FAILED FDA REFORM

by Henry I. Miller

THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) in recent years often has touted its efforts to streamline requirements and procedures so that needed pharmaceuticals and other regulated products can be delivered to patients as quickly as possible. The agency has dismissed criticisms of its approval system as ill-founded or outdated. But its rhetoric does not withstand scrutiny.

In past years the FDA has introduced new requirements and policies that have increased the regulatory burden on drug companies without adequate consideration of how they hinder the delivery of new and innovative therapies. For example, the FDA has unilaterally and dramatically expanded the definition of what constitutes inappropriate "promotion" of a drug, unnecessarily increased reporting requirements for drugs' side effects, and intruded into cost-saving relationships among health care providers.

The drug development system in the United States has become the slowest and most expensive in the world. Increasingly, testing, production, and timely access to important new products have shifted from this country to European and other countries. Inasmuch as the FDA's efforts at self-reform have been unsuccessful, legislative intervention seems the only means to lower the costs and time required for drug development in the United States. However, Congress also has been unwilling to implement meaningful reform and, until it acts, many Americans will needlessly suffer or die waiting for federal officials to approve healing or lifesaving drugs, vaccines, and medical devices.

PROTECTOR, OR PERSECUTOR AND PROCRASTINATOR?

The Food and Drug Administration is arguably the nation's most ubiquitous regulatory agency, with regulatory authority over more than $1 trillion worth of consumer products annually. They range from tongue depressors and x-ray machines to drugs, vaccines, home pregnancy tests, and artificial sweeteners. The FDA's regulatory regimes are sometimes referred to as the world's "gold standard," meaning that the agency's standards are the most difficult to meet and implying that FDA-approved products are the world's safest.

But the FDA's regulatory zeal has a dark side. The agency has constantly sought new mandates and promulgated new requirements, regardless of the costs to patients and to regulated industries. According to the 1996-97 Annual Report of the Tufts University Center for the Study of Drug Development, since the 1960s the total time required for drug development—from synthesis in the laboratory to the patient's bedside—has almost doubled, from 8.1 years to 15.2 years. From 1990 to 1993 alone, according to estimates by a Boston Consulting Group analysis, as quoted by the Office of Technology Assessment in its 1993 report *Pharmaceutical R&D: Costs, Risks, and Rewards,* the average cost of bringing a single drug to market increased from $359 million to $500 million—in pretax 1990 dollars, the highest price tag in the world.

The effects of the FDA's regulations are pernicious. As a result of rising costs and lower returns on investments, American pharmaceutical companies have fewer resources available for research and development than they would otherwise. As a result, more drug development moves offshore; according to a Tufts study, 73 percent of drugs approved by the FDA during the 1987-93 period had already been approved abroad. Patients find increasingly that only by forming vocal interest groups—as individuals suffering from AIDS have done—can they force the FDA to expedite approval of medications to treat their afflictions.

FDA officials claim that past inefficiencies and excesses have been remedied, that review times are shrinking, and that critics are complaining about "the FDA of another era." They tout recent decreases in the time required for reviewing submissions for marketing approval. Yet they pointedly ignore more-than-offsetting increases in the overall time for drug development. For example, according to the Tufts University Center for the Study of Drug Development study, while the time required for the FDA's review of new drugs for marketing approval (the final phase of the multistep approval process) did decrease from 2.8 years to 1.8 years during the 1987-96 period, the overall mean time from synthesis of a new drug to marketing approval increased from an average of 14.1 years between 1980 and 1989 to 15.2 years between 1990 and 1996.

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In the past few years the FDA has proposed or implemented new rules and redefined part of the approval process in ways that will add further costs and time to the development of new drugs, with little or no additional protection of public health. Patients ultimately will bear the costs in terms of morbidity, mortality, and higher prices for pharmaceuticals.

REPORTING DRUG SIDE EFFECTS: THE RULES

In 1995 the FDA proposed a new rule, "Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products" (*Federal Register* 1995; 59) that would mandate new reporting requirements on the side effects of drugs in clinical tests. That regulation was the brainchild of then-FDA Commissioner David Kessler, who directed that it be prepared and published on the basis of a 1994 incident with fialuridine, or FIAU. That drug was at the time being tested at the National Institutes of Health (NIH) to treat chronic active hepatitis, and actually worsened liver failure in dozens of patients, causing several deaths and requiring liver transplants in others. It was difficult at first to determine that the drug was causing those problem because the side effects were so similar to usual progression of the illness.

