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# Assessing the FDA via the Anomaly of Off-Label Drug Prescribing

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**I**t is commonly thought that the U.S. Food and Drug Administration (FDA) regulates the use of all pharmaceutical drugs in the United States. In fact, most hospital patients are given drugs that are not FDA-approved for the prescribed use. The FDA does require that drugs undergo extensive testing before they are released onto the market and, if it concludes that a new drug is unsafe or not effective, the FDA can decline to approve it. The agency can also recall a previously approved drug. The FDA is the final authority on a drug's approved uses, which are indicated on its label. Despite these considerable powers, the agency is limited in important ways.

Once a drug has been approved for some use, the FDA has almost no control over how that drug is actually prescribed. The prescribing of drugs for non-FDA-approved uses, called "off-label prescribing," is widespread. Drugs prescribed off-label have not met the FDA's requirements for proving efficacy in the off-label applications. The practice of off-label prescribing therefore raises interesting questions. Why does the FDA, in effect, require that some drugs be tested for efficacy but not others? If there are good reasons for the FDA to have strong pre-approval powers regarding efficacy, shouldn't FDA post-approval powers be commensurate? Alternatively, if there is good reason for widespread off-label prescribing, doesn't this call into question the FDA's pre-approval powers?

In this article, I review the extent of off-label prescribing in the United States and explain why physicians prescribe off-label. Next, I evaluate the costs and benefits

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of off-label prescribing and assess the advertising ban on off-label uses of pharmaceuticals. I conclude by discussing the implications of off-label uses of pharmaceuticals for the FDA's regulatory power over new drugs.

## **The Extent of Off-Label Prescribing**

A number of studies have documented the extent of non-FDA-approved (off-label) prescribing in a variety of medical fields. According to a study by the U.S. General Accounting Office, 56 percent of cancer patients have been given non-FDA-approved prescriptions, and 33 percent of all prescriptions in cancer treatment were off-label (General Accounting Office [GAO] 1991). Another survey, of AIDS patients, found that 81 percent of patients received at least one drug off-label, and 40 percent of all reported drug use was off-label (Brosgart and others 1996). Experts have estimated that nearly all pediatric patients (80 to 90 percent) are prescribed drugs off-label (Jaffe 1994; Kauffman 1996; Goldberg 1996).

Prescribing for non-FDA-approved uses is, for reasons that will be discussed below, most widespread in the treatment of AIDS, cancer, and pediatric illnesses, but it is by no means limited to those areas. A survey of more than one thousand patients receiving antidepressants found that a majority of usage (56 percent) was for conditions other than those for which the FDA had approved the drugs (Streator and Moss 1997). Antidepressants are commonly prescribed, for example, to treat anxiety and alcohol dependence; such uses are supported in the scientific literature but are not approved by the FDA. Similarly, a survey of fifty-five dermatologists found that every one of them commonly wrote off-label prescriptions, even though many believed (incorrectly) that they were at risk of legal action from the FDA by doing so (Li and others 1998). Another survey, of 731 pregnant women, found that 23 percent had taken at least one drug for an off-label indication during their third trimester (Rush 1998).

In summary, off-label prescribing is common in every field of medicine, and in a large number of fields most patients are prescribed at least one drug off-label. It is clear that if the FDA were to attempt to prohibit doctors from prescribing off-label, current practices would have to change significantly.<sup>1</sup>

## **Why Physicians Prescribe Off-Label**

Off-label prescribing is common for at least three reasons. First, new discoveries change the "best practice" standard of care much more rapidly than the FDA approves new uses for existing drugs. Second, it is an ineluctable fact that in many cases

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1. At several times in the past the FDA has tried to restrain such prescribing and in particular to prevent manufacturers from promoting off-label uses of their drugs (Christopher 1993; Shapiro 1979). Many of the FDA's regulations prohibiting promotion by manufacturers of off-label drug uses were recently ruled an unconstitutional abridgment of freedom of speech (*Washington Legal Foundation v. Friedman*, D.D.C., July 30, 1998). The FDA has appealed this decision.

best practices fail to stem a patient's disease. When best practices fail, patients demand innovation. Patients with terminal diseases rationally demand new approaches, despite possible dangers and low odds of success, because they face low costs of experimenting with new therapies. Third, getting the FDA to approve a new use for an old drug is an expensive and lengthy process. In many cases, the costs of the required testing exceed the benefits of FDA approval. Each of these reasons for off-label prescribing merits additional discussion.

Medical practice moves far faster than the FDA and often in surprising ways. For almost a century, for example, doctors thought that stomach ulcers were caused by diet and emotional stress. In 1982, Barry Marshall and Robin Warren discovered in the stomachs of ulcer sufferers a new bacterium, *Helicobacter pylori*, which they hypothesized was the cause of the ulcer. Their theory was initially highly controversial, but it is now believed that most stomach ulcers (perhaps 90 percent or more) are caused by *Helicobacter pylori*.<sup>2</sup> Using antibiotics such as amoxicillin and tetracycline, these ulcers can now be cured. Although hundreds of thousands of prescriptions have been written to this effect, all have been off-label. Neither amoxicillin nor tetracycline is approved for use in the treatment of stomach ulcers.

The examples can easily be multiplied. The drug mitomycin is approved for use in the treatment of gastric and pancreatic carcinomas. It also complies with the accepted standard of care in the treatment of lung, bladder, breast, cervical, and other carcinomas, even though these uses are not approved by the FDA. More surprisingly, given the difference in the conditions, mitomycin is also used in the treatment of certain forms of leukemia, and it is widely used by glaucoma surgeons and ophthalmologists.<sup>3</sup> Taxol was labeled for use in treating ovarian cancer, but after published reports indicated its effectiveness, it was used to treat breast cancer years before this use was approved. Among AIDS physicians the drug trimethoprim/sulfamethoxazole complied with the community standard of care for treating pneumonia long before it was labeled for this use by the FDA. The same drug is also used in non-approved ways to treat chlamydia, meningitis, and sinusitis, among other conditions.<sup>4</sup>

Many non-approved uses of drugs are for conditions and populations quite different from those for which the drugs are approved. Aspirin is used for headaches and also to prevent and ameliorate heart attacks. Propranolol was approved for the treatment of cardiac arrhythmia, but it was discovered to be useful in the treatment of angina pectoris when it was given to patients with both conditions. Even more

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2. For a review, see "Helicobacter pylori in peptic ulcer disease" (NIH Consensus Statement 1994, January 7-9; 12 (1): 1-23).

3. Medscape ([www.medscape.com](http://www.medscape.com)) offers a search engine that, for any drug, will list labeled and unlabeled uses. The United States Pharmacopoeia Drug Indications, known as USP DI, is an annual compendium of drugs and their uses that also lists labeled and unlabeled uses. On the uses for mitomycin, see the Medscape drug search engine and Craven and Moran 1996.

4. See the Medscape ([www.medscape.com](http://www.medscape.com)) drug search engine and Brosgart and others 1996.

surprising, when propranolol was given to patients with arrhythmias or angina who also had migraines, it was found to prevent migraines. After many years of off-label use it was approved for this use in 1979 (Farley 1992). Propranolol is currently used off-label to treat hyperthyroidism and anxiety.<sup>5</sup>

The second reason for off-label prescriptions is that patients with terminal diseases may rationally demand “experimental” treatments. Although doctors are reluctant to label any treatment experimental, it remains true that many new and beneficial treatments are discovered when conventional treatments fail. Clinical trials are an important way of substantiating new therapies, but such trials do not arise out of a vacuum. Often, especially in the case of older drugs no longer under patent, there is no large-scale effort to discover new uses, and therefore such uses must be discovered by physician experimentation. Many nonbeneficial and sometimes even harmful treatments are also discovered in this way. In both cases, future patients benefit from experimentation, but obviously current patients benefit only in the former case. Failed gambles, however, are not the same as irrational gambles. Preventing experimentation when conventional treatments fail will not benefit current patients whose gambles are rational despite having low odds, and it will certainly harm future patients.

