's did not have much luck in either of these areas. One day, though, Anji Reddy stumbled upon an article in a journal about a company called Sankyo that was conducting research on a new class of compounds called glitazones for treating diabetes.

Glitazones promised a very different way of treating diabetes. In the most common form of diabetes, the body fails to utilise insulin properly. The common drugs for treating diabetes, till glitazones came along, essentially induced the body to produce more insulin to make up for its inefficient use. Now, glitazones held the promise of helping the body use the insulin itself in a better fashion.

The other interesting point about glitazones, as far as Anji Reddy was concerned, was that its chemical structure was relatively simple. He faxed across a copy of Sankyo's molecule to his research chemist and asked her whether a similar — though not same — compound could be developed. The answer was yes. Dr. Reddy's started their research on glitazones.

The first few glitazone compounds that the lab produced initially seemed promising, but did not last the full course. Many of them failed at the pre-clinical phase. A couple of them went on to phase II of human testing but failed to cross

The next three promising candidates...

Company	Molecule	Phase	Therapeutic category
Dr. Reddy's	DRF 10945	Phase II	Dislipidemia
Dr. Reddy's	DRF 1042	Phase II	Cancer
Glenmark	GRC8200	Phase I	Diabetes

that barrier. As it lacked money to develop a drug all the way, Dr. Reddy's followed the 'outlicensing' strategy. That essentially meant Dr. Reddy's created what would seem like a promising compound and then licensed it to a multinational with deeper pockets to carry out the rest of the development. The multinational would have rights to market the drug if it succeeded, but it would also bear the costs of the testing and pay Dr. Reddy's a certain amount as and when the compound crossed each stage of clinical development.

Dr. Reddy's worked out a deal with Novo Nordisk to conduct trials on a few glitazones it had developed. This included both DRF 2593 as well as Ragaglitazar. Two of the compounds failed to clear the first test — the toxicity test, which checks whether the drug induces poisonous reactions in the human body. The third compound — DRF 2593 or Balaglitazone — was returned by Novo Nordisk because though it worked, it didn't seem to show any great advantage over the glitazones already present in the market. Dr. Reddy's, however, found another partner — Rheosciences, a Danish company — that was willing to take a bet on the compound and take it up after phase II (B).

Meanwhile, some of the other companies had started pursuing their own original research plans. In 1997, Habil Khorakiwala of Wockhardt had commissioned a state-of-the-art

The birth of a new drug:



1 Development of a compound

Chemists in a laboratory develop certain compounds. These are expected to alleviate certain symptoms of a disease, or even cure it.

2 Pre-clinical testing

The compound is first tested on animals (mice, dogs, monkeys). This is done to determine the efficacy of the compound and check for possible side effects. Animal studies also seek to prove that the drug does not cause cancer, foetal malformations or change the genetic material and also to understand how the drug is absorbed and excreted. This sets the stage for human trials. For this, an Investigational New Drug (IND) application is filed.



3 Clinical studies: Phase I

Now begin the tests on humans. These tests are typically done on a small number of healthy volunteers (20-100). The tests look at how the drug is absorbed, metabolised and excreted. Side effects — such as when the dosage levels are increased — are also monitored.



new drug research facility to focus on new generations of antibiotics. He points out that the biggest area of concern in India is infections. And with bacteria getting resistant to antibiotics at a rapid rate, it made sense to focus on developing new antibiotics that would stay ahead of bacterial resistance. Meanwhile, also in 1997, Ranbaxy had started pursuing its own research in half a dozen areas. One of the first new compounds it tried to develop was a drug that would help in a condition called benign prostatic hyperplasia (BPH) or prostate enlargement. This was given out to Schwartz, a German company in a deal similar to the one Dr. Reddy's did with Novo Nordisk. However, this molecule failed at an early stage of testing. Over the years, Torrent, Lupin, Sun Pharmaceuticals and several others got into original research as well. Some of them genuinely wanted to graduate to the league of new drug developers. For many others, the push came because the generic game was becoming both competitive and expensive. And they simply wanted to hedge their bets even while they were pursuing the generic opportunities.