ALL NEW DRUGS ARE PRESUMED GUILTY UNTIL CONCLUSIVELY PROVEN INNOCENT.

Under the new rule (which has not yet been made final) the FDA requires more frequent reporting of side effects and requires notification not only to the FDA but to research institutions' Institutional Review Boards, which are ill-equipped for such an avalanche of paperwork. The regulations reconfigure the burden of proof so that if a patient gets sick or sicker during any clinical trial, the new drug is assumed to be culpable until another cause can be ascertained; in other words, all new drugs are presumed guilty until conclusively proven innocent.

That approach ignores the fact that in many trials the medication being tested is not responsible for a patient's additional health problems, though that is often not readily provable. It also ignores two analyses of the FIAU incident: one by the NIH the other by the Institute of Medicine. Neither found any deficiency in the existing system for reporting side effects.

The proposed change in the reporting of side effects and a lower regulatory threshold for stopping a clinical trial will make the entire drug development process even more risk averse, slower, and more expensive. When published as a final rule, the regulation will send the cost of clinical trials off the charts.

The comments on the proposal to the official FDA docket from industry and academia are revealing. The Dupont-Merck Pharmaceutical Company in its submitted comments estimated that, under the proposed regulations, its reporting burden would double for each prospective drug in development. Amgen, Inc., in its comments on the rule, described the practical difficulties of estimating the expected incidences of death and serious adverse events that arise, not from the drug, but from underlying disease or concomitant medications. Consider, for example, that in a terminal cancer patient with multiple organ failure, an episode of lightheadedness, cardiac arrhythmia, or an abnormal laboratory finding could be due to the test drug, to another drug the patient is taking, or to the underlying disease itself.

Medical researchers at the Johns Hopkins University Center for Clinical Trials led by Dr. Curtis L. Meinert compared two clinical trials, one performed with reporting according to the old requirements and one under the new rules. Their conclusions, published in *Controlled Clinical Trials* (August 1996, vol. 17, pp. 273-284) were that the FDA's proposed changes would increase the cost per patient and the paperwork generated per patient to an extraordinary extent: on a per patient basis, the costs increase from $151 to $9407—a whopping 62-fold increase; and the paperwork increases from 135 to 8500 pages—63-fold! The researchers estimated that the hugely increased costs and complexity of clinical trials were not accompanied by commensurate advantages to patients.

FDA DRUG "PROMOTION" POLICIES

The FDA has the authority to regulate labeling and therapeutic claims for a drug. "Promotion" of an as-yet unapproved use of an approved drug is prohibited. The FDA has interpreted promotion to encompass any printed materials or advertisements, as well as a range of other activities. Companies have been barred from distributing to physicians peer-reviewed journal articles or textbook chapters that unequivocally support important new, but as yet unapproved, uses of certain products. Yet some 40 percent to 50 percent of all drugs are prescribed for such "off-label" uses, including 60 percent to 70 percent of drugs used to treat cancer and 90 percent of drugs used in pediatrics.

Those restrictions hinder the effective practice of medicine. Physicians' own opinions about the FDA's policies are revealing. An August 1995 survey of clinical oncologists conducted by the Competitive Enterprise Institute (CEI) found that nearly two-thirds of respondents believed the FDA has "hurt their ability to give the best possible care to a patient on at least one occasion," and over one in ten believed this has happened "frequently." Three-quarters of respondents "oppose FDA restrictions on off-label information," and 60 percent believe those restrictions make their job more difficult. Similar results were obtained in a subsequent CEI survey of cardiologists, in July 1996 published: half maintained that FDA regulations prevent them from using promising new drugs or medical devices, 71 percent felt that FDA's approval process had hurt their ability to give patients the best care, and 57 percent said that unnecessary delays in product approval by FDA actually cost lives. And 80 percent of the respondents to a CEI survey of neurologists and neurosurgeons, published in October 1998, said the FDA process hurt their ability to treat patients.

