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IT could be the blockbuster that Dr. Reddy's has been waiting for. Then again, it may turn out to be a big, fat dud. The Hyderabad-based company is racing to become the first pharma company in the world to introduce the controversial polypill, a superdrug combining several active drugs for the treatment of cardiovascular disease (CVD).

Why CVD? Well, because it is actually a bigger killer than more feared ailments like cancer or HIV/AIDS. Estimates suggest that CVD accounts for 29.3 per cent of deaths globally every year compared to 12.5 per cent for cancer and 4.9 per cent for HIV/AIDS. Predictably, treatment of CVD is big business. According to the World Health Report 2004, healthcare expenses related to CVD (including surgery, hospital stay, medication, etc.) accounted for more than \$350 billion in the US in 2003, which was 40 per cent of its total healthcare industry.

But why a polypill? Take Surekha Khanna, a 66-year-old housewife in Delhi, for instance. In 2002, Khanna suffered a mild heart attack. She suffers from hypertension, high cholesterol and diabetes, and none of them are coming under control. Reason: too many pills, nine tablets every day, to be precise. "I hate it. Taking nine pills daily makes me feel ill," she fumes. So, here's what she does: skip the fattest pill, and take any pill whenever she feels like it.

Now, this problem (of compliance as well as cost) could be solved if people like Khanna could take one pill instead of several. This simple logic caught the imagination of the global medical community, and the idea of the polypill was born in the early 2000s. But it has been mired in controversy since. Despite that, Dr. Reddy's went ahead and developed a modified version of the polypill, which is slated to go in for clinical trials in early April.

We'll go into the details of Dr.



HERE WE COME: Dr. Reddy's API lab in Hyderabad

Reddy's effort a little later. First, a small backgrounder on the polypill.

Polypill: The Genesis

The polypill was first mooted at a meeting of the Wellcome Trust and World Health Organization at Cambridge in 2001. But the real thing came later.

In the 28 June 2003 edition of the *British Medical Journal (BMJ)*, Nick J. Wald and Malcolm R. Law, professors at London's Wolfson Institute of Preventive

Medicine, suggested that a polypill — comprising a statin (lipid lowering agent), aspirin (blood thinner), folic acid (to prevent the build-up of plaque in blood vessels) and three anti-hypertensives (to reduce blood pressure), all in half doses — could reduce ischaemic heart disease (IHD) by 88 per cent and stroke by 80 per cent.

They said that the pill could be safely administered to everyone aged 55 and older, and everyone with existing heart

The world's first polypill, a multiple-product pill for heart ailments, has been developed by Dr. Reddy's. Next step: clinical trials. By Gina S. Krishnan

C  **om**  **ound**

The heart of the matter

Across urban and rural India, all age groups are likely to see almost equal increase in incidence of coronary heart disease.

| Year/area | 20-29 yrs | 30-39 yrs | 40-49 yrs | 50-59 yrs | 60-69 yrs | Total |
|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 2000 | | | | | | |
| Urban | 2.71 | 2.64 | 2.78 | 2.29 | 1.89 | 12.31 |
| Rural | 1.80 | 2.85 | 3.34 | 3.59 | 3.15 | 14.73 |
| Total | 4.51 | 5.49 | 6.12 | 5.88 | 5.04 | 27.04 |
| 2005 | | | | | | |
| Urban | 4.14 | 3.87 | 4.12 | 3.17 | 2.58 | 17.88 |
| Rural | 2.01 | 3.38 | 4.22 | 4.54 | 3.85 | 18.00 |
| Total | 6.15 | 7.25 | 8.34 | 7.71 | 6.43 | 35.88 |
| 2010* | | | | | | |
| Urban | 5.99 | 5.15 | 5.61 | 4.22 | 3.71 | 24.68 |
| Rural | 2.32 | 3.94 | 5.37 | 5.82 | 4.83 | 22.28 |
| Total | 8.31 | 9.09 | 10.98 | 10.04 | 8.54 | 46.96 |
| 2015* | | | | | | |
| Urban | 8.17 | 7.93 | 8.49 | 6.16 | 5.35 | 36.10 |
| Rural | 2.32 | 4.52 | 5.82 | 6.85 | 5.91 | 25.42 |
| Total | 10.49 | 12.45 | 14.31 | 13.01 | 11.26 | 61.52 |

Figures are number of cases (males and females) in million of coronary heart disease in India
Source: National Commission on Macroeconomics and Health

*Projected

disease. With widespread use, it "would have a greater impact on the prevention of disease in the Western world than any other single intervention".

