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Accutane: Has Drug Regulation in the United States Reached its Limits?

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ACCUTANE: HAS DRUG REGULATION IN THE UNITED STATES REACHED ITS LIMITS?

JOAN H. KRAUSE*

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I. INTRODUCTION

"[N]othing on the scale of the thalidomide tragedy has occurred in the United States, even though potent teratogens do exist."1

"Accutane is as bad as thalidomide, but it doesn't have the emotional connotation of thalidomide."2

The regulation of pharmaceuticals is a controversial task: a constant battle against limited resources, newly-discovered diseases, and the uncertainties of science itself. Yet a system of governmental regulation is

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1 Evelyn Zamula, Drugs and Pregnancy: Often the Two Don't Mix, FDA CONSUMER, June 1989, at 9.

2 Dr. Adrian Ive, quoted in Gina Kolata, Europeans Placed Stiffer Curbs on Acne Drug, N.Y. TIMES, Apr. 28, 1988, at A25.
preferable to allowing ineffective and potentially dangerous "medicines" to flood the marketplace. With administrative controls, however, come time-consuming procedures and institutionalized cost-benefit decisions. Since we lack the resources to investigate all potentially beneficial drugs, special interest groups fight against the government, manufacturers, and each other in a quest to get "their" medications developed, tested, and marketed.

Pharmaceutical regulation is complicated by a variety of intractable dilemmas. The most basic is the choice between safety/efficacy and availability: to withhold approval until tests have shown that a drug is completely safe and effective denies access to people who may desperately need the drug in the interim. Depending on the need for the drug, the balance may shift; we are swayed by fewer studies when the drug is indicated for a life-threatening illness, such as AIDS, than when the drug is merely a new pain reliever. The problem is further complicated because very sick patients want access to potentially effective drugs now, while the information from continuing clinical trials is vital for a determination of the drug's ultimate safety and efficacy. The history of U.S. drug regulation illustrates this tension between the claim that no drug should be sold until we know it is totally safe and effective, and the reminder that a drug is useless unless those who need it can get it.

Historically, many changes in pharmaceutical regulation have come about in the face of "highly dramatic and publicized disasters." The Federal Food, Drug, and Cosmetic Act ("FDCA") of 1938 was passed in response to the deaths caused by "Elixir Sulfonilamide," an untested "drug" that contained a deadly poison. The European tragedy of thalidomide, a sedative that caused thousands of birth defects, led to a rethinking of regulation in England and a tightening of U.S. restrictions. Starting in the mid-1980's, the specter of AIDS has led the Food and Drug Administration ("FDA") to create "fast-track" procedures, allowing promising therapies to reach needy patients sooner. These public tragedies have produced public outrage and demands for change.

Yet other "tragedies," other problems with our regulatory system, don't receive this attention. Although we have improved our procedures, we are still far from being able to claim that approved drugs are safe for the people who take them. For example, the drug Accutane is used to treat

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5 "Accutane" is the trade name for isotretinoin, marketed by Roche pharmaceutical company, a division of Hoffman-LaRoche. Since isotretinoin is commercially available only under the trade name "Accutane," I will refer to it as such. Accutane has also been the subject of extensive products liability litigation, which will not be addressed by this article.
a rare but severely disfiguring form of acne. It is highly effective, but has a number of severe side effects; in particular, like thalidomide, it causes severe birth defects. Unlike thalidomide, however, our experiences with Accutane have not spurred sweeping changes of regulatory policy. Accutane is a story about selective clinical testing, about the documentation of severe side effects, and about efforts to educate and warn the public of its dangers. It is, perhaps, a "success" story, an example of what innovative measures can be used to minimize the dangers of a potent drug. Yet Accutane also illustrates the shortcomings of our current regulatory policy, and highlights the dilemmas inherent in any attempt to control pharmaceuticals.