With the 1997 FDA Modernization Act (FDAMA), Congress made a half-hearted attempt to check regulators' excesses. Inexplicably, the details of the legislation were dic-

tated largely by FDA officials themselves, and by such Democratic members of Congress as Sen. Edward M. Kennedy (D-Mass.) and Rep. John Dingell (D-Mich.) and Rep. Henry Waxman (D-Calif.) who have been advocates of an intrusive, aggressive FDA. It should come as no surprise, then, that a scant two months after the passage of the FDAMA, the agency again was pushing the regulatory envelope. In January 1998, the FDA published a draft guidance document aimed at regulating "medical product promotion" among health care providers and professionals. Although its stated goal is to deter pharmaceutical manufacturers from promoting their own products through health care organizations and insurers, the FDA proposal could reduce industry competition, increase drug prices, and damage public health. Further, the draft plan could exert a chilling effect on the beneficial exchange of information among various segments of the health care industry. In any case, the plan duplicates oversight functions already performed by other government agencies.

The FDA's statutory authority allows it to regulate a manufacturer's product labeling and advertising, primarily to prevent false or misleading claims. But the new plan would extend the agency's regulatory authority to any "relationships" it deems promotional that occur between different members of the health care professions. Not only is this a giant step beyond the FDA's legal authority, but the wording of the proposal is so deliberately vague that it could effectively shut down vital communication among health care professionals and patients. For example, the FDA asserts that if any "subsidiary" of a drug manufacturer promotes a drug, the parent company bears full legal responsibility. But the agency says that "subsidiary" is "to be interpreted in its broadest sense to include any corporate relationship," no matter how remote, and that a company that has a relationship with "an independent contractor or agent becomes responsible criminally for the failure of the person to whom he has delegated the obligation to comply with the law." The manufacturer is responsible, even if it neither approved nor knew about the actions in question.

In theory, that wording could make the manufacturer share the legal "blame," were a pharmacist to give a patient a medical journal article that was circulated by a health care organization and that contained current and accurate information about an off-label use of a drug. While this might sound far-fetched, it must be remembered that the FDA already prohibits the distribution of textbooks and journal articles to health care professionals if they allude to off-label uses. (A federal district court recently found that those FDA actions violate constitutional guarantees of free commercial speech, but the agency is expected to appeal the decision. See below.) The FDA has even prohibited manufacturers from holding focus groups, before a drug's approval, to determine how to make their labeling and packaging more user-friendly for doctors and patients.

As in any other profession, individuals in the health care field talk with one another. But under the new FDA proposal, even the most basic health care communications between individuals in the industry could be labeled "promotional" and therefore prohibited by FDA censors. Health care organizations might well decide what information to distribute to patients not on the basis of its accuracy and usefulness, but according to their perceived "relationship" with manufacturers; conversely, manufacturers might make decisions about what information to distribute to health care providers on the basis of potential liability.

THE FDA'S MISSION IS, AND SHOULD BE LIMITED TO, THE ASSURANCE OF PRODUCTS' SAFETY AND EFFICACY.

The ambiguous yet imperious nature of the FDA proposal could stifle competition and drive up costs. Organizations that deliver health care depend on peer-reviewed clinical information about drugs' effectiveness to enhance the quality of health care and to lower costs. They also use their purchasing power to receive discounts from manufacturers, thus bringing competition to the market for medicines. Such organizations thus can hold down costs for their patients or pass along benefits to patients in the form of lower copayments. Under the draft proposal, sharing that kind of information or having such volume-based discount arrangements could constitute a "relationship" that could make drug manufacturers liable for any misconduct on the part of health care deliverers. That would likely create a chilling effect on such arrangements and could discourage or eliminate such cost-saving, competitive influences and ultimately increase health care costs.

The FDA proposal wanders into areas where other agencies already are responsible for consumer protection; the FDA cannot, therefore, claim to be filling a regulatory void. State attorneys general and the Federal Trade Commission, for example, set industry standards for disclosing manufacturer relationships and for assuring clinicians' independence and credibility. Clinical professionals are regulated by state boards of medicine and pharmacy. The Health Care Finance Administration regulates reimbursement, discounting, self-referral, kickbacks, fraud, and abuse under rules that bind all health care organizations. Those regulatory bodies are better suited to monitoring health care communications than is the FDA, whose mission is (and should be limited to) the assurance of products' safety and efficacy.

