THE SAFETY AND EFFICACY OF NEW DRUG APPROVAL

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> The perception that agencies are out of control arises from the fact that in being called on to make fundamental value judgments they have moved outside their accustomed sphere of activity, outside their expertise, and outside the established system of controls. This perturbation of the regulatory process will not be corrected until the agencies are relieved of the necessity of making judgments they are not equipped to make.
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> —Richard M. Cooper[1]

Introduction

The U.S. Food and Drug Administration (FDA) has been widely criticized for obstructing the development and use of new pharmaceutical drugs. Under present law, no new drug or medical device may be brought to market until it has been officially approved as "safe and effective" by the FDA. Unapproved products may not legally be sold and are available only on a highly restricted basis in investigational studies specifically preapproved by the FDA. Critics have frequently accused FDA of failing to permit potentially valuable drugs on the market. The ironic effect is that consumers are denied access to drugs that could benefit them on alleged grounds of public health.

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[1]Richard M. Cooper (FDA chief counsel), "The Role of Regulatory Agencies in Risk-Benefit Decision-Making," *Food, Drug and Cosmetic Law Journal* 33 (December 1978): 772.

The present approval system was established by the Food, Drug and Cosmetics Act of 1938, which required that all new drugs be approved for safety by the FDA; this was extended to include medical devices in 1976. Approval criteria were substantially strengthened in 1962 by the Kefauver-Harris amendments, which added the requirement that drugs be proven "effective" as well as safe. In addition, the 1962 amendments placed stringent controls on the use of investigational drugs, which had previously not been regulated.

In the wake of the 1962 amendments, the FDA's regulation of new drugs became increasingly stringent and risk averse, leading critics to complain of overregulation. The bureaucracy at the FDA acquired a reputation for remarkable inefficiency and delay, with processing times for new drug applications (NDAs) typically extending to two years or more, and paperwork reaching into tens of thousands of pages.[2] Meanwhile, the time and expense of new drug development increased dramatically. By 1976 the cost of developing a new drug had risen to an estimated $24 million, 10 to 20 times as much as in the early 1960s, while development times had climbed from a couple of years to the better part of a decade.[3]

By the mid-1970s critics began to argue that FDA regulation was causing the United States to suffer a so-called drug lag, a slowdown in the development of new pharmaceutical drugs. Many critics pointed to a dramatic decline in the number of innovative new drugs approved by the FDA: from an average of 50 per year in 1955–60 to only 17 per year in 1965–70 and after.[4] In a notable cost-benefit study of the 1962 amendments, Sam Peltzman argued that the consumer costs of the post–1962 slowdown in drug development substantially outweighed benefits from improved drug efficacy and safety.[5] It is unclear, however, how much of the apparent slowdown in new drug development can be attributed to FDA regulation since it began some

[2]U.S. General Accounting Office (GAO), *FDA Drug Approval—A Lengthy Process that Delays the Availability of Important New Drugs,* Report to the House Committee on Science and Technology, Subcommittee on Science, Research and Technology (May 1980).

[3]W. Wardell, M. Hassar, S. Anavekar, and L. Lasagna. "The Rate of Development of New Drugs in the United States, 1963–1975," reprinted in U.S. House of Representatives, *The FDA's Process for Approving New Drugs: Hearings of the House Committee on Science and Technology, Subcommittee on Science, Research and Technology* (96th Congress, 1979), pp. 543–63.

[4]Henry G. Grabowski and John M. Vernon, *The Regulation of Pharmaceuticals: Balancing the Benefits and Risks* (Washington, D.C.: American Enterprise Institute, 1983), pp. 29–30.

[5]Sam Peltzman, *Regulation of Pharmaceutical Innovation: The 1962 Amendments* (Washington, D.C.: American Enterprise Institute, 1974).

months before the 1962 amendments took effect, and a similar decline occurred in foreign countries.[6]

More substantive evidence for drug lag is that by the late 1960s new drugs were coming into use in foreign countries months and years before receiving FDA approval. In a comparative study of the United States and Great Britain, William Wardell and Louis Lasagna found that U.S. physicians were at a relative disadvantage in the number of potentially valuable new drugs available to them because of the greater stringency of FDA regulation.[7] A General Accounting Office (GAO) study found that in four out of five foreign countries, regulatory approval times were 6 to 18 months shorter than in the United States.[8] Meanwhile, there was evidence of a growing number of so-called orphan drugs—potentially useful drugs that were not being brought to the U.S. market because the costs of FDA approval would exceed their potential sales revenues.[9] This evidence was accompanied by reports of patients suffering from lack of access to unapproved drugs or denial of FDA permission for investigational treatment; other Americans sought treatment abroad or resorted to black- or gray-market suppliers for unapproved products.[10]

Until recently, the problem of FDA overregulation received little public attention. Throughout the late 1960s and 1970s critics complained that the political pressures on the FDA were such as to systematically favor overregulation. This complaint was explained by the fact that new drug accidents, such as with thalidomide, were more widely publicized by the press than casualties from the drug lag, whose victims were largely anonymous.[11] However, criticism of the drug-lag problem finally mounted to the point where the FDA was forced to respond. In 1979 Congress held hearings on the drug-lag problem,[12] prompting the FDA to establish a new "fast-track" approval system for important new drugs. Reforms to streamline new

[6]Donald Kennedy, "A Calm Look at 'Drug Lag'," *Journal of the American Medical Association* 239 (1978): 423–26.

[7]William Wardell and Louis Lasagna, *Regulation and Drug Development* (Washington, D.C.: American Enterprise Institute, 1974).

[8]GAO, "FDA Drug Approval," p. 7.

[9]Louis Lasagna, "Who Will Adopt the Orphan Drugs?" *Regulation* (November/December 1979): 27–32.

[10]For examples, see John Kelly, "Bridging America's Drug Gap," *New York Times Magazine*, 13 September 1981; the testimonies of William Regelson and J. Kiffin Penry, in *The FDA's Process*, pp. 288–89 and p. 101; and David L. Shanks, "Chance Denied," letter to the *Wall Street Journal*, 4 April 1985, p. 33.

[11]Compare Milton Friedman, *Free to Choose* (New York: Avon Books, 1980), pp. 193–200.

[12]*The FDA's Process*.

drug regulation were further pressed by the Reagan administration. These efforts succeeded in reducing approval times for important new drugs by as much as 40 percent, to an average of 19 months, while new drug approvals reached their highest level since the early 1960s.[13]

While the thrust of recent FDA reforms has been to speed new drug approvals, the drawback of this strategy is that it inevitably raises the risk of new drug accidents. Efforts at deregulation have accordingly been attacked by consumerist opponents on grounds of safety. These concerns were born out in 1982 by the highly publicized case of Oraflex, an innovative arthritis drug that received "fast track" approval from the FDA—partially on the basis of foreign data, which had hitherto been disallowed by FDA policy. Oraflex subsequently had to be withdrawn from the market when it proved toxic to 61 British and 11 American victims, prompting critics to call for stricter regulation. Some patients, however, claimed to enjoy unique benefits from Oraflex, which may have had the unique ability to arrest progress of arthritis.[14]

The Oraflex dispute illustrates a fundamental problem of the present approval system for new drugs; namely, the assumption that new drugs be approved as "safe and effective" on a collective, societywide basis. The problem is that safety and efficacy are inherently subjective concepts, whose meaning inevitably varies from individual to individual. As noted by one observer, "No one has yet defined safety and efficacy. Nevertheless, distinguished panels attempt to make what are termed 'scientific assessments' in the absence of objective basing points."[15] In practice, safety and efficacy depend strongly on individual circumstances such as age, sex, genetic makeup, and a host of other medical and personal factors that are often difficult for regulators to know. Even more important, the meaning of safety and efficacy depends crucially on personal values and attitudes toward risk: what seems safe to one person may well seem unsafe to another in similar circumstances. By imposing collective choice in drug risk, the present system is therefore inherently controversial, requiring the arbitrary imposition of values by technocratic authority. In this light, the debate over drug lag can be understood as a value dispute

[13]The FDA has also recently announced further reforms to reduce new drug approval times to 17 months: *Federal Register*, 22 February 1985, p. 7452.