Off-label prescribing is also common when doctors must prescribe drugs for so-called orphan populations and orphan diseases—populations too small and diseases too rare to justify the expense of petitioning the FDA for new labeling. Even when the off-label use is similar to the labeled use, the FDA requires a “supplemental new drug” application and, just as with new drugs, supplemental applications require extensive clinical trials. (Typically, clinical trials for safety are not required for a supplemental use, but efficacy trials are required.) On average, the development of a new drug currently costs more than a third of a billion dollars (\$326 million in 1997 dollars).<sup>6</sup> A substantial fraction of these costs arises not from pure research but from clinical trials that would also have to be conducted to gain FDA approval of a supplemental use. Furthermore, clinical trials take years to complete and, once they are completed, the approval process itself takes more than two years on average and in many cases substantially longer (DiMasi, Brown, and Lasagna 1996). The FDA took nearly seven years to approve acyclovir for supplemental use in *Herpes zoster* cases. (The original application was approved in only 9.6 months).

In recent years, the FDA has claimed to be speeding up and simplifying the supplemental approval process, especially with regard to the most significant “orphan” population, children. Although the agency periodically makes such claims,

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5. The discovery of propranolol is discussed briefly in Shapiro 1979. Current off-label uses can be found in the Medscape search engine or the USP DI 1997. See also note 8.

6. DiMasi and others (1991) give a figure of \$231 million in 1987 dollars. Using the consumer price index to update to 1997 produces the figure in the text. Because of increased development costs during the past decade, the figure is now probably an understatement (Institute for Policy Innovation 1997, 5).

however, rarely are they substantiated by data (Kazman 1990). The most recent full study of this issue does not show a decrease in approval times for non-pediatric uses (DiMasi, Brown, and Lasagna 1996), although there may have been a simplification of the process for some pediatric uses.<sup>7</sup> To extend labeling to pediatric patients the FDA will in some cases accept data from well-controlled studies of adults, together with other evidence supporting pediatric use in lieu of clinical studies on children (DeMasi, Brown, and Lasagna 1996). Even more dramatically, William Schultz (1996), deputy commissioner for policy at the FDA, has claimed, “some off label uses could be approved by the FDA if the sponsor would simply compile the existing literature and submit it to us.”<sup>8</sup> If the FDA were actually to implement this policy, it would in effect be returning responsibility for deciding how drugs are to be used and labeled to the medical marketplace. Compiling and evaluating the existing literature is exactly how expert panels of the AMA and the drug compendia currently recognize and support the use of drugs in an off-label manner.

### Evaluation of Off-Label Prescribing

S. A. Shapiro (1979) calls off-label prescribing a “regulatory anomaly which deprives some consumers of the protection of the [Federal Food, Drug, and Cosmetic] Act” (801). Shapiro is correct to describe off-label prescribing as an anomaly: new drugs are regulated quite differently than new uses of old drugs. On balance, however, consumers have *benefited* from the lack of FDA “protection.”

The FDA requires that drugs be tested for safety and efficacy, and it approves only the drugs that meet its standards on those two criteria. Both aspects of the FDA’s authority have significant and often overlooked costs. Testing takes time and money. The additional testing required by the FDA may have the beneficial effect of improving the safety of the drugs that reach the market, but it has at least two negative effects. First, because increased testing delays the commercial availability of improved drugs, it results in the premature death or the unnecessary suffering of many people whose conditions could have been alleviated had the new drugs been available sooner. Second, increased testing raises the costs of bringing a new drug to market; hence, the more testing that is required, the smaller the number of drugs brought to market.

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7. DiMasi, Brown, and Lasagna 1996 covers drug approval up to 1994. In 1992 the Prescription Drug User Fee Act was passed. Data from the late 1990s suggest that review times have declined as the FDA used the users’ fees to hire more reviewers. Interestingly, the FDA now takes pride in pointing out that speedier review times have not led to greater withdrawals for safety reasons (see the comments from FDA official Janet Woodcock in Tufts Center for the Study of Drug Development, *Impact* V.1, June 1998). Thus, implicitly the FDA now acknowledges that longer review times in the past led to significant loss of life as beneficial new drugs were kept off the market—something the FDA never previously acknowledged. Whether or not the gains of the late 1990s are permanent, the drug-approval process takes much longer today than in the 1960s.

8. There is a precedent for approval based on studies published in the medical literature. After significant criticism from the medical community, the FDA approved the use of propranolol for angina pectoris based on such studies.

Prior to the 1962 amendments of the Food, Drug, and Cosmetic Act, which considerably enhanced the FDA's powers, the average time from the filing of a New Drug application to its approval was seven months. The 1962 amendments gave the FDA authority to prescribe how the drug companies must conduct their clinical trials, adding years to the development process. Time to approval, which now included approval of an Investigational New Drug application (for conduct of the clinical trials) as well as a subsequent New Drug application, continued to rise, reaching 6.5 years in the 1970s, 8.3 years in the 1980s, and 8.9 years for the period 1990–96 (Tufts Center for the Study of Drug Development 1998).<sup>9</sup> Time to approval is typically shorter by years in Europe than in the United States, and as a result drugs are often available in Europe long before they are available in the United States.<sup>10</sup> The difference between the time of a drug's availability in Europe and that in the United States has come to be called the "drug lag" (Wardell 1973, 1978a, 1978b; Wardell and Lasagna 1975; Kaitin and others 1989; Grabowski 1980).

Deaths due to the drug lag have been numbered in the hundreds of thousands. Wardell (1978a), for example, estimated that practolol, a drug in the beta-blocker family, could save ten thousand lives a year if approved in the United States. Although the FDA first approved a beta blocker, propranolol, in 1968, three years after that drug had become available in Europe, it waited until 1978 to approve propranolol for the treatment of hypertension and angina pectoris, its most important indications. Despite clinical evidence available as early as 1974, only in 1981 did the FDA approve a second beta-blocker, timolol, for prevention of second heart attack. The agency's dilatory action with regard to beta blockers alone was thus responsible for probably tens of thousands of deaths.<sup>11</sup>

Drug lag is not *necessarily* a sign of failure, because the lag might be accompanied by a proportionately greater level of safety for the drugs that are approved, but any benefits from increased safety appear considerably smaller than the costs of extra delay. Dale H. Gieringer (1985), for example, uses data on drug disasters in countries with less stringent drug regulations than the United States to create a rough estimate of the number of lives saved by extra FDA scrutiny. He then computes a

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9. Pre-clinical research time is not included in these figures because this is the aspect of drug development least influenced by the FDA. Total time from synthesis of a new chemical entity to its marketing approval now runs about fifteen years (Tufts Center for the Study of Drug Development 1998).

10. This last fact is important, because it demonstrates that Europe is not merely free-riding on the FDA's investigations. Because drugs are available in Europe sooner, the FDA should free-ride—that is, take into consideration drug approvals by authorities in other nations—but it does not do so in any official manner. The FDA monitors the European (ethical) drug market mostly in order to gather information that might lead to a rejection of a new drug or the withdrawal of an older drug rather than to obtain data that might advance the acceptance of a new drug.

11. Kazman (1990) gives a number of estimates of this sort; see also Gieringer 1985. Unfortunately, no large-scale study of the excess deaths caused by drug lag has been undertaken, although Kazman proposes that the FDA be required to undertake such studies so that a proper accounting of the costs and benefits of FDA testing can be made.

similar estimate of the number of lives lost due to the delay of beneficial new drugs and concludes:

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. . . . Given the uncertainties of the data, these results must be interpreted with caution, although it seems clear that the costs of regulation are substantial when compared to benefits. (196)

Similarly, W. M. Wardell and L. Lasagna (1975) concluded their investigation comparing drug approvals in the United States and those in Great Britain by noting, "In view of the clear benefits demonstratable from some of the drugs introduced into Britain, it appears that the United States has lost more than it has gained from adopting a more conservative approach" (105).