Vague directives like the draft FDA proposal allow wide governmental discretion about what is regulated and what is prohibited; such discretion is a very big stick that can be and is used on regulated industry. The proposal is an example of what economist Milton Friedman has called a government agency contravening the free market because it mistrusts freedom itself.

SMALL STEPS ON BIOLOGICALS

Various supposed FDA reforms that have been launched in the past several years, with great fanfare, have accomplished little. Often, they have simply codified or taken credit for changes

that already had evolved or been implemented. For example, in a grandly titled 6 April 1995, press release, "Reinventing Drug and Medical Device Regulation," the FDA announced a lengthy list of "reforms" that had minimal impact and that were, in any case, already well within the agency's practices. In another 1995 press release, the FDA announced that it would modernize and streamline oversight of a class of therapeutic products called "biological" drugs, or biologicals. Historically, those products—blood and blood products, vaccines, derivatives of natural substances for treating allergies, extracts of living cells, and most products of the new biotechnology—had been approached differently from other products. The reason is that the difficulty in producing biologicals meant that they were often rather impure compared to other drugs.

THE CLINTON ADMINISTRATION WAS TOUTING AS A MAJOR REFORM THE RECOGNITION OF WHAT WAS ALREADY FDA POLICY.

Biologicals also tend to be poorly characterized and inconsistent: one batch might contain 2 percent of the active substance and another batch might contain 4 percent, with varying amounts of other constituents. Those attributes do not imply that biologicals are dangerous or that they do more harm than good to patients; in fact, they include some of the most ubiquitous, useful, and safe pharmaceuticals, including childhood vaccines and material for allergy shots. Because of the difficulty of demonstrating that each batch meets specified standards of purity and potency, traditionally the FDA has granted marketing approval not only for the product itself, which had to be safe and effective, but also for the manufacturing establishment, certifying that there is adequate control and rigor in production. In addition, samples from every production batch had to be submitted for certification by the FDA.

Nonbiological drugs—for pain, ulcers, high blood pressure, and so forth—traditionally are smaller, simpler, chemically synthesized molecules that can be purified and characterized much more easily than biologicals. In contrast to biologicals, neither licensing of the manufacturing facility nor batch certification for those products was required.

Advances in technology have blurred the distinction between biological and other drugs. Many biologicals—particularly those made with the techniques of the new biotechnology such as recombinant DNA, or gene splicing—are now highly purified, well-characterized preparations that can be regulated the same as other drugs. Biologicals' manufacturing facilities continued to be certified, but in practice the inspections are not very different from those that are performed on the plants that make nonbiological drugs. The FDA's 1995 policy change enabled biologicals that are "well characterized biotechnology products" to be regulated as though they were nonbiological drugs. For that subset of biotechnology products, the requirements for licensing of the manufacturing facility and for batch certification were eliminated. Those were hardly dramatic changes from the status quo, especially in view of the fact that only about two dozen biotechnology-derived biologicals have been approved by the FDA during the past decade. Taking a cue from the FDA, in the 1997 FDA Modernization Act, section 123, Congress eliminated from the statute the requirement for biological drugs to obtain separate product and establishment licenses.

SURROGATE ENDPOINTS

Another example of the government putting public relations before public health came on 29 March 1996. The day after three FDA reform bills were introduced in the House of Representatives, President Clinton, Vice President Al Gore, Health and Human Services secretary Donna Shalala and then-FDA commissioner David Kessler announced that henceforth the FDA would permit the use of so-called surrogate endpoints "to speed up the entire process" of cancer-drug development. More specifically, the FDA asserted in a press release that "It is appropriate to utilize objective evidence of tumor shrinkage as a basis for approval, allowing additional evidence of increased survival and/or improved quality of life associated with that therapy to be demonstrated later."

Though the ultimate indicator of the clinical benefit of a drug may be unambiguously positive outcomes such as survival or complete disappearance of disease, these are often difficult and hugely expensive to demonstrate as the endpoint of a clinical trial. Therefore, physicians and others involved in clinical testing, including the FDA, have over a period of decades devised appropriate "surrogates" as measures of a disease's regression or prevention. For drugs that lower blood pressure or serum cholesterol, for example, the FDA no longer requires a demonstration that treatment actually increases survival or reduces the incidence of heart attacks and stroke: significant improvement of "the numbers"—that is, lowering of blood pressure or of cholesterol, or an improvement in the pattern of serum lipids (more "good" lipids)—is sufficient. If clinical trials of every new cholesterol-lowering agent and blood pressure drug still had to demonstrate improvement in the "ultimate endpoints" of increased survival or fewer heart attacks, the costs of developing those drugs would be dramatically and unnecessarily increased.