[14]*Wall Street Journal*, 3 August 1982, p. 3; *WSJ* 24 November 1982, p. 12; *WSJ* 27 December 1982, p. 5.

[15]Joseph Cooper, "Purpose, Technique and Strategy in the Regulation of New Drugs," in Richard Landau, ed., *Regulating New Drugs* (Chicago: University of Chicago Press, 1973), p. 30.

between "pharmacophobes" and "pharmacophiles," that is, those who are respectively more and less risk averse to new drug hazards.

An evident solution to the drug safety problem is to make all drugs available for those who want them with appropriate informational warnings. In principle, this might be done through a system of "informed choice," where the basic object of drug policy would be to inform, not to restrict, consumer choice. Under such a policy, the basic role of the FDA would no longer be to determine whether or when drugs could be made available, but rather to assure that patients were adequately informed of the risks. In contrast, the present regulatory system often fails to provide consumer information on drug hazards. For example, prescription drugs are regularly sold without consumer labeling or warnings from the manufacturer. Thus Oraflex patients had no way of knowing that it was a relatively untested drug when it first came on the market unless their physicians or pharmacists happened to tell them. Under an informed-choice policy, new drugs like Oraflex would be sold with appropriate warnings about the increased risk of unknown new reactions, so that patients and physicians could decide for themselves whether to try them. In effect, the drug-lag debate would be resolved through consumer choice in the market.

Informed choice has occasionally been mentioned as an attractive alternative to the present system of mandatory approval,[16] but rarely seriously discussed.[17] Informed choice has been virtually ignored in legislative reform proposals, as the present regulatory system has developed with little consideration of other alternatives. In the meantime, the FDA has in some ways actively discouraged informed choice, for example, by exempting manufacturers from providing written consumer warnings with prescription drugs.[18] As with most FDA regulations, the consequences of this policy have never been fully evaluated.[19]

[16]Henry Grabowski, *Drug Regulation and Innovation* (Washington, D.C.: American Enterprise Institute, 1976), p. 82; and Grabowski and Vernon, "Regulation of Pharmaceuticals," pp. 71–72; compare Kenneth Arrow, "Uncertainty and the Welfare Economics of Medical Care," *American Economic Review* 53 (1963): 967.

[17]For a full analysis of informed choice in drugs, see Dale Gieringer, "Consumer Choice and FDA Drug Regulation," Ph.D. Dissertation, Department of Engineering-Economic Systems, Stanford University (1984).

[18]See Peter Temin, "The Origin of Compulsory Drug Prescriptions," *Journal of Law and Economics* 22 (April 1979): 91–105.

[19]For further analysis of the present prescription drug system, see Peter Temin, *Taking Your Medicine: Drug Regulation in the United States* (Cambridge, Mass.: Harvard University Press, 1980).

This paper considers the costs of FDA regulation of new drugs in greater detail. The following section, in accordance with Peltzman's results, argues that the costs of regulatory approval may well outweigh the benefits. But, unlike Peltzman's analysis, this argument is based entirely on an examination of the real public health benefits and risks of available drugs. More important, it will be shown that new drug casualties could be reduced at least as effectively through informational warnings as through regulatory prohibition from the marketplace. From this analysis, it follows that an informed-choice policy would be superior to any new-drug approval system, no matter how well balanced the latter system is from a cost-benefit viewpoint. This conclusion stems from the fact that the informed-choice policy would not require sacrificing drug benefits for one class of patients in order to protect others.

Risk-Benefit Tradeoffs of FDA Approval

The FDA typically has avoided any attempt to apply cost-benefit methodology to the regulation of new drugs, and it has tended systematically to overstate the dangers of approving new drugs relative to the dangers of delaying them.[20] There has been one cost-benefit study with conclusions apparently favorable to the FDA—namely, that of James Jondrow, who argued that the consumer benefits of the 1962 efficacy requirement exceeded the expenses of additional testing. Jondrow's study, however, is flawed by its failure to account for the cost of delay in introducing new drugs.[21] This shortcoming was addressed in Peltzman's cost-benefit study. Based on an econometric analysis of drug company sales, Peltzman estimated the cost to consumers of the 1962 amendments at $350–450 million versus benefits of only $100 million.[22] The assumptions of Peltzman's study, how-

[20]Rita Ricardo-Campbell, "Risk-Benefit, Cost-Benefit: Improving Government Regulation of Approval of New Drugs," in J. Van Der Gaag, W. B. Neenan, and T. Tsukahara, Jr., eds., *Economics of Health Care* (New York: Praeger Publishers, 1982), chap. 2.

[21]James Jondrow, "A Measure of the Monetary Benefits and Costs to Consumers of the Regulation of Prescription Drug Effectiveness," Ph.D. dissertation, University of Wisconsin (1972); as discussed in Leonard Schifrin, "Lessons from the Drug Lag," report prepared for the Office of Technology Assessment (June 1980). For further discussion of FDA cost-benefit studies, see Temin, *Taking Your Medicine*, pp. 141–51; and Grabowski and Vernon, pp. 37ff.

[22]Peltzman also estimated an additional $200 million in unmeasurable costs owing to delays in approving particularly efficacious drugs, versus less than $50 million in unmeasurable benefits from reduced new drug casualties. Peltzman, p. 81.

ever, have been disputed on various grounds, including charges of there being certain problems of economic methodology.[23]

Perhaps the most important criticism of Peltzman's study is that it assumes that the entire post–1962 slowdown in new drugs is attributable to regulation. Yet, as noted above, there is considerable evidence to suggest that the slowdown was at least partially independent of the 1962 amendments. In fact, a good case can be made that it was at least partly a voluntary response by the drug industry to increased public demand for drug safety in the wake of the thalidomide tragedy.[24] Nevertheless, economic studies have generally concurred that FDA regulation has had some adverse effects on new drug development.[25] For example, in a more recent study relying exclusively on data from the 1970s, Steven Wiggins has argued that regulation reduced new drug introduction rates by 60 percent.[26]

A second criticism of Peltzman's study is that his economic methodology evaluates drug costs and benefits exclusively in monetary terms, and in particular on the basis of revenues earned by drug manufacturers. The connection between industry revenues and real health benefits, however, seems dubious at best, given that the market for worthless and even harmful patent medicines has often been extremely lucrative.[27] In addition, the attempt to evaluate human life and health in monetary terms involves controversial problems, since it is not always possible to place a specific monetary value on life.[28]

Because of these criticisms, it is useful to try to evaluate the costs and benefits of regulation in terms of real public health effects. In

[23]For critiques of Peltzman's study, see Richard Nelson and Thomas Spavins, "An Evaluation of Consumer Protection Legislation: The 1962 Amendments, A Comment," *Journal of Political Economy* 83 (1975): 655–61; and testimony of Leonard Schifrin and Samuel Baker in U.S. Senate, Select Committee on Small Business, *Hearings on Competitive Problems in the Drug Industry* (93rd Cong., 1st sess., 1973), Part 23, pp. 9766–9801.

