Biotech Pipeline: Bottleneck Ahead

A vast array of new genetically engineered drugs are heading for market—but an FDA backlog is holding them up

AT THE RECENT ANNUAL MEETING OF THE Industrial Biotechnology Association, analysts, biotech executives, and regulators were making grand predictions for the biotech industry. The 1990s, they said, would finally be a boomtime for the industry that has been banking on its promise for 25 years. First, Ernst & Young analyst Steven Burill predicted that the industry would earn $30 billion by the year 2000 (compared with worldwide sales of $3 billion this year). As proof, he pointed to the "spectacular" pipeline of new drugs awaiting Food and Drug Administration (FDA) approval. Then, FDA deputy commissioner Mike Taylor stepped up to the speaker's podium to pronounce that "the biotech industry has very much arrived."

An examination of the biotech pipeline—the drugs moving inexorably through the long process of research, development, and FDA approval—does indeed show that a whole host of new drugs is nearing the market. And a recent survey by the Pharmaceutical Manufacturers' Association (PMA) shows that at least 21 new biotech drugs have completed clinical trials and are awaiting final approval, while another 111 are currently being tested in human beings. Those 132 drugs—including an array of anticancer and anti-AIDS agents—represent a whopping 63% increase over the volume in the pipeline as recently as 1988 (and the PMA figures fall short of the actual numbers at the FDA). Yet patients may have to wait far longer than the biotech enthusiasts suggest before they reap the benefits of those new drugs. In fact, at the moment the biotech industry could be on the verge of becoming a regulatory victim of its own research and development successes.

Even as they publicly tout the good times just ahead, industry insiders openly worry that the FDA is falling behind in its ability to review and approve medicines quickly. Indeed, the management firm of Booz, Allen & Hamilton concluded the agency needed another 100 to 180 scientists in the next few years to handle its growing workload. Yet FDA officials point out that their staff is actually down from a high in 1979.

And the problems aren't due only to the volume of new products in the pipeline. They're also due to the fact that many second- and third-generation biotech products are much more complex scientifically than their earlier counterparts. Early biotech drugs were usually well-understood substances, such as insulin and other hormones, that function as therapeutic agents just as they do naturally. But many of the new agents—such as the anti-AIDS drug CD4—may work as drugs in ways that are far different from their natural functions. And their effects as drugs aren't well understood. As a result, the FDA is struggling to approve more drugs whose reviews are more complex. Yet there is little hope the FDA will get the money it needs to do the job. Therefore, it could be that the biotech industry—just as it hits its stride—is about to run into a stumbling block.

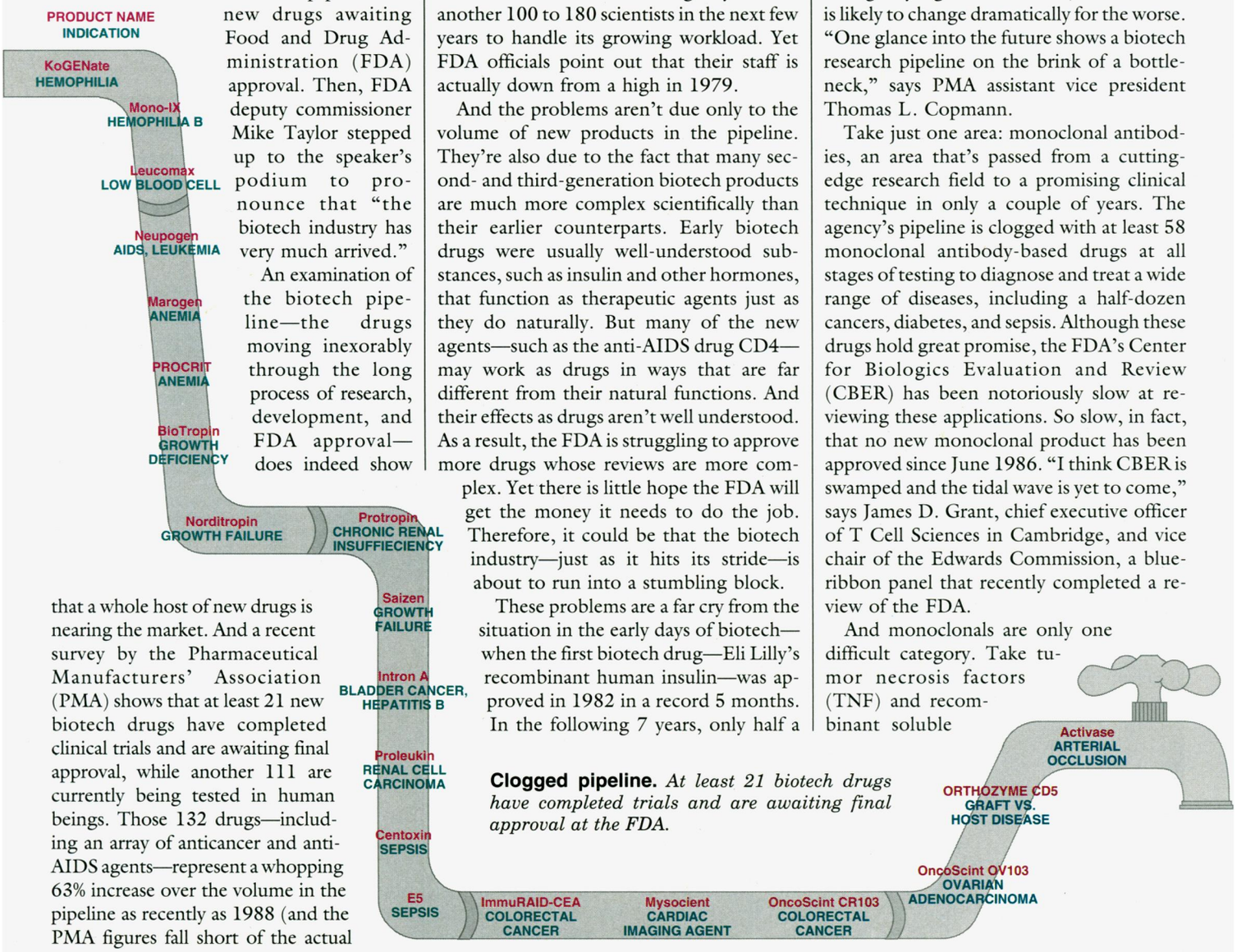
These problems are a far cry from the situation in the early days of biotech—when the first biotech drug—Eli Lilly's recombinant human insulin—was approved in 1982 in a record 5 months. In the following 7 years, only half a dozen more were approved, not because they were too challenging but because there weren't many.