By a careful examination of the Accutane experience, both here and abroad, I will illustrate some of the shortcomings of the current American system of drug regulation. There are a number of ways in which this system fails to live up to the strict regulatory philosophy that it purports to follow; in particular, there are systemic inadequacies in the design of clinical trials, the official labeling received by drugs, and the manner in which adverse reaction reports are collected and assessed. Additionally, although the system often works well, there are natural limitations to a system of pre-approval testing; for some drugs, such as Accutane, it is foreseeable that the current U.S. approach will not provide an adequate degree of patient safety. It is my position that we must both improve current regulatory safeguards to meet the stringent standards we have set up, and also be willing to implement stricter post-approval controls for the few distinct cases where pre-approval safety in the relevant patient populations cannot be adequately assured.

Part II of this paper will provide background information on the history and procedures of the FDA and the drug Accutane. Part III will analyze the regulatory problems of our current system, as illustrated by our experience with Accutane. Part IV will explore an alternative method of regulation, illustrated by that used in England.

II. BACKGROUND

A. Drug Regulation in the United States

The United States has regulated drugs in some form since 1906, although the actual procedures have changed over time. While early laws concentrated on the prevention of misbranding and adulteration, tragic experiences led to the adoption of stringent requirements of safety, efficacy, and quality. Yet there remains a great deal of flexibility in these procedures, which allows the system to adapt to the changing realities of scientific discoveries, patient needs, and pharmaceutical production.
1. An Historical Overview

The Food and Drugs Act of 1906 was aimed at preventing the adulteration and misbranding of drugs. It required drugs to meet standards of strength and purity, but not safety or efficacy. In addition, the Act failed to provide for preventive remedies, and judicial interpretation severely curtailed its effectiveness. Attempts to remedy the Act's loopholes were drafted so poorly that prosecution was nearly impossible.

Although a bill to revise the obsolete 1906 act was introduced in the Senate in 1933, it took the tragedy of "Elixir Sulfonilamide," in which 107 people died, to prompt the passage of new legislation. The Federal Food, Drug, and Cosmetic Act of 1938 required manufacturers to provide scientific evidence of drug safety, beginning what would become the major means of drug regulation in the United States. The Act also removed the intent requirement in misbranding cases, authorized factory inspections, provided injunctive remedies, and regulated cosmetics and foods. However, still no proof of drug efficacy was required. The FDA quickly took advantage of its new powers, and a variety of new regulations were promulgated through the mid-1940's. In particular, statutory definitions of "prescription drugs" were passed in the Humphrey-Durham Amendment of 1951, and regulations were proposed to require full disclosure in sales literature and information accompanying drug packaging.

Public outcry over the European thalidomide tragedy prompted Congress to strengthen FDA control over new drugs in the Drug Amendments of 1962. Thalidomide, a tranquilizer, was widely marketed as a sleeping pill and morning sickness remedy. In the early 1960's, it became clear that the drug had also caused grotesque deformities in thousands of European babies. The drug was never marketed in the U.S. because Dr. Frances O. Kelsey, an FDA medical officer, determined that it failed to meet the safety requirements of the 1938 Act. However, the experience convinced Congress to amend the 1938 act, requiring by a unanimous vote that new drugs be proven both safe and effective for their intended uses. The Amendments created a detailed system of approval procedures,
including requirements for both animal studies and human clinical trials, and in some cases applied the efficacy requirements retroactively to 1938. Although subsequent amendments have updated and expanded specific provisions, the basic framework of the 1962 system remains in place.

2. An Overview of FDA New Drug Approval

Before a new drug can be tested in humans, the manufacturer must carry out a variety of tests in laboratory animals. Many of these address the drug’s ability to cause toxic side effects (“toxicity”), the relationship of safety and dosage, and how the drug is absorbed and broken down by the body. Since drugs may affect different animals in different ways, two or more species are commonly used. However, humans may react very differently to the drug than any test animal; for this reason, animal studies are only the first step towards drug approval.