[24]Temin, *Taking Your Medicine*, pp. 146–48.

[25]For additional discussion of FDA cost-benefit studies, see Grabowski and Vernon, pp. 37ff.; and Temin, *Taking Your Medicine*, pp. 141–51.

[26]Steven Neil Wiggins, "Product Quality Regulation and New Drug Introductions: Some New Evidence from the 1970's," *Review of Economic Statistics* 63 (November 1981): 615–19; and Wiggins, "The Impact of Regulation on Pharmaceutical Research Expenditures: A Dynamic Approach," *Economic Inquiry* 21 (January 1983): 115–28.

[27]See James Harvey Young's account of the early U.S. patent medicine market, *The Toadstool Millionaires* (Princeton, N.J.: Princeton University Press, 1961).

[28]While it is often possible to impute a monetary value to life on the basis of consumers' willingness to pay for risk reduction, this is generally true only at limited levels of risk. At higher levels of risk, the monetary value of life tends to increase, becoming infinite beyond a certain point. For an analysis, see Ronald Howard, "On Making Life and Death Decisions," in R. C. Schwing and W. A. Albers, Jr., eds., *Societal Risk Assessment* (Milford, Mich.: General Motors Research Labs, 1980).

doing so, it should be noted that any estimate of drug costs and benefits is inevitably fraught with uncertainties. It is generally not possible to know what would have happened in the absence of regulation, especially with regard to any additional drug casualties that may have occurred or with regard to other new drugs that may have been developed. In addition, there is a notable lack of reliable information on the actual health benefits and costs of existing medicine. A simple, rough estimate of the real health costs and benefits of drug regulation, however, can be obtained by considering the two most salient, relevant data sets presently available. One set consists of known casualties from new drug reactions in the United States and foreign countries, as reported in the world press and medical journals. The other set consists of reductions in the mortality rate, as reported by the U.S. Bureau of the Census, for diseases in which it is generally agreed that advances in drug therapy have played a major role in recent decades.

With regard to known casualties, it is possible to use worldwide new drug reaction reports to obtain a rough gauge of the value of FDA new drug approval. This is because most new drug casualties have occurred in foreign countries where regulation has been more liberal than the United States, at least until recent years. The difference between U.S. and foreign casualty rates may thus be taken as a rough gauge of the marginal benefits of the post–1962 FDA regime.

With regard to mortality rate declines, the benefits of new drugs may be estimated from the reported declines in mortality rates for major diseases recorded in U.S. vital statistics. (Unfortunately, corresponding statistics on disease morbidity are lacking, so it is necessary here to confine the discussion of new drug benefits entirely to the prevention of deaths.) By estimating the contribution of new drugs to observed mortality rate declines, it is possible to estimate the potential cost of delay in new drug approval. This may be done by assuming that the effect of delay is to postpone all subsequent new drug benefits accordingly. Thus, if a new drug saves 1,000 lives per year, a one-year delay in its introduction may be estimated to cost 1,000 lives. While this is clearly a simplifying assumption, which is subject to qualification in many instances, it may serve as a useful rough indication of the potential costs of new drug delay.

Cost of Delay in New Drug Introductions

Table 1 contains a summary of mortality rate declines for diseases where advances in drug therapy are thought to have played a signif-

TABLE 1

ESTIMATED MORTALITY RATE REDUCTION ATTRIBUTABLE TO NEW DRUGS: 1950–77

Disease	Mortality per 100,000 Age Adjusted (1977 Base) 1950	1960	1977	Est. Reduction in Mortality Rate Attrib. to Drugs 1950–60	1960–77
Hypertension[a]	74.8	53.8	24.0	6–12	10–21
Cerebrovascular Disease	142.0	136.0	84.0	3–6	20–33
Tuberculosis[b]	23.4	6.5	1.4	6–10	1–4
Pneumonia	32.6	37.1	23.1	—	2–6
Kidney Infection	2.3	4.9	1.7	—	0.3–2
Polio	1.3	0.0	0.0	1.3	—
Rheumatic Fever	16.4	11.0	5.9	0–1	0–1
Nephritis and Nephrosis	21.0	8.8	3.9	1–3	—
Meningitis	1.0	1.1	0.7		
Peptic Ulcers	6.1	7.1	2.7	0–1	0–1
Asthma	3.3	3.2	0.8		
TOTAL REDUCTION IN MORTALITY RATE[c]				17–34	33–68

[a]Data for hypertension and hypertensive heart/renal disease are adjusted to their 1950 base definition using adjustment factors supplied in U.S. Bureau of the Census, "Comparability of Mortality Statistics for 7th and 8th Revisions of the International Classification of Diseases," *U.S. Vital and Health Statistics*, Series 2, No. 66. (Washington, D.C.: Govt. Print. Office, various years).

[b]Drugs to treat tuberculosis were introduced in 1946–47; see also accompanying text.

[c]Estimates refer to average annual reductions in mortality rates per 100,000 people.

SOURCE: Cols. 1–3, U.S. Bureau of the Census, National Center for Health Statistics, *Vital Statistics of the United States*, various years. Cols. 4–5, author's estimates based on mortality statistics and discussions with medical experts (supra, note 30).

icant role in the period 1950–77.[29] In the two righthand columns is displayed, for each disease, a range of plausible estimates of that portion of reduced mortality that may reasonably be attributed to drugs. Unfortunately, there is a lack of epidemiological and drug usage statistics to directly measure the total impact of drug therapy in the population (with the important exception of hypertension and stroke, as described below). Therefore, the estimates in Table 1 are

[29]For a more detailed discussion see Cieringer, "Consumer Choice."

by necessity "best guess" estimates, based on the author's reading of mortality statistics and discussions with medical experts.[30]

Estimates of the contribution of drugs in Table 1 have been adjusted to discount preexisting secular trends in mortality, and have been further reduced on the side of conservatism where considerable uncertainty or disagreement among experts is apparent or where a prominent contribution from other extraneous factors seems likely. The estimates in Table 1 are for the period 1950–77, and have been adjusted to exclude the impact of any drugs introduced before 1950. While mortality statistics have been broken down into two periods, 1950 to 1960 and 1960 to 1977, no attempt is made to separate the effects of drugs introduced before and after 1960.

