Protection or Overprotection in Drug Regulation?

The Politics of Policy Analysis

David Seidman

If thalidomide cured leukemia, it would be on the market today," or so a Food and Drug Administration lawyer told me.[1] The claim is surely correct. But thalidomide is only a sedative, and an army of deformed babies is too high a price to pay for the bit of calm that thalidomide might produce.

The decision to approve or prohibit the marketing of a drug is often a difficult one, because no drug is perfectly safe if it is powerful enough to be useful. Aspirin, for example, "has been said or shown to interfere with platelet function, to cause allergic reactions in the sensitive, to induce exfoliation of renal epithelial cells, to initiate gastric and to exacerbate duodenal ulcer, and to aggravate liver disease under certain circumstances," and is known to cause gastric bleeding in normal use.[2] The decision to approve a drug turns on its possible risks and benefits to health and even life. Assessing the balance is difficult, because neither the risks nor the benefits can be known precisely, and in any case depend upon values which cannot easily be stated or quantified and which may not be consensual.

Since 1962, U.S. policy on this matter, roughly speaking, has been to allow marketing of only those pharmaceuticals demonstrated to be safe *and effective.* The way this policy is to be carried out by the Food and Drug Administration (FDA) is, of course, not fully specified by law: the FDA writes regulations to implement the law and has discretion within those regulations. Both the legislated policy and the way the FDA implements it have effects going well beyond the availability of any particular drug, because FDA decisions on marketing become part of the costs of developing new drugs.

Criticism of both the legislated policy and FDA's actions is common. There are, in broad outline, two schools of critical thought on drug regulation. One holds that drugs are too readily approved for marketing, the other that they are too readily rejected. There is, unfortunately, no obvious way to decide who is right, but several attempts have been made. This essay examines these attempts and their exceedingly chilly reception by the policy community. This is, then, a case study in the politics of policy evaluation.

The Regulatory Context

An understanding of the issues involved requires some familiarity with the nature of an unregulated market for pharmaceuticals and the nature of the regulatory structure.

An Unregulated Market for Pharmaceuticals. The ultimate consumer of pharmaceuticals, the patient, is not like the consumer in the classical model of the free market because, presumably incompetent himself to evaluate pharmaceuticals, he must leave the choice to

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the doctor. The patient-consumer is therefore not sovereign. Rather, it is the doctor's preferences, willingness to run risks, and information that govern drug selection.

As for the doctor, he makes the choices but does not bear the financial and other costs of taking the drugs. Being partially insulated from the consequences of his actions, he may not have the consumer's normal incentive to be well informed. Without conducting large controlled experiments, he will generally not learn greatly from experience, and the professional literature is too vast for anyone to master. Typically, the doctor relies heavily upon information provided by the drug manufacturer.

A pharmaceutical firm will provide doctors with vast quantities of information because sales depend upon it. But the firm has less incentive to provide information that is full and accurate because doctors and patients cannot independently check its reliability or adequacy, at least not in the short run. Word may eventually get around, but until it does, manufacturers operating in an unregulated market are generally free from the consequences of providing misleading information. Tort law, a potential spur to accurate information, is difficult to use against manufacturers of prescription drugs. Concern for reputation, another spur, also seems to be insufficient. Thus, manufacturers generally make more extensive promotional claims but provide less information about potential hazards when selling their drugs in the relatively free markets of Latin America than when selling in the United States where promotional information must meet FDA standards.[3]

A free market for prescription drugs is thus imperfect, and may even be perverse. Regulation seems required to correct the imperfections, particularly those related to information.

Regulation before 1962. The first food and drug act, that of 1906, regulated a drug market that was chaotic and dangerous. Three decades later, the Food, Drug, and Cosmetic Act of 1938 created something resembling the present regulatory structure. Under it, manufacturers had to file a New Drug Application (NDA) with the FDA presenting evidence that the drug was safe for use under certain specified conditions. Unless the FDA rejected the application within sixty days (and the grounds for rejection were limited), the NDA became "effective," and the drug could be marketed. (Actually, although the distinction is not often important, it was the entry of a "new drug" into interstate commerce which the NDA governed.)

In order that the drug could be tested before marketing, investigations by "qualified" investigators were exempt from these requirements. The tests—including those on human subjects—were, for all practical purposes, unsupervised by the FDA or anyone else.

The act spoke only of safety, but safety is closely linked to the effectiveness of a drug, so the FDA in principle took effectiveness into account in considering the NDA. FDA Commissioner Larrick explained the pre-1962 FDA approach in testimony given in 1964:

> If we had used the term "safety" in the dictionary definition, we would have taken nitroglycerin off the market, sulfanilamide off the market, and drugs of the value of insulin off the market. It was obvious to us as administrators that was not what Congress intended. So taking what we thought was the legislative history of this section into account, we then announced to the world . . . that in dealing with lifesaving drugs we would have to consider whether a drug was effective in considering safety.[4]

Attention to effectiveness was, however, limited: the FDA could not require evidence of effectiveness in an NDA.

The system allowed widespread use of a drug—for investigational purposes—with virtually no government controls, required some evidence that the drug was safe before it could be marketed, and almost totally ignored the drug after marketing approval was given. The consumer-patient therefore had some reasonable assurance that, at one point in their history, the drugs he bought had been shown, on the basis of some evidence, not to be strikingly unsafe. There was less (if any) assurance that the drugs were useful. And there was no assurance of safety or efficacy in the case of drugs which the consumer did not buy, but rather was given by a doctor conducting an informal bit of research with an "investigational" drug.

Thalidomide. This was the regulatory structure that existed when thalidomide was kept off the

market in the United States, thereby preventing here the sort of tragedy which occurred elsewhere. But the American experience with thalidomide was unsettling anyway. Disaster was prevented through what would appear to have been a combination of luck and the sort of dedication and courage which any system would be unwise to assume as typical. (FDA medical officer Dr. Frances O. Kelsey blocked the marketing of thalidomide on the grounds that it had been inadequately tested, for which she received a distinguished government service medal from President Kennedy.) Furthermore thalidomide had been widely distributed and used within the United States under the investigational exemption. Over 2.5 million "experimental" thalidomide tablets had been distributed to 1,200 physicians, about 20,000 patients had received thalidomide, and 624 were reported as pregnant. In all, there were ten deformed babies born to American women who had received thalidomide from domestic sources and taken it during the critical first three months of pregnancy.[5] Physicians were under no legal obligation to inform those patients who took the drug that it was experimental.