Once animal testing is completed, the sponsor must submit the research to the FDA, along with detailed descriptions of proposed human studies, in the form of an “investigational new drug application” (“IND”). If the agency believes the drug can safely be given to human volunteers, controlled testing may begin. Clinical testing generally consists of three phases of experiments, although this is not required by law. Phase I trials are primarily concerned with the safety of the drug, and involve fewer than 100 healthy, paid volunteers. These trials provide information about how the drug is broken down in the body, what effects it has on the body, and what side effects appear as the dosage is increased. They generally last several months.

If unacceptable safety problems do not occur in Phase I, Phase II trials may begin. These trials are designed to study the drug’s efficacy for its intended purpose, although short-term side effects in target patient populations may also be discovered. They usually involve several hundred patients with the particular disease or condition indicated, and last for several months to two years. Phase II studies are randomized control trials, in which a “treatment” group (which receives the drug) is compared to a “control” group (which receives a standard treatment or placebo). These trials are often “blinded,” with neither patient nor doctor aware of

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14 See generally Jeffrey P. Cohn, The Beginnings: Laboratory and Animal Studies, in FROM TEST TUBE TO PATIENT, supra note 6, at 8; Ken Flieger, Testing in ‘Real People’ in FROM TEST TUBE TO PATIENT, supra note 6, at 13; Dr. Frank E. Young, Experimental Drugs for the Desperately Ill, in FROM TEST TUBE TO PATIENT, supra note 6, at 24; Nelson, supra note 3.
15 See Cohn, supra note 14, at 10.
16 See, e.g., Teff, supra note 4, at 577 n.52 (penicillin is lethal to guinea pigs); Zamula, supra note 1, at 9 (human sensitivity to thalidomide is 100 times that of rats and 50 times that of rabbits).
17 See Nelson, supra note 3, at 470, n.52.
which treatment is being received. Finally, Phase III trials may involve several thousand patients with the indicated disease, and may last four years or more. They are designed to approximate normal medical usage of the drug, and to discover less common side effects and other information. Upon completion, the sponsor files a “New Drug Application” (“NDA”) with the FDA. Final approval of the drug will depend on whether the manufacturer has proven that the drug is safe and effective, and the development of satisfactory official labeling. A drug’s labeling contains the approved indications, recommended dosage levels, and lists of warnings, contraindications (conditions in which the drug should not be used) and reported side effects. It is usually found in the form of a “package insert” accompanying a drug, but versions may also be tailored specifically to patients or to prescribing physicians.

Some drugs reach patients by alternate means. For many years the FDA permitted investigational new drugs to be used for treatment in particular cases under ad hoc “Treatment INDs” or “Compassionate INDs.” In 1987, the FDA revised its official IND policies to allow patients with immediately life-threatening or serious illnesses to obtain experimental drugs without enrolling in research trials. Drugs for immediately life-threatening diseases may receive such approval near the end of Phase II trials; drugs for serious diseases may receive approval during Phase III. The controversial measure also allows drug companies to charge for these drugs. The FDA then proposed a “fast track” to approval for drugs for life-threatening or severely debilitating illnesses, which includes a greater interaction between drug sponsors and the FDA in designing Phase II trials and a more lenient FDA risk-benefit analysis. The ultimate effects of these controversial changes are not yet fully apparent.

Although the FDA requires proof of safety and efficacy in the drug’s intended conditions, an approved drug may be prescribed for conditions other than those indicated. However, the FDA has a number of regulations

