Can David Kessler Revive the FDA?

The new commissioner has all the qualifications—but he's got his work cut out for him in an ailing, overburdened, and demoralized agency

FROM THE DAY DAVID A. KESSLER TOOK the oath of office as the new commissioner of the Food and Drug Administration (FDA) last December, he has been taking a tough line: "The FDA is a policeman," Kessler said in his oath of office speech. "We're going to take up enforcement a notch in this agency." The tough talk, he hoped, would prevent any repeat of last year's conviction of five FDA employees for accepting bribes from generic drug companies. So he must have been discouraged to wake up last week to headlines in *The Washington Post* that read, "Grand Jury Investigates FDA Leak—Drug Approvals Said Tied to Insider-Trading Profits." Yet another scandal at the FDA—and this time on his watch.

By any measure, the FDA has been a sick agency in recent years. The symptoms were manifest long before Kessler arrived. In 1989, the generic drug company scandal made national headlines: One drug company's private investigator found that at least three generic drug companies were getting preferential treatment on drug approvals in exchange for payoffs. One year later came reports that more than a dozen generic drug companies and "scores of individuals" were under suspicion of fraud and bribery. At the same time, the FDA announced that blood banks had been blatantly ignoring its regulations, resulting in the infection of some blood transfusion patients with AIDS. And now we read that another group of FDA employees is under investigation for using inside knowledge about drug approvals to play the stock market. "This is the lowest point in terms of scandal in the FDA's history," says Peter Barton Hutt, former chief counsel of the FDA.

As if this weren't enough to debilitate the FDA, AIDS activists and drug companies—not often allies—charge that the slow-moving bureaucracy delayed the approval of critical drugs such as ganciclovir, which is used to prevent blindness from one of the opportunistic infections of AIDS. At the same time, consumer advocates complain the agency is too quick to approve some products, such as heart valves that later cracked, an arthritis drug that caused more than 100 deaths, and several brands of antidepressants that led to 300 cases of acute kidney failure.

Meanwhile, Congress has heaped new responsibilities on the agency—but provided too little in the way of funds to carry out all those responsibilities. It has mandated that the FDA hasten the approval of more generic medicines and drugs for rare diseases. When Congress did consider giving the FDA more money, the General Accounting Office said the agency's management methods were too poor to assess where new people were needed most. On top of that, a parade of witnesses openly criticized the agency in public hearings in the past year, held by a blue ribbon panel of experts reviewing the FDA (the Edwards Commission, whose final report is due in May). "The FDA is everyone's whipping boy," says William W. Vodra, former associate chief counsel for drugs at the FDA.

Now, David Kessler becomes the latest physician to try and heal the FDA. While it is unlikely that any one commissioner can rid the agency of all its ills, Kessler has as good a chance as any. Interviews with FDA insiders, Washington policy makers, scientists, and drug company officials paint a promising portrait of Kessler who, at 39, has all the right credentials for the job—including an M.D., a law degree, management training, and a winning manner (see box on next page).

Now, 4 months into the job, he's had time to diagnose the agency's problems and prescribe a treatment. His prescription has four parts. First: Restore the agency's credibility. Second: Clear the backlog of drugs and products that are months, if not years, behind schedule for final approval. Third—and perhaps most difficult: improve management. Finally: seek staff, funds and regulatory authority to improve morale and build a stronger agency.

Whether he succeeds is a matter of great importance. No less is at stake than the public health and the economic stability of major industries—the FDA is entrusted with guaranteeing the safety of products that account for 25 cents of every dollar of American consumer spending. Not only must the FDA approve the safety and effectiveness of every drug, it also certifies blood supplies and medical devices ranging from IUDs to surgical lasers. At the same time, FDA regulators inspect food, test food coloring and sweeteners, and approve the labels and advertising campaigns for food, drugs, and, to a lesser extent, cosmetics.