The thalidomide incident (along with other events) suggested at least four conclusions. First, the regulatory structure prior to 1962 allowed somewhat precipitous investigational use of drugs in humans: often it occurred before the potential benefits of tests on animals were exhausted. Second, investigational use was, at least in some cases, extremely casual. Third, the evidence upon which the FDA relied in considering NDAs was often weak, much of it amounting to testimonials (or "uncontrolled clinical trials") rather than careful studies. Fourth, the procedure for considering NDAs was not well-designed either to facilitate detailed consideration of the evidence by FDA medical officers or to allow the FDA to resist industry pressures for approval of drugs. The Kefauver-Harris drug amendments of 1962 were designed to take account of these points and others.

Regulation after 1962. Under the 1962 amendments, premarketing requirements and implementing regulations became considerably more elaborate than they had been before. The sequence is now roughly as follows.

A new substance is invented (or a new use found for an old one). Various studies of safety and efficacy are carried out in the laboratory, without the use of human subjects. Then, in order to receive permission for human testing (actually permission to introduce the drug into interstate commerce for the purpose of human tests), the manufacturer must file with the FDA a Notice of Claimed Exemption for a New Drug (IND). This document, which describes the testing already done and sets out a detailed plan for subsequent testing, is a crucial addition to the regulatory structure. The proposed tests must be "adequate" and are subject to elaborate rules, including one requiring consent of the subjects. Once the IND receives FDA approval and becomes effective, the tests which will later provide the basis for the NDA may begin.

Following testing in the IND phase, the manufacturer submits the NDA. Another crucial difference between the old and the new system is found here: the tests must not merely demonstrate that the drug is safe, but also provide "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested . . .," where " 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. . . ." [6] This can be interpreted as a requirement that experimentation be conducted according to the highest standards of design and analysis. (Achieving this standard is difficult. Indeed, a statistical consultant to the FDA told me that if the highest standards were applied, none of the tests that he examines would be passed. It is notoriously difficult to carry out a perfect experiment outside the laboratory.)

In principle, only when safety and efficacy have been established according to these rigorous standards is the NDA approved and the drug released for marketing.[7] Even if the standards are applied with something less than full rigor, the cost (in both time and money) of developing a new drug and bringing it to market can be very high:

The impact of these requirements on a

drug maker was considerable. For example, a Parke-Davis official reported that when the company first marketed a particular epinephrine preparation in 1938, all it had to submit was a 27-page report concerned primarily with safety. In 1948, when it introduced a new expectorant, only a 73-page report was required. Another new drug marketed in 1958 needed a 430-page submission. But in 1962, when Parke-Davis requested FDA approval of its contraceptive Norlestrin, it had to present a report amounting to 12,370 pages. And in 1968, when approval was requested for its new anesthetic Ketamine, the required documents totaled slightly more than 72,000 pages in 167 volumes.[8]

It is, in large measure, these costs which raise the question of protection and overprotection.

Protection or Overprotection: The Dilemma of Regulation

The present regulatory structure for new drugs is designed to prevent physical harm by keeping "unsafe" drugs off the market. It is also designed to prevent the physical harm which may result from taking an ineffective drug—a harm which may occur simply because an effective drug, if available, would have cured the disease—and the economic harm of spending money on drugs which do no good. But these worthy aims cannot be achieved without some costs. The cost of bringing a drug to market has been substantially increased by the new testing requirements. Either manufacturers absorb this new cost, which means lower profits, or part or all of the cost is recovered through the market, which means higher prices. In some cases, for example, that of the drug treating a rare disease, these costs may be unrecoverable. If the cost of developing new drugs has increased, standard economic theory would suggest that there is, in consequence, less development.

There are also costs in time. The requirement of more extensive testing, along with the resulting need for more consideration by the FDA, must delay the movement of new drugs to the market. This is not surprising: many who supported the 1962 amendments argued that drugs were being brought onto the market entirely too quickly. However, suppose a safe and effective new drug is developed. The period during which it is being tested is a period in which its therapeutic benefits are not generally available. As an American Medical Association spokesman put it, "it is entirely possible that more lives could be lost by keeping a valuable drug off the market during extensive clinical trials than would be saved by gaining a precise knowledge of the exact type and incidence of all side effects." [9]

One final potential cost should be mentioned. Under the present regulatory structure, it is almost always the case that a drug is either not permitted on the market or is permitted on the market with almost no controls over its use by doctors. We enforce, so to speak, a simple all or none choice.[10] But the pattern of a drug's effects is not that simple. A drug may help some individuals while injuring others. The doctor, exercising care and judgment (as he sometimes does not), may be able to determine that a dangerous drug is in fact not so dangerous to his particular patient. Thus an absolute ban against a generally unsafe drug may deprive individual patients of important therapeutic benefits. As Wardell and Lasagna put it, "this type of risk-benefit decision should ultimately be made by single physicians for individual patients, rather than by a regulatory agency for society as a whole." [11] Even if this recommendation is not accepted, it is clear that making decisions for society as a whole does not necessarily maximize the expected benefit for particular individuals.

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The present structure for regulating the safety and efficacy of new drugs entails, then, certain costs in precisely those areas where we seek benefits through regulation—that is, in terms of the well-being of the patient. The more

exacting the requirements of regulation, the higher these costs are likely to be. An absolute standard of safety would prevent all drugs from being marketed. On the other hand, a permissive standard that amounted to allowing anything and everything on the market might recreate the conditions that led to regulation in the first place. The ideal is presumably somewhere between the extremes of no drugs and no regulation, at a point where the benefits of regulation in terms of consumer protection still outweigh the costs.

But where is that point? This question has stirred increasingly lively debate ever since the implementation of the 1962 amendments—a fact which is not surprising. Therapeutic accidents are dramatic. The amendments have profoundly altered the operating conditions of a major industry, and they impinge upon the status of doctors as well. Moreover, they are vigorously supported by consumer groups. Finally, the recent revival—on the campus and in policy circles—of interest in the nature and consequences of government regulation in general has also fed the debate.

Let us look at four different approaches taken in the debate on evaluation of drug regulation and then consider how officials within the policy community reacted to the approaches taken outside that community.

Four Alternative Approaches

The Economist. As I described the problem above, evaluation of the 1962 amendments is a relatively straightforward question of costs and benefits. Chicago school economist Sam Peltzman has produced such an evaluation.[12] It is a highly technical work of empirical analysis, relying upon both the economic theory of consumer surplus and data analysis linked to a long chain of assumptions. I attempt here only a very crude sketch.

Consider efficacy first. Peltzman notes that the amendments appear to assume that, before 1962, consumers (doctors) were making excessive purchases of new drugs—that is, their demand curves were "too high"—because they were acting upon exaggerated claims of efficacy. If the assumption were valid, demand would have fallen over time as consumers learned that the claims were exaggerated. Using data on market shares and prices for new and old drugs within therapeutic categories, Peltzman estimates pre-1962 demand curves for new drugs shortly after introduction and four years later. He finds little difference, and therefore concludes that there was in fact little waste as a result of ineffective drugs. Thus the potential gain to consumers that the amendments could have produced was small. The same analysis for the post-1962 period produces similar results—which implies the same conclusion.

