FDA: Congress Mixes Harsh Medicine

Bills to reform the Food and Drug Administration are expected to be introduced this fall. They could change the way drugs and biotech products are approved

Regulatory agencies routinely attract the ire of Congress these days. But even in this hot political climate, the Food and Drug Administration (FDA) seems to have a special flair for making lawmakers' blood boil. Accused by its critics of everything from intimidating drug companies to stifling the nascent biotechnology industry with red tape, FDA has become a lightning rod for the anti-government sentiments that changed the face of American politics last year. As David Kessler, FDA commissioner since 1990, puts it dryly, "It's not fashionable these days to be a regulator."

Over the next few months, Kessler and his agency will find out just how unfashionable government regulation has become. This fall, the House and Senate will begin considering legislation that would overhaul the agency and have a major impact on how the United States approves new drugs, biotechnology products, and medical devices—as well as on the future of the companies and researchers who depend on those approvals for their livelihood. Any reshuffle is also likely to have a direct impact on the 1150 researchers who work for the agency: Some of FDA's critics are talking about narrowing the kinds of research the agency conducts or even slashing in-house research drastically (see box on next page).

"We're turning up the front burner" on FDA reform, says Representative Fred Upton (R–MI), who introduced a bill in July that would loosen FDA rules that restrict exports of drugs not approved in the United States. Upton's measure is the first drop in what could be a flood of legislation to reform agency practices. And Democrats are jumping on the bandwagon, too. "There is a growing consensus on both sides of the aisle for comprehensive FDA reform this year," says Representative Ron Wyden (D–OR), a member of the Commerce Committee, which oversees the agency.

Just what shape that reform will take is far less clear. Critics contend that FDA takes too long to approve new products, is loath to seek outside expertise in reviewing applications, and is so ardent in enforcing regulations that it is pushing factories and jobs overseas. But the myriad groups scrutinizing the FDA—from cancer patients to biotech managers to conservative politicians—so far have no common blueprint for overhauling the agency. At least a dozen different reform proposals, floated by think tanks, industry associations, and congressional staff, are circulating in Congress.

The challenge for FDA reformers, say industry executives, scientists, and congressional staffers, will be to craft a single piece of legislation capable of winning widespread support from lobbyists and lawmakers. Associations like the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Organization (BIO) prefer a cautious approach, leaving FDA's structure essentially intact while removing what they see as bureaucratic roadblocks to speedy product approvals. At the other extreme, influential conservative groups like the Progress and Freedom Foundation, which has links to House Speaker Newt Gingrich (R–GA), are pressing for a radical overhaul that would turn over a large measure of control to industry.

KENNETH LAMBER/*THE WASHINGTON TIMES*

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Critic and target. Commerce Committee Chair Thomas Bliley *(right)* claims FDA Commissioner David Kessler *(above)* has taken FDA into areas where it doesn't belong, such as tobacco regulation.

"What's missing is a common vision—you don't see anyone sitting back and looking at the big picture," says William Vodra, a Washington lawyer and former FDA associate chief counsel for drugs. "And I don't see a broad-based consensus on where we want to go." Adds Louis Lasagna, dean of the Sackler School of Graduate Biomedical Sciences at Tufts University: "Everybody is for change. But the spectrum of suggestions is so broad that Congress may say 'a pox on all your houses.' "

Yet some basic elements of FDA reform are already gelling, say congressional aides. One is a clear mission statement for FDA that would limit the agency's purview. "Dr. Kessler has led the agency away from its core mission into areas that are either peripheral to the public health or for which other agencies hold the statutory mandate," insists Representative Thomas Bliley (R–VA), chair of the powerful House Commerce Committee. Bliley, whose Richmond district is near the headquarters of Philip Morris Co., is particularly incensed by recent moves by Kessler to regulate nicotine as a drug. To speed FDA's review process, Congress is also expected to call for outside reviewers to take over at least some portion of it, possibly through certified bodies such as those used in Britain, composed largely of academic scientists. Bliley's panel will take the lead next month by preparing legislation and holding public hearings. The Senate will also begin its debate this autumn, but no bill is expected to reach either floor of Congress until well into next year.