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18 The sponsor must prove that the drug is safe for “its intended conditions of use . . . by adequate testing by all methods reasonably applicable . . . A higher degree of risk may be considered acceptable when no alternative treatment is available or when a drug is indicated for use after alternative treatment has been unsuccessful.” 1 Food Drug Cosm. L. Rep. (CCH) ¶ 71,010 (Aug. 6, 1990).
19 According to 1988 estimates, approximately 70% of drugs complete Phase I clinical trials, 33% complete Phase II, and 25-30% complete Phase III. Of 100 INDs, only an average of 20 will be approved for marketing. Flieger, supra note 14, at 14.
22 See Young, supra note 14, at 24-25. But see Nelson, supra note 3, at 472-73, 478-79 (claiming that drugs for serious diseases may actually be approved dangerously early in Phase II).
designed to assure the continuing safety of marketed drugs. In large part, the FDA relies on reports and records kept by drug sponsors. For example, the sponsor must notify the FDA of all "adverse drug experiences," defined as "any adverse event[s] associated with the use of a drug in humans, whether or not considered drug-related." The deadlines for these reports vary with the severity of the reaction. If such reports indicate a safety problem, the FDA can withdraw the drug from the market. As the story of Accutane illustrates, however, the FDA also has a variety of less drastic ways to address a potential problem.

B. Accutane: An Overview

Accutane was developed as an acne treatment in Switzerland in the 1950's, but awareness of the drug's teratogenic properties (ability to cause birth defects) convinced the company not to pursue marketing approval. In the late 1970's, Hoffman-LaRoche began testing the drug for use in treating severe recalcitrant cystic acne, a disfiguring and debilitating form of acne caused by a chronic oil gland disorder. Mindful of the drug's teratogenicity, most test centers excluded women from the trials; the drug was tested in only 550 people before receiving FDA approval. In May 1982, the U.S. became the first country to approve Accutane for use in the treatment of severe recalcitrant cystic acne. The unusually quick FDA approval, coming only nine months after the NDA submission, alarmed some doctors. The original package insert contained warnings against the drug's use in pregnant women, but noted only that the drug caused birth defects in animals.

By mid-1983, Roche became aware of at least three cases of malformed children born to women who had taken Accutane, and passed this information along to doctors in the form of "Dear Doctor" letters. In August,

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24 Records and Reports for Approved Products, 1 Food Drug Cosm. L. Rep. (CCH) ¶ 71,040 (Aug. 6, 1990). Note that the burden of reporting falls on the drug’s sponsor, and generally not on the prescribing physician. Realistically, however, if physicians do not report adverse events to the sponsor, the latter may not know of the reactions.

25 For example, "15-day alert reports" are required when a "serious and unexpected event" has occurred, or when there is an "increased frequency of expected event[s]." Id.

26 According to the drug's inventor, ["In the 1970s], in the psychological climate engendered by the thalidomide tragedy, it would have been inconceivable to develop an agent with teratogenic properties for the treatment of such a common complaint as acne." Dr. Werner Bollag, quoted in Diane A. Nygaard, Accutane: Is the Drug a Prescription for Birth Defects?, TRIAL, Dec. 1988, at 81.

27 Id. In the United States, the drug was only tested in 170 patients at four universities and the National Cancer Institute. See Penny Chorlton, FDA Outpaced Firm on Acne Drug, WASH. POST, Sept. 14, 1982, at A17.

28 See, e.g., Dr. Frank Yoder, Isotretinoin: a Word of Caution, 249 JAMA 350 (1983) (letter from Dr. Frank Yoder, a former NIH researcher, claiming that the toxicity of Accutane was "seriously underemphasized").
the FDA published a description of 12 reported cases of "adverse pregnancy outcomes" with Accutane. In September, after the consumer advocacy group Public Citizen claimed that the drug's warnings were inadequate and that it was being oversold, Roche revised Accutane's labeling to include information about human birth defects.

By 1984, 21 cases of Accutane-associated birth defects and 24 spontaneous abortions had been reported to the FDA. At this point, Dr. Paul J. Benke published a study of two infants born to mothers who had taken Accutane. Benke identified an "isotretinoin teratogen syndrome," consisting of abnormalities of the central nervous system, ear, and face. For many, Accutane was even more dangerous than thalidomide; while the victims of thalidomide suffered from shortened and deformed limbs, the victims of Accutane are often retarded, with serious brain and central nervous system damage. In addition, Accutane's effects may occur if the drug is taken even briefly during the first trimester, a time when many women do not yet know they are pregnant. As a result, Accutane's warnings about birth defects were strengthened in 1984; suggestions included the use of contraception for a month before and after therapy, pregnancy tests prior to therapy, and advice that blood banks refuse exposed donors. Roche embarked on a program to educate prescribing physicians about the dangers of the drug, even taking out a "Medical Director's Page" in the Journal of the American Medical Association to stress that Accutane was contraindicated in pregnancy.