Such a tall claim naturally generated intense interest, both positive and negative. Richard Smith, the (then) editor of *BMJ*, remarked that it was perhaps more than 50 years since the journal had published something as important. And Anthony Rodgers, director, Clinical Trials Research Unit, University of Auckland, who was involved in trials of polypill components in the 1990s (see interview on page 96), wrote a highly supportive editorial in the same issue of *BMJ*.

But not everyone loved the idea. Sceptics pointed out that the study was based on a meta-analysis — a statistical run in a computer program — of 750 trials on over 400,000 patients, and till actual clinical trials were conducted on humans, safety would remain an issue.

Then, it was said that dosages of the

component drugs (statin, aspirin, etc.) need to be tailored to a patient's condition and cannot be fixed for everyone. The suggestion that everyone aged 55 or above could be given the polypill (essentially as a prophylactic or preventive measure) came in for flak. There were fears that the polypill could lead to prescription abuse. Others felt that in an age where medicine seeks to work on people based on individual gene profiles, the polypill is a step backward. Finally, it was feared that the polypill would encourage people to skip other important steps like exercise and dieting.

Despite the opposition, the polypill has found pockets of support. In January 2005, a group of experts of the US Centers for Disease Control and Prevention in Atlanta supported the polypill and suggested that placebo-controlled clinical trials be held. However, trials have not yet begun.

The India Connection

While the debate on the polypill still rages, there was no doubt that a single pill to treat CVD, if it actually worked, would be immensely useful for the developing world. That's because the cost of the combo, which used off-pat-

ent drugs, would likely be cheaper than that of the individual drugs combined.

In his editorial in the 28 June 2003 issue of *BMJ*, Rodgers wrote: "The most important challenge is ensuring such interventions reach the many people at high risk in developing countries who currently receive little or no preventive care. Compared with developed countries many times more lives could be saved, mostly among middle aged people, if combination medications were made affordable and accessible."

India comes into the picture in two ways. One, that India is on the threshold of a virtual CVD epidemic, according to a study conducted last year by the National Commission on Macroeconomics and Health (see 'The Heart Of The Matter'). The study also revealed that Indians are three to four times more at risk to CVD than Caucasians, six times more than Chinese and 20 times more than Japanese.

And two, making the polypill required combining several active drugs into one, a kind of reverse engineering that Indian pharma companies, with their experience in generics, have become adept at. K. Srinath Reddy, head of cardiology at AIIMS, and a prolific researcher of CVD prevention methods, took advantage of that. Reddy, who has emerged as an evangelist of sorts for the polypill, approached Dr. Reddy's in early 2003. "They had the scientific capability to develop the polypill," he says.

Dr. Reddy's, for its part, took up the challenge and Rs 25 crore was set aside for project Little Red Heart Pill (LRHP). A team of international advisers led by Rodgers and including people like professors Stephen MacMahon and Anushka Patel, and associate professor Bruce Neal of the George Institute of International Health, University of Sydney; professors Richard Grimm and Jim Neaton of the University of Minnesota; Krishnam Raju of CARE Hospital; and Srinath Reddy worked with Dr. Reddy's research team and studied various combinations of molecules, dosage forms and therapeutic categories.

After going through multiple iterations, the project team settled on the following combination: two hypertensives, a blood thinner and a lipid lowering agent. Folic acid was eliminated due to lack of sufficient data.

cure

Bioavailability studies were done on healthy volunteers specified by the Drug Controller General of India to understand the plasma concentration of the polypill. And comparative bioequivalence studies were done to ensure that the bioavailability of the polypill was equal to those of the component pills. Says M.S. Mohan, vice-president (research & development), Dr. Reddy's: "It was technically and scientifically the most challenging project for us."