This conclusion of small benefits implies that the initial demand for new drugs in the pre-1962 period was close to the "true demand." Peltzman then compares pre- and post-1962 initial demand for new drugs and finds that the new demand curve is lower. He attributes the decline to the reduction in information provided to the consumer, a reduction that has occurred because the 1962 amendments severely restrict the claims which manufacturers may make. Consumers, it is implied, would demand more of these new drugs if the 1962 amendments allowed more information. Since additional benefits to consumers would be generated through the additional demand, the effect of the amendments is a loss in consumer welfare. (Peltzman's analysis uses the more technical term "consumer surplus.")

Consumers also lose, Peltzman argues, for two additional reasons. First, the amendments retard innovation in drugs so that some drugs which would appear on the market were it not for the amendments do not appear. Consumers would benefit from these as well. To establish that a decline in innovation has in fact occurred, Peltzman analyzes the annual number of new chemical entities (a smaller category than new drugs) introduced, and con-

In sum, Peltzman finds [that the 1962 amendments have produced] both benefits and costs to the consumer. The benefit from decreased spending on ineffective drugs is estimated to be roughly $100 million annually, while the costs from a reduced flow of both drugs and information are roughly $300-$400 million . . . and those from decreased competition are roughly $50 million. . . .

cludes that there has in fact been a substantial decline attributable to the amendments. Second, the amendments lead to higher prices for existing drugs, because the higher costs to new firms (or new drugs) of entering the market reduce competition.

In sum, Peltzman finds both benefits and costs to the consumer. The benefit from decreased spending on ineffective drugs is estimated to be roughly $100 million annually, while the costs from a reduced flow of both drugs and information are roughly $300–$400 million annually and those from decreased competition are roughly $50 million annually. Overall, there is a substantial net loss to the consumer.

The question of safety is more difficult to address, but Peltzman bravely makes the attempt. His strategy is to compare the cost of an occasional thalidomide tragedy with the costs of delay in the introduction of major therapeutic advances. The analysis is necessarily highly speculative, because no one knows how many major therapeutic disasters there would be with or without the amendments, what major therapeutic advances are or would be likely, how much they would be delayed, or how to put dollar values on death and disease. Peltzman thinks the safest conclusion is that the amendments have neither produced significant safety benefits so far, nor foreclosed or delayed extraordinary therapeutic advance. On the other hand, he suggests that the procedures required by the amendments go too far in avoiding risk, that we would probably be better off if we accepted a higher likelihood of thalidomide tragedies in return for speedier introduction of major therapeutic advances. Once again, the 1962 amendments are seen as providing a net loss to society.

In the discussion that follows, two points should be kept in mind. First, Peltzman focuses entirely upon results and ignores the process through which the FDA reaches its decisions. Second, he uses aggregate data almost entirely. He does not, except in the tentative discussions of safety, point to any single drug as exemplifying his points. He has chosen to avoid pharmacological issues, no doubt wisely—for he is an economist, not a pharmacologist.

The Pharmacologist. A second major line of criticism of the 1962 amendments concentrates on particular drugs. This approach is most closely associated with the name of William M. Wardell, professor of pharmacology, toxicology, and medicine at the University of Rochester.[13] Wardell's strategy is to compare the availability of drugs in the United States and in Great Britain in the post-1962 period. His assumption is that the patterns of regulation in the two countries were far more similar before the 1962 amendments than after.

Taking the 1962–71 decade, Wardell tabulates drugs introduced according to whether they were exclusively available in the United States, exclusively available in Great Britain, or available in both. He concludes that at least in numerical terms, the United States lagged considerably behind Britain. This, of course, may be good or bad for the United States, depending upon the value of the drugs foregone.

[Wardell concludes:] "In view of the clear benefits demonstrable from some of the drugs introduced into Britain, it appears that the United States has, on balance, lost more than it has gained from adopting a more conservative approach than did Britain in the post-thalidomide era."

Wardell approaches this problem of value in three ways. First, he examines the medical evidence on the uses, effectiveness, and safety of most of these drugs, generally concluding that they should have been available in the United States. Second, he surveys British and U.S. doctors and discovers that British doctors consider these drugs important, while U.S. doctors are generally unaware of them. In those cases where the U.S. doctors are aware of the drugs or of unapproved uses of available drugs, they generally think that the drugs should be available or the uses approved. Finally, he attempts an analysis of the safety question that is similar to Peltzman's except that it takes into account the impact of particular drugs actually available in Britain. He concludes that "it is difficult to argue that the United States has escaped an inordinate amount of new-drug toxicity by its conservative approach," and "it is relatively easy to show that Britain has gained by having effec-

tive drugs available sooner." Furthermore, the costs to Britain of higher levels of adverse drug reactions have been small. "In view of the clear benefits demonstrable from some of the drugs introduced into Britain, it appears that the United States has, on balance, lost more than it has gained from adopting a more conservative approach than did Britain in the post-thalidomide era." [14]

Whereas Peltzman concludes that the 1962 amendments ought to be repealed, Wardell's recommendation is rather more complex. He would keep a regulatory structure, but he would rely less than we do today upon the all-or-none marketing decision and more upon release subject to postmarketing surveillance and he would institute new controls (or at least influences) upon the actual use of the drugs by doctors.

While Wardell speaks to the mechanism of regulation, his analysis is primarily in terms of results, not of the process through which they are achieved. In this it is similar to Peltzman's. It parts company with Peltzman in that it does not avoid pharmacological issues and does not provide an overall measure of the impact of the 1962 amendments, as Peltzman's measure of consumer surplus does.

The Politician. Evaluation of results is one way to judge the impact of regulation. Another way, generally less explicit, is to evaluate the specific regulatory process.

A process approach commonly found on Capitol Hill makes use of the political science model of interest-group conflict or pressures. (Model as used here means a simplified representation, or image, of reality, one which focuses on central elements and strips away nonessential detail. This simplification facilitates coherent analysis.) In this model, FDA decisions are seen as heavily influenced by drug industry pressures, by constant contact between regulators and regulated in which the regulated seek to have their drugs approved. This perspective is nicely captured by the following exchange between Senator Edward Kennedy and Ralph Nader:

> Senator KENNEDY. . . . Commissioner Schmidt of the FDA has put the question . . . that the agency is caught between the devil and the deep blue sea. On the one hand [there are] the pressures of the various drug industries, and on the other hand the harassment by active consumer groups. . . . Is [this] a fair description of the dilemma?
>
> Mr. NADER. Not at all.
>
> Senator KENNEDY. Are the two forces equal?
>
> Mr. NADER. They are basically magnified 1,000 times greater on the part of industry.[15]

This model has led many to conclude that the 1962 amendments do not provide sufficient protection for the public. And, indeed, some analyses of results appear to support this view and validate the model. It is possible, for example, to take almost any FDA decision approving a drug for marketing and demonstrate both that the evidence upon which the decision was based does not meet the rigorous standards supposedly required and that injury or death will result in at least some instances from use of the released drug. If the benefits resulting from the decision are ignored, any FDA drug approval will therefore appear to be unwise. And it is easy to ignore the benefits, because they are rarely so colorful or identifiable as the injuries that may be directly traced to the drug.