To give this vital agency back its self-respect, Kessler is focusing first on the black eye the organization received in the generic drug scandal. Many FDA staffers hoped they could put the scandal behind them with the conviction last year of five former agency em-

FDA SYMPTOMS AND DR. KESSLER'S PRESCRIPTION

CREDIBILITY DAMAGED
The recent conviction of five FDA employees for accepting bribes from generic drug companies tarnished the agency's image.
Solution: *Kessler is beefing up inspections of drug and product companies, and is calling for new civil and criminal authority to prosecute.*

BACKLOG OF DRUGS AND OTHER PRODUCTS
More than 70 drug applications are overdue and a similar backlog of vaccines and other biological products is growing.
Solution: *The FDA is considering computerizing applications, and speeding up the approval process for drugs for treating fatal diseases.*

LACK OF RESOURCES
The agency's budget and personnel have barely kept pace with inflation in the past decade, yet Congress has assigned significant new duties to the FDA.
Solution: *The proposed 1992 budget of $770.2 million for the FDA includes an 11% increase over the 1991 budget, but $197.5 million of that will be financed by "user fees."*

POOR MANAGEMENT SYSTEMS AND DOCUMENT TRACKING
The GAO and consultants say the agency has a poor system for tracking product reviews, measuring employee performance, and setting priorities.
Solution: *New workload assessments are under way, a computerized data system is being investigated, and Kessler is hiring a special assistant for management.*

ployees. But those wounds were reopened with the new investigation of employees accused of using their knowledge of upcoming drug approvals to play the stock market. Some FDA staffers said they felt "betrayed," because they genuinely think of themselves as "good guys," protecting the public from unsafe food, drugs, and products, says Henry Dausch, deputy director of external operations at the FDA.

Kessler has responded by beefing up enforcement. He is dispatching more investigators to inspect drug and product manufacturing plants and records before their new products are approved. "The thing I learned most from the generic drug scandal is that data coming to the agency have to be audited," he says. "The honor system is out the window."

Like the other problems facing the FDA, the enforcement quandary has been a while building. Some observers say the reason enforcement has gotten out of hand is that the agency has been perceived as a "paper tiger." "It would write a nasty letter and let 2 more years go by before it did anything," says Vodra. "FDA just sat on its hands and the industry ran amok." And throwing out the honor system is just the first step in bringing things back under control. Kessler has also met with lawyers at the Department of Justice to find out what legal muscle he has to back up his threats, and he has sent a signal to Congress that he wants new legislation to expand his authority to inspect plants, recall harmful products, press civil charges against errant manufacturers, as well as to prevent a company convicted of illegal activity from seeking the approval of any product for a set time.

While most people welcome Kessler's new get-tough stance, drug company representatives—and even some FDA researchers—grumble that it will divert resources from another absolutely key need—speeding up drug approval. Says Irwin Lerner, chief executive officer of Hoffmann-LaRoche Inc.: "Companies have written and documented examples where pre-approval inspection has cost them months or even years." Even the FDA admits the process takes too long. "We do a very good job of making decisions, but we don't make them in a timely manner," says Gerald Meyer, deputy director for the Center for Drug Evaluation and Research (CDER). Adds Meyer ruefully, "We draw a lot of heat for that."

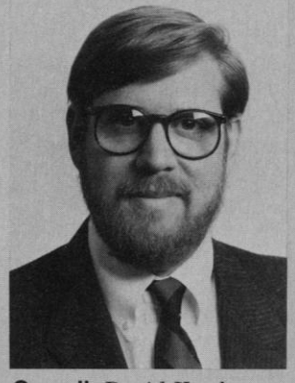
How slow is too slow? The CDER's track record last year was an average of more than 2 years (27.7 months), with one drug taking an incredible 7 years (84.3 months). Those figures are way over the statutory limit requiring the FDA to make a decision within 6 months of the filing of a new drug application (which comes only after years of clinical trials in humans and animals are completed).

And because the approval process is so stately, the backlog of new drug applications is piling up. It now includes 70 applications—the lowest number since December 1989. Particularly embarrassing is a bottleneck of 21 overdue cases in a pilot study division that was set up to try new methods for streamlining drug approval.

Every delay means patients are deprived of potential treatments and drug companies lose profits—no small consideration when those companies now claim to spend $231 million and 12 years on average to produce a new drug. The Administration worries that continued bottlenecks could cost the United States its competitive advantage in new medical products, whose export cut $1.8 billion off the U.S. trade deficit in 1989. In particular, the Administration would like the United States to retain its lead in the key area of biotechnology products (see box on next page).

Yet in the face of this considerable economic and political pressure, Kessler has

New FDA Head: Profile of an Overachiever



On call. *David Kessler*

When David Kessler taught a course on the Food and Drug Administration (FDA) at Columbia University School of Law in New York, he sometimes asked his students a hypothetical question: "You're the commissioner of the FDA. It's 4 a.m. and you get a phone call that X product is contaminated. What would you do?" Little did he suspect that one day his phone would ring and *he* would be the commissioner.