There is little question that the greatest mortality savings attributable to drugs since 1950 have occurred in the related areas of hypertension and cerebrovascular disease or stroke. Mortality from hypertension has declined in parallel with the introduction of antihypertensive drugs, beginning in the 1950s. This has been accompanied by a parallel decline in stroke, for which hypertension is a leading risk factor.[31] It is widely believed that drugs have been a major factor in the control of hypertension and stroke. Most experts estimated that drug therapy has reduced mortality rates by 60–75 percent.[32]

Fortunately, there exist drug-use surveys from which it is possible to confirm this estimate. The National Health Examination Survey of 1960–62, for example, found that 11.9 percent of all hypertensives were under therapeutic control. Following a nationwide public education campaign in the early 1970s, control levels of 45 percent or

[30]Various expert physicians and pharmacologists were asked to help estimate the percentage of disease mortality declines attributable to drugs as precisely as possible. In many cases it was felt that exact numbers could not be meaningfully assigned, and many answers were qualified to exclude the effect of secular trends or other uncertain factors. While there was an unavoidably conjectural element in this process, numerical estimates tended to converge in precisely those areas where it was felt that the contribution of drugs had been greatest, whereas greater divergence of opinion was expressed where the contribution of drugs seemed more marginal.

[31]Hypertension has been associated with 85 percent of all cerebrovascular problems. See W. B. Kannel, P. A. Wolf, J. Verter, and P. M. McNamara, "Epidemiological Assessment of the Role of Blood Pressure in Stroke: The Framingham Study," *Journal of the American Medical Association* 214 (1970): 301ff.

[32]Compare Boranhi's estimate that "at least 40 percent" of the observed decline for hypertension is attributable to better treatment. See N. O. Boranhi, "Mortality Trends in Hypertension," in National Heart, Blood, and Lung Institute, *Proceedings of the Conference on the Decline in Heart Disease Mortality*, NIH Publication 79-1610 (October 1978), p. 227.

more were being reported.[33] All in all, it may reasonably be estimated that 35–50 percent of the hypertensive population came under control in the period 1950–76, or 25–40 percent since 1960. Given that about 25 percent of the adult population is hypertensive, that this proportion accounts for 85 percent of all cases of stroke, and that antihypertensive drugs have been shown to reduce the risk of stroke by a factor of 3 or 4,[34] it can be estimated that stroke mortality would be reduced by some 60 percent if all hypertensives were treated. From the drug-use surveys, therefore, it follows that drugs would have caused total stroke mortality rates to decline by 21–30 percent from 1950 to 1976, or by 15–24 percent since 1960—declines that are in agreement with the estimates given in Table 1.

A major breakthrough in tuberculosis therapy occurred with the introduction of streptomycin and PAS in 1947. Although these drugs were later displaced by others, the major advances must be said to have begun three years before the start of the period covered here. For this reason, mortality savings for tuberculosis as included in Table 1 should be considered optional. Also, in estimating the contribution of drugs to tuberculosis mortality savings, it is necessary to adjust for a preexisting, secular mortality decline of over 4 percent per year dating back to the early 1900s.[35] Discounting for this, about one-half of the observed post–1950 mortality decline seems attributable to drugs.

Antibiotics account for most of the other gains shown in Table 1. It is generally agreed that antibiotics have played a major role in the control of pneumonia and kidney infections plus some other conditions for which separate mortality data are lacking. They also appear to have played a more modest and uncertain role in the treatment of other diseases, such as meningitis. In the case of pneumonia and other infections, it is necessary to adjust for occasional upswings in mortality statistics owing to epidemics, although the long-term trend has been downward.[36] In addition, it is necessary to adjust for preex-

[33]For a summary of evidence, see G. W. Ward, "Changing Trends in Control of Hypertension," *Public Health Reports* 93 (January/February 1978): 31–34; M. P. Stern, "The Recent Decline in Ischemic Heart Disease Mortality," *Annals of Internal Medicine* 91 (1979): 630–40; and Boranhi, "Mortality Trends."

[34]H. M. Perry, "The Treatment of Mild Hypertension," in Elliot Rapaport, ed., *Cardiology Update: Reviews for Physicians* (New York: Elsevier Publishing, 1981), pp. 145–63.

[35]For a similar analysis, see Peltzman, pp. 58–63.

[36]Thus, the anomalous rise in pneumonia deaths around 1960 was caused by the Asian flu epidemic. It seems likely that flu vaccines have been a factor in the subsequent decline of pneumonia mortality to historic lows.

isting mortality declines owing to the use of penicillin, which dates from around 1941 (well before the 1950 start date used here). Nevertheless, new antibiotics have been necessary to deal with the resistant strains of bacteria that are continually emerging, as well as to treat patients with special allergies.

Other areas in which advances in drugs have been cited include ulcers, asthma, and kidney conditions such as nephrosis.[37] However, in most of these areas, the impact of drugs seems marginal or uncertain at best. One exception is polio, which has been largely eradicated as a result of the widespread use of polio vaccines.

Not included in Table 1 are advances in cancer chemotherapy, for which the National Cancer Institute attributes some 11,000 to 46,000 cures per year.[38] These are omitted here because of a lack of adequate cancer mortality statistics and because most of the cures appear to be attributable less to the introduction of new drugs than to the more effective application of existing ones.[39]

In sum, Table 1 shows estimated mortality reductions attributable to the use of new drugs of 50–102 per 100,000 from 1950 to 1977 (or 43–88 per 100,000 if tuberculosis is excluded). At this rate, it follows that a one-year delay in new drug benefits would cost 37,000 to 76,000 lives per decade in the U.S. population (32,000 to 65,000 excluding tuberculosis). By comparison, FDA delays in approving new drugs have often been estimated at two years or more.

Caution must be used in extrapolating from these figures to estimate new drug approval costs. The assumption that every delay in approval postpones all subsequent drug benefits equivalently may in fact result in an overestimation of the costs of delay. It seems likely that some drug benefits are partly attributable to events that are independent of the exact date of new drug approval. For example, the use of antihypertensive drugs languished for many years until finally being stimulated by public education efforts over a decade after the first drugs were approved. However, this problem may well have been aggravated by restrictions on drug labeling and advertis-

[37]The Pharmaceutical Manufacturers' Association's *Prescription Drug Industry Fact-book* for 1980 (p. 46) also lists arteriosclerosis and infectious hepatitis, but with little apparent foundation.

[38]According to the director of the National Cancer Institute, *Washington Post*, 18 October 1981, p. A-15.

[39]See Alfred G. Gilman, Louis S. Goodman, and Alfred Goodman, *The Pharmacological Basis of Therapeutics*, 6th ed. (New York: Macmillan, 1980), p. 1249. Nevertheless, it has been reported that the use of certain cancer drugs has been impeded by the difficulty of obtaining NDA approval for new indications. See the testimony of C. Gordon Zubrod, in *Hearings on Competitive Problems*, Part 23, pp. 9672–88.

ing, which prohibit the mention of any drug uses or indications that have not been specifically approved by the FDA.[40] For many years, the FDA restricted approval of antihypertensives to cases of severe high blood pressure only and may have accordingly retarded their application to moderate hypertension, where they have also proved valuable.[41]

Another factor that may reduce the impact of FDA delay is that the delay itself may bolster consumer confidence in drug safety, thereby enabling new drugs to reach a wider market more quickly once they are finally approved. However, this factor is not relevant where delays are caused by sheer bureaucratic inefficiency. In this connection, it should be noted that approval times for important new drugs have been reported to average from 8 to 19 months in the wake of recent FDA reforms.[42] At the lower rate, the cost of regulatory delays could be estimated between 21,000 to 51,000 lives per decade; at the higher rate, it could be estimated at between 51,000 and 120,000 lives per decade.