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Public display of these disasters has become a major congressional activity. As FDA Commissioner Schmidt has said, "The occasions on which hearings have been held to criticize approval of a new drug have been so frequent in the past ten years that we have not even attempted to count them." [16] The hearings serve two purposes, one within the context of the model and one outside it: they provide a counterweight to industry pressures, and they serve the publicity needs of congressmen. For both purposes, press coverage is essential. As one congressional staffer deeply

involved in drug hearings told me, there is "no sense in having hearings unless you are going to get coverage." Since the hearings usually deal with dramatic subjects, that coverage is generally forthcoming (perhaps particularly in Washington, where Morton Mintz, himself a leading exponent of the interest-group or pressure model of FDA decisions, covers them for the *Washington Post*).

There is a variant of the pressure model which leads in a very different direction. It sees the balance of pressure as resulting in overprotection. Central to this view are precisely these "counterbalancing" congressional hearings, which teach bureaucrats that procrastination in approving new drugs is the route to salvation. As FDA Commissioner Schmidt has said, reflecting a view shared by industry:

> In all our history, we are unable to find one instance where a Congressional hearing investigated the failure of FDA to approve a new drug. . . . [T]he message conveyed by this situation could not be clearer. . . . Until perspective is brought to the legislative oversight function, the pressure from Congress for FDA to disapprove new drugs will continue to be felt, and could be a major factor in health care in this country.[17]

The pressure model, then, leads in two directions and implies two different answers to the evaluation problem.

The FDA Official. Another process approach to assessing a regulatory system holds that what is important is the procedure through which decisions are made: procedure determines substance. The approaches discussed above seem most congenial to the economist, the doctor, and the politician. This one seems peculiarly lawyerly, though it is shared by non-lawyers at FDA. The director of FDA's Bureau of Drugs has argued that to "be credible, regulatory decisions must not only be scientifically sound and legally correct. They must be made for the right reasons and result from a valid, open decision-making process administered by persons of integrity." [18]

In essence, the FDA's decision is a judgment of costs (or risks) and benefits. The problem, according to one official, is that cost-benefit analysis, though proper in principle, cannot be carried out because neither costs nor benefits can be quantified. Consequently, the only thing to do is to rely on proper procedures and a well-designed process. In recent years, the FDA has attempted to structure the process so that "a lot of reasonable people have input"—which has meant, in practice, the multiplication of advisory committees through which the best available judgment can be brought to bear on regulatory decisions. The result may be good decisions within the statutory framework. But if that framework is faulty, as Peltzman and Wardell suggest, the FDA's reliance on advisory committees does not meet the problem and the major questions of regulatory policy remain unanswered. It should be kept in mind, however, that in our political system, the place where these questions should be decided is the Congress and not at the agency level.

The FDA's reliance upon outside advice can also be explained as a means of diffusing responsibility for decisions. One FDA official has said as much: "the responsibility that is imposed on us by law is too heavy for a government agency to bear alone. When we speak of outside advice . . . what we are actually seeking is a means of widening the base of decision-making, and thus, broadening responsibility." [19] Even so, the view from the evaluation standpoint is that procedure determines substance.

Reactions and Interactions

As we have seen, the critiques that Peltzman and Wardell leveled at the status quo in drug regulation clashed head on with the perspectives of major policy officials within Congress and the FDA. A review of the clash provides useful insights on the impact of policy evaluation.

Reactions to Peltzman: The Nelson Hearings. The first major public response to Peltzman and the drug-lag theorists (other than Wardell, whose work had not yet been published) came in the form of five days of hearings held in February and March 1973 before Senator Gaylord Nelson's Subcommittee on Monopoly of the Senate's Select Committee on Small Business. This subcommittee had long been interested in pharmaceutical regulation, and its

staff explicitly saw the hearings as a chance to refute criticism of the 1962 amendments, particularly that of Milton Friedman (who had publicized Peltzman's findings in a *Newsweek* column). In the view of staff members, Chicago-school economics is a closed deductive system at odds with the scientific method, so that Peltzman's findings were both without value and "dangerous." Senator Nelson's opening statement makes clear the purpose of the hearings: "Since these are serious charges, the subcommittee would be happy to have Dr. Dripps [who had charged the FDA with creating a 'drug lag'], Mr. Peltzman, and Mr. Friedman come to document them or withdraw them." [20] Nelson clearly preferred the second alternative.

The major burden of discrediting the "charges" fell to the FDA itself, which provided the first witnesses. The FDA's defense of American drug regulation had five major points.

(1) Innovation has not declined as a result of post-1962 practices. The FDA noted that the decline began before 1962. (Peltzman had realized this. He modeled innovation as a response to growth in the demand for drugs and showed that the relationship changed with the amendments. The FDA did not comment on this.) Then the FDA argued that Peltzman (and others) were looking at the wrong data: "The relevant question is not now and never has been how many new drugs are marketed each year, but rather how many significant, useful and unique therapeutic entities are developed. . . . [T]he rate of development and marketing of truly important, significant, and unique therapeutic entities in this country has remained relatively stable for the past 22 years. . . ." [21] (Responding to this some time later, Peltzman pointed to the highly subjective character of the criteria and noted that "an unpublished version of the same FDA listing" shows a statistically significant shift.) [22]

(2) In any case, if there is a drug lag, it comes about because the 1962 amendments require decent testing of drugs rather than "subjective impression"; the alternatives to controlled clinical trials are not as scientifically reliable. The fault, if there is one, does not lie with the FDA. (While Peltzman had never suggested it did, some of the drug-lag theorists had.)

(3) In any case, comparison with other countries does not show that the United States has been hurt by the amendments. An exchange between Senator Nelson and Dr. Henry Simmons, then director of FDA's Bureau of Drugs, illustrates the argument:

> Senator NELSON. Are you aware of any significant drug entity marketed in any foreign country that is not available here and for which there is no viable alternative available here?
>
> Dr. SIMMONS. . . . I do not know of such a drug and the key phrase there, Mr. Chairman, . . . is known to be safe and effective.[23]
>
> . . . In our judgment, there is no condition amenable to drug therapy that cannot be treated as safely and effectively in this country as any place in the world. The American public is not deprived of significant therapeutic drugs whose safety and effectiveness have been adequately substantiated.[24]

The key phrase is indeed "known to be safe and effective," for it comes close to reducing the FDA's position to a tautology. In order for the FDA to consider a drug as "known to be safe and effective," it must consider the evidence of safety and effectiveness to be sufficient to justify approval of the drug for the U.S. market. (In theory the FDA could be aware of such evidence even though no NDA had been submitted, but this is a rare situation.) The more important question is whether drugs are available in other countries which ought to be on the U.S. market even though they are not, by the FDA's standards, "known to be safe and effective."