FDA officials, not surprisingly, don't relish this critical attention. What's more, they say the agency is already addressing some of the critics' concerns, and they fear a lengthy debate could disrupt their own reform efforts. "A big concern is that [legislation] could slow us down," says William Schultz, FDA policy chief. Most of the criticisms, Kessler maintains, don't take into account "the enormous progress" the agency has made since he came on board. He says that in the past 5 years, the median time it takes to approve products has dropped, drugs for AIDS and cancer patients are put on the market faster, and a new generation of managers is in place. "I'm not sure I fully understand why the pounding," Kessler adds.

A new era

This is not the first time Congress has been bent on reforming FDA. In the late 1970s an attempt to streamline its drug approval process failed when consumer and industry groups withdrew support for legislation pushed by Senator Edward Kennedy (D–MA). The intervening 2 decades, however, have seen enormous change in the pharmaceutical industry as scores of new companies

The Science of Regulation

When critics question the need for the Food and Drug Administration's (FDA's) research programs, agency officials have a story they are fond of telling. Three years ago, National Institutes of Health (NIH) virologist Arthur Nienhuis discovered a potential problem with a mouse retrovirus used to deliver genes to target cells in dozens of gene-therapy experiments. In monkeys with suppressed immune systems, Nienhuis found, a fraction of injected retroviral particles—which are engineered not to be infectious—somehow regained the ability to infect new cells.

The discovery rang alarm bells at the Center for Biologics Evaluation and Research (CBER), an FDA branch that regulates biotech products and experimental protocols, including monoclonal antibodies, vaccines, and gene therapy. "It was a totally unexpected finding," says Philip Noguchi, director of CBER's cellular and gene therapies division, who had to decide quickly whether FDA should call for a moratorium on clinical trials of gene therapy using the popular retrovirus. Noguchi and other scientists at CBER, which is located on the NIH campus in Bethesda, Maryland, shuttled back and forth between their labs and others on the campus to follow up on Nienhuis's findings. Within a few months, the FDA decided that the potential benefits of gene therapy outweighed the possible risk of retroviral infection in humans. But the agency did require more stringent testing for infectious retroviral particles in gene-therapy patients. The result of this "good synergy between FDA and NIH investigators," says Kenneth Seamon, CBER's associate director for research, is "a more rational policy for safety testing of gene-therapy vectors."

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Cutting edge. FDA scientist Philip Noguchi says lab work keeps regulators scientifically sharp.

FDA officials point to this episode as just one indication of the extent to which FDA's regulatory decisions are rooted in cutting-edge science—and hence the need for FDA to maintain strong research labs. "We're confronted with molecules we only dreamed about 2 decades ago," says FDA Commissioner David Kessler. At CBER, the connection between science and regulation is direct: CBER scientists spend about half their time reviewing drug applications from industry and the other half at the bench, studying everything from the safety of gene-therapy vectors to the toxicity of neurotrophic growth factors. Says Noguchi: "Our scientists have to be at the same cutting edge as the drug applications that come in."

But FDA's large science budget—it spends $190 million on research, 20% of the agency's total budget—is attracting attention from critics in industry and Congress. The Biotechnology Industry Organization (BIO), for instance, has accused the FDA of engaging in "unfocused research activities." "FDA's research provides a useful function, but it must support the agency's regulatory mission," says Alan Goldhammer, director of technical affairs at BIO. More zealous critics concerned with cutting the federal budget deficit simply see no need for a regulatory agency to do research. Charges a former FDA employee who is now an industry official: "What you have is largely a bunch of bored bureaucrats who want to dabble in labs."

