When Pharma Merges, R&D Is the Dowry

Pharmaceutical companies' continuing quest to get bigger is not just megalomania. Staying on top in the global drug market requires doing more and better research. And unit costs keep rising

Around the time that Britain's giant Glaxo Wellcome PLC first began talking with the equally huge SmithKline Beecham PLC about a merger that would create the largest pharmaceutical research and development machine in the world, Glaxo chair Sir Richard Sykes declared the death of the traditional approach to drug discovery—screening thousands of chemical compounds to find one that works. "The future," Sykes said, "is in molecular genetics, cell biology, and the modern sciences." It would take more than 2 years for senior management from both companies to agree on who would call the shots in the new enterprise and to proclaim, on 17 January of this year, that they had achieved a "merger of equals." But nobody disputed the unspoken message behind Sykes's vision: The pharmaceutical company in the best position to exploit nascent discoveries would be the one with the fattest research budget.

The idea that bigger is better in R&D has become an article of faith in the pharmaceutical industry. Just 3 weeks after the Glaxo SmithKline announcement, Pfizer Inc. and Warner-Lambert Co. linked hands to create a behemoth with an even bigger R&D platform. And Pharmacia & Upjohn Inc.—itself the product of a 1995 merger—beat them both to the altar by announcing in December that it would merge with Monsanto Co. to create "a first-tier pharma company with a first-tier growth rate."

The forces driving this mania for mergers—there have been 30 in the past 15 years—are straightforward. Although no company has even a double-digit slice of the global prescription drug market, each must have enough market share and product lines to maintain "a significant presence" in the United States, Europe, and Japan, the three major world markets, says Sergio Traversa of Mehta Partners, a pharmaceutical and biotech investment firm in New York City. With nearly 7% of the world pharmaceutical market each, Glaxo SmithKline and the merged Pfizer may be big enough for the time being, says Traversa, but others will try to catch up.

Other forces behind the recent mergers stem from the need for ever-larger R&D establishments, both to take advantage of new opportunities and to cover the continuing rise in the cost of developing new drugs. The Human Genome Project—the effort to identify all 3 billion nucleotide bases in human DNA—is yielding clues to thousands of new research targets for drug development. But following up on those clues will be hugely expensive and will require a supersized scale of operation. The easiest way to achieve that magnitude quickly is to merge.

Rising costs

Already, the pharmaceutical industry is spending a hefty sum on R&D. The Washington, D.C.–based Pharmaceutical Research and Manufacturers of America (PhRMA), the industry's U.S. trade association, estimates that U.S.–based research by its members topped $21 billion last year; worldwide, it exceeded $24 billion. That's nearly three times the 1990 level and a robust 21% of sales, up from 16% in 1990. The Centre for Medicines Research International in the United Kingdom, which surveys more companies, pegs the global figure at $43 billion.

This growth mirrors the steady rise in the cost of bringing a drug to market. Although exact numbers remain elusive, the most widely quoted figure, from a 1993 study by the Boston Consulting Group, is about $500 million in R&D for each new drug that makes it to market. Others place the cost lower, at $300 million—still a hefty amount. These estimates, of course, include projects that are canceled along the way.

The cost per drug is likely to go higher, say industry R&D chiefs, for several reasons. One is the slew of new drug targets emerging from the genomics revolution, which is dramatically widening the playing field for companies. "We've gone from a period, not long ago, where pharmaceutical companies all were working on the same targets," says Göran Ando, Pharmacia's executive vice president and president of R&D, who will oversee a pharmaceutical R&D budget that may reach $2.4 billion this year. "Now we are into an abundance of novel targets."

"Abundance" may be an understatement. The full human genome sequence will contain "all of the targets for drug intervention in mankind" except for antimicrobials, notes Tadataka Yamada, who will be the R&D chair in the new Glaxo SmithKline. "The territory has been staked out. Now, people have to go out and identify the opportunities for pharmaceutical intervention within that territory. It's going to be a very competitive effort," says Yamada, who will have $4 billion a year to spend on that task. Industry analyst Hemant Shah of HKS and Co. in Warren, New Jersey, agrees: "Look at the kind of research targets these companies are going after. They are far more difficult, far more complex, and far more uncertain."

The cost of identifying the potential drug targets from among an estimated 80,000 to 100,000 human genes is one of the reasons why Pfizer Inc. fought so hard to corral Warner-Lambert. The merged company will boast the biggest R&D budget in the industry, an expected $4.7 billion this year. Pfizer chair and CEO William Steere Jr. is betting that amount will help make the new entity "the fastest growing major pharmaceutical company in the world." And pharmaceutical companies will need all the muscle they can muster.

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R&D AT TOP 11 BIG PHARMA

Company	Prescription sales*	Total revenues (in billions)	R&D (1999)
Glaxo Wellcome/ SmithKline Beecham	$20.1	$26.3	$3.7
Pfizer/Warner-Lambert	18.7	29.1	4.0
AstraZeneca	12.6	18.5	2.5
Merck	12.5	32.7	2.1
Aventis	12.1	17.9	2.7†
Novartis	11.5	21.6	2.4
Bristol-Myers Squibb	11.3	20.2	1.8
Johnson & Johnson	10.3	27.5	2.6
Roche	8.9	18.4	1.9
American Home Products	8.5	13.6	1.7
Pharmacia & Upjohn/ Monsanto	8.3	16.4	2.8‡

* (12 months ending 9/30/99) Excludes mail order and sales in the Netherlands.
† 1998 ‡ Includes $600 million in agricultural R&D.