"Viable alternative" is also a key phrase. At the time of the hearings two of the drugs marketed in Great Britain but not in the United States were practolol and oxprenolol, both "beta-blockers," a type of cardiovascular drug. An alternative to these drugs is propranolol, another beta-blocker which was available in the United States. Is propranolol a "viable alternative," as Senator Nelson and the FDA suggested? Perhaps, but "both practolol and oxprenolol have less cardiac and bronchial side effects than propranolol. They can therefore be used in some of these patients with asthma or heart failure who do not tolerate propranolol and for whom in the United States

propranolol is specifically contraindicated."[25] Some patients might be better served by the unavailable drugs than by the available ones.

(4) The attempt to measure the overall cost of tighter safety regulations is simply unacceptable: "The difficulty we have with Peltzman's analysis is that we do not know how to put a dollar value on a human life. . . . I do not know what dollar value to put on a child born without arms or legs. . . . That is why it is so difficult to argue with economists. . . ."[26] One could, of course, avoid using dollar values and balance the physical harm from the use of drugs against the physical harm that results from delay and failure to develop drugs. But since the FDA denied that regulation had kept any valuable drug off the U.S. market, it saw no point to this accounting scheme either.

(5) In spite of the preceding argument, the FDA ventured a cost-benefit conclusion: "The allegation has been made that the cost to our society to prevent a thalidomide-type tragedy far exceeds the benefits of a regulatory system developed to prevent such a tragedy. We disagree. We believe that benefits which accrue to society because of our regulatory system are worth the cost and far outweigh any risks."[27] But the FDA did not attempt to justify this conclusion by actually measuring the costs and benefits.

The FDA, in short, used the hearings to enter a sweeping defense of both the regulatory structure and the agency's practices, paying scant attention to the details of Peltzman's analysis and not much more to questions of pharmacology (since the then-existing statements of the drug-lag argument did not themselves present much pharmacological argument). If Peltzman's critique raised important questions, they were left unresolved at the conclusion of the FDA testimony.

Peltzman's critique got more attention on the final day of the hearings. Two economists raised some technical questions about his analysis, but the main event was the rather hostile interrogation of Peltzman by Senator Nelson and the subcommittee staff. Two points were made time and time again. First, noting that Peltzman's analysis depends upon estimates of market demand for various drugs, questioners contended that marketplace tests were inappropriate: what counts, they insisted, is expert judgment. One exchange captures much of the flavor of the dispute:

> Senator NELSON. Well, do I understand correctly, what you are saying is that the marketplace demand determines the scientific value of a product?
>
> Mr. PELTZMAN. No, but turn that around, Senator. If the drug has scientific merit, if it is truly a significant advance as some of these statements say, somebody ought to be buying it. They ought to be buying it more than the average drug.[28]

Senator Nelson then cited one drug which, according to most experts, is prescribed frequently when it should hardly be used at all, and he implied that the therapeutic choices of the typical doctor should not be taken as indicating the worth of drugs.

This view of the average quality of prescribing decisions in the United States may well be central to the position of those who support the 1962 amendments. If doctors generally prescribe poorly, the appropriate governmental response might be to approve drugs with great hesitancy, not because the drugs are unsafe or ineffective when used properly, but rather because they are likely to be used improperly. As one congressional staff assistant told me, "Putting a new drug on the market is putting another weapon in their hands, another killer drug in the hands of doctors who will misuse it." This is a peculiar defense of the 1962 amendments and the FDA, for it implies that the need is less to control drugs and drug companies than to control the practice of medicine—which the present regulatory structure is not well designed to do.

The other central point in Peltzman's exchange with the subcommittee was Peltzman's failure to list specific drugs available in other countries but not in the United States. To no avail Peltzman pointed out, first, that he was not a pharmacologist and, second, that his analysis did not require such a list because it depended as much upon drugs never developed because of the amendments as upon drugs available abroad but not here. Though he mentioned practolol and oxprenolol and cited Wardell's unpublished work, he was repeatedly attacked:

> Senator NELSON. I say to you name one, just one significant drug entity [available

in Great Britain but not in the United States].

Mr. PELTZMAN. Now, Senator, you know I am not going to do that. I told you—

Senator NELSON. Well, then you have no case at all, do you?

. . . So what I am saying is that your whole case just collapses unless you can prove that we are being deprived of valuable drugs. And if we are not being deprived of valuable drugs, I must say with all due respect, your study is totally useless.[29]

The Nelson hearings, then, can be seen as a hard-line defense of the FDA and of a policy that significant congressional actors had embraced. Serious criticisms of the agency and its policy were not so much refuted as dismissed out of hand.

Reactions to Wardell. Wardell added something new to the debate, an answer to the pharmacological and therapeutic questions which had been used in the subcommittee's attempt to discredit Peltzman. Peltzman could be dismissed as irrelevant because his intellectual framework was foreign to the policy community (as one high FDA official said, "an economic analysis is kind of ridiculous"). His and others' previous drug-lag arguments lacked detailed specifications. However, Wardell provided evidence within a framework the FDA could accept (thus, the same high FDA official called Wardell's work "important"). There is reason to think that arguments of the kind Wardell advanced and facts such as those he presented have had an impact at the FDA.

While the FDA's decision-making process tries to involve many individuals in decisions on new drugs, there are points in the process where single individuals can block approvals. According to several members of the FDA staff, there had been one individual with such power over cardiovascular drugs, a person who was suspicious of anything he was told by the drug companies and who believed that in general there were already enough drugs on the market. ("Both are sound attitudes, but he carried them to extremes.") As a result, between 1968 and 1972, no new cardiovascular drugs were approved. Then FDA management became convinced that there was in fact a lag, at least in cardiovascular drugs. Begining in 1970 it took steps to remove what it saw as bottlenecks in the drug approval process. In September 1974, Wardell testified before two subcommittees chaired by Senator Kennedy that the situation had improved: "I have been critical of the FDA in the past but I must acknowledge that in the last 2½ years the FDA has improved markedly. Large anachronisms still remain, which I pointed out 2 or 3 years ago. But I have found they are decreasing in most areas and in some cases have vanished. . . ." [30]

. . . Growing dissatisfaction with the results of the new drug approval process led the FDA to recognize it had a problem. . . . In response, it improved the process and continued to support the basic outlines of the policy. Why the policy itself is to be supported remains obscure.