Surrogate endpoints in some form already had been used for decades before the Clinton-Gore-Shalala-Kessler "bombshell" announcement. More to the point, starting in 1991 as a result of reforms stimulated by President George Bush's Council on Competitiveness, the FDA had formally adopted, at least in theory, a policy of using "flexibility in the current statute to develop and adopt surrogate endpoints whenever possible to measure the efficacy of drugs used to treat life-threatening diseases." (See Council on Competitiveness Fact Sheet, "Improving the nation's drug approval process," November 1991.) In other words, the Clinton administration was touting as a major reform the recognition of what was already FDA policy.

FAILED LEGISLATIVE EFFORTS

Recognizing the need for genuine FDA reform, members of the 104th Congress crafted the landmark Drugs and Biological Products Reform Act of 1996, HR 3199. Introduced by a bipartisan group of a dozen members of Congress and eventually boasting more than 160 cosponsors, the bill sought to ameliorate in a number of ways the FDA's contribution to the expense and delays of drug testing and evaluation. It would have allowed the FDA in many cases to dispense with the requirement that manufacturers turn over voluminous raw data from clinical trials, often hundreds of thousands of pages long. The FDA would have been allowed to accept condensed, tabulated or summarized data that often are adequate for determining the safety and efficacy of products, with FDA officials having access to additional material if needed.

THE SHEER VOLUME OF THE LEGISLATION AND THE LAUNDRY LIST OF PROVISIONS OFFER THE IMPRESSION OF SUBSTANCE—WHICH WAS EXACTLY CONGRESS'S INTENTION.

The legislation would have established a new, more liberal approval standard for drugs intended to treat any "serious or life-threatening" condition. Like the current standard for AIDS drugs, the new standard would have allowed easier access by patients with other serious illnesses to a drug when there was "a reasonable likelihood that the drug will be effective in a significant number of patients and that the risk from the drug is no greater than the risk from the condition." That is a commonsense, humane principle. It would have extended to patients with diseases like stroke, multiple sclerosis, Alzheimer's disease, emphysema, crippling arthritis, and heart failure the benefits currently reserved for those with AIDS.

The bill would have reduced the FDA's censorship of scientific and medical information concerning off-label uses of drugs by permitting the legitimate dissemination of information via textbooks and articles from peer-reviewed journals. It also would have permitted retrospective evidence from clinical research to be used for approval of additional, off-label uses of drugs already approved for some uses. Normally, expensive and time-consuming new studies are required for every phase of tests for new uses, even when some data from the original tests are adequate. Such a reform would have cut down on both the time and the costs of securing FDA approval for additional uses of drugs.

Perhaps the legislation's most significant reform would have been to turn over part of the evaluation of drugs to nongovernmental entities; the bill would have introduced nongovernmental alternatives to some FDA oversight. Pharmaceutical manufacturers could have opted to have their products reviewed by nongovernmental organizations, which could be private- or public-sector entities (universities, for example), profit-making or nonprofit. Those organizations would be subject to FDA accreditation and auditing. Strict requirements, backed by civil and criminal sanctions, would have assured the confidentiality of data and the absence of conflicts of interest. The manufacturer still could have chosen to have the FDA perform the review, and in all cases the agency would retain the responsibility for final sign-off. The new mechanism closely resembles regulatory apparatuses already operating elsewhere. Medical device regulation in the European Union is currently performed solely by nongovernmental organizations accredited by national authorities.

Eliminating the FDA's regulatory "monopoly" has been recommended repeatedly by blue-ribbon expert groups convened to improve the drug-approval system at various times during the past quarter century. In 1973, the President's Science Advisory Committee concluded that it may "be worth adapting U.S. regulations so that not even a single important new entity introduced into selected foreign countries during the previous year fails to become available in the U.S." In 1976, the President's Biomedical Panel concluded that delays and costs that the FDA's protective systems impose on drug development constitute a "hazard to public health." But the FDA's policies and procedures were to become progressively more intrusive and expensive for drug manufacturers and patients alike. President Bush's Council on Competitiveness induced the FDA to announce various reforms in 1991, but the agency studied many of them, literally, to death, and turned its bureaucratic talents toward vitiating the others in a variety of ways.