These complaints are likely to be echoed in reform proposals now being put together in Congress. BIO, for example, is working with House and Senate Republicans to draft language that would call for the creation of a scientific review board—composed of scientists from academia, industry, and federal agencies other than FDA—to oversee FDA's research activities. Congressional staffers say the board would be empowered to identify, and perhaps shut down, research projects that do not directly support FDA's regulatory mission. And FDA officials fear that Congress may take a more drastic step: making wholesale cuts in the agency's research budget. That, they argue, would be especially unfortunate, because the complaints now ring hollow: Reforms instituted in the past few years, they maintain, have focused research more tightly on FDA's regulatory mission than at any time in the agency's history.

Take the changes that have swept through the National Center for Toxicological Research (NCTR) in Jefferson, Arkansas, which spends $40 million a year on toxicology testing and exploring the mechanisms of drug toxicity. In 1991, a blue-ribbon panel chaired by former FDA Commissioner Charles Edwards criticized NCTR for having strayed too far from FDA's mission. "We were doing a lot of good stuff, but some of it had no immediate impact on regulatory decisions," says NCTR toxicologist William Allaben. In the wake of the Edwards report, Kessler issued a simple directive to the lab: NCTR scientists must show how their research is linked to FDA decisionmaking. "In every protocol, we have to justify how our research is relevant to FDA's mission," says NCTR neurotoxicologist Syed Ali. The transition to doing more FDA-relevant research has gone smoothly, insists Allaben. "Sure there were guys who questioned the long-term effect on their scientific careers, but the bottom line is that the refocusing initiative has gone remarkably well," he says.

The task of further strengthening the links between NCTR and FDA regulators fell to toxicologist Bernard Schwetz, whom Kessler hired in 1993 from the National Institute of Environmental Health Sciences to head the lab. This year, says Schwetz, about 25% of NCTR's budget is being spent on toxicology tests. In addition, says Schwetz, "we're getting away from doing research in rodents for the sake of rodents"—animal experiments that have no relevance to human health. For instance, NCTR researchers have just launched a collaboration with scientists at the Veterans Administration to study drug-induced DNA damage in cancer patients given chemotherapy. Finally, scientists at FDA's product centers now have more input into the kinds of testing NCTR does. "Regulators are sitting with us and helping us plan the protocols," says Allaben.

Pleased with Schwetz's efforts at NCTR, Kessler gave him an additional title last year—associate commissioner for science—with responsibilities to coordinate science activities across the agency. Schwetz plans to convene a panel of FDA scientists to conduct a broad review of agency science, from identifying holes in the research program to ferreting out redundant projects.

FDA officials hope that these changes will strengthen FDA's research—and help stave off major cuts. But with Congress poised to bring FDA research under scrutiny, CBER Director Kathryn Zoon, an immunologist, says it will be difficult to maintain morale. "With shrinking resources, it will be hard to keep people engaged in cutting-edge science," Zoon says. But necessary, says Schwetz: "Science underlies all the decisions we make."

–R.S.

have sprung up to exploit novel techniques ranging from gene splicing to rational drug design. In the late 1980s, industry began complaining that FDA was not keeping up with those changes. Approval times lagged and regulations proliferated.

Kessler's 1990 appointment by President George Bush raised hopes of change. The young and dogged regulator—one of only two top Bush appointees kept on by the Clinton Administration, the other being National Aeronautics and Space Administration chief Dan Goldin—promised to streamline FDA's procedures (*Science*, 12 April 1991, p. 200). But he also quickly made it clear that he would vigorously enforce the food and drug laws. Among his first major enforcement acts, for example, was to haul thousands of gallons of orange juice off the market for mislabeling—a move he has described as being a wake-up call to the food and drug industry.