O. M. Bakke and others (1995) studied safety-related withdrawals of official drug approvals in the United States, Britain, and Spain. If the U.S. system resulted in appreciably safer drugs, we would expect to see far fewer post-market safety withdrawals in the United States than in Britain or Spain, each of which approved more drugs than the United States during the same period. Yet approximately 3 percent of all drug approvals were withdrawn for safety reasons in the United States, about 3 percent were withdrawn in Spain, and about 4 percent were withdrawn in Great Britain. In no case was the difference in withdrawal proportion statistically significant at conventional test levels.<sup>12</sup>

Even if FDA regulations have not improved safety, they could be beneficial if they reduced the proportion of inefficacious drugs that are marketed. Using a variety of tests, however, Sam Peltzman (1973) finds little evidence to suggest a decline in the proportion of inefficacious drugs reaching the market since 1962. Therefore, he concludes, "[the] penalties imposed by the marketplace on sellers of ineffective drugs prior to 1962 seem to have been enough of a deterrent to have left little room for improvement by a regulatory agency" (342). Similarly, in their survey of the literature, Henry G. Grabowski and John M. Vernon (1983) conclude, "In sum, the hypothesis that the observed decline in new product introductions has largely been concentrated in marginal or ineffective drugs is not generally supported by empirical analyses" (34).

The costs of developing a new drug have also risen, in large part due to expanded regulatory requirements, so that today developing a new drug costs more than one-third of a billion dollars. As a result, the number of new drugs has fallen dramatically

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12. Author's calculation using the data in Bakke and others 1995.

since the 1962 amendments. In parallel with the “drug lag” terminology, Grabowski and Vernon (1983) dub this reduction the “drug loss.” It has been estimated that without the 1962 reforms the yearly flow of new drugs would have been two to three times larger than it was (Peltzman 1973, 1974; Wiggins 1981). Again, a large decline in the number of new drugs is not *necessarily* a sign of failure. If many inefficacious drugs were released onto the market prior to 1962 and if after 1962 the FDA successfully identified such drugs in the testing process and removed them from the pipeline, then a decline in the number of new drugs would be expected and applauded. But, as noted previously, the empirical evidence does not indicate a decline in the proportion of inefficacious drugs (Grabowski and Vernon 1983).

Because the proportion of inefficacious drugs reaching the market has not declined since 1962, it follows that the large reduction in the total number of new drugs has imposed large costs on society. It is difficult to know how many lives have been lost due to drug loss. Studies of drug lag, however, indicate that the number might well be very large. The decline in drug development has been especially important in the treatment of rare diseases, the so-called orphan diseases. By definition, each rare disease afflicts only a small number of people, but there are thousands of rare diseases and, all together, rare diseases afflict millions of Americans, perhaps as many as 10 percent of the population according to an estimate by the American Medical Association (1995). Thus, millions of Americans have few or no therapies available to treat their diseases because of increased costs of drug development brought about by stringent FDA “safety and efficacy” requirements.<sup>13</sup>

Apart from the costs of testing, the FDA’s exercise of its approval authority is also costly. The FDA allows onto the market only those drugs it considers “safe,” which suggests a bright-line standard for distinguishing safe and unsafe drugs.<sup>14</sup> In reality, all drugs have side effects, and what is safe enough depends on available alternatives and personal preferences.<sup>15</sup> AIDS activists, for example, argued that the “safety” of drugs was of little concern to people with terminal diseases.<sup>16</sup> Furthermore, people with the same disease may experience different levels of pain, different

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13. In January 1983 the Orphan Drug Act (Public Law 97-414) was passed to provide tax relief and exclusive marketing rights to firms developing drugs for diseases affecting 200,000 or fewer Americans (AMA 1995).

14. The original impetus for the congressional hearings that led to the modern FDA was not the thalidomide disaster but a concern that consumers were being fleeced by manufacturers who produced too many drugs similar to those already on the market. Another unfortunate aspect of the FDA’s power is that by design or effect it has prevented so-called “me-too” drugs from reaching the market. L. G. Thomas (1990), for example, finds that smaller pharmaceutical firms that specialized in these sorts of drugs “suffered devastating reductions in research productivity because of FDA regulations” (497). So-called me-too drugs have several useful purposes. First, they increase competition, resulting in lower prices; and second, they allow for better matching of drugs to patients. Because patients are heterogeneous, the same drug can cause different reactions in different patients, and chemically similar drugs can cause different reactions in the same patient. Moreover, the FDA’s record at predicting which drugs are “me-too” drugs and which actually represent important new therapies has been poor (Yasuda and Woosley 1992).

impairments, and different levels of interference with their life plans. A college professor and a superstar athlete with the same disease may rationally choose quite different courses of treatment. Or the college professor and the athlete may opt for the same drug, but because of physical differences the drug may cause strong side effects in one but not the other. A third cost of the FDA's authority is that its crude yes-or-no approval decision fails to account for individual differences in either preferences or biology.

To summarize, the FDA's regulation of new drugs entails three kinds of costs: First, requirements for additional testing delay the introduction of new beneficial drugs; second, testing costs reduce the total number of new drugs; and third, the FDA's one-size-fits-all rules are insensitive to individual trade-offs and cost-benefit decisions. Each of these issues is also relevant to an evaluation of off-label prescribing but, so to speak, in reverse. Whereas these FDA requirements entail costs of the current regulatory system for new drugs, their absence is a benefit of the current system of unrestricted off-label prescribing. Drugs prescribed off-label are available in a timely manner; they do not have to undergo expensive testing that would still further reduce the number of new therapies; and they may be prescribed by physicians in consultation with their patients on an individualized basis that takes into account personal trade-offs.

Physicians attach great importance to each of these benefits of off-label prescribing. In a letter to the FDA, John Durant, the executive vice president of the American Society of Clinical Oncology (the national organization of cancer specialists), stated, "The labeling of anticancer products frequently presents an incomplete or even inaccurate picture of the current state of medical knowledge. For virtually every cancer drug, appropriate medical usage differs from the terms of the product labeling."<sup>17</sup>

As Durant's statement indicates, the medical literature advances at a far faster rate than the FDA. J. H. Beales (1996) found that journal articles substantiating new uses for old drugs appeared in print years before FDA approval. On average the new uses were recognized in the U.S. Pharmacopoeia Drug Information (USP DI), an

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15. The FDA does recognize that the determination of safety depends on the potential benefits of a drug. If a drug used to treat cancer and a drug used to treat athlete's foot had the same serious side effects, then the former might be approved and the latter not. What the FDA does *not* take into account (or allow to be taken into account) is that trade-offs differ by individual, not just by disease (Higgs 1994, 1995). Stephen A. Eraker and Harold C. Sox (1981) document how widely attitudes toward risk vary and how these varying attitudes affect treatment choices.

16. In October 1988 the FDA issued an Interim Rule on Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illness, which was designed to decrease approval times for new drugs intended to treat rapidly progressing terminal illnesses. Although this was a welcome change in policy, it begs the question of whether the FDA or patients and their doctors should have the authority to make the difficult and inherently individual trade-offs involved in choosing a therapy.

17. Letter from John R. Durant, M.D., executive vice president of the American Society of Clinical Oncology, to Michael A. Friedman, acting Commissioner of Food and Drugs, July 21, 1998.

authoritative compendium of prescription drug information, a full two and half years before FDA approval.