LESS THAN SECOND BEST

Because of the Clinton administration's opposition to HR 3199 and the threat of a presidential veto, Congress abandoned that bill. The 105th Congress tried again. This time there was an important "carrot" that reformers could dangle in front of the Clinton administration to secure approval of a new bill. The authorization for the agency's critical "user fees"—an approximately $100 million tax paid annually by regulated industry to help the FDA expedite the approval of new medicines, and supplementing the congressional appropriation—was set to expire on 1 October 1997. Leaving aside the wisdom of this discriminatory tax on the pharmaceutical industry, the need for another five-year reauthorization provided a strong incentive for the Clinton administration to accept meaningful reforms.

However, the 1997 FDA Modernization Act, passed on 9 November and signed by President Clinton on 20 November was a profound disappointment. In spite of the lever that regulatory-reform-minded members of Congress possessed to move reluctant colleagues and administration officials, the legislation is the moral equivalent of the proverbial elephant laboring to bring forth a mouse. At best, it includes only minor reforms. To the uninitiated, the sheer volume of the legislation and the laundry list of provisions offer the impression of substance—which was exactly Congress's intention. It is instructive to observe that even the bill's most ardent advocates have not claimed that it will reduce the overall time or costs of drug development.

Section 903(b) of the law changes the FDA's mission,

adding the obligation for "promptly and efficiently reviewing clinical research" and making decisions "in a timely manner." But it is naive to think that this symbolism will have any impact on the agency's thirty-year-plus tradition of risk-aversion and foot-dragging. This section, as well as section 803(c)(3), requires the FDA to meet with foreign governments and to participate in efforts at international harmonization of regulation. However, the level of commitment to these efforts is reflected in the comment of a high-ranking European official, in response to this author's enquiry about the progress of negotiations with the FDA on European-United States reciprocal drug approvals, "It's like discussing the Thanksgiving menu with the turkeys." What many FDA officials lack in productivity and efficiency, they more than make up for in skills related to obstructionism and self-preservation.

Section 903(f)(2) of the legislation calls upon the FDA to develop a plan by the year 2000 for clearing the legendary backlog of products awaiting approval. With this provision, Congress has made itself a hostage to an endless series of demands for additional resources the agency will claim are essential for meeting the required goal.

Section 115(a) of the new law permits the FDA to approve a drug for marketing on the basis of a single clinical trial where previous statutory language referred to "trials," plural, but that pronouncement is largely symbolic. The FDA easily could have made a case for approval on the basis of a single, definitive trial under the previous language. But the point is moot: The average number of trials performed to support approval of a new drug is currently more than fifty! Permitting the FDA to do what it is disinclined to do in any case is unlikely to speed up the approval process.

Several sections of the new law codify policies that were already in place or make inconsequential changes by conferring on the FDA flexibility it already exercised; this is a strategy similar to that of the Clinton administration's "recycling" of extant policies, as discussed above. For example, Section 124 provides that a drug manufactured in a pilot or other small-scale facility can be used to establish safety and effectiveness for the purpose of approval, before scale-up to a full-scale manufacturing facility; this had already been permitted by the FDA.

Section 123 eliminates the requirement for separate product and establishment licenses for biological drugs (discussed above), a provision that is desirable but inconsequential, because the FDA had already eliminated most distinctions between biological and other drugs. These kinds of statutory changes add little or nothing to the status quo but attempt to convey the impression of a lengthy list of reforms.

Section 401 of the legislation ostensibly offers drug companies greater latitude in supplying scientifically sound information to doctors about drugs' off-label uses, a reform that was sorely needed. Yet unlike the provision in the failed 1996 legislation, this reform comes at a high price. It requires substantial additional paperwork to convince the FDA that formal applications for approval of the new uses are forthcoming. A manufacturer can disseminate information only if it has submitted to the FDA a supplemental application covering the new use or if the manufacturer certifies that it will soon submit such a supplement, or in the unlikely event that the FDA grants an exemption from the supplement requirement. In essence, the provision offers little more than a modest acceleration of approval of submitted or soon-to-be-submitted supplemental applications. Moreover, the FDA's discretion in these matters provides yet another "stick" for regulators to use on drug companies.