Whatever the accuracy of these estimates, there are important respects in which they may actually understate the true costs of regulation. In particular, they completely ignore the drug benefits of reduced morbidity from crippling strokes, polio, and other nonfatal illnesses, the value of which in many cases may be comparable to that of life itself.[43] Moreover, they do not account for lost benefits from drugs that may otherwise have been marketed but were entirely suppressed by regulation during the period of mortality data covered here. In short, while numerical estimates are admittedly rough, the evidence suggests that regulatory delays in new drug approval may be quite costly, with casualties on the order of tens of thousands of lives per decade.

In confirmation of these conclusions, it is useful to cite one or two specific cases in which FDA approval delays have been plainly costly.

[40]Current law does not actually forbid the use of approved drugs in unapproved indications; however, only FDA-approved indications may be mentioned in labeling or usage instructions, and many doctors are reportedly reluctant to prescribe such drugs for unapproved indications.

[41]Testimony of William Wardell, in *The FDA's Process*, p. 62.

[42]"FDA Approval of New Drugs is Speedier, But More Progress is Needed, GAO Says," *Wall Street Journal*, 16 September 1981, p. 8.; "DHHS New Drug Regulations," *Federal Register*, 22 February 1985, p. 7452.

[43]In this connection, Peltzman estimated the economic benefits of tranquilizers in reduced hospital days to be greater than the total mortality and morbidity savings attributable to tuberculosis drugs and polio vaccines; however, he neglected to account for the considerable costs of addiction, accidents, and adverse reactions owing to tranquilizers. Peltzman, pp. 63–66.

Most of the mortality reductions shown in Table 1 happen to be from drugs approved prior to 1962, when FDA approval delays were relatively small. While this fact may itself possibly be attributed to the tightening of FDA regulation after 1962, it may also be attributed to extraneous factors.

However, one important class of drugs that clearly suffered from post–1962 FDA regulation was the beta blockers, an innovative treatment for a variety of cardiovascular conditions. The FDA approved the first U.S. beta blocker, propranalol, in 1968—three years after it had been approved in Great Britain. In subsequent years, the FDA was criticized for delaying the introduction of other, newer beta blockers and for restricting approval of propranalol to only limited indications, against the advice of expert cardiologists.[44] Finally, in November 1981, the FDA announced its approval of a new beta blocker, timolol, for an innovative indication, the prevention of second heart attacks. The FDA's action was based on a study published seven months earlier, showing that timolol could reduce mortality from second heart attacks by enough to save an estimated 6,500 to 10,000 lives per year in the United States.[45] At this rate, it can be estimated that some 4,000 to 5,800 preventable deaths occurred during the seven months required by the FDA for its purportedly expedited approval. However, as noted by Wardell, there had been clinical evidence for the efficacy of beta blockers in preventing second heart attacks as early as 1974.[46] The total cost of this seven-year delay could then be put at some 45,000 to 70,000 lives—several times greater than all the casualties resulting from thalidomide and other major new drug disasters.[47]

FDA regulation also may be responsible for major adverse public health effects in the area of cancer prevention. In recent years, there

[44]Wardell and Lasagna, pp. 61–64, 110–13.

[45]According to FDA estimates; quoted in the *Wall Street Journal*, 27 November 1981, p. 5.

[46]W. Wardell, "Are These Requirements Enough or Too Much?" in A. F. De Schaepdryver, L. Lasagna, F. H. Gross, and D. R. Laurence, eds., *The Scientific Basis of Official Regulation of Drug Research and Development*, Proceedings of the 7th International Congress of Pharmacology (1978), reprinted in *The FDA's Process*, pp. 527–42.

[47]Theoretically, given that the alternative beta blocker propranalol was available in the U.S. market, there was nothing to prevent physicians from venturing to prescribe it for second heart attacks, even though this was an unapproved and unproven indication for this drug. However, as noted previously, physicians are usually reluctant to prescribe for unapproved indications. Compare the *Wall Street Journal* editorial of 2 November 1981, "100,000 Killed," and the response by FDA Commissioner Arthur Hayes, Jr., *WSJ*, 18 November 1981 (letter to the editor).

has been growing evidence that certain vitamins and minerals may have significant potential for blocking cancer.[48] While the evidence is far from certain, it seems possible that substantial benefits could be obtained from prophylactic use of vitamins and minerals as dietary supplements.[49] Vitamins and minerals are presently classified as "food supplements" and are exempt from drug regulation under special legislation that Congress passed in 1975 to prevent the FDA from banning over-the-counter sales of megavitamins. However, it is illegal for manufacturers to make any reference to possible health benefits of vitamins without becoming subject to new drug application (NDA) approval requirements for proof of efficacy. In prohibiting the advertising of possible anticarcinogenic benefits of vitamins and minerals, present regulations may be having a substantially adverse effect on consumer education and health. For example, assuming that food supplements could reduce the risk of cancer by 10 percent, some 3,500 lives per year could be saved if only 10 percent of the population were persuaded to take them.

Finally, in projecting the costs of new drug delays, the question must be asked as to whether drug development can be expected to continue at its historic rate. In recent years there have been such major developments (not shown in Table 1) as the introduction of cimetidine for ulcers, cyclosporine for transplants, and the use of beta blockers to prevent second heart attacks. As noted above, beta blockers have been estimated to have the potential of saving 6,500 to 10,000 lives per year, and comparable gains may be achieved through the use of various other kinds of heart drugs now being developed.[50] Even greater gains may result from advances in cancer treatment through recombinant DNA technology; a mere 10 percent reduction in cancer mortality would save 35,000 lives per year.

Costs of Reactions to New Drugs

Table 2 lists the casualties associated with the introduction of new drugs. The table is limited to incidents in which more than 100 deaths

[48]Vitamins A, C, and selenium have commonly been mentioned. For further discussion, see Bruce Ames, "Dietary Carcinogens and Anticarcinogens," *Science* 221 (23 September 1983): 1256–64.

[49]There is evidence that these effects could range as high as 50 percent in the case of certain cancers. Although many authorities, including a recent panel of the National Research Council of the National Academy of Sciences, have begun to advocate dietary changes to prevent cancer, most have shied away from advocating the use of supplements for lack of further evidence. See, for example, "Scientists Conduct Research on Nutrients That May Block Cancer," *Wall Street Journal*, 15 November 1982, p. 1.

[50]"Anti-cholesterol Treatment Can Cut Risk of Heart Attacks Up To 50%, Study Says," *Wall Street Journal*, 13 January 1984, p. 9; "The Scramble for the Next Superdrug," *Fortune*, 19 October 1981, pp. 94 ff.