Christopher (1993) has written:

It is tempting to ask Congress to give the FDA the power to forbid off-label use. The logic supporting such a ban is that a drug that has not been determined scientifically to be safe and effective for a given use should not be so used. This logic runs up against medical reality, however. The FDA, even with cooperation from drug manufacturers, could not review drugs in its lengthy testing process at a pace equal to that at which physicians discover beneficial off-label uses. (261)

Christopher is correct that the FDA cannot review drugs as fast as physicians discover beneficial new uses. But Christopher begs an important related question when he implicitly accepts that only the FDA can scientifically determine whether a drug is safe and effective. Off-label drug uses typically have extensive scientific support. Such uses come to be accepted through research, discussion, testing, and especially through the publication of peer-reviewed studies. FDA-required clinical trials are often (although not always) among the best sources of scientific information concerning a drug's safety and efficacy, but they are hardly the only sources of such information. As noted earlier, what is "safe" and "effective" depends in part on judgment and preferences; safety and effectiveness are not dictated exclusively by objective fact. Off-label prescribing offers patients and doctors a choice between the judgments of the medical and scientific communities and the judgments of the FDA. For at least some of their therapy, most patients and doctors choose the judgment of the medical and scientific communities.<sup>18</sup>

If off-label prescribing were outlawed, many therapies would be lost, because they would be too expensive to test clinically. Writing about off-label drug prescription in dermatology, Li and others (1998) note that "Once a drug is approved, its approval for another indication is a costly and lengthy process that few pharmaceutical firms can justify as the clock on their patent protection winds down." Also, if physicians were limited to labeled uses, they would in many cases have no therapies at all to employ. The 1991 GAO study that found more than half of all patients received at least one off-label drug also found that off-label use was more likely when standard treatment regimes did not exist or when standard treatment regimes failed. Similarly, according to Li and others (1998), "off label drug use broadens the clinician's ability to relieve the symptoms of patients with diseases that are refractory to standard therapy or for which there is no effective standard therapy."

Old drugs used in new ways can sometimes substitute for new drugs, which brings into focus a peculiar aspect of the current regulation of drugs. If a drug has not

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18. Recall that a large majority of AIDS patients, a majority of cancer patients, a majority of patients treated with antidepressants, and many others have been prescribed at least one drug off-label.

received FDA approval for *some* condition, then it is illegal for a doctor to prescribe the drug for *any* condition, even if clinical studies indicate that the drug is effective for the intended use and even if the drug has been approved for that use in other countries. But doctors are allowed to try to save the lives of their patients with old drugs (that is, drugs approved for some other use) even if those drugs have been less studied than unapproved drugs. Exactly this situation existed when the FDA prohibited physicians from prescribing practolol and alprenolol even though large clinical studies indicated that these drugs could reduce the mortality rate of heart attack patients by 40 percent. The FDA, however, could not prevent physicians from prescribing propranolol, a close relative. Off-label prescribing is thus similar to the illegal practice of prescribing non-approved experimental drugs. Many thousands of lives were saved because the FDA lacked the power to prevent off-label prescribing of propranolol, which illustrates both the benefits of off-label prescribing and the costs of the FDA's approval powers over new drugs.<sup>19</sup>

Significantly, in the medical literature on off-label use the main issue discussed is not the utility of off-label prescribing, about which virtually all physicians agree, but rather the issue of reimbursement. As recently as ten years ago it was often difficult to get insurance companies, HMOs, and government plans such as Medicare to reimburse patients for off-label drug therapies. The GAO (1991) found that 62 percent of doctors had admitted patients to hospitals rather than treating them as outpatients solely in order to circumvent these policies.<sup>20</sup> Another 23 percent of doctors reported that they had been forced to change their preferred treatment regimes.

Spurred by frustrated patients and doctors, the Association of Community Cancer Centers, AIDS activists, and other interested groups lobbied extensively in the 1990s to mandate coverage of off-label prescriptions for drugs that would otherwise be covered. Medicaid and Medicare now cover off-label prescriptions, as do insurance plans in twenty-three states.<sup>21</sup> New Mexico's law is typical. It states that no managed health care plan can refuse to reimburse the cost of drugs on the basis of their off-label

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19. The levamisole episode is the opposite of the propranolol episode. Levamisole was an anti-worm drug for which the manufacturers filed an application in the early 1970s. The application was not approved, ostensibly because other anti-worm drugs were available. It appears, however, that the FDA actually rejected levamisole because reports of its immunity-boosting effects were already circulating, and the agency feared that it would be prescribed off-label for other uses. (Interestingly, levamisole was approved for nonhuman use). The early reports turned out to be correct, and in 1990 levamisole was approved for use against colon cancer. Thousands of lives may have been lost because the FDA had the power to prevent the approval of a new drug for which a good substitute was lacking. Most of the information in this note is from Kazman 1990.

20. At the time, Medicare gave hospitals a fixed fee for treating covered inpatients regardless of the actual cost of the treatment. Because the payment was fixed, Medicare scrutinized physician choices far less in hospital settings than in outpatient settings (GAO 1991).

21. The states with laws mandating coverage for off-label prescriptions (some apply only to cancer drugs) are Alabama, California, Connecticut, Florida, Georgia, Illinois, Indiana, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, North Dakota, Mississippi, New Mexico, Ohio, Oklahoma, Rhode Island, South Carolina, Tennessee, Virginia, and Washington. Most of these laws have been passed since 1994. Compiled from data in Young 1996 and 1997.

status so long as “the drug has been recognized as safe and effective in ... one or more of the standard reference compendia, including the *AMA Drug Evaluations*, the *American Hospital Formulary Service Drug Information* and [USP’s] *Drug Information for the Healthcare Provider*” (Young 1997). New Mexico takes “safe and effective” to mean recognized as such by at least one reference compendia. Other states will reimburse provided the off-label use is recognized in one of the compendia *or* in the medical literature. In either case, note that Christopher’s implicit argument that only the FDA can determine whether a drug is safe and effective is rejected (Christopher 1993).

### **Off-Label Prescribing and Improper Prescribing**

Off-label prescribing should be distinguished from improper prescribing. All improper use is, by definition, off-label, but not all off-label use is improper. Improper use is unintended; it occurs when a physician prescribes a drug that he would not prescribe if he were following the standard practices of the accepted community of care. It is better to reserve the term *off-label* (as most of the literature does) for the intended prescribing of a drug according to the practices of an accepted community but not according to FDA labeling. Drugs are often prescribed improperly because of inertia and dated information. It may happen, for example, that although a drug in widespread use has been superseded by a safer substitute, most doctors continue to prescribe the older drug for a while before learning of the better one. Or it may be discovered that the side effects of a particular drug are more serious than first thought, perhaps not serious enough to prompt a recall but serious enough to make the drug a second-line rather than a first-line therapy. Doctors who have prescribed the same drug for years, however, may not immediately change their prescribing habits.

Off-label use should be distinguished from improper use not because the former is desirable and the latter undesirable, but because public policy affects these uses in different ways. *Outlawing off-label use will not prevent improper use*. Doctors will always be less than perfectly informed, and the law is not an effective means for improving this state of affairs. Improper use is best remedied by lowering the costs of information, by better training, refresher courses, more informed patients, and so forth. The Internet, for example, is making it easier for doctors and patients to obtain authoritative, up-to-date information at low cost, and this information can be expected to reduce improper prescribing. Notice, however, that improved information is likely to *increase* off-label prescribing. It is plausible, for example, that the Internet will increase the speed at which information in peer-reviewed studies reaches doctors more than it increases the speed at which the FDA conducts its reviews. The gap between best practices and FDA-approved practices will therefore widen, making off-label prescribing more likely.