Dr. Richard Crout, director of the FDA's Bureau of Drugs, appeared with Wardell and retracted previous FDA statements on the drug lag. Senator Kennedy reminded the witnesses that an FDA official had told the Nelson subcommittee that "there is no condition amenable to drug therapy which cannot be treated as effectively in the United States as anywhere in the world and that the American public is not being deprived of safe and efficacious drugs." Dr. Crout replied that "we would modify that statement today. . . ." He explained that in the list of drugs available elsewhere but not in the United States, "you can pick out drugs . . . that we recognize are potential gains from the standpoint of somewhat improved effectiveness, improved safety and convenience gains." He later pointed directly to the cause of the drug lag: "it is evident that regulatory requirements are an important influence on the availability of new drugs in this or any other country, and any drug lag that exists in this country regarding important drugs is an inevitable result of the standards set by our laws on safety and effectiveness." He rejected, however, suggestions that the 1962 amendments be repealed.[31]

It is difficult to reconcile such statements with earlier FDA testimony. Presumably what happened is that growing dissatisfaction with

the results of the new drug approval process led the FDA to recognize it had a problem. (Personnel changes in top management speeded this recognition.) In response, it improved the process and continued to support the basic outlines of the policy. Why the policy itself is to be supported remains obscure.

In any event, Wardell's analysis, or something similar to it, appears to have contributed to a modest reorganization within the FDA. Congress showed no great enthusiasm for Wardell and gave the reorganization a very chilly reception. What from one perspective looked like a reorganization of the agency for the purpose of better serving the public interest appeared from another perspective to be a purge of those who were protecting the public from the drug industry. Such a pressure model interpretation was suggested by associates of Ralph Nader in 1972:

> In the past three weeks, an acute and deepening crisis has developed at the Food and Drug Administration which seriously threatens the health of American citizens. Two medical doctors, John Nestor and John Winkler, both specialists in cardiovascular disease with unassailable records of protecting the public from harmful drugs, have been removed from their positions and assigned new tasks.
>
> ...By these adverse actions against two doctors who have served the public in an exemplary way, FDA officials are supporting fears that they are more responsive to complaints from industry than to their responsibility to protect the public health.[32]

The reorganization led to the approval of certain drugs. Subsequently, in 1974, procedures used by the FDA in reaching these approvals were attacked in hearings before a subcommittee of the House Committee on Government Operations, and the matter of the purges was aired in hearings before two of Senator Kennedy's subcommittees. A Morton Mintz story in the *Washington Post* captures the sense of the hearings: "Eleven Food and Drug Administration scientists charged yesterday that the FDA's top echelon always supports them when they recommend approval of new medicines for the market but commonly harasses and intimidates them when they question the safety or effectiveness of new drugs." The FDA responded with a 900-page report which, not surprisingly, concluded that on the whole the charges were without foundation and that the agency was neither improperly subject to industry influences nor biased towards approval of drugs.[33] Caspar Weinberger, then secretary of the Department of Health, Education, and Welfare, appointed a Review Panel on New Drug Regulation to look into the charges and the FDA's investigation of its actions. The panel's first report (1976) concluded, in a mere 524 pages, that the FDA's investigation was inadequate and advised David Mathews, HEW's new head, that some of the charges should be reinvestigated.

Reluctant at first to authorize a new investigation, Secretary of HEW David Mathews later did so, and the 700-page report of that investigation was released in April 1977.[34] Findings were mixed. There was indeed a purge at the FDA (the report uses more neutral terminology), and improper (in some cases unlawful) methods were used to carry it out and cover up what had been done. The aim of the purge was to "neutralize" some medical officers who took an "adversarial" stance toward the drug industry in reviewing NDAs. There were also improper contacts with the drug industry. However, the purge did not result from these relatively infrequent improper contacts, and the FDA was not dominated by the drug industry. Rather, top FDA officials appointed during the Nixon administration independently believed that an extreme adversarial position was inappropriate and that drug approval should be facilitated. In other words, while the results were those predicted by the pressure model, they came about for different reasons. The report makes it exquisitely clear that policy changed at the FDA, but it does not say whether the change was desirable or undesirable. The panel is also considering the substance of drug approval decisions, but its conclusions have yet to be released.

In summary, Wardell's approach to evaluation was received far more sympathetically at the FDA than was Peltzman's, which called for a way of looking at the world radically different from that normally found at the FDA. But politicians and officials who view the world in pressure terms saw the FDA's efforts to shorten the drug lag as capitulation to industry. There is little or no evidence, for example, that mem-

bers of Congress were moved greatly by Wardell's arguments. Indeed, in a strict sense there is little evidence that Wardell influenced the FDA either. It is possible that FDA officials responded not to Wardell, but rather to industry pressures—or to their own views, as the review panel suggests—concerning the drugs Wardell considered significant. I cannot resolve this question, except by saying that the FDA treated Wardell's critique as if it were important.

Conclusions

Conclusions drawn from a case study apply only to that single case. Nevertheless I offer several generalizations—hypotheses—here. I think they make sense in light of the material in this article, but I make no greater claim for them.

On Congress and Policy Analysis. Hypothesis: Congress is almost totally impervious to systematic policy analysis, particularly in the short run.

It is possible to examine the Peltzman and Wardell analyses carefully and then reject the conclusions because of shortcomings in the analyses. But on Capitol Hill the rejection had nothing to do with careful examination. Several reasons, taken together, suggest an explanation for this.

(1) Members of Congress and staffers involved with drug regulation have substantial investments in at least the general outlines of current policy and practice. They have staked out positions as defenders of the "public interest" against the drug manufacturers, positions that are useful in generating political support and needed publicity. To have bought the conclusions of Peltzman and Wardell would have required reversing positions and liquidating investments, not politically attractive steps. In general, policy analysis is more likely to be dangerous than helpful to politicians because it often finds flaws in programs that they and their constituents support.

In this context, careful consideration of analysis becomes wasteful: the sensible response to unwelcome conclusions is to ignore them as long as possible and then try to discredit them. Such was the fate of Peltzman. As for Wardell, once the FDA came to agree with some of the particulars of his analysis, a new strategy was required: congressional attention turned from the substance of policy to the FDA "purge." This brought good publicity, and the difficult policy questions could be ignored.