TABLE 2

REPORTED CASUALTIES FROM NEW DRUGS, 1950–80
(Accidents Involving 100 Major Casualties or More)

Drug	Period/Location	Effects	Deaths	Other Casualties
Thalidomide	1960–61/worldwide	Birth defects		>10,000
Isoproterenol (inhalers)	1962–69/U.K. et al.	Asthma deaths in children	3,500	
Clioquinol	1956–70/Japan	SMON victims[a]	500	5,700
DES[b]	1970/U.S.	Vaginal cancer in daughters	150	400
Practolol	1969–75/U.K.	Misc. claims[c]		1,000
Chloramphencicol	c. 1950/U.S.	ADRs from misprescription	753[d]	
MER-29	1960–62/U.S.	Misc. claims[e]		400–500
Cutter Vaccine	1955/U.S.	Polio cases	11	204
Aminorex	1966–68/Europe	Cases of pulmonary hypertension	>30	>300
Orabilex	1958–64/U.S.	X-ray patients poisoned	25–100	
Stalinon	1954/France	Encephalitis victims	110	

[a]11,000 total victims including minor casualties. SMON = subacute myelo-optical neuropathy.
[b]Diethylstilbestrol. Death figure given represents ultimate casualties projected from data in A. L. Herbst, ed., *Intrauterine Exposure to Diethylstilbestrol in the Human*, Proceedings of 1977 Symposium on DES.
[c]Including 100 severe claims.
[d]Sam Peltzman's estimate; Peltzman op. cit., pp. 52–54.
[e]Fewer than 100 major settlements.

SOURCES: Testimony of Barbara Moulton in *The FDA's Process;* M. N. Dukes, ed., *Side Effects of Drugs*, 8th and 9th eds. (New York: Elsevier, 1975, 1980); Edward C. Lambert, *Modern Medical Mistakes* (Bloomington: University of Indiana Press, 1978).

or disabling casualties have been reported worldwide since 1950. It should be noted that the overwhelming number of casualties is from three major disasters, any one of which could have caused as many as 10,000 casualties in the U.S. population. In fact, all three occurred during the 1960s in foreign countries where regulation was less strict than in the United States. Avoidance of these accidents may thus be taken as a useful indication of the value of present FDA regulation.

In comparison, the number of drug casualties reported in recent years appears relatively insignificant. Although critics of FDA reform have pointed to several drug accidents since 1981, none of these is above the 100-casualty cutoff of Table 2: the most significant include Oraflex, which claimed 11 lives in the United States and 62 more in Great Britain; Selacryn, which caused 25 deaths; Zomax, which caused 5 deaths; and E-Ferol, a vitamin product that was marketed without FDA approval, which killed 38 infants. In sum, these casualties amount to less than one-twentieth of those casualties associated with any of the three major drug disasters involving thalidomide, isoproterenol, and clioquinol.

Thalidomide is the only example of a major disaster involving a drug for which the FDA actually denied approval. In 1961 an epidemic of birth defects was observed in West Germany among babies born of mothers who had taken the tranquilizer thalidomide during pregnancy. News of the disaster broke out after the FDA had postponed approving an NDA for thalidomide. Worldwide, some 10,000 babies were born with severely defective limbs and other birth defects attributable to thalidomide. Had thalidomide been approved in the United States, an additional 10,000 to 19,000 casualties might have occurred.[51]

The FDA's success in averting disaster, however, appears to have been largely fortuitous, given the scientific knowledge of the time. Had FDA ordered further laboratory studies, it seems quite possible that the problem with thalidomide would not have been found. Subsequent animal studies failed to reveal thalidomide's effects in 13 out of 22 animal experiments, including those conducted with the most commonly used laboratory species.[52] It therefore seems altogether possible that the FDA would have eventually approved thalidomide had it not been for the tragic reports based on human experience in Europe. Ironically, even though the thalidomide dis-

[51]The estimate of 10,000 is based on worldwide incidence rates; 19,000 is Peltzman's worst-case estimate based on West German incidence rates. See Peltzman, p. 55.

[52]Robert L. Brent, "Drug Testing in Animals and Teratogenic Effects: Thalidomide in the Pregnant Rat," *Journal of Pediatrics* 64, no. 5 (1964): 762–70.

aster was widely interpreted as evidence of the need for longer premarket review, it actually illustrated the basic unreliability of premarket studies. Had other nations adopted the same cautious policies as the FDA in reviewing thalidomide, the United States itself might well have suffered disaster.

The other two major drug disasters in Table 2 both involved unusual usage problems with old drugs that were already on the market in the United States. In the late 1960s asthma inhalers containing the widely used drug isoproterenol were found to be causing an epidemic of deaths among children in Great Britain, Australia, and elsewhere. The cause of the reactions appears to have been an unusually concentrated dosage form (other kinds of isoproterenol inhalers were and still are available in the U.S. and elsewhere, delivering the drug in a less concentrated dosage that has turned out to be safe). Between 1962 and 1970, it is estimated that some 3,500 children died from isoproterenol overdoses.

A similar disaster in the United States might have resulted in some 8,000 deaths.[53] That this did not happen seems largely fortuitous. Although the more dangerous form of isoproterenol was never submitted for FDA approval, it is doubtful whether its hazards could have been detected in premarket testing. Adverse reactions to isoproterenol appear to have been specifically connected with excessive use, and they were never observed in a clinical setting.[54] Wardell and Lasagna concluded, therefore, that isoproterenol was "precisely the type of adverse reaction that could not be reliably detected and intercepted in the premarketing phase" of drug testing.[55] However, casualties in foreign countries might have been reduced had more attention been paid to early warnings; deaths were linked to isoproterenol as early as 1964, three years before the first public warnings were issued.

During the 1960s thousands of Japanese users of the antidiarrhea drug clioquinol were left crippled, blinded, or otherwise disabled by a nerve disease known as subacute myelo-optical neuropathy (SMON). As with isoproterenol, diagnosis was complicated by the fact that clioquinol had been widely used in other countries for many years with no major ill effects. The peculiarity of the Japanese experience has never been adequately explained. It may have been the

[53]Based on British mortality data in Paul Stolley, "Asthma Mortality: Why the U.S. Was Spared an Epidemic of Deaths Due to Asthma," *American Review of Respiratory Disease* 105 (1972): 883.

[54]P. J. D. Heaf, "Deaths in Asthma: A Therapeutic Misadventure?" *British Medical Bulletin* 26 (1970): 245.

[55]Wardell and Lasagna, p. 99.

result of ethnic or environmental factors unique to Japan, or to the fact that the drug was more routinely prescribed in heavy chronic dosages by Japanese doctors. The Japanese government recognized about 11,000 SMON victims, 4,700 of whom had filed damage claims as of 1979.[56] Scaled to the U.S. population, a similar disaster involving clioquinol would have claimed twice as many victims.

The FDA played no direct role in the clioquinol tragedy. Clioquinol had been on the market for many years and, thus, had avoided the rigors of the modern new drug approval process. The FDA, however, had outlawed over-the-counter sales of clioquinol in 1961, nine years before the drug was banned in Japan, and it had been used cautiously in the United States for many years due to suspicions of toxicity.[57] It therefore seems likely that an FDA-style new drug approval review of clioquinol could have prevented the SMON outbreak in Japan.

In sum, only one major drug disaster, that involving thalidomide, was actually averted by FDA intervention, and this may well have been by accident. One other major disaster, that involving clioquinol, was probably preventable by tighter premarket approval procedures. The third disaster, involving isoproterenol, probably was not preventable.