There are examples of deleterious use of off-label drugs that do conform to the current standard of care. One frequently cited case involves the anti-arrhythmia drugs encainide and flecainide. These drugs were widely prescribed in the late 1980s for patients who had survived a first heart attack and who had premature beats of the heart known as PVCs (premature ventricular complex). A number of researchers thought that preventing PVCs would help to prevent cardiac arrest. Encainide and flecainide were better at preventing PVCs than other drugs used for that purpose, and they caused fewer side effects such as nausea and headaches (Moore 1995). On this basis, the FDA approved these drugs for treatment of life-threatening arrhythmias and also less severe but symptomatic arrhythmias (those that caused the patient to have some symptoms rather than being detectable only by use of a heart monitor).

In 1989, preliminary results of the Cardiac Arrhythmia Suppression Trial (CAST), a double-blind clinical trial conducted by the National Heart, Lung, and Blood Institute, were released at a hastily arranged press conference (Moore 1995). Instead of preventing cardiac arrest, encainide and flecainide caused cardiac arrest. Some 800,000 people were then taking these or closely related drugs, and if the CAST results applied to this population, the drugs could have been responsible for tens of thousands of excess deaths (Moore 1995).<sup>22</sup> In congressional inquiries and later statements, the FDA responded to this disaster by shifting blame onto off-label prescribing of anti-arrhythmic drugs (see Moore 1995, 263; Gelb 1995; Schultz 1996; Suydam 1999). Although some doctors had prescribed anti-arrhythmia drugs for *asymptomatic* patients, this practice was not in fact common (Anderson and others 1997). Moreover, except in the most extreme cases, there was no evidence that the benefits of anti-arrhythmia drugs exceeded the costs even in those uses approved by the FDA; that is, the drugs resulted in excess deaths even when used as approved.

Moore (1995) blames the FDA for letting encainide and flecainide onto the market. Certainly one lesson of the anti-arrhythmia disaster is that using surrogate end points to evaluate drugs is risky. Encainide and flecainide prevented PVCs, but the real question was whether they prevented death. A clinical study with mortality as the end point is typically much more expensive than one allowing a surrogate. It is less expensive and time-consuming, for example, to discover that a drug lowers cholesterol than it is to discover whether the reduction in cholesterol saves lives (Moore 1995). Thus, it is standard procedure for the FDA to approve drugs based on surrogate-end-point data from clinical trials when the costs of obtaining mortality data are high. Moreover,

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22. J. L. Anderson and others (1997) find no excess deaths in the heart-related mortality data for the nation as a whole. They conclude that Moore's estimate of tens of thousands of deaths is far larger than actually occurred. Their reasoning, however, is flawed. The CAST study compared encainide and flecainide to a placebo and found excess deaths. In practice, encainide and flecainide were used as a substitute for older drugs in the same class. If the older drugs were just as deadly as the newer drugs, as some studies appear to indicate, we would expect to see no jumps in the national mortality data.

the FDA knew that some anti-arrhythmia drugs were already on the market and that the new drugs were more effective and better tolerated than the older drugs. Given these facts, the FDA is not necessarily to be blamed for the anti-arrhythmia disaster. The policy of accepting surrogate end points in clinical trials is sometimes costly, but those costs are unavoidable consequences of getting life-saving drugs approved sooner. In any case, off-label prescribing appears to have played only a minor role in this terrible episode.

The FDA and groups such as Public Citizen also argue that the problems discovered with the diet drug fen-phen illustrate the dangers of off-label prescribing (FDA 1997; Public Citizen 1999; Arnst 1998). Fen-phen was a combination of two drugs, fenfluramine (or the closely related dexfenfluramine) and phentermine, used to aid weight loss. The FDA approved phentermine in 1959, fenfluramine in 1973, and dexfenfluramine in 1996, all for short-term appetite suppression. Fenfluramine and dexfenfluramine used by themselves often caused fatigue, but in the 1990s physicians found that this did not occur when these drugs were combined with phentermine. The discovery led to a large increase in the number of “fen-phen” prescriptions. Although fenfluramine, dexfenfluramine, and phentermine were all approved by the FDA, and the former two had been prescribed for more than twenty years, the combination “fen-phen” was never separately approved by the FDA and so was considered off-label. In July 1997 the Mayo Clinic announced that it had discovered twenty-four cases of heart-valve disease in women taking fen-phen. Further small studies indicated that heart-valve disease might be shockingly common in women taking fen-phen. Fenfluramine and dexfenfluramine were withdrawn from the market in September 1997.<sup>23</sup>

Opponents of off-label prescribing drew attention to the fact that the combination of fenfluramine and phentermine was never tested for safety or effectiveness and thus was prescribed off-label. The opponents, however, have not realistically evaluated the implications of a policy of testing every combination drug. Ex post, it is easy to point out dangerous combinations, but to do so implies nothing about the desirability of ex ante regulation. Because combination drug regimes are very common, the FDA could not test every combination in use without a massive increase in manpower and without significantly slowing down drug adoption and raising the costs of drug innovation.<sup>24</sup> Because most combinations are safe and effective, increased testing of combinations probably would reduce, rather than improve, patient health.

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23. Studies completed since the withdrawal support the association between fen-phen and heart disease, although considerable uncertainty remains regarding the severity of the disease, especially when fen-phen is taken for short periods. See “Appetite Suppressants and Valvular Heart Disease,” an editorial in the *New England Journal of Medicine* 339, no. 11 (September 10, 1998), summarizing three studies published in that issue.

24. Apart from combination drug regimes, drugs and foods often combine in surprising ways. Recently it was accidentally discovered that grapefruit juice can enhance the absorption of a number of drugs, including the sedative Halcion (triazolam), the antihistamine Seldane (now off the market), and the immunosuppressant cyclosporine, among others (Rodvold and Meyer 1996).

More important for the fen-phen case, it is significant that the FDA has withdrawn only fenfluramine and dexfenfluramine, not phentermine. As the FDA (1997) notes, “At the present time, no cases of heart valve disease meeting FDA’s case definition have been reported with phentermine alone. Analysis of the data points to an association of heart valve disease with fenfluramine and dexfenfluramine.” It appears, therefore, that a drug the FDA approved in 1973, fenfluramine, and approved again in slightly different form in 1996 has been causing heart disease for twenty-seven years.<sup>25</sup> The discovery of the problems with fenfluramine occurred only because of increased usage and inspired medical detective work by doctors at the Mayo Clinic. The fen-phen episode does not speak to any problems with off-label prescribing, but it does remind us that no drug is perfectly safe, not even FDA-approved drugs.

The debate over off-label prescribing is not about perfect safety; it is about whether unavoidable trade-offs are best made for everyone by a centralized authority such as the FDA or whether those decisions are best made by patients and doctors acting independently. Whoever makes a decision to try (patient), prescribe (doctor), or approve (FDA) a drug must face the trade-off between the costs of prescribing a potentially unsafe medicine (a type II cost) and the costs of not prescribing a drug that could have saved a life (a type I cost).

The origins of type I and type II costs (or errors) are shown in the following illustration.

		<b>True State of the World</b>	
		New therapy is safe and effective	New therapy is not safe and effective
<b>Decision</b>	Try, prescribe, or approve	Correct decision	<i>Type II cost</i>
	Reject	<i>Type I cost</i>	Correct decision

The FDA tends to overemphasize the cost of using a potentially unsafe medicine, because type II costs are highly visible and result in punishment of the FDA, whereas type I costs are invisible and do not result in punishment.

25. Given that the FDA failed to find any problems with fenfluramine or dexfenfluramine in two rounds of clinical testing and twenty-four years of use, it is disingenuous of the agency to use the fen-phen episode as a justification for further FDA regulations. The FDA (1997) gives reasons, generally sound, for not having discovered the problems with fenfluramine earlier.

If the FDA approved a drug that killed thousands of people, that story would make the front page of every newspaper in the nation. Congressional hearings would certainly be held, the head of the FDA would probably lose his or her job, and the agency would be reorganized. But if the FDA rejected a drug that could save thousands of people, who would complain? When a drug kills a patient, that person is identifiable, and family and friends may learn the cause of the death. In contrast, the patient who would have lived, had new drugs been available, is identifiable only in a statistical sense. Family and friends will never know whether their loved one could have survived had the FDA not delayed the introduction of a new drug. In some cases the drug that could have saved the patient's life is never created, because the costs of the FDA's testing procedures make the necessary research and development appear unprofitable.