Far more relief on this issue came to drug manufacturers—and also to health care professionals and patients—in a 30 July 1998 court decision in *Washington Legal Foundation v. Friedman*, (94-1306, D.D.C.). In that case a federal judge struck down the FDA's prohibition of drug manufacturers' distributing peer-reviewed medical literature. On First Amendment grounds, the court found that while the FDA could properly block drug companies from distributing their own marketing materials to physicians if they claim nonFDA approved uses, it is an infringement of their commercial speech rights to prevent them from handing out journal articles, textbooks, and the like that describe new uses for a drug already approved for other purposes. The federal judiciary has moderated the FDA's regulatory scope where the Congress was unwilling to do so.

Section 114(a) does permit manufacturers to submit "health care economic information," such as data on a drug's cost-effectiveness, to hospitals and health-maintenance organizations. This could be a small help in holding down health care costs.

The bill also contains other minor improvements, such as loosened restrictions on health claims for food products and expanded use of third parties, including academic institutions, to review medical devices.

But amidst these small changes, some for the good, is one devious provision, Section 410, that actually increases the scope of FDA regulation. Specifically, it expands the agency's jurisdiction to activities pertaining to any potentially regulated products that occur completely within a single state. Before this change in the law, intrastate research or treatments generally were not subject to federal regulations. Now all such activities are now considered to be interstate commerce. For the first time, the FDA explicitly will have regulatory authority over small-scale research by an academic or practicing physician testing an innovative drug therapy within a single state.

WHAT IS NOT THERE

What is most disappointing about the legislation is what it fails to do. Many critical reforms were conspicuously absent. For example, all proposed clinical trials are currently reviewed by Institutional Review Boards (IRBs) at the hospitals where the studies will be performed, as well as by the FDA. Students of FDA regulation have argued that Phase 1 studies (small, early-stage trials that often provide data leading to the drug being abandoned) could be overseen only by the IRBs, as is done in the United Kingdom and elsewhere. This pivotal change would have reduced significantly the time and costs

involved in clinical trials, a particular advantage for smaller companies.

Perhaps the most striking deficiency in the law is its treatment of third-party review—the contracting out of reviews and/or approvals—which was all but ignored. Pilot programs undertaken by the FDA in the past, in which drug reviews were contracted out to private sector organizations, were generally judged to be successful. However, Section 210 of the new law commissions only a minuscule pilot program for third-party review of certain noninnovative medical devices.

The FDA's slow approval process is often contrasted with the greater efficiency of equivalent European agencies. An example is the FDA's pan-European counterpart, the European Agency for the Evaluation of Medicinal Products (EMEA), which ensures the safety of medicines in a more timely and less expensive fashion, while maintaining constructive relationships with drug manufacturers. Moreover, the EMEA's mean processing time for marketing applications received in 1997 was 207 days, while the FDA required approximately 460 days for the marketing approvals that were announced in 1997. The FDA reports data in this way intentionally to make its numbers look more favorable. In other words, reporting only approvals announced in 1997 tends to minimize the statistical effects of applications that were received in that year or even in earlier years but that languished unapproved for extended periods.

With such data in mind, many public health advocates have suggested binding reciprocity provisions that, for example, would limit FDA review of a new drug to a maximum of, say, sixty days after its approval in the United Kingdom or by the EMEA. The FDA would then have to show cause why the drug should not be marketed in the United States, or it would be approved automatically.

CONCLUSION

The failure of the 104th Congress to accomplish any FDA reform and the weak bill passed by the 105th means that the time and costs of drug development will continue to rise, fewer drugs will be developed, market competition will erode, and prices to patients will increase. Ultimately, patients will be the victims. To protect public health and stimulate pharmaceutical innovation in the United States, the incremental, minimal changes wrought by the 1997 FDA Modernization Act must be supplemented by meaningful reform. However, having produced what it considers to be a voluminous and significant revision of the Food, Drug and Cosmetic Act and Public Health Service Act—which achieved little—Congress still has a long way to go before it puts patients first.

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