Publicity efforts and minor labeling changes continued for the next few years. By April 1988 the FDA had concluded that the education and warnings had not been effective, and asked the Dermatologic Drugs

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31 *See Janice S. Lewis, Accutane and Birth Defects, TRIAL, April 1985, at 16.
34 *See Nygaard, supra note 26, at 82. An exposed woman has a 40% chance of having a miscarriage, and at least a 25% chance of producing a deformed baby. Id.*
37 An FDA study released on April 22, 1988, estimated that 16,000-24,000 pregnant women were exposed to Accutane between 1982 and 1986. Although only 62 formal reports of birth defects had been filed, the FDA estimated the actual number to be 900 to 1300 cases. Michael Abramowitz & Philip J. Hilsa, *FDA Eyes Ban on Acne Drug: Study Links Use by Pregnant Women to Birth Defects*, WASH. POST, April 23, 1988, at A1.
Advisory Committee for recommendations. The Committee suggested stronger package warnings, greater physician education efforts, and written patient acknowledgements. The FDA adopted stringent changes, including informed consent forms, large-sized boxed contraindications sections, inclusion in the labeling itself of a depiction of an infant with the syndrome, use of a "nonpregnancy" symbol, increased educational efforts through "Pregnancy Prevention Kits," and new packaging. The FDA declined to accept the Committee's recommendation that only certain types of physicians (i.e., dermatologists), be allowed to prescribe the drug. Although such an approach is common in Europe, it would have been a drastic departure from U.S. norms. In May 1990, the FDA took further steps under consideration, including preparation of a videocassette to be shown in doctors' offices and further encouragement of pretherapy pregnancy testing.

Not all the news about Accutane has been grim, however. Since 1988, researchers have studied the use of Accutane as a cancer treatment. Accutane appears to be a promising therapy for certain types of skin and head and neck cancers. Although the drug is not officially indicated for use in the treatment of cancers, under the U.S. regulatory system physicians may continue to investigate and prescribe the drug for these and other uses without such formal approval. For now, Accutane remains a controversial drug. Yet its story is a useful illustration of the U.S. philosophy of drug regulation, and the potential problems with this approach in the areas of pretrial testing in relevant patient populations, tracking adverse drug events, and reacting to newly discovered dangers.

III. REGULATORY PROBLEMS ILLUSTRATED BY ACCUTANE

A. Drug Regulatory Philosophy in the United States

The choice between safety and availability clearly influences the type of regulatory system that is imposed. A country that favors safety will require prolonged testing of the drug, but at the expense of the patients who need the drug in the interim. A country that favors early availability

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References:


39 See Nygaard, supra note 26, at 82.


will require less testing, but will carefully monitor post-approval drug experiences; however, patients may suffer severe reactions before decision-makers respond to the post-market reports. Although a regulatory system usually favors one such approach, many nations are flexible when it comes to particularly necessary but potentially dangerous drugs.

In striking the balance between drug safety and availability, the U.S. comes down firmly in favor of stringent pre-market safety requirements. As one commentator has put it, the exacting demands of the U.S. process reveal a perceived need to go to extreme lengths in an effort to establish drug safety prior to marketing . . . . FDA supervision commences at an early stage . . . and has paid relatively little attention to post-market surveillance.42

Consistent with this philosophy, the U.S. has strict procedural requirements (described in Part II) to assure that the drug is safe for its intended conditions. The U.S. also monitors adverse drug reactions, and has a great deal of flexibility in responding to such reports. Yet despite these safeguards, serious adverse reactions still occur; for example, the arthritis/pain-killing drugs Oraflex (benoxaprofen, Lilly), Zomax (zomepirac, McNeil), and Suprol (suprofen, McNeil) were all removed from the market in the 1980's after causing deaths, kidney or liver disease, or severe allergic reactions.43 In light of the number of drugs that have been taken off the market or have been forced to change their official labeling, the adequacy of the U.S. system is by no means clear. The history of Accutane is one example of how these procedures both do and do not work.