Richard Merrill, a former chief counsel of the FDA, wrote that

it is always safer for agency officials to prevent the marketing of products that entail physical risk—regardless of what benefits they provide. No FDA official has ever been publicly criticized for *refusing to allow* the marketing of a drug. Many, however, have paid the price of public criticism, sometimes accompanied by an innuendo of corruptibility for approving a product that could cause harm.<sup>26</sup>

Patients and doctors do not face the same biased incentives as the FDA and thus tend to pay more attention to the costs of *not* using a drug that could save a life. Because doctors and patients pay more attention to type I costs than the FDA does, it would not be surprising if they suffered more from the costs of using a potentially unsafe medicine than they would if the FDA had greater regulatory powers. But if the goal is to minimize *total* costs, an increase in type II costs does not necessarily reflect poorly on off-label prescribing. What the evidence seems to suggest, however, is that off-label prescribing results in significant reductions in type I costs—drugs reach patients sooner, doctors have a greater choice of drugs, and the costs of drug innovation are lower—with only small increases in type II costs. This outcome attests that the FDA greatly overemphasizes type II costs.

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26. Richard A. Merrill was chief counsel for the FDA from 1975 to 1977; quotation from Shapiro 1979, n.86. In recent years the imbalance has been altered somewhat by AIDS activists who have criticized the FDA for holding back the approval of new AIDS drugs. Inspired by the success of AIDS activists, other groups representing patients with life-threatening illnesses have also petitioned the FDA for early release of new drugs. The FDA has responded to such criticism by speeding the approval of some drugs meant to treat life-threatening illnesses. Although patients can be grateful that the FDA responded to criticism, that responsiveness only confirms that the FDA always emphasizes type II costs, because they are more visible and punishable than type I costs, notwithstanding occasional efforts by activists.

Former FDA commissioner Alexander Schmidt was also clear about FDA incentives, stating, "In all of our history, we are unable to find one instance where a Congressional hearing investigated the failure of FDA to approve a new drug. 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." Statement of Alexander M. Schmidt in Senate hearings, 1974, quoted in Hutt and Merrill 1991, 1318.

## Promotion of Off-Label Drugs

In 1972 the FDA proposed extensive regulation of off-label prescribing, but the new rules were tabled after vehement objections from the medical community (Shapiro 1979; Kessler 1978). Since then the FDA has periodically tried to bring off-label prescribing under its control. The most recent attempt was made in December 1991, when the agency announced that the 1972 rules, which had been neither implemented nor withdrawn, were once again being actively considered (Christopher 1993). Furthermore, a series of regulations in the 1990s increased the FDA's powers over drug promotion and advertising by manufacturers. The rulings prohibit drug manufacturers, except in limited circumstances, from disseminating to physicians peer-reviewed journal articles, textbooks, compendiums, and other information supporting off-label uses of drugs (Morgan, Lewis & Bockius LLP 1998).<sup>27</sup>

The costs of prohibiting promotion run parallel to the costs of prohibiting off-label use or requiring extensive testing of new drugs. They include (1) reducing the speed at which beneficial new drugs are widely adopted; (2) reducing the size of the market for drugs, thereby increasing the costs of innovation and reducing the incentive to research and develop new drugs; and (3) reducing the number of treatment options, making it more difficult for physicians to provide therapies optimally adjusted for each individual patient.

There have been numerous instances in which the FDA has reduced the speed at which beneficial new drugs, and beneficial new uses of old drugs, have been widely adopted. Perhaps the most important example is that the agency prevented aspirin manufacturers from advertising that clinical studies had shown that the use of aspirin during and after heart attacks could save thousands of lives (Rubin 1995; Keith 1995). When, years after the clinical studies had been completed, the FDA finally sanctioned aspirin for heart-attack patients, Dr. Carl Pepine, co-director of cardiovascular medicine at the University of Florida College of Medicine, estimated that as many as ten thousand lives annually could be saved. Noting that the decision should have come years earlier, Pepine said, "I'm disappointed that something that has such potential to save so many lives took so long. But it's better late than never."<sup>28</sup> Despite studies showing benefits, the FDA still does not allow aspirin manufacturers to advertise the benefits of aspirin as a preventive measure for people at high risk for a first heart attack.

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27. These regulations were declared unconstitutional in 1998 by the U.S. District Court for the District of Columbia because the court held they were "considerably more extensive than necessary" to advance any legitimate interest of the FDA (*Washington Legal Foundation v. Friedman*, D.D.C., July 30, 1998). The FDA has appealed.

28. Quoted by Melanie Fridl Ross in a University of Florida news release, "FDA Proposes Labeling Aspirin for Use at Onset of Heart Attack," June 14, 1996. News releases from the University of Florida can be found at <http://www.napa.ufl.edu/>. See also Cannon 1996. Also relevant is the 1997 report from the American Heart Association (1997) recommending aspirin use beyond that approved by the FDA. Rubin 1995 examines the costs of the FDA's advertising restrictions.

In 1992 the federal Centers for Disease Control and Prevention (CDC) recommended that women of childbearing age take folic acid supplements, which had been shown to reduce neural-tube birth defects such as anencephaly and spina bifida. The FDA immediately announced, however, that it would prosecute any food or vitamin manufacturer that placed the CDC recommendation in its advertising or product labeling (Calfee 1997). The importance of folic acid did not enter public consciousness until several years later, when Congress passed the Dietary Supplement Health and Education Act of 1994 and thereby checked the FDA's efforts to clamp down on the advertising of vitamins and other dietary supplements. Amazingly, within only a few years of its ban on publicizing the CDC recommendation, the FDA made a complete turnabout. As of 1998, the agency has *required* manufacturers to fortify a variety of grain products with folic acid (*Seattle Times* 1998).

Proponents of information restrictions argue that such restrictions have benefits because manufacturers of drugs are a biased source of information. For example, manufacturers are likely to provide physicians with only those studies that support the use of their drugs. Physicians may be unduly swayed by this bias and by unscientific or low-quality studies. Promotion could therefore increase sales of unsafe or nonbeneficial drugs (Schultz 1996; Suydam 1999; Public Citizen 1999). But the opponents of drug promotion ignore the costs of banning advertising (as exemplified in the cases of aspirin and folic acid), they exaggerate the incentive of drug manufacturers to provide biased information, and they further exaggerate the effect such bias has on physicians' behavior.

One important role of advertising in any market is simply to inform consumers about the existence of a product. Bias is not a serious problem with regard to such "existence claims." Prior to the development of Rogaine, for example, there were few treatments to increase hair growth, so Rogaine's manufacturer had to inform physicians about the existence of this new option. Nor is bias a serious problem in relation to a seller's provision of price information. Even with respect to safety and effectiveness, the incentives to provide biased information are weaker than commonly imagined. To be credible, manufacturers must present information from peer-reviewed journals and independent clinical studies. And to avoid lawsuits, bad publicity, and loss of reputation, manufacturers want physicians to be aware of contraindications, dangerous interactions, and potential side effects.