Only in the past 2 years has the pace of approvals quickened considerably. Since 1989, the FDA has approved more biotech drugs than it had in all the preceeding years—half of the 14 drugs ever approved. What's more, the agency has been doing better on biotech drugs than other types. The average biotech drug is approved 21.4 months after its manufacturer submits an application to the FDA—10 months faster than the average approval for traditionally synthesized chemicals, says Henry Miller, the physician who is director of the FDA's Office of Biotechnology. "So the way I look at this is that on each and every biotech product, we're giving them an advantage of about 10 months," says Miller.

But if that sounds like boasting, why are biotech and pharmaceutical company officials so gloomy? The reason is that despite the agency's good intentions, the situation is likely to change dramatically for the worse. "One glance into the future shows a biotech research pipeline on the brink of a bottleneck," says PMA assistant vice president Thomas L. Copmann.

Take just one area: monoclonal antibodies, an area that's passed from a cutting-edge research field to a promising clinical technique in only a couple of years. The agency's pipeline is clogged with at least 58 monoclonal antibody-based drugs at all stages of testing to diagnose and treat a wide range of diseases, including a half-dozen cancers, diabetes, and sepsis. Although these drugs hold great promise, the FDA's Center for Biologics Evaluation and Review (CBER) has been notoriously slow at reviewing these applications. So slow, in fact, that no new monoclonal product has been approved since June 1986. "I think CBER is swamped and the tidal wave is yet to come," says James D. Grant, chief executive officer of T Cell Sciences in Cambridge, and vice chair of the Edwards Commission, a blue-ribbon panel that recently completed a review of the FDA.

And monoclonals are only one difficult category. Take tumor necrosis factors (TNF) and recombinant soluble



Clogged pipeline. *At least 21 biotech drugs have completed trials and are awaiting final approval at the FDA.*

CD4s, two groups of promising drugs that are in the early stages of safety and efficacy testing in humans. As early as 1975, it was learned that TNF can inhibit tumor growth by triggering the deployment of immune cells that damage tumor-nourishing blood vessels. Now Genentech, Biogen, and Knoll Pharmaceuticals are all testing recombinant TNFs to treat cancer in humans. The problem is that this work strains the limits of the hottest researchers, because it still isn't clear exactly how TNFs work. And the FDA has a tough time recruiting the scientists it needs to review these drugs.

Nor are they likely to make quick intellectual work of CD4s, recombinant copies of the cellular receptor that the AIDS virus binds to. Two companies, Genentech and Biogen, have just started testing genetically engineered CD4s in humans, where they hope the drugs will act as decoys to bind the virus, protecting white blood cells from infection. Although the method copies nature through the use of CD4 receptors, it isn't using CD4 in the way that nature intended—and large quantities of the molecule circulating in the blood could have a wide variety of unintended consequences, since CD4 is a key element in immune system regulation.