Among the lesser drug accidents shown in Table 2, there is only one case—namely, that of practolol—in which it has been argued that FDA regulation might have played a role in preventing U.S. casualties.[58] Practolol, however, was never actually submitted for FDA approval, and its side effects were discovered only after 250,000 patient-years of experience in the British market.[59] In other instances, it is dubious whether any amount of premarket testing could have averted disaster. The antiobiotic chloramphenicol, for example, was discovered to cause fatal reactions in one out of 25,000–50,000 patients, an order of magnitude more that the number of subjects normally enrolled in clinical testing. Similarly, the effects of DES did not manifest themselves until nearly a generation had passed (however, DES would have failed the post–1962 requirement for efficacy testing).

[56]William Chapman, "A Japanese Tragedy, Dirodohydroxyquinoline," *Washington Post* 18 March 1979; reprinted in *The FDA's Process*, pp. 1288ff.; other information on clioquinol taken from M. N. Dukes, ed., *Side Effects of Drugs*, 8th ed. (New York: Elsevier, 1975), p.794; and Gilman, et al., pp. 1064–65.

[57]Testimony of Barbara Moulton, in *The FDA's Process*, pp. 425, 1228. Clioquinol has since been withdrawn from the market in most developed countries but continues to be exported to the Third World despite medical misgivings about its use. See Gilman et al., pp. 1064–65.

[58]Testimony of Barbara Moulton, in *The FDA's Process*, p. 425.

[59]Testimony of Matthew Connolly, in *The FDA's Process*, p. 303.

Thus, there have been only one or two major drug accidents that could have been averted through stricter premarket testing, and one or two that could not have been prevented. Altogether, the worldwide 30-year total of new drug casualties shown in Table 2 comes to about 5,100 fatalities and 18,000 disabling injuries, of which approximately 1,000 deaths and 1,000 injuries occurred in the United States. Had the United States experienced the same casualty rate as other developed nations, another 1,000 deaths and 8,000 injuries might have occurred—the rough equivalent of one major thalidomide-type disaster in two or three decades. This is about the rate at which other developed countries have experienced major disasters.

At this rate, the benefits of FDA regulation relative to that in foreign countries could reasonably be put at some 5,000 casualties per decade, or 10,000 per decade for worst-case scenarios. In comparison, it has been argued above that the cost of FDA delay can be estimated at anywhere from 21,000 to 120,000 lives per decade. These figures would seem to support the conclusion that the costs of post–1962 regulation outweigh benefits by a wide margin, similar to Peltzman's results of a 4:1 cost-benefit ratio for the 1962 amendments.

Given the uncertainties in the data, these results must be interpreted with caution, although it seems clear that the costs of regulation are substantial when compared to benefits. However, one conclusion that can be drawn with certainty is that the FDA fails its own criterion for public health: *the FDA's new drug approval system is in no way proven "safe and effective."* It is therefore worth considering alternatives to the present system.

The Case for Consumer Choice

To this point, it has been assumed that new drug approval is the only means of preventing new drug accidents. The risk of drug accidents, however, can also be limited by means of usage warnings. Ideally, warnings could be designed to protect consumers from unnecessary risks while providing access to potentially valuable unproven drugs for those consumers who want them. Unfortunately, there has been relatively little scientific research on the design and impact of consumer drug information, possibly because the present regulatory system has largely preempted research in this area. Nevertheless, an examination of the drug accidents cited in Table 2 strongly suggest that usage warnings would have been as effective as regulatory approval in preventing major new drug disasters.

In this respect, it should be noted that the majority of adverse drug reactions are associated with relatively prolonged use and heavy

dosages.[60] This was true in the case of isoproterenol and clioquinol, as well as in numerous other cases (MER-29, Aminorex, practolol, Oraflex). In addition, the risk of adverse reactions is concentrated in certain especially susceptible populations: the elderly, people using other drugs, children, and pregnant women. It seems likely, therefore, that the risk of adverse reactions could be greatly reduced if consumers—especially those in the most susceptible populations—were cautioned against prolonged and heavy use of new drugs, and if physicians and patients were alerted to be on the lookout for unknown reactions.

An important shortcoming of the present drug system is that it has no mechanism for informing consumers of the risks associated with new drugs. Once a product has been approved by the FDA as safe and effective, it is essentially indistinguishable from other drugs on the market. Furthermore, prescription drugs are commonly sold with no patient warnings or usage instructions from the manufacturer; present law requires only that pharmacists supply a typewritten label with the physician's instructions from the prescription (for example, "Take once a day").[61] Patients accordingly are dependent on the advice of their physicians, who are notably unreliable in providing drug information and warnings.[62] A solution to this problem would be to provide consumer warnings via written prescription drug "patient package inserts." Such inserts have been advocated by numerous consumer groups and have been considered by FDA, although proposals to require them have been shelved by the Reagan administration.[63]

Another way in which new drug risks could be reduced is through better postmarketing surveillance and testing. Many drug hazards go

[60]Inappropriate dosages have been found to account for as many as 80 percent of all drug accidents, including those attributable to familiar "old" drug reactions. See K. L. Melmon, L. B. Sheiner, and B. Rosenberg, "Medical Benefits and Risks Associated with Prescription Drugs: Facts and Fancy," *New England Journal of Medicine* 284 (1971): 1361, reprinted in Robert B. Helms, ed., *Drug Development and Marketing* (Washington, D.C.: American Enterprise Institute, 1975), pp. 5–13.

[61]Additional information is sometimes required by state law.

[62]According to a recent FDA survey, 80 percent of patients received no information from prescribing physicians. See the *New York Times*, 26 Feb. 1983, p. I–48. Physicians themselves are often woefully ignorant about the drugs they prescribe. See, for example, Milton Silverman and Philip R. Lee, *Pills, Profits, and Politics* (Berkeley: University of California Press, 1974), pp. 282–304; and Temin, *Taking Your Medicine*, pp. 88–119.

[63]It seems likely that modern product liability laws would have obliged prescription drug manufacturers to provide patient package inserts had FDA regulations not specifically relieved them of this obligation. See Robert Temple, "Legal Implications of the Package Insert," *Medical Clinics of North America* 58, no. 5 (September 1974): 1151–59.

undetected for a prolonged period of time, as suggested in Table 2. For example, casualties from both isoproterenol and clioquinol occurred over the better part of a decade. Substantial mortality savings, therefore, might be achieved by earlier detection of adverse reactions. The United States has often been criticized for inadequate postmarketing surveillance, especially relative to other countries such as Great Britain and New Zealand.[64] It may be noted that the British surveillance system appears to have failed in the case of isoproterenol. This case, however, was a particularly difficult disaster, and there is little reason to believe that any other system, including premarket testing, would have worked any better.

For other major drug accidents, it seems likely that a combination of consumer warnings and postmarketing surveillance would have been roughly as effective as new drug approval in averting casualties. In the case of clioquinol, it seems likely that a British-style surveillance system in Japan would have detected the unusual symptoms of SMON poisoning early on and greatly reduced the number of casualties, although casualties might have been even lower if detected in premarket testing. Moreover, insofar as clioquinol's toxicity was suspected at the time, warnings against overdosage would have been appropriate.