Let us accept, however, that a manufacturer is unlikely to present the same information about a drug that an independent panel of physicians would choose to present; in this sense, information from manufacturers is biased.<sup>29</sup> The issue, however, is not the bias of a single manufacture but rather the overall consequences of allowing

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29. Of course, independent panels of physicians do not have the same resources as drug companies or the same incentives to present their (presumably unbiased) information. We face a choice of low or zero levels of "unbiased" information or high levels of possibly "biased" information. The latter is preferable when the biases are small or can be filtered out by the information recipients.

advertising and promotion. Even though every manufacturer is biased about its own products, competition and comparative advertising can result in the revelation of significant negative information. In the 1950s, for example, following publication of the first persuasive reports linking smoking and lung cancer, cigarette manufacturers launched advertising campaigns that emphasized how safe their own cigarettes were compared to their competitors' brands. Each manufacturer's advertising was biased, but the net result was that the dangers of smoking were clearly conveyed to the public. According to a *Consumer Reports* article from that time, "ads claiming health advantages for a particular brand merely underscore the possible dangers from smoking, to the detriment of the whole industry." As a result of this cutthroat advertising, cigarette consumption declined more during that period than in any period since. Unfortunately, in 1955 the Federal Trade Commission (FTC) prohibited manufacturers from making any health claims, and cigarette sales rebounded.<sup>30</sup>

The critics of off-label drug promotion repeatedly make a simple mistake related to the surprising history of cigarette advertising. Consider this statement by William B. Schultz, FDA deputy commissioner for policy, before the U.S. Senate, February 22, 1996:

Another example relates to the widespread off label use of a class of drugs called calcium channel blockers (CCBs). These drugs are effective for patients suffering from angina, which is chest pain caused by insufficient oxygen to the heart muscle. CCBs have no established role in patients who have had a heart attack but have no symptoms. These patients do, however, benefit from another class of drugs, beta-blockers, which are known to reduce mortality by 25–30 percent after heart attacks. Nevertheless, CCBs are widely used in this patient population and there are publications that could be interpreted as supporting this use. Because CCBs and beta-blockers generally should not be used simultaneously, patients are receiving CCBs in lieu of clearly life-saving beta-blockers. Many, probably thousands, of lives are lost each year because a drug of no known benefit is being used for an unapproved use in place of a drug with known value. Widespread promotion of this use would make the problem even worse.

Obviously, widespread promotion of this particular use of CCBs would make it more prevalent; but the relevant question is, What would happen if there were widespread promotion of both CCBs *and* beta-blockers? Schultz's error is one of composition. From "advertising would increase the share of drug X" it does not follow that lifting an advertising ban on all drugs would lead to an increase in the share of drug X.

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30. The information in this paragraph, including the quotation from *Consumer Reports*, is from Calfee 1997, 46-55.

In this case the opposite is more likely. Assuming that Schultz is correct about the health effects of CCBs and beta-blockers, if both were allowed to advertise, the market for CCBs would be likely to decrease and that for beta-blockers to increase, thereby saving thousands of lives. Indeed, given Schultz's assumptions, what could possibly explain why CCBs are used in place of beta-blockers except that doctors lack the right information? And what better way to bring the right information to their attention than by advertising targeted at them? Advertisers know how to transmit information memorably, effectively, and at low cost. Despite its best efforts, the FDA has by its own admission failed to make doctors aware of the superiority of beta-blockers over CCBs. The CCB story is not an indictment of off-label prescribing but rather another example of FDA failure.

Schultz's comments indicate the failure of the FDA in a second, ironic manner. Beta-blockers were available in other countries at least a decade before they became available in the United States; and even then, years passed before any of them were approved for prophylactic treatment after a first heart attack. Large-scale studies of practolol and alprenolol in the mid-1970s suggested that these drugs could reduce by 40 percent the mortality rate of patients in the first year or two after a heart attack (Wardell 1978a). Because neither practolol nor alprenolol was approved for use in the United States, physicians began off-label prescribing the closely related drug propranolol. (Propranolol was finally approved for prophylactic use after a first heart attack in 1986.) The FDA's record on practolol and alprenolol is thus one of delay leading to many premature deaths, a misfortune moderated only by the fortuitous circumstance that physicians had access to a close substitute product that they could prescribe off-label.

The FDA tends to argue as if physicians were extraordinarily naive processors of information. But physicians are not ciphers; they have an independent ability to evaluate information presented to them not only by drug manufacturers but also by colleagues, journal articles, compendia, textbooks, and other sources. Opponents of drug promotion worry about preliminary reports from lower-quality journals unduly influencing prescribing decisions, as if physicians had no ability to judge quality. But physicians, like other professionals, are well aware of the value of alternative sources of information. Moreover, many drugs are administered through HMO and hospital formularies. Drugs are not admitted to formularies without being evaluated by a panel of expert physicians who are unlikely to be swayed by low-quality information.

Furthermore, all else equal, the promotion of beneficial drugs is more profitable than the promotion of nonbeneficial drugs.<sup>31</sup> Promotion of a nonbeneficial drug is clearly wasted if the sieve of physician judgment cuts the link between promotion and the writing of prescriptions. Even if the sieve of physician judgment is

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31. The "all else equal" covers variables such as market size, consumer income, and other determinants of advertising expenditure.

weak, advertising works best when product quality is high, so that consumers initially convinced to buy the product through advertising become repeat customers when they learn through experience about product quality. A firm that uses massive promotion to squeeze a drug with few benefits through the sieve of physician judgment will lose the value of that investment when physicians realize that the drug doesn't work. It is more profitable to heavily promote a drug that is likely to retain a high market share, because then a single investment today pays off in years of repeat purchases (Nelson 1974).<sup>32</sup> Firms that massively promote poor products will also find future products more difficult to sell, as the firms' reputations deteriorate.

Like other consumers in other markets, physicians undoubtedly have a healthy skepticism of drug promotion and advertising, but also like other consumers in other markets, they find that on balance advertising is an important and useful source of information.<sup>33</sup> In a poll, 79 percent of neurologists and neurosurgeons, 67 percent of cardiologists, and 76 percent of oncologists said that the FDA should not restrict information about off-label uses. In response to a follow-up question, similar numbers indicated that the FDA policy of limiting information had made it more difficult for them to learn about new uses of drugs and devices (Conko 1998).

The evidence on the promotion of off-label uses has been especially well studied in a closely related area, direct-to-consumer advertising of health claims in the food market. In the early 1960s, scientists established a link between high-fat diets and increased heart disease. In response to those discoveries, manufacturers began promoting low-fat, low-cholesterol foods as heart-healthy, but such claims were soon banned. Until 1973, manufacturers were not even allowed to label the fat, cholesterol, or other nutritional content of their foods! In 1984, however, the National Cancer Institute and Kellogg's cooperated to produce an advertising campaign to promote the use of fiber that had been found to reduce certain types of cancer. The Kellogg's challenge created a furor in Washington and led to congressional hearings and a formal review of food labeling and advertising law (Ippolito and Mathios 1990). The FDA wanted the campaign stopped and considered suing Kellogg's, arguing that it had the authority to stop the campaign because All-Bran was being marketed as a drug, for which any health claims were off-label. The FTC's Bureau of Consumer Protection, however, encouraged the ads, arguing that they presented "important public health recommendations in an accurate, useful, and

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32. The logic of advertising better products leads to a corollary: more advertising can "signal" higher product quality (see Klein and Leffler 1981).

33. When asked whether advertising is often deceptive, about 70 percent of people answer yes, but when asked whether advertising contains useful information, about 70 percent also say yes (Calfee 1997). The two perspectives are not inconsistent. Advertising is deceptive in a face-value sense—drinking beer won't get you the girls—but everyone knows this reality, and recipients screen advertising accordingly in order to extract useful information.

substantiated way.”<sup>34</sup> The FTC won the political battle, which led to a lifting of the ban on health claims for food in 1985.<sup>35</sup>

The lifting of the ban on health claims was controversial and, as noted, opposed by the FDA. Opponents of promotion argued that manufacturers of food were biased and would use advertising of health claims to deceive consumers into buying less healthy foods at higher prices—the same sorts of arguments used to prohibit promotion of off-label uses for drugs. What actually happened when food manufacturers were allowed to advertise the health benefits of their products?