When the phone did ring, Kessler had been FDA commissioner for only 4 months. It was midnight on a weekend, and on the other end of the line was an aide telling him that in Washington State several Sudafed capsules had been laced with cyanide; three people were dead.

Perhaps because of the preparation from his Columbia course, Kessler was ready. He ordered an immediate recall of the Sudafed 12-hour cold capsules, and the FDA came through with high marks. Will Kessler do as well with the other challenges the job holds? It's much too soon to tell, and those challenges are much tougher; none of them is going to yield to a quick fix. But if Kessler fails, it won't be for lack of preparation.

He breezed through congressional confirmation hearings in March, largely because he's one of the most qualified commissioners in FDA history. He has not only an M.D. from Harvard but also a law degree (earned simultaneously) from the University of Chicago—where, to top everything off, he was associate editor of the law review.

And the penchant for doing several things at once seems to have persisted. While a resident in pediatrics at Johns Hopkins University in Baltimore at night, he was working for the Senate Committee on Labor and Human Resources by day, as a consultant to Senator Orrin G. Hatch (R–UT). "I caught up on sleep on the train" between Washington, D.C. and Baltimore, he says. The dual employment wasn't just overachievement; Kessler had a shrewd, future-oriented purpose in mind. "I wanted to learn how this town [Washington] worked," says Kessler.

Having acquired the insider's viewpoint, he decided it was critical that he leave Washington to get a perspective "outside of the Beltway." So in 1984 he returned to his native New York City to become medical director of the Hospital of the Albert Einstein College of Medicine. Just to round things off, he got the professional manager's viewpoint by earning an advanced professional certificate from the New York University Graduate School of Business Administration and taught food and drug law at Columbia University and medicine at the Albert Einstein College of Medicine.

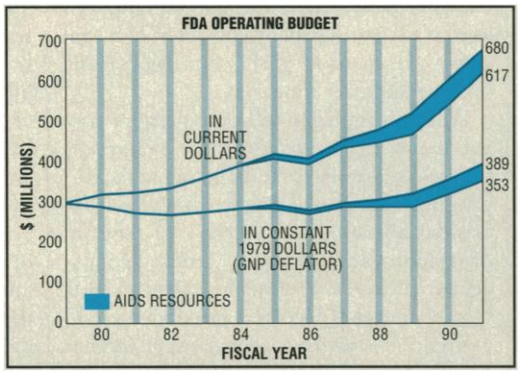
If David Kessler's résumé testifies to a certain driven quality, insiders at the FDA say he also has a personable manner that has helped in dealing with the staff. He seems to have all the requisites for his new job. Says Peter Barton Hutt, former FDA chief counsel: "If Kessler can't do it, nobody can." Which only raises the real question: Can anybody straighten out the FDA? ■ **A.G.**

been cautious. He is giving measured support to efforts to get drugs to patients with life-threatening diseases before the drugs win final approval—as has been tried with AIDS medications. To streamline the approval process further, he is calling for use of independent committees of non-FDA scientists to help review drug applications.

Another fix is technical: bringing the reviews, currently all conducted on paper, into the computer age. An independent management consulting firm, Booz, Allen & Hamilton, predicted computerized filings could reduce the time to review data from large clinical trials by 15% to 25%, says Mary Jo Veverka, vice president of the firm.

But in grappling with the question of speed, Kessler faces a particularly severe challenge, because he must attempt to accelerate the approval process without sacrificing safety. Last year the General Accounting Office (GAO) found that more than half the nearly 200 drugs approved by the FDA between 1976 and 1985 caused "serious" adverse reactions. Should the agency become even more cautious than it already is? Perhaps not, says former chief counsel Hutt, who notes that the FDA already is a "risk-averse system." According to Hutt, the entire drug approval process "is broke. It has to be fixed, but it's doubtful it can be. We'd have to re-educate the public and Congress that there are no drugs without risks."

Short of a national re-education campaign, there is one solution that could help streamline drug approval without sacrificing safety: improving FDA management. Another GAO report noted last year that although the FDA appears to need more money and more staff, poor management has prevented it from setting priorities based on a comprehensive assessment of needs. "I liken it to a research department in a company or within academia where you have highly qualified scientific and technical people who have been asked to take on management responsibilities," says Veverka, whose firm did the study for the Edwards Commission. "But they're not trained to be managers, so what you end up seeing is very ineffective management." In her report to the Edwards Commission, she recommended that a dual career path be developed so that good scientists don't have to go into management to be rewarded, while those who do show an aptitude for management are given more training and encouragement.