(2) The dominant mode of analysis on Capitol Hill, the pressure group model, is uncongenial to policy analysis based on other models. Seemingly locked into their own approach, members of Congress and staffers respond to evaluations based on other approaches by placing them within the pressure model. Policy analysis is seen as merely the continuation of pressure politics by other means, another weapon to be used to support predetermined positions. What counts is not whether an analysis is technically competent, or even correct, but which side it supports. In his study of how congressmen decide how to vote, John Kingdon said: "When asked . . . how he sorted out the conflicting scientific claims, one congressman snorted: 'We don't. That's ridiculous. You have a general position. Once you assume that posture, you use the scientists' testimony as ammunition. The idea that a guy starts with a clean slate and weighs the evidence is absurd.' " [35]

For many congressmen, to accept Wardell's or Peltzman's conclusions would be to cave in under pressure from the drug manufacturers. Senator Nelson gave Peltzman's testimony roughly the same reception that F. Lee Bailey gave the testimony of Dr. Joel Fort in the Patty Hearst trial, and for much the same reason: it was for the wrong side. FDA actions producing results suggested by Wardell's analysis were viewed by Congress entirely in terms of the pressure model. (As noted above, that model can lead in a different direction, but supporters of that side of the model do not generally surface in Congress.)

. . . There appears to be a congressional bias towards specific and visible victims, and against unknown and unidentifiable (perhaps merely hypothetical) ones. . . . The implication of this is that the political system—and Congress in particular—will be inefficient in the saving of lives. In some situations, this will lead to overprotection. . . .

(3) Two risks are inherent in drug regulation, the risk of harm from approved drugs and the risk of the consequences of delay in marketing new drugs (or of failing to develop them at all). In a sense, these risks are symmetrical. As economist Stanley Lebergott told the Nelson subcommittee in its 1973 hearings, "the central point is, you are choosing one set of deaths and suffering and illness and cost against another. That is the only choice open to us." [36] In another sense, however, the risks are not symmetrical. On the one side, therapeutic accidents often produce identifiable victims. Horrible pictures can be shown; grieving families can testify; particular decisions can be blamed. On the other side, the victims are not so easily identified, and their injuries are not so easily traceable to particular decisions and causes. While policy analysis may weight the two sides equally, congressmen do not. Rather, there appears to be a congressional bias towards specific and visible victims, and against unknown and unidentifiable (perhaps merely hypothetical) ones.

This bias is surely not limited to Congress. It appears whenever we must balance "statistical lives" against the lives of identifiable individuals: we spend almost unlimited amounts to rescue a trapped miner, but comparatively little per life saved for improvements in mine safety. But congressmen, oriented as they are towards distributive benefits, may be particularly susceptible to this bias: diffuse benefits have something of the character of public goods, for which it is hard to claim credit. The implication of this is that the political system—and Congress in particular—will be inefficient in the saving of lives. In some situations, this will lead to overprotection in consumer protection legislation. Of course, as the mine safety example suggests, the bias may also lead to underprotection when unidentifiable victims predominate.

On the FDA and Policy Analysis. Hypothesis: The FDA is less impervious to systematic analysis of policy results than is Congress because its ways of thinking are more congenial to such analysis than is the congressional way of thinking.

FDA officials reacted to Peltzman much as congressmen did: they rejected his entire approach out of hand, finding its economic framework so foreign to their modes of analysis that they felt no call to take it seriously. Wardell, however, approached the problem in precisely the terms normally used within the FDA in deciding on drug approval: what is the evidence of effectiveness, and how safe is the drug? The FDA appears to have accepted much of what Wardell said about particular decisions, but to have translated his critique of the regulatory structure into more congenial terms, a critique of process within the structure. In a sense, then, the FDA reacted to Wardell just as Congress did: it placed his analysis within its own models and treated it only in those terms. But on the FDA's terms, Wardell had something to say.

On the Potential Impact of Policy Analysis. Hypothesis: the potential impact of comprehensive, systematic analysis of the effects of policy is limited.

If an analysis does not produce results consistent with the needs, preconceptions, and perspectives of policy-makers, it is likely to be ignored—even attacked. Indeed, because no analysis is perfect and complete, "even those who would like to see more analysis in policy making will not wholly endorse it, will never wholly accept its results, and will obviously want some kind of political machinery to make policy decisions. . . ." [37]

This limited role for analysis may be entirely appropriate. Peltzman's work is interesting, but the framework of his analysis is open to question, and even within that framework his results may be subject to dispute—with the dispute being, of necessity, highly technical. The point is not whether Peltzman is right or wrong, but that a congressional committee could hardly hope to resolve the technical issues involved; if it could, the resolution might not be the correct one. One economist on the staff of HEW's review panel concluded, perhaps correctly, "that it is impossible on

If an analysis does not produce results consistent with the needs, preconceptions, and perspectives of policy-makers, it is likely to be ignored—even attacked.

the available evidence to draw firm judgments about the amendments' overall impact on consumer welfare." [38] Under the circumstances, what can the policy-maker do? The congressman can take the side of his traditional allies, which is precisely what Senators Nelson and Kennedy did. The bureaucrat can say he is just doing his job, which is what the officials at the FDA did. Politics is one mechanism for evaluating evidence. It may even be an adequate one.

On Pharmaceutical Regulation. Some of the critics and some of the defenders of the 1962 amendments share an interest in how drugs are actually used by doctors. This is not surprising. Because the present system of regulation is a blunt instrument that either blocks a drug from almost all use or makes it available to all doctors to use as they please, it will always be possible to show both that useful drugs are not available (when they presumably should be) and that patients are being injured in appalling numbers by drugs already approved. This suggests that perhaps something should be done about the way doctors prescribe drugs.

Proposals to accomplish this abound. Wardell suggests greater reliance on postmarketing surveillance for evidence concerning safety and efficiency, combined with additional controls on drug utilization. "If the initial release of new drugs were restricted to individuals or institutions with special facilities to monitor them, drugs could be released at a considerably earlier stage than at present." [39] He also would permit the therapeutic use of drugs still in investigational status. Finally, he gives consideration to systems of control which would allow use of certain drugs by some doctors but not by others.

Richard Merrill, now FDA's general counsel, proposes alterations in the rules governing malpractice suits against doctors (and in the rules governing suits against drug manufacturers) so as to more tightly control the use of drugs.[40] The effect would be to turn drug descriptions and labels—which the FDA must approve—into a set of rules controlling how drugs may be used.

Senators Kennedy and Javits have proposed legislation which would, among other things, create a new stage in the regulation of some drugs (S. 2697, 94th Congress). Once safety had been reasonably established, a drug would be placed on a "conditional release" status for the purpose of obtaining information about effectiveness and other matters. During the period of conditional release, doctors not approved by the government would not be allowed to use the drug, and approved doctors would not be allowed to use the drug for unapproved purposes. Congressman Paul Rogers has proposed a different kind of controlled release (H.R. 1603, 95th Congress). While neither bill would do much to regulate the use of drugs that are already on the market, both would provide some kind of control over the use of new drugs by the medical profession.

Whether any of these proposals will become law is uncertain. Given the intent to control aspects of the practice of medicine, the opposition of the organized medical profession seems guaranteed. In any event, agreement on controlling the use of new drugs masks underlying disagreement on balancing the risks and benefits of these new drugs. Senator Javits said of his proposal that it "seeks to respond to the problem of 'drug-lag,' but at the same time protect the public health." [41] I suspect that it would not fully accomplish this. Rather, it would shift the controversy to somewhat different decisions in the regulatory process. That process would still require a risk-benefit calculus and, as this essay has argued, consensus on the results of that calculus is not easily reached.