The Kellogg’s and related campaigns led to a revolution in cereal advertising and production and hence to higher-fiber, lower-fat cereals and much greater consumer awareness of health issues (Ippolito and Mathios 1991; Calfee 1997). The lifting of the ban on health claims for other products also had large benefits. In an exhaustive study for the FTC, Ippolito and Mathios (1995a, summarized in 1995b) found that fat consumption fell at a significantly faster rate after the ban on advertising health claims was lifted than when the ban was in effect. Ippolito and Mathios concluded:

The available evidence is consistent with the view that the relaxation of the rules governing producer health claims contributed to a better information environment, leading to improvements in consumers’ food choices. The data do not support the alternative view that producer health claims in advertising and labeling had adverse effects. . . . [In short,] diets improved faster in the years when health claims rules were relaxed.

In summary, the evidence indicates that forbidding drug manufacturers from promoting off-label uses of their products can have high costs. Moreover, the evidence from the food and cigarette markets demonstrates that the fears of promotion opponents are unfounded. When cigarette manufacturers were allowed to make health claims (“low tar is better for the lungs”), cigarettes became safer, and total cigarette consumption decreased. When food manufacturers were allowed to advertise health claims, fat and cholesterol content decreased, fiber content increased, and consumers became better informed. We can expect the same benefits of advertising and promotion in the market for off-label uses of drugs.

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34. The quotation is from remarks of Carol T. Crawford, director of the FTC’s Bureau of Consumer Protection, quoted in Calfee 1997, 25.

35. The lifting of the ban was short-lived. In 1990 the Nutrition Labeling and Education Act imposed new restrictions. In a comprehensive analysis of the new rules, P. M. Ippolito and A. D. Mathios (1993) write, “Our primary conclusion is that in the attempt to prevent deceptive claims, the new rules also eliminate the potential for many types of truthful, nonmisleading claims . . . there is reason to be concerned that the restrictions on such truthful claims will generate unnecessary losses for consumers.”

## The Promotion Ban as an Inducement to Conduct FDA Trials

The last argument against promotion to be examined is quite different from the others. Opponents of promotion argue that forbidding promotion will encourage firms to conduct the clinical trials and submit the paperwork necessary to obtain on-label approval. Because the right to advertise is valuable, some firms (that would not otherwise do so) will pay for the necessary trials, but for other firms the costs of the trials will exceed the value of the right to advertise. The net benefit depends on the number of firms in each category, the costs of the promotion ban for those firms that do not complete the necessary trials, and the net value of completing the trials.

Although it is difficult to assign precise numbers, it is likely that the promotion ban induces only a small number of firms to conduct the trials required to gain FDA approval for supplemental uses. First, there is little inducement to conduct trials for drugs that have gone off patent or are within several years of going off patent, and those two categories account for a large majority of drugs. Second, some firms will conduct clinical trials regardless of the advertising ban, because more information about a drug makes the drug more valuable. Third, the right to advertise tends to be of little value for drugs with small potential markets, whereas the costs of conducting FDA-approved trials are large and independent of market size. Therefore, few sellers of small-market drugs will be induced to conduct trials by the promise of advertising rights. These considerations suggest that the majority of off-label drug uses will never be submitted to the FDA and that many of the supplemental uses that are submitted would have been submitted even without the promotion ban.

The cost of the promotion ban in excess deaths and less informed consumers has been discussed already. Because the majority of off-label uses will not be submitted to the FDA, the costs of the promotion ban will accrue to many more drugs than will any benefits.

Taken together, the costs of the trials, the delay in getting new drugs to market, and the reduction in new drugs suggest that the net value of FDA policy with regard to new drugs is negative. Because the process for supplemental trials is very similar, the net value of these trials probably is also negative. It is certainly not positive and large enough to overcome the large costs of the advertising ban.

### Conclusion: End the Anomaly

In the United States, new drugs are regulated extensively but new uses of old drugs are regulated much less extensively.<sup>36</sup> Every drug available for prescription in the United States must have gone through at least phase I clinical trials. Phase I trials examine a drug for toxicity in healthy volunteers and establish that the drug meets a minimum level of safety. Drugs used in FDA-approved ways have also been through

phase II and phase III “efficacy” trials. Drugs prescribed off-label, however, have not been through this process; hence, off-label drugs are regulated essentially according to the FDA’s pre-1962 rules whereas drugs prescribed for labeled uses are regulated according to the post-1962 rules.

Studies of the FDA’s post-1962 powers consistently find few benefits and large costs. Despite these studies, the system has not been reformed. Convincing people of the benefits of a system with fewer FDA powers may require a direct comparison of a regulated and an unregulated system. This study provides such a comparison. I find that the largely unregulated system of off-label prescribing has large benefits and few costs. Off-label prescribing speeds medical innovations to patients, increases the number of drugs available to doctors, and lowers the costs of medical innovation. Because of these benefits, off-label prescribing is common in the United States today. The largely unregulated system of off-label prescribing is working well, and it should be extended.<sup>37</sup> The FDA may be able to perform a useful service by certifying drugs,<sup>38</sup> by encouraging and supporting, in cooperation with the National Institutes of Health, clinical studies of drugs (especially those that have gone off patent), and by monitoring and serving as a national and international repository for information concerning adverse reactions. But an analysis of off-label prescribing strongly suggests that the FDA’s authority over new drugs, particularly the requirement that new drugs be tested for efficacy, is detrimental to the public’s health and welfare and therefore should be abolished.

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36. Common law rules of tort apply to physicians as to any other profession, of course, so physicians face penalties for negligence. Essentially, the common law requires physicians to practice according to recognized community standards of care. Further details on the common law regulation of off-label prescribing can be found in Shapiro 1979, Christopher 1993, and Krauss 1996. The common law also regulates drug manufacturers. American Home Products, the producer of the fen-phen diet-drug combination settled a class action suit in October of 1999 for \$3.75 billion (*New York Times*, October 8, 1999).

J. Serradell and A. I. Wertheimer (1989) surveyed national drug regulatory agencies in eleven countries and found that most did not regulate off-label prescribing. There are three important exceptions: Israel, Greece, and New Zealand (the latter is not mentioned by Serradell and Wertheimer but is discussed in Wardell 1974). In Israel it is illegal for a doctor to prescribe a drug for a non-approved use. It would be interesting to examine the situation in Israel in further depth. Is the Israeli law enforced, and if so, how do the authorities monitor prescriptions? Are supplementary indications easily approved in Israel? Do Israeli doctors chafe at the restrictions? In Greece and New Zealand, doctors may prescribe approved drugs for any use, but the respective national health services will not pay for the drug if the use is not indicated on a national list. The New Zealand national list of approved uses is created by experts in a manner similar to the creation of the U.S. drug compendia, so it is possible that many more uses may be approved in New Zealand than in the United States. See Wardell 1974 for further details.

37. The ban on advertising and promoting off-label products appears to be unconstitutional and a detriment to patient health; it would be best if the lower court ruling overturning the ban were upheld.

38. In a certification system the FDA, possibly in competition with private agencies, would certify that drugs had or had not met the FDA’s standards of safety and efficacy. Firms would seek out FDA approval in order to increase sales, just as they seek the Underwriters Laboratory (UL) seal of approval for electrical appliances. On a certification system for the FDA, see Grabowski and Vernon 1983, Krauss 1996, Kazman 1990, and Campbell 1999. Klein 1998 and the essays in Klein 1997 examine issues of quality assurance in voluntary systems more generally.

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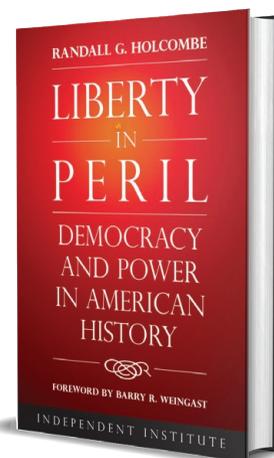
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