Analoguing and Outlicensing — Smart Ways to Conserve Cash

One point that needs to be understood about new drug research is that it costs enormous amounts of money. The expenses are high because of two reasons. One, a compound needs to go through various steps before it graduates to become a new drug (See 'The Birth of a New Drug...'). The second reason is that a large number of compounds fail and that increases the overall costs of research.

PhRMA, a global pharma association, estimates that while last year multinational drug firms spent around \$39.5 billion on new drug discovery research, only 26 new chemical entities were granted patents. They have a long way to go before they hit the market. It is estimated that Indian companies have, so far only devoted a total of \$450 million on new drug research. Dr. Reddy's has spent some \$57 million on taking its first eight

new compounds up to the pre-clinical stage.

Though costs of conducting research in India are lower than in the West — primarily because of vastly cheaper scientific manpower — it is also true that no Indian company has the scale or resources to pursue cutting-edge research, or even to take a new compound through all the stages on its own. This is precisely why all Indian firms are pursuing two basic strategies that vastly lower their costs and risks. The first is a research strategy called analogue research, while the second is termed outlicensing.

Let's take the analogue strategy first. What it essentially means is this: the Indian firms are not pursuing research to find a completely new family of drugs; their research is aimed at finding a new drug within an existing family that has already been discovered. It is called the analogue strategy because it involves finding a compound that is analogous to an already discovered compound.

To understand this, let's take the example of Dr. Reddy's diabetes compound again. Here, it was Sankyo that originally figured out that glitazones could provide an alternative way of treating diabetes and probably also tried to develop the first glitazone. Dr. Reddy's, though, got into the game very early and started working on creating a number of glitazones that would work better than the originals. DRF 2593 or Balaglitazone will be the third glitazone to hit the market if it eventually crosses the final hurdle. Dr. Reddy's is promising that it will be the glitazone that works the most effectively with the least amount of side effects.

The analogue strategy is important because it cuts down on your risk. By working on protein targets that are already well established, and developing a new drug within a family that has been extensively researched, a company can reduce at least some of the uncertainties of new drug research. The downside is that the new drug developed by this strategy will not be as big a blockbuster as the first drug in a new family

A step-by-step account

4 Clinical studies: Phase II (A)

Next, the safety and efficacy levels are checked on patients suffering from the particular disease, which the drug is expected to cure. The trial may be carried over 100 or more patients. One group of patients receives the experimental drug, while a second group receives a placebo.



5 Clinical studies: Phase II (B)

These are designed to arrive at optimum dosage levels. Different doses and their efficacy are studied. Only one-third of drugs successfully complete both phase I and II of trials. Studies to check that these drugs are not cancer causing are also carried out.

6 Clinical studies: Phase III

In this final phase, the drug is tested on several hundred to several thousand patients suffering from the disease. The large-scale testing provides the pharmaceutical company with a more thorough understanding of the drug's effectiveness, benefits and severity of possible adverse side effects. Seventy to 90 per cent of drugs successfully complete this phase of testing.



(or first in class, as the pharma industry prefers to dub it). But sometimes, a second or third drug in a new family also turns out to be a bigger blockbuster simply because it is overall a better drug. A classic example was Pfizer's cholesterol busting champion Lipitor, which was not the first drug in its class to hit the market, but became the best seller anyway.

The analogue strategy was very successfully used by the Japanese drug industry when it was venturing into new drug development. Many observers think that Indian industry will also rapidly build up scale by using the same tactics.

If analogue research helps cut down research risks, the outlicensing strategy drastically reduces the financial risk and, in fact, helps a company earn some money even before the drug is fully developed.

The outlicensing strategy works this way. An Indian company identifies a number of new compounds in a family that are likely to work, and then takes them up to the pre-clinical trial phase. After that, they strike a deal with a multinational operating in the same area. The deal is structured this way: the multinational has the rights to market the compound in a particular market if it clears all the tests. The Indian company gets 'milestone payments' — a certain amount for each stage of clinical trials that its compound clears. If the compound successfully clears all tests, it also gets royalty when the drug is introduced in a market.