PHARMACEUTICAL regulation takes place in a world of uncertain and incomplete information. It touches upon fundamental values and attitudes and profoundly affects the lives of nearly all of us—and the fortunes of some. The power of analysis to resolve such highly charged conflict is, as we have seen, limited. Political decisions are made politically, with the analysts on the sidelines.

An earlier version of this paper appeared as chapter 10 in PUBLIC LAW AND PUBLIC POLICY, *John A. Gardiner, ed. (New York: Praeger Publishers, 1977).*

Notes

[1] This statement, like others in this paper, is from interviews I conducted with various officials in Washington. While not all interviewees wished to remain anonymous, all quotations from them will be anonymous here.

[2] F. J. Ingelfinger, "The Side Effects of Aspirin," *New England Journal of Medicine,* November 1974, p. 1197.

[3] Milton Silverman, prepared testimony before U.S. Congress, Senate, Select Committee on Small Business, Subcommittee on Monopoly, May 26, 1976.

[4] U.S. Congress, House, Committee on Government Operations, *Hearings on Drug Safety,* Part 1, 88th Congress, 2d session–89th Congress, 2d session (1964), p. 185.

[5] Morton Mintz, *By Prescription Only* (Boston: Beacon Press, 1967), pp. 260-61.

[6] 21 United States Code §355 (d).

[7] If a drug is intended for long-term use, showing that it is safe for such use may take decades. FDA has therefore devised a sort of half-way house—rarely used—for important drugs of this kind.

[8] Milton Silverman and Philip R. Lee, *Pills, Profits, and Politics* (Berkeley: University of California Press, 1974), p. 119.

[9] *Hearings on Drug Safety,* Part 1, p. 224.

[10] There is one major exception. FDA controls apply to each use of the drug claimed by the manufacturer. If a drug is approved for one purpose, doctors may use it for another, though the manufacturer neither claims this use nor provides suitable directions, cautions, and the like. The absence of claims and information may discourage doctors from using a drug in this way, but there is little evidence on this point.

[11] William M. Wardell and Louis Lasagna, *Regulation and Drug Development* (Washington, D.C.: American Enterprise Institute, 1975), p. 63.

[12] Sam Peltzman, "The Benefits and Costs of New Drug Regulation," in Richard L. Landau, ed., *Regulating New Drugs* (Chicago: University of Chicago Center for Policy Study, 1973), pp. 113-211; "An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments," *Journal of Political Economy,* September-October 1973, pp. 1049-91; *Regulation of Pharmaceutical Innovation* (Washington, D.C.: American Enterprise Institute, 1974).

[13] William M. Wardell, "Developments in the Introduction of New Drugs in the United States and Britain, 1971-74," in Robert B. Helms, ed., *Drug Development and Marketing* (Washington, D.C.: American Enterprise Institute, 1975), pp. 165-81. Earlier papers by Wardell are reviewed and updated in Wardell and Lasagna, *Regulation and Drug Development.*

[14] Wardell, "Therapeutic Implications of the Drug Lag," *Clinical Pharmacology and Therapeutics,* January 1974, p. 90.

[15] U.S. Congress, Senate, Committee on Labor and Public Welfare and Committee on the Judiciary, *Hearings on Regulation of New Drug R. & D. by the Food and Drug Administration,* 93d Congress, 2d session (1974), p. 466.

[16] Ibid., p. 207.

[17] Ibid. There is reason to think that at least one drug, L-dopa, was approved for marketing in part because of congressional interest (Joseph D. Cooper, "Purpose, Technique, and Strategy in the Regulation of New Drugs," in Landau, ed., *Regulating New Drugs,* pp. 21-32).

[18] Richard J. Crout, "New Drug Regulation and Its Impact on Innovation," in Samuel A. Mitchell and Emery A. Link, eds., *Impact of Public Policy on Drug Innovation and Pricing* (Washington, D.C.: American University, 1976), p. 243.

[19] Joseph D. Cooper, *Philosophy and Technology of Drug Assessment* (Washington, D.C.: Interdisciplinary Communications Associates, 1971), vol. 2, *The Quality of Advice,* pp. 8-9.

[20] U.S. Congress, Senate, Select Committee on Small Business, *Hearings on Competitive Problems in the Drug Industry,* Part 23 *(Development and Marketing of Prescription Drugs),* 93d Congress, 1st session (1973), p. 9107.

[21] Ibid., p. 9387.

[22] Peltzman, *Regulation of Pharmaceutical Innovation,* p. 86.

[23] *Hearings on Competitive Problems in the Drug Industry,* p. 9377.

[24] Ibid., p. 9382.

[25] Wardell and Lasagna, *Regulation and Drug Development,* p. 62; citations to the medical literature, here omitted, show this information was available several years before the hearings. Other side effects became known after introduction of these drugs in Britain.

[26] *Hearings on Competitive Problems in the Drug Industry,* p. 9383.

[27] Ibid., p. 9367.

[28] Ibid., p. 9820.

[29] Ibid., pp. 9834-35.

[30] *Hearings on Regulation of New Drug R. & D. by the Food and Drug Administration,* p. 490.

[31] Ibid., pp. 477 and 505.

[32] Sidney Wolfe and Anita Johnson, "Conflict against the Public Interest at the Bureau of Drugs," in Alexander M. Schmidt, *The Commissioner's Report of Investigation of Charges* (Washington, D.C.: Food and Drug Administration, 1975), pp. 242-51.

[33] Schmidt, *The Commissioner's Report of Investigation of Charges,* pp. 895-96.

[34] Department of Health, Education, and Welfare, Review Panel on New Drug Regulation, *Investigations of Allegations Relating to the Bureau of Drugs, Food and Drug Administration,* a report to the Review Panel on New Drug Regulation by Its Special Counsel and His Staff, April 1977.

[35] John W. Kingdon, *Congressmen's Voting Decisions* (New York: Harper and Row, 1973), p. 223.

[36] *Hearings on Competitive Problems in the Drug Industry,* p. 9859.

[37] Charles E. Lindblom, *The Policy-Making Process* (Englewood Cliffs, N.J.: Prentice-Hall, 1968), p. 20.

[38] Charles F. Stone, "Economic Effect of New Drug Regulation in the United States," prepared for the Review Panel on New Drug Regulation, November 1976.

[39] Wardell and Lasagna, *Regulation and Drug Development,* p. 147.

[40] Richard A. Merrill, "Compensation for Prescription Drug Injuries," *Virginia Law Review,* January 1973, pp. 1-120.

[41] *Congressional Record,* November 20, 1975, p. S 70512.