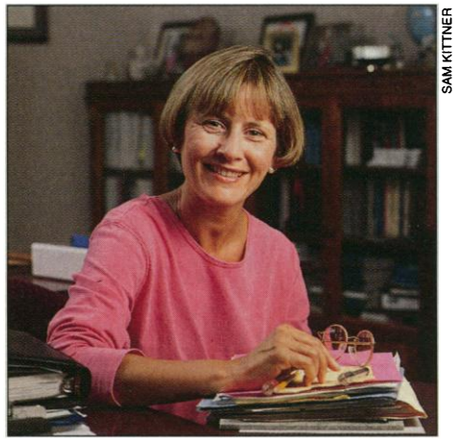
A lawyer, medical doctor, and former consultant to Senator Orrin Hatch (R–UT), Kessler "took an agency that was viewed as a paper tiger in the '80s and turned it into a tough enforcement agency in the '90s," says Vodra. But Kessler's promise to shorten the paper trail for industry never materialized, claims Carl Feldbaum, president of BIO: "There was a lot of jawboning on the issues. But little progress was made." And the combination of tough enforcement and Kessler's own confrontational style irritated companies and increased tensions, say both supporters and detractors.

So when Republicans gained control of Congress in January after campaigning in part against government intervention, the stage was set for a concerted effort to alter the way FDA does its job. This Congress is more attuned to industry complaints than to consumer concerns, say FDA officials. But critics insist that legislation is the only way to force changes at FDA. "Kings don't just give up their power," says Peter Hutt, a former FDA general counsel and a vocal agency critic who now works in a Washington law firm.

The $350 million maze

The hot-button issue for FDA critics like Hutt is the amount of time it takes to approve new products. This is a critical point for smaller companies funded by impatient investors who want a quick return. BIO estimates that it now costs at least $350 million to bring a single drug to market, a sum the organization says has increased over the past decade at an annual rate of more than 8% a year above inflation. Those costs are keeping valuable therapies away from patients, say Hutt and others. "We need an FDA that's not so busy screwing Americans' health," he says.

Kessler maintains, however, that FDA has made substantial progress in speeding up critical parts of the drug approval process. He points out, for example, that the average period between submission of a new drug application (NDA)—after a company has completed the required clinical trials—to final approval has been halved during his tenure. It dropped from 30 months to 20 months between 1992 and 1994 alone. Kessler credits this speedup in part to a 1992 law that allows FDA to charge a fee for reviewing NDAs. These so-called user fees are funneled into a pot that has enabled FDA to hire about 600 additional review staffers. "There is no question in anyone's mind that review times are coming down pretty dramatically," Kessler says.



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Conflict concerns. Biologics chief Kathryn Zoon says relying on outside reviewers could raise conflict-of-interest problems.

In addition to speeding up reviews, FDA last April reduced the amount of paperwork companies have to file when they make changes in the manufacturing process that do not "adversely affect the safety, purity, or potency of a product." And it followed up that reform in July by dropping a requirement that biotech companies must complete a pilot production plant before FDA will give them a green light to distribute an approved drug.

"The progress has been helpful," acknowledges Feldbaum. But, he adds, the changes have "been grudging on [FDA's] part." Kessler, however, defends his record in dismantling barriers for the fledgling industry. "We've streamlined the entire process," he says. "I just don't get it—I think we've delivered."

Industry groups argue, however, that although approval times are down, companies are spending an increasing amount of time and money completing a labyrinth of tests before they can even apply for approval to market a new drug—the NDA. BIO estimates that it now takes an average of 6 years of animal and clinical testing before a company files for an NDA, up from 4 years a decade ago. And it puts most of the blame on increasingly burdensome requirements for conducting clinical trials. According to BIO, depending on the nature of the trial, costs shot up 50% to 100% between 1989 and 1993.

FDA is requiring more patients in clinical trials and is demanding additional safety tests during the course of a trial, says Alan Goldhammer, director of technical affairs at BIO. "That's where the real problem is," he says. BIO also argues that FDA is swamped with investigational new drug (IND) applications—which are required for clinical testing—many of which are unnecessary. Last year, more than 80% of INDs were filed by individual scientists and academic health centers whose investigations, states a BIO concept paper on FDA reform, "rarely lead to commercial therapies" and whose consideration at FDA "delays approval activities by FDA reviewers."