Why would a global company be interested in 'inlicensing' a compound from an Indian company? Why doesn't a multinational prefer to develop its own drug from scratch? The reason can be traced to the high levels of failure in the new drug discovery game. For every 1,000 compounds that are identified by a company, only about 30 show promise. And for every 30 compounds that show promise, three get past the first round of clinical trials and finally, only one hits the market. Thus, to introduce one new drug, you need to start with many thousands of compounds.

Even multinational companies do not have the wherewithal to test each and every compound in a family. Hence,

licensing deals are quite common. Apart from their own compounds under development, multinationals routinely scour the globe for promising compounds developed by other companies in therapeutic areas that interest them, and put them through clinical trials. While some succeed, others fail. But some of the biggest blockbusters in the market are currently those that have come as a result of licensing deals. For example, Pfizer's \$10-billion (in sales) Lipitor was actually discovered by Yamanouchi, a Japanese company, while Bristol Myers Squibb's three biggest drugs — Pravachol, Glucophage and Taxol — are compounds developed by other companies.

Ranbaxy, Dr. Reddy's, Glenmark and practically everyone else follows this outlicensing strategy. But the undisputed champion of this game is Glenmark Pharmaceuticals. The Glenmark story is instructive as it shows that a smart company can practically get its entire research expenses paid for by big global pharma.

Glenmark was originally a medium-sized family-run pharmaceutical company specialising in skin care products. That was until Glenn Saldanha, the son of the founder, took charge of the company in 2000. Saldanha decided to build a new drug research laboratory and commissioned Aftab Lakdawala to build it. (Lakdawala, incidentally, is a sort of new drug lab specialist — he also set up Wockhardt's laboratory.) Saldanha hired a team of researchers and started focusing on a number of targets. One of the promising molecules the Glenmark team identified in 2002 belonged to a family of compounds called PDE4 inhibitors. Essentially, PDE4 is a protein that triggers off inflammation in various organs of the body. A compound that targets this protein and stops it from going berserk is called a PDE4 inhibitor.

There has been a lot of work that has been conducted around the globe on PDE4 inhibitors. The big problem is that most PDE4 inhibitors have such terrible side effects that the cure is often worse than the disease. Very few PDE4 inhibitors have been successfully introduced in the market and even these aren't particularly good drugs.

Glenmark's PDE4 inhibitor was code-named GRC 3886 or Oglemilast by the company. And the early indicators are that it will work rather well against asthma and another breathing problem called chronic obstructive pulmonary disorder (COPD). Inflammation of the airways is a problem in both asthma and COPD, and the Glenmark compound, so far, seems to be working well.

Having identified the compound, Glenmark did a really smart thing. It first cut a deal with US-based Forest Labs, which has a number of drugs for pulmonary (lung) diseases. Forest Labs picked up the rights to develop the compound for the North American market against a payment of \$190 million. That means Forest Labs will not only bear the costs of taking the compound through the different phases of clinical trials, it will also pay Glenmark \$190 million as upfront and milestone payments. Six months later, Glenmark licensed the Japan

...And the others being worked on

Company	Categories worked on	Number of promising compounds	Stage of Development
DR. REDDY'S	Cardio vascular diseases, diabetes and cancer	37	9 in phase I and II
RANBAXY	Infectious respiratory and urinary diseases, and diabetes	11	2 in phase I
ORCHID	Inflammatory and infectious diseases, cancer and diabetes	8	3 in phase I and II
GLENMARK	Respiratory and inflammatory diseases, diabetes and obesity	6	4 in phase I and II

Discovering India

EVEN as Indian firms learn the ropes of new drug research, some MNCs are attempting to exploit India's potential as a drug discovery base. Two approaches are seen: opening independent R&D labs in India, and partnering with Indian drug discovery services companies and research institutes.