In the case of thalidomide, the argument for warnings is even stronger, given the likelihood that premarket testing could not have detected the hazard of birth defects. Even today, animal testing is considered to be a remarkably unreliable guide to teratogenicity in humans. It would therefore seem hazardous to rely on premarket testing as a strategy for preventing future thalidomide-like disasters. There seems little question though that the risk of thalidomide-like casualties could be greatly reduced by warning pregnant women and their physicians to be cautious when using new drugs that have not specifically been tested for their effects during pregnancy. The presence of such a warning may actually be the reason why a major thalidomide-like disaster has not recurred. In fact, the FDA commonly approves drugs without any testing in pregnant women, but there is a specific warning to this effect on the package inserts, and physicians and women are widely aware of the need to be cautious in using new drugs during pregnancy.

It seems likely therefore that the risk of new drug accidents could be controlled as well by informational warnings as by strict premarket approval standards. While further behavioral research on consumer drug information is necessary, existing evidence strongly suggests

[64]Wardell and Lasagna, pp. 97–107.

that informational warnings could be designed to assure informed consent even for the most dangerous drugs.[65] Studies of patient package inserts already have revealed a strong consumer interest among people of all educational backgrounds in written prescription drug information.[66] It is also well known that drug warnings can be overdesigned so as to frighten patients away from beneficial medication.[67] In addition, given the publicity accorded to new drug accidents, there is reason to believe that the public is sensitive to their danger. In a recent poll, for example, only 18 percent of the respondents thought there is "very little" danger in taking new drugs, 38 percent said there is "great" danger, and 48 percent said there is "some danger."[68] Finally, a striking demonstration of the feasibility of informed choice in drugs is now taking place in Great Britain, where thalidomide has been administered to women of childbearing age for treatment of a rare condition known as Behcet's Syndrome.[69] This has been done by having the women sign a statement affirming that they have been warned of the drug's dangers and that they do not intend to get pregnant during treatment.

Further research is necessary to determine the best design of a consumer drug warning system. However, an informed choice system would most likely feature the following four measures:

1. Written patient package insert warnings with prescription drugs.
2. Improved postmarketing surveillance of adverse drug reactions.
3. A system of graded safety and efficacy ratings for unproven drugs instead of the present simplistic categories of approved/not approved "safe and effective."

[65]Noninformational measures could arguably be necessary to prevent drug misuse (1) in the case of antibiotics, overuse of which may have deleterious third-party effects in breeding resistant organisms, and (2) in the special case of psychoactive or addictive drugs (for example, tranquilizers, painkillers, amphetamines, and illegal narcotics), which pose unique problems in an informed-choice framework because they appear to challenge the fundamental assumption of consumer free choice. The latter are now strictly regulated under the Controlled Substances Act, a full treatment of which is beyond the scope of this article. Nevertheless, it seems posible that the risk of accidental addiction could be satisfactorily minimized with no further legal restrictions other than perhaps some limitation on over-the-counter sales.

[66]Readership of patient package inserts has been reported at 70 percent and higher for first-time drug users, independent of educational level. See D. E. Kanouse, S. H. Berry, B. Hayes-Roth, W. H. Rogers, and J. D. Winkler, "Informing Patients About Drugs: Summary Report on Alternative Designs for Prescription Drug Leaflets," prepared for FDA (Santa Monica, Calif.: Rand Corp., August 1981), p. 3.

[67]Ibid., pp. 32–33; see also L. C. Epstein and L. Lasagna, "Obtaining Informed Consent," *Archives of Internal Medicine* 123 (June 1969): 682–88.

[68]Trendex survey for General Electric, cited in *Public Opinion* (June/July 1983): 31.

[69]*San Francisco Chronicle*, 3 October 1983, p. 3.

4. Special precautions in the case of especially risky or unproven drugs, such as prominent oral and/or written warnings explicitly acknowledged by patients and/or physicians with written signatures.

Given the preceding measures, it would seem possible to abolish mandatory drug approval entirely in favor of an informed choice policy. One way this could be done is to make unapproved drugs available with the explicit warning "NOT FDA APPROVED," and with whatever other warnings the FDA felt appropriate.[70] This would provide access to unapproved drugs for those who wanted them while maintaining the present level of FDA protection for those who did not. It would even be possible to raise FDA standards to a higher level than presently by establishing a new category of "especially safe and effective" drugs, while allowing other drugs to be sold with additional safety warnings. Moreover, it seems possible that drug warnings could be provided more efficiently through private-sector institutions such as medical advisory boards, health insurers, or consumer groups, than via government agencies, which may lack adequate incentives for providing consumers with the relevant information.[71]

An information-oriented drug policy offers certain advantages over the present approval system. The proposed drug policy would allow new drugs to be introduced more quickly, thereby reducing the costs of the present drug lag, and it would provide warnings so that only those consumers who preferred a new drug would be exposed to the increased risk. It has been argued above that the public health benefits of reduced regulatory delay would probably far outweigh costs, by as much as a few thousand lives per year. Although the proposed policy would probably entail some increase in the total number of new drug casualties, due to greater use of experimental and high-risk drugs, it is conceivable that an overall reduction in new drug casualties could result. This overall reduction could stem from the better information available to consumers about potential new drug

[70]For similar proposals, see Durk Pearson and Sandy Shaw, *Life Extension* (New York: Warner Books, 1982), pp. 590 ff.; and Murray Weiner, "Should the Public Have the Legal Right to Use Unproven Remedies? Yes," in Louis Lasagna, *Controversies in Therapeutics* (Philadelphia: W. B. Saunders, 1980).

[71]Political pressures may make it difficult for public agencies to act quickly and fairly, and action may be delayed through legal appeals. The FDA has taken some 20 years to review over-the-counter drug efficacy with comparatively little effect on improving consumer drug education. Similarly, FTC regulation of drug advertising has been notoriously ineffectual. See Bruce Yandle, "The Cost of Getting Nowhere at the FTC," *Regulation* (July/August 1981): 43–47.

risks. More important, drug label warnings would give consumers better information about the hazards of existing, "old" prescription drugs that are now on the market. Since present evidence suggests that the overwhelming number of drug accidents are due to old, not new, drugs,[72] it seems quite possible that there would actually be a substantial reduction in the total number of drug-induced injuries under an informed choice system. Furthermore, those casualties that did occur, in general, would be limited to people who had been specifically informed of the risks, which often is not the case under the present system. Finally, informed choice would encourage a more open attitude toward the use of experimental and unproven drugs, increasing medical knowledge for the benefit of everyone.

Conclusion

There appears to be little justification for the present FDA approval system. From a public health standpoint, the FDA's post–1962 approval policies appear to be neither safe not effective. Reforms to speed up new drug approval may mitigate, but not eliminate the basic contradictions of a system based on societywide approval of safety and efficacy.

The evidence suggests that drug consumers can be protected as well by informational warnings as by restrictions on market choice. The most promising alternative appears to be an informed choice drug system, where individual consumers and physicians could choose for themselves what drugs to take given appropriate informational warnings.

[72]Wardell and Lasagna, pp. 100–3.