Top R&D dogs. The latest merger partners—Pfizer and Warner-Lambert—are also the king of the research hill, although Merck leads in overall revenue and Glaxo in drug sales.

SOURCE: IMS HEALTH, PLYMOUTH MEETING, PA; *SCIENCE*

targets—PhRMA guesses 3000 to 10,000 targets, compared with 500 that the drug industry has so far exploited—the trick will be to recognize and then validate them. By itself, Ando observes, the raw genome sequence "is sort of like getting the Manhattan phone book with only the numbers, not the names."

Both Ando and Yamada expect that some of the nameless gene sequences will stand out as more interesting than others. For instance, genes coding for a family of receptors known as G protein–linked receptors—which are key interchanges in cell signaling—will be recognizable because of sequence similarity to known receptors. So if a gene sequence seems likely to encode such a receptor, "that's a clue that the gene encodes a potential pharmaceutical target," Yamada says. The crucial tip-offs will be "relationships, similarity to other structures, clues derived from computer algorithms. This is what bioinformatics is all about."

As industry researchers try to determine where a protein fits in a biochemical pathway and what happens if it's eliminated or augmented, the industry will be drawn more deeply into functional genomics. Ando notes that pharmaceutical labs have been doing some of this work all along. But the current era requires a stronger commitment, which translates into greater resources spread over a wider area. "Researchers may find themselves studying a receptor and find a compound that inhibits it without [having] any idea what disease the compound might be most useful against," says Yamada. "The receptor may be important in cardiac function, or bladder function, or bowel function." In cases like this, he adds, only a company that is active in all those therapeutic areas can truly capitalize on that discovery.

Raising the bar

It's not just the genomics revolution that is pushing up the costs of R&D. For a variety of reasons, drug development has become more costly and more complicated. In a major switch from just 20 years ago, a growing proportion of drugs is now prescribed for chronic conditions rather than as short-term antibiotics or pain-killers. This change has forced government regulators to look more closely at each drug's long-range effects. "We keep raising the bar on what our performance should be," says Roger Perlmutter, executive vice president for basic research at Merck Research Laboratories in Rahway, New Jersey.

Therapies aimed at conditions such as hypertension, high cholesterol, diabetes, or neuropsychiatric diseases, he notes, "are in principle going to be taken day in, day out for years. And they have to have a squeaky-clean safety profile." In addition, many of these drugs are being taken by older patients who also are on other medications. Eliminating the potential negative side effects of such drug interactions is "paramount," says Perlmutter, adding that a drug that might have been marketable 20 years ago is no longer acceptable if it shows signs of inhibiting the body's metabolism of other drugs.

On the other hand, companies can't always pass along to consumers the full cost of drug R&D. In a Catch-22, drugs already proven safe, tolerable, and efficacious must also be "cost effective," says Yamada, if they are to succeed in the current era of managed care. Without such proof, managed care operators and national governments—which, in most of the world, are at least partial payers for prescription drugs—will not include a drug among the medications they will pay for. "These [outcomes] studies are very expensive, and they extend the length of time that research must be done on a drug," says Yamada.

Companies are also striving to shorten the time from discovery to marketing—to get the most out of the finite length of a patent and, often, to beat a competitor to market. But this competition raises costs by forcing companies to juggle more balls. "You need to run more things in parallel, rather than sequentially," says Ando. As a result, "you do a few more things than you would have."

The cost of clinical trials makes up a huge share of pharmaceutical companies' R&D budgets, nearly 40% by one independent estimate, and both per-patient costs and the costs of sophisticated tests seem likely to keep rising. Another 10% goes toward developing processes to synthesize compounds on a huge scale while controlling their production so precisely that, as one official puts it, "the billionth pill is identical to the first." In addition, a substantial fraction of R&D money goes to screen compounds that might produce a new or improved drug—such as the search for a more effective inhibitor of the COX-2 enzyme, which promotes inflammation, pain, and fever, to develop a better arthritis therapy.

A gripping story. Such handshakes by corporate chieftains—Pfizer's William Steele and Warner-Lambert's Lodewijk de Vink *(left)* and Glaxo's Richard Sykes and SmithKline's Jean-Pierre Garnier *(above)*—are likely to be repeated often as companies seek bigger R&D budgets.

Although the proportion of industrial budgets taken up by basic exploratory research is quite low, says Perlmutter, it is not irrelevant to the overall biomedical research enterprise. For example, Merck researchers were the first to determine the three-dimensional structure of the HIV-1 protease enzyme in 1989 (see p. 1954), "and we published that structure so that everybody else could work on it, too," Perlmutter notes. Earlier, Merck researchers had performed the mutagenesis experiments demonstrating that disabling the protease enzyme halted HIV-1 propagation.

For all those reasons, being the biggest kid on the block has become the hottest game in town. Unless government antitrust agencies step in, several of the recent proposed mergers are expected to be finalized later this year. The newly created Glaxo SmithKline and the new Pfizer certainly seem big enough to tackle all these challenges. Pharmacia, with a relatively large R&D budget in proportion to overall drug sales, is getting there, and it may have a new growth surge before the year is out—industry analysts believe it is eyeing another potential partner, American Home Products Corp. Whether or not these deals go through, Traversa of Mehta Partners predicts that such corporate ballroom dancing will continue: "You don't want to be the last one left without a partner."

–BRUCE AGNEW

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