Struggling to keep pace. *In real terms, the FDA budget has lagged behind its growing responsibilities.*

Kessler has already asked Veverka to put her money where her study is by joining him as a senior adviser for management. He is also recruiting other senior advisers for strategic planning, operations, policy, and external affairs—as well as for science. "In 6 months, you will see significant changes," he promises.

But there's still a long way to go to improve morale, particularly in parts of the agency where overworked regulators are choking on backlogs of applications. To eliminate those bottlenecks, it's clearly going to take not only good administrative ideas but also more money. "I'd say that the agency would have problems regardless, because the Congress keeps passing new legislation, with new tasks, without worrying about whether the agency has the bud-

The Biotech Pipeline Is All Clogged Up

Delays by the Food and Drug Administration (FDA) in approving drugs have long angered pharmaceutical companies, who think they're losing profits. Yet a Merck or Hoffmann-LaRoche isn't likely to go bankrupt because the FDA moved slowly. But for the fledgling biotech industry, largely populated by tiny companies with only one or two products, the consequences could be lethal. "Delays in drug approval already have been a setback to the biotech industry," says Bruce Merchant, a vice president at Viagene in San Diego. In fact, he says, "many companies are now planning their initial clinical work abroad." Among those who are is Viagene's parent company, Gensia Pharmaceuticals of San Diego.

The problem is that it takes 34 months, on average, for the FDA to approve genetically engineered products once they've completed years of tests in humans and animals. And the trend is even worse: Only 4 years ago that part of the process took a third less time. As a result, though more than 104 biotech drugs are in the final FDA pipeline, only 13 have so far won approval.

The consequences of FDA delay in biotech are not theoretical: Merchant argues that some small manufacturing firms have already died, in part because the business they expected from biotech companies never materialized. Those firms, he claims, include Damon, Bio Response, Invitron, and Helix Biocore.

And things could get worse. The industry is concerned about proposals—which surface sporadically—to require the FDA to regulate genetically engineered products differently from standard products. The industry fears that would mean further regulation. And indeed, a former member of the House Science, Space and Technology Committee, who asked not to be identified, told *Science* he thinks there should be additional regulations partly to make the public feel confident in the manufacturing process of genetically engineered products.

But on that issue, the biotech industry has an ally in the FDA. The agency believes, says Henry Miller, director of the FDA's Office of Biotechnology, that what matters is the safety of the final product—and not the specific manufacturing process, even if that process is genetic engineering. In general, the FDA has no special procedures for evaluating genetically engineered products.

Instead, Miller says, the agency has chosen to concentrate its resources on improving management and increasing staff in the Center for Biologics Evaluation and Research (CBER), where 80% of biotech products are reviewed. Improvements now being considered include better systems for tracking approval of products and predicting workloads.

Those systems could be crucial to handling the glut of biotech products entering the FDA pipeline. The 100 or so drugs in the pipeline have been joined by 800 other genetically engineered products, such as diagnostic tests and drug delivery systems. And it's clear that this number will explode in the next decade. "We have barely scratched the surface," says Miller. Which highlights one of the key tests before new FDA commissioner David Kessler: Can he move new products to market quickly enough to avoid a biotech industry that chokes on its own innovation? ■ **A.G.**

get or personnel to do those tasks," says Louis Lasagna, academic dean of the School of Medicine at Tufts University and chair of a committee that last year reviewed the FDA's approval process for cancer and AIDS drugs. Congress did give the FDA a significant increase last year and the proposed 1992 budget of $770.2 million includes an 11% increase over the 1991 budget, but $197.5 million of that would be financed by "user fees" charged to industry.

Even that infusion, however, will fall short of what Kessler needs to really get the job done. The Booz, Allen & Hamilton study estimates that just the two centers that approve new drugs and biologics need another 100 to 180 scientist/physicians and another 50 to 100 support staff, with projected estimates of 400 to 600 new people in the next few years—particularly in the Center for Biologics, where a backlog of genetically engineered drugs already is building. That doesn't take into account new staff needed in the field to inspect plants, dock shipments, and enforce statutes, or in food regulation, animal drugs, and medical devices. Those needs will be large, because the workforce at the FDA has been dwindling over the years: Overall staff fell from more than 8000 in 1979 to fewer than 7000 in 1987; it is expected to catch up again only this year, when it will reach a peak of 8400.