The earliest example of an MNC lab in India (after Hoechst's lab wound up in the early 1990s), is the R&D centre in Bangalore of UK-based AstraZeneca, set up in 2003 to research on tuberculosis. More recently, Altana Pharma, a \$3.6-billion (euro 2.4 billion in 2005) German company, set up a drug discovery lab in Mumbai (it will be operational by end-September). This lab will focus on drugs for gastrointestinal and respiratory diseases as well as oncology. But Antal J. Hajos, managing director (India), is unwilling to reveal more.

The partnership route has been taken by other large pharma companies, including Wyeth (with GVK Biosciences) and Eli Lilly (Jubilant Organosys). Aurigene, Dr. Reddy's collaborative discovery services company, works with international pharma companies such as Denmark-based Rheosciences on early discovery work.

MNC pharma companies are also partnering with leading Indian research institutes. For instance, Swiss biotech company Evolva and Indian Institute of Chemical Technology (IICT), Hyderabad, are to set up a drug research facility under a five-year agreement to work on diabetes and cancer. APIDC, the only Indian biotech fund, invested \$2.5 million in it along with a consortium of smaller investors. Besides IICT, international pharma companies are also working with National Chemical Lab, Pune; National Institute of Immunology, New Delhi; Indian Institute of Science, Bangalore; and Centre for Cellular and Molecular Biology, Hyderabad.



Photo courtesy: ALTANA PHARMA

rights of the same compound to Teijen Pharma, a Japanese drug company, for \$53 million. The deals were structured so that Glenmark would receive some cash upfront and the rest as milestone payments. Industry observers reckon that the money Saldanha has received so far has more than paid for the cost of setting up the lab and all the research his team has done so far. In contrast, Dr. Reddy's had received barely \$3 million when it had licensed its compounds to Novo Nordisk.

Drugs Under Development and New Organisation Structures

Dr. Reddy's potential diabetes drug is in phase III while Glenmark's asthma compound has successfully completed one of the phase I clinical trials. This means that both of them seem to be working on patients and have side effects within acceptable limits. Both, therefore, have a fairly good chance of taking the honour of being the first new Indian drug.

There are two other contenders in the fray. The first is Wockhardt with a compound codenamed WCK 771/2349. It belongs to a class of antibiotic drugs called fluoroquinolones. These are broad spectrum antibiotics that work against a number of bacteria, and Wockhardt is confident that it has developed a new generation that will work even against those bacterial strains that have developed resistance to other antibiotics. The 771 version is an injectable one, while the 2349 version is meant to be swallowed. Khorakiwala is chary of divulging any details of his compound but market observers think that his drugs won't have much problem crossing phase II, in which they are currently. Their calculation is based on the fact that because of the sheer body of existing research on antibiotics, it would have been easy for Wockhardt to develop a new version. Top notch research scientists often look down upon antibiotic research as being less challenging, though there is obviously a big need for such drugs. Meanwhile, Ranbaxy is the fourth contender with an anti-malarial compound that is a synthetic version of a natural compound called artemisinin derived from the bark of sweet wormwood tree grown in China. The costs of the natural product is shooting up, one reason for a cheaper synthetic version. Ranbaxy remains tightlipped about its compound though it is supposed to have cleared phase II clinical trials.

Just a step behind these four are half a dozen compounds, ranging from an anti-obesity compound by Orchid to a potential arthritis cure from Glenmark. (For the full list, log on to www.businessworldindia.com)

Meanwhile, as they learn the rules of the game and sniff out new opportunities, some Indian firms are toying with the idea of a new drug R&D lab as a standalone commercial organisation. The thinking behind this structure goes like this: freed of the controls of the parent company, the lab could raise resources, conduct research in areas not necessarily of interest to the parent, and pursue partnerships. And by spinning it off as an independent entity, the parent reduces its own risks. Sun Pharma, run by Dilip Shanghvi, has been the first to adopt this approach, and has spun off its new drugs division as an independent entity called Sun Pharma Advanced Research company (SPARC). Others are closely watching its progress to see whether they need to adopt a new organisational structure even as they seek to develop many more new compounds. ■