Is anyone besides the manufacturers worried? In a report earlier this year, the Vice President's Council on Competitiveness said—in what might be taken to be a bit of hyperbole—that it is concerned that regulatory delays at all agencies could jeopardize the nation's lead in the international biotechnology industry. And beyond the fashionable buzzwords like competitiveness, there is a hard, underlying reality in the potential biotech bottleneck: Delays keep drugs from dying patients.

At least eight of the monoclonal antibodies in the pipeline are intended to treat life-threatening diseases. Genentech's president, G. Kirk Raab, says the most powerful argument for speedy approval is "to get the drugs to the people who need them. The FDA's role is not to protect small industry or American competitiveness."

The FDA responds that drugs for life-threatening diseases—particularly AIDs—are already fast-tracked. Says Miller, "The argument that the agency is in big trouble just doesn't hold water." Nonetheless, he is concerned about the growing workload for those at the FDA who approve new biotech drugs. More than two-thirds of all active investigational new drug (IND) applications to one FDA center are for biotech products, and that number is expected to grow from 2600 this year to 3250 during 1992.

Although a large infusion of new resources for the FDA may not be a realistic possibility, Grant, an M.B.A. who was on the Edwards Commission, has some suggestions that might help avoid a bottleneck without too much new cost. One would be to convene an outside group of expert medical and scientific authorities who would help the FDA "rethink the whole process" of how it reviews drugs. In particular, it should consider new ways of streamlining the way it measures the safety and efficacy of new biotech products, Grant says.

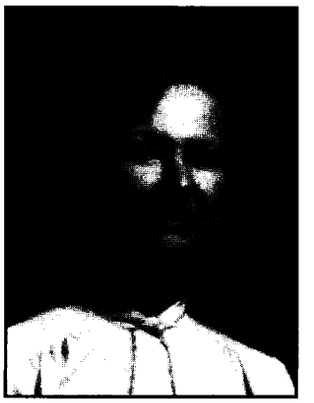
"One glance into the future shows a biotech research pipeline on the brink of a bottleneck."

—Thomas L. Copmann

New FDA head David Kessler apparently is listening to such ideas. Earlier this week, in a speech to 100 biotech company leaders, he said he had hired a new senior science advisor, and had set up an in-house committee to reconcile differences between the two main FDA centers that approve biotech products to help speed up the review time. Changes also are being made in the agency's management, including better computer systems to track and evaluate the approval of drugs. Whether Kessler, with his limited resources divided among many congressional mandates, can reduce the bottleneck that so many industry insiders fear won't be known for a while. But the answer will determine whether the 1990s is to be a decade like the 1980s for the biotech industry—a time full of promise but only moderate hard payoff—or a decade that sees the promissory notes, for the first time, redeemed in a big way. ■ ANN GIBBONS

They'd Rather Switch Than Fight

The huge number of college students who choose science, math, or engineering majors only to drop out is alarming the National Science Foundation (NSF), and members of the scientific community generally. As NSF calculates it, the attrition rate is as high as 60%. Just why it's so high is a puzzle. Faculty members often blame the students, arguing that the dropout rate is due to educational weaknesses among the students who switch. Alternatively, they cite factors over which teachers have little control, such as large classes or inadequate lab facilities. But maybe it's time to focus on the quality of teaching itself—at least that's the conclusion of a preliminary study by two sociologists at the University of Colorado at Boulder.



Switch analysts. *Nancy Hewitt* (left) *Elaine Seymour.*

Work by Nancy Hewitt and Elaine Seymour, research associates at the university's Bureau of Sociological Research, takes issue with the "weak students" hypothesis. The two researchers interviewed 149 students at four colleges and universities, including 61 switchers and 88 nonswitchers, and found that "the switchers and the nonswitchers are essentially not two different kinds of people," as Seymour puts it. "They're not the untalented versus the talented or the lazy versus the hard-working or people who have problems of some kind versus people who don't have problems."

What all share are problems with the science faculty at their schools, the sociologists discovered. The chief complaints were poor teaching and unapproachability on the part of the faculty members, who didn't seem to have much time for undergraduates. And here came a pointed difference between the two groups: The switchers didn't find any way to cope with these difficulties; the persistent nonswitchers did. Yet even among those who stuck it out, a telling 40% reported being "turned off" to science by the experiences they had as undergraduates.

A quarter of the nonswitchers added another telling observation to their complaints about faculty laissez-faire: They had come to believe, they reported, that other majors were intrinsically more interesting than sci-