Chief among the personnel problems that Kessler is going to have to grapple with is recruiting top-level scientists and physicians. Those are people who can draw much larger salaries in industry and even academia—and as a result, it's hard to attract them and hard to keep entry-level scientists once they're trained. Furthermore, the FDA lags in keeping labs and equipment up to date. Kessler doesn't have answers to these problems. In fact, he complains: "I don't have salaries. I don't have space. The only thing I have is convincing people of the importance of this agency."

In the face of all these competing, sometimes contradictory demands, how will David Kessler fare? It's not easy to predict. All those interviewed by *Science* acknowledge he's a capable man. He's got a new, tough attitude toward enforcement, he's got good ideas about management, and he's energetic. He's also coping with huge inertia, a demoralized agency, and a chronic lack of money. Perhaps the right attitude is that of many FDA staffers, who say they are taking a wait-and-see approach. The problems he faces, they say, are so big that it's unclear how big a dent any single person can make. Yet if anybody can do it, the consensus seems to be that Kessler can.

■ ANN GIBBONS

Candidate in Sight to Head Salk

San Diego—For the second time in a year, a search committee at the Salk Institute for Biological Studies has homed in on a choice for the institute's president. Its latest pick is Arnold Levine, 51, chairman of molecular biology at Princeton University. The Salk board of directors is expected to vote to make Levine an offer during its next meeting on 17 April in La Jolla.

Princeton

Arnold Levine

"It's a little premature to talk about it because they've made no offer and we haven't negotiated any details yet," Levine told *Science*. "But I'm both honored by the possibility and would look forward to the opportunity to lead the Salk Institute."

Renato Dulbecco, Salk's interim president, cautiously calls Levine "the most serious candidate." He and the board want to avoid an embarrassing repeat of the unsuccessful negotiation they engaged in last year with James E. Darnell of Rockefeller University. Darnell declined the Salk presidency in March 1990 after months of discussion about salary and housing.

Dulbecco says of Levine: "He has a good reputation as a scientist and for having built up two rather strong departments of biology." Before taking the Princeton post in 1984, Levine was chairman of the department of microbiology in the medical school at the State University of New York at Stony Brook. His research involves DNA tumor viruses and tumor suppressor genes.

Dulbecco, a 77-year-old Nobel laureate, has served as interim president since 1988, when the late Frederic de Hoffmann stepped down. When the Darnell negotiations fell through, Dulbecco agreed to remain in the post until 1992. During his tenure, he launched a $25-million fund-raising campaign and led the planning for a major expansion of the private research facility.

■ YVONNE BASKIN

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French AIDS Researcher Cleared

Paris—AIDS researcher Daniel Zagury has been cleared by the French government of allegations that he conducted unethical research on human subjects. The allegations stemmed from tests at the Saint-Antoine Hospital in Paris in 1988 and 1990, in which Zagury administered a candidate AIDS vaccine to seronegative volunteers and tested active immunotherapy on AIDS patients. The research was conducted in collaboration with researchers at the U.S. National Cancer Institute (NCI), including Robert C. Gallo.

French authorities investigated the tests after the U.S. National Institutes of Health (NIH) suspended collaboration between NCI researchers and the Université Pierre et Marie Curie, where Zagury works. The suspension was imposed when NIH's Office for Protection from Research Risks found that the NCI scientists had failed "to provide and document adequate protections" for human subjects involved in Zagury's research (*Science*, 15 March, p. 1306). Last week, however, Minister of Health Bruno Durieux announced that "the results of the [French government] investigation show that legislative texts, procedures, and recommendations of ethical committees have been respected by the teams that carried out the trials."

A report of the investigation, which was conducted by François Stasse, director general of the Assistance Publique, the body that administers public hospitals in Paris, points out that the French National Ethics Committee had approved trials of AIDS vaccines prepared in France. The ethics committee had also sanctioned tests of immunotherapy on patients whose chances of survival were poor and who could not be given AZT. Moreover, the report said, Saint-Antoine's own ethics committee had authorized comparative trials of immunotherapy alone and immunotherapy in conjunction with AZT.

The French government did not investigate controversial trials of a candidate AIDS vaccine Zagury conducted in Zaire as far back as 1987. These tests, some of which involved young children whose mothers were being treated for AIDS, were reportedly approved by Zairian ethics committees.

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