BIO has its own prescription for reform: better communication between companies and the FDA during the IND process. That way, scientists on both sides can agree on a clinical trial design and stick with it—rather than have FDA dictate additional requirements during the course of a trial. BIO says Congress should "encourage FDA ... to work with sponsors so that one pivotal clinical trial can serve as the basis for approval of breakthrough drugs," eliminating the need for additional safety trials. In addition, BIO argues that FDA could move with more alacrity on company INDs if review of INDs from academics was farmed out to institutional review boards certified by the FDA or the National Institutes of Health (NIH) for this purpose.

Kessler acknowledges that the agency can improve how it interacts with industry during the IND phase of drug development. But he says that FDA reviewers must continue to be demanding to ensure that clinical trials are up to snuff. Kessler says it's up to the companies to commit the time and resources to designing clinical trials adequately so as to avoid delays at FDA. "The vast majority of that time is not in our control; it's on the company's clock," he says. More interactions between FDA and industry early in drug development are fine, Kessler says, but attempts by Congress to prescribe the nature of these interactions are unlikely to do any good. "I've not seen additional tools in legislation to speed up the review process," he says.

Decentralizing approval power

Although industry's chief goal is to speed up the process of getting a new drug to market, some of FDA's critics would like to go one step further: They are arguing that the agency should be forced to relinquish some of its monopoly over approving new drugs. Currently, the agency has advisory committees that review clinical trial data on potential drugs, but the final decisions are made entirely by FDA employees. This reliance on in-house staff is designed to minimize conflicts of interest, but university scientists like

Lasagna say the FDA could safely farm out many reviews. "The notion that only the FDA has the expertise is silly," he adds. Expanding the pool of expertise could improve both the quality and timeliness of product approvals, critics say.

Others prefer a more drastic approach. The drug industry could mimic the industry-funded Underwriters Laboratory, which sets standards and tests products in the electrical sector, says one congressional staffer. And the Progress and Freedom Foundation envisions organizations with an FDA stamp of approval scattered throughout the country—an arrangement similar to the British model. The FDA in this scheme could object to a drug approval, but a final decision would rest with an independent arbitrator.

FDA officials, on the other hand, see few advantages in shifting review activities outside the agency. "I haven't seen a plan that makes any sense," says Schultz. He and others rattle off a litany of obstacles to increased outside review. "Conflict of interest is a real problem," says Kathryn Zoon, director of FDA's Center for Biologics Evaluation and Research (CBER). She says it's already hard to find academics or even NIH scientists who are free of ties to industry to serve on advisory panels.

In addition, FDA officials say they would have a hard time ensuring the consistency of outside reviews. In rapidly developing fields, "you see a finding published in *Science*, and 2 days later it's on your desk as an IND," says Kenneth Seamon, CBER's associate director for research. "You really don't have time to generate an external network familiar with the regulatory issues to help evaluate the risks of a novel therapy," he says. "You can get reviews all over the place depending on who you send it out to," adds Zoon. "In my personal opinion, outside review isn't going to move things faster."

Kessler: A lightning rod

With the FDA's enemies massing for an assault, you might think the agency's chief would be avoiding further confrontations. But as always in his tenure, Kessler is not shying away from taking on powerful interests and controversial issues. Take his relentless investigation of the tobacco industry. For more than a year, Kessler has been conducting a broad review of whether FDA has the evidence and the authority to regulate nicotine as a drug. His efforts have put the agency in a bitter confrontation with the tobacco companies. Earlier this month President Clinton shied away from endorsing sweeping regulations on tobacco, but he did call for strict rules that would reduce the availability of cigarettes to minors. Kessler's aggressive stance on tobacco infuriates many Republicans and some Democrats in southern states, including Representative Bliley.

Kessler makes no apologies: "Add up the risks posed by everything else that we regulate, and look at the risk posed by tobacco, and then ask me about priorities," he says. But others say they are baffled by his penchant for antagonizing key lawmakers at such a delicate time for the agency. "He is a very complicated man," says Lasagna. "He tends to be confrontational. You'd think he'd be good at [working Congress]. He trained with Republicans, and you'd think he would have friends on both sides of the aisle. Instead, he has enemies."