Dr. Reddy's Strategy

Dr. Reddy's looks at the polypill as a product for the world market. To make that happen, the company claims it is following stringent global quality requirements of different regulatory bodies. Says Satish Reddy, managing director and COO: "The magnitude of the

problem was such that the only way it could be looked at was globally." To begin with, it is looking at India, Russia, Brazil, Australia and New Zealand.

That will give Dr. Reddy's something it needs in its desire to be a research-led pharma company: experience in launching an NCE (new chemical entity or original molecule) in different markets, although the polypill itself will not be an NCE. The marketing team was brought into the picture early last year. Says Sandeep Sahney, executive vice-president: "We are very excited. It is the first time that an Indian company is looking at a product in the global context."

Each market is being studied to forecast requirement and sales (Dr. Reddy's has offices in 35 countries and its products are marketed in 110). "We have been collaborating with business heads

in each country," says Sahney. The business heads are assessing market potential as well as regulatory timelines, which are different for each country.

Within India, 35,000-40,000 doctors (specialists and general physicians) will be targeted for detailing on the polypill.

Pricing is another important factor. The idea is to make the product at the lowest possible cost. Says Raghu Cidambi, head (IPR and strategic planning), Dr. Reddy's, and mentor of the polypill project: "We are looking for the cheapest manufacturer of the API in the world." However, multiple pricing or higher pricing for the developed market to cross-subsidise the cost for developing market have not been considered, according to G.V. Prasad, executive vice-chairman and CEO, Dr. Reddy's.

Meanwhile, Dr. Reddy's polypill follows a completely new approach that has deviated from the original combination prepared by Wade and Law. That's not to say that it won't work, but there are attendant risks that have not been tested yet.

Besides, questions dogging the polypill still remain. Doctors are not happy about the fact they will not be able to regulate the dose per patient.

Counters Satish Reddy: "Doctors would ideally like to titrate the dose with every patient, but aren't compliance and cost equally significant issues?" Srinath Reddy says that it will be a cost-effective solution, particularly for the poor, who cannot remain on expensive multi-pill medication for long.

Dr. Reddy's contention is that at this point, one can only theorise about possible risks. The clinical trials, scheduled for April, should provide some answers. Says J.S. Bakshi, corporate medical director: "In India, clinical trials in phase III will be held in 10 institutes. They would be held at referral hospitals with a mix of rural and urban population."

The financial implications of a successful polypill launch for Dr. Reddy's are not known yet. "There is no formula that can be applied to cover our investment," says Satish Reddy.

Pharma analysts, though, are gung-ho about the prospects of the polypill. Gushes an analyst: "Given time, there is no way that it would not be a blockbuster, at whatever price."

Blockbuster or no, time will tell. ■



Anthony Rodgers, director, clinical trials research unit, University of Auckland, is an ardent advocate of the polypill. He spoke to *BW's* Gina S. Krishnan. Excerpts:

- *What is your interest in the polypill?*
- It is the public health potential. In India, about 2.1 million people die from CVD each year and (this number) is projected to increase to 3.5 million by 2020. Much of this burden is suffered by people in middle age. The polypill, if it is effective, safe and affordable, has the potential to make huge inroads into this public health priority. Also, I was involved in trials of polypill components in the 1990s.
- *How did you identify the component molecules for the polypill?*
- These were chosen to be evidence-

'The polypill needs top quality clinical trial evidence'

based, with direct evidence of benefit for each. The lowest effective dose of aspirin was used (75mg), since above this dose side effects increase, but efficacy does not.

- *What kind of support does it need as it moves for regulatory approval?*
- The polypill needs a full programme of clinical trials testing bioequivalence, adherence, tolerability and effects on cardiovascular risk. The regulatory requirements are not confirmed for many countries, but these should be less onerous than for an NCE, since the component drugs have an established safety and efficacy profile after a few decades of research. Affordability will be key, but this has to be backed up with top quality clinical trial evidence.
- *Do you anticipate major opposition to a fixed dose combination pill?*
- There will be a change in approach needed for some. The key is identifying the patients for whom improved long-term adherence outweighs any issues with tailoring the component drugs.