1. Pre-Approval Clinical Testing

For pre-approval testing to function as proof of drug safety, the tests must use patients and conditions that closely resemble those in which the drug will be used in practice. On the other hand, ill patients must not be exposed to excessive dangers, and the drug should reach the market in a reasonable amount of time. The U.S. guidelines attempt to take all this into account. But recent evidence suggests that there still is inadequate testing in the patients who will eventually receive the drug.

42 Teff, supra note 4, at 579.
43 Other drugs removed from the market for similar reasons include the antidepressants Merital (nomifensine, Hoechst) and Wellbutrin (buproprion, Burroughs-Wellcome), as well as the high-blood pressure drug Selacryn (ticrynafen, SmithKline Beckman). In addition, the FDA lowered the recommended doses of the anesthetic Versed (midazolam, Roche), and Merrell Dow halted production of the morning sickness remedy Bendectin after allegations that it caused birth defects. See Sidney M. Wolfe, FDA Approval Doesn't Guarantee a Drug's Safety, WASH. POST, July 19, 1989, at A22; Company Stops Making Morning Sickness Drug, N.Y. TIMES, June 10, 1983, at A16.
For example, certain patient populations have traditionally been excluded from clinical trials on ethical grounds, due to the excessive risks involved. A pregnant woman cannot participate in pre-market studies because untested drugs may harm the fetus; pre-market pregnancy data comes only from laboratory animals. Other populations have also been traditionally overlooked. Because menstrual cycle fluctuations can confound research, even female laboratory animals have been excluded from some clinical trials. Since drugs may be metabolized differently by children and the elderly, these groups are rarely included in initial trials. Despite increasing knowledge of the different ways in which different ethnic groups metabolize drugs, minorities are often underrepresented in clinical trials. The problem with such selectivity is that these drugs are often used by such "excluded" patients, and the precise factors that made these patients hard to study (e.g., menstrual cycle fluctuations) make it likely that the drug will affect them differently.

Accutane is a good example of this. Aware that laboratory tests showed the drug was teratogenic in rabbits and rats, most test centers excluded women from the studies; at other centers, women were required to have a negative pregnancy test before starting therapy, to use an effective contraceptive, and to agree to undergo an abortion if they conceived. As a result, there was no documentation of birth defects caused in humans, and the original drug labeling said as much. Nor did the labeling require the stringent anti-pregnancy measures that were required at the trial stage. Although severe recalcitrant cystic acne occurs more frequently in males, it was clear that some women of childbearing age would be proper candidates for Accutane therapy. Given this knowledge, a much stricter warning against use during pregnancy would have seemed proper from the start.

Accutane is by no means the only drug whose clinical trials produced little information about much of the patient population. As one commentator has noted, "[t]he net result is that the potential effects of drugs are often most conjectural for the categories of patients whose drug consumption is the greatest." While the elderly are often excluded from trials because of their reduced ability to remove drugs from the body (via the liver and kidneys) and their frequent use of many medications at
once, they also consume a great deal of medication. For example, the anti-
arthritis pain-killer Oraflex was tested in only 52 people over the age of
65 in English trials. Yet as an arthritis treatment, the drug was largely
used by the elderly. It was withdrawn from the market in 1982 after being
linked to deaths from liver and kidney damage.

The lack of clinical studies using women subjects has been the topic of
much debate since Congress asked the General Accounting Office ("GAO")
in 1989 to analyze the practices of the National Institutes of Health
("NIH") in this area. A 1990 report found that NIH had made little
progress in implementing a four-year-old policy to include more women
in government-funded studies. Much of the controversy has focused on
recent studies of heart disease, such as the National Heart, Lung and
Blood Institute's aspirin study and the Multiple Risk Factors Intervention
Trial (referred to, ironically, as "Mr. Fit"). As a result of these practices,
physicians are often unsure whether the data from these studies can be
applied to their female patients. Those who do extrapolate are, in essence,
running small-scale experiments on their patients rather than providing
proven therapy.

It is clear that clinical trials do not provide an adequate assessment of
drug safety for many of the ultimate consumers of the drug. For many
groups, such as women and the elderly, the solution is clear: study these
subjects, either as part of the regular trials or in separate studies. The
answer is less obvious for patient groups, such as pregnant women, where
ethical constraints are more compelling. Yet one lesson of Accutane is
that, if the risks are too high to justify testing in a particular population,
that information must be publicized from the start.

2. Pre-Approval Testing and Unlimited Drug Access

Presently, a drug approved in the U.S. may be prescribed by any li-
censed physician for any ailment, not just those for which the drug offi-
cially received approval; ideally, a drug's other uses and abuses will be
taken into account by the FDA during its initial safety assessment. While
many beneficial uses are discovered in this manner, potential dan-
gers also exist in a system stressing pre-approval testing. In practice, a

60 Id. at 588-89, n.96.
61 See, e.g., NIH Has Not 'Adequately' Implemented Policy to Enroll More Women
in NIH-Sponsored Clinical Trials, THE BLUE SHEET, June 20, 1990, at 3; Susan
Okie, Study: NIH Slow to Include Women in Disease Research, WASH. POST, June
19, 1990, at A10; Diana Morgan, Unlocking Research Barriers: Feds Promise to
Include Women in Clinical Trials, AARP BULL. at 1. In response, NIH set up the
Office of Research on Women's Health in September 1990.
62 1 Food Drug Cosm. L. Rep. (CCH) ¶ 71,010 (Aug. 6, 1990) (stating that
"[w]hen there has been specific evidence of other probable use or potential abuse
of a drug, these have been considered by the FDA in evaluating safety.")
drug may be prescribed for patients who were not included in clinical trials because they did not have the “indicated condition” that was being studied. If this actual patient population is a distinct clinical group (e.g., the elderly), the differences in the way patients react to drugs (and vice versa) may mean that little real proof of safety exists. If the actual patient population is much larger and more varied than the test population, as with Accutane, the incidence of side effects may vary greatly. In either case, it is difficult to extrapolate from clinical studies when patients use the drug for purposes different from those studied.

Accutane is an example of both the positive and negative side of this system. On the positive side, Accutane is now under investigation as a therapeutic and preventive agent for various forms of cancer. Many beneficial new uses are discovered when physicians observe patients who use the drug for its approved indications, long before any full-scale clinical research is contemplated. Limiting a drug to use for only its approved conditions might deprive scientists of such incidental discoveries. Requiring every possible new use of a drug to begin at the laboratory stage would also use a great deal of time and money.

The evidence on the negative side of the Accutane story, however, weighs heavily against unlimited access. By September 1983, the Public Citizen Health Research Group had charged that the drug, prescribed by 90% of U.S. dermatologists in its first year on the market, was being given to patients with less severe and easily treatable forms of acne.53 This meant that a great deal more women of childbearing age were exposed to Accutane than was clinically necessary. In 1988, one FDA staffer estimated that only 4,300 women each year truly had acne severe enough to warrant the use of Accutane.54 According to these statistics, about 15,000 women between the ages of 15 and 44 fell within this category between 1982 and 1987, but 270,000 to 390,000 actually received the drug.

The simple fact that the drug could be prescribed for conditions other than severe recalcitrant cystic acne did not necessarily mean that it would be; a great deal of blame rests on the media attention and promotion received by the drug.55 Opponents contend