To Kessler, that's just a sign of a job well done. He readily cites statistics that show that 70% to 80% of Americans support the current FDA. The criticism, he maintains, is coming from "people who want us off their back"—that is, the industries he regulates. "And the fact is, when you are a regulator, you have to say no. ... That's not going to make you friends. If you want to make friends, get a different job." But in the coming battle the commissioner may find that he will need all the friends he can get to keep his agency intact.

–Andrew Lawler and Richard Stone

GEOSCIENCES

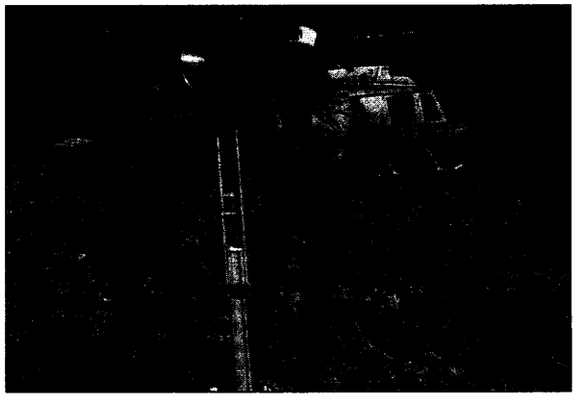
525 Laid Off As USGS Looks Ahead

Although Congress has promised to shrink the federal work force as part of its campaign to reduce the deficit, layoffs are still only a rumor at most agencies. But not at the U. S. Geological Survey (USGS). Last week the survey announced that 525 employees in its Geologic Division—including hundreds of scientists—would be out of a job as of 15 October. Ironically, the staff cuts came even though the division's budget appears to have weathered this year's flurry of budget cuts (*Science*, 11 August, p. 748). USGS officials say the layoffs are a belated response to years of stagnant funding and an attempt to spread research dollars across fewer activities.

The jobs lost, mostly in the Geologic Division's main offices in Reston, Virginia; Denver; and Menlo Park, California, include 345 permanent and 180 nonpermanent positions. About three fourths of those laid off were scientists and technical staff, with the remainder administrative and support personnel, says minerals specialist William Cannon, who coordinated the cuts. About 200 others will be demoted or moved to other positions. USGS employees had known for several weeks that job losses of this magnitude were coming (*Science*, 30 June, p. 1840), but researchers didn't know exactly where the ax would fall until the pink slips were handed out last week.

The layoffs pare the Geologic Division's staff from about 2200 to 1970. Scientists in the agency's two other divisions, Water Resources and National Mapping, have been spared for now. And there are winners and losers even within the Geologic Division's six major program areas. A reorganization of the division is aimed at making its research "reflect national needs and priorities," says David Russ, associate chief geologist of the division.

Russ says that minerals research—especially studies of rock and mineral formation—is being cut by about 40% because mineral resources are "less of a policy concern" in the aftermath of the Cold War. Also sharply cut were some areas of energy research, such as uranium and shale studies, which have fallen out of favor with Congress. Other programs will be refocused—marine studies, for example, will do less deep-water surveying and more environmental work near coastal areas. "You might actually be able to do more with fewer people if you've got the money to send people to the field," says seismologist Robert Hamilton.



USGS

Hard landing. USGS layoffs will free up funds to send mappers like this California team into the field.

Indeed, USGS officials say that savings from the layoffs and reorganization will be used to upgrade lab equipment and provide more direct support for field research, which has accounted for a dwindling share of USGS's budget. Having "geologists sitting in the office is really not the way to do science," says Patrick Leahy, head of the Geologic Division. Cannon adds that shifting funds from salaries into research support will permit the division to lift the fraction of its budget going into operations from its current level of between 5% and 10% to 20% next year, which officials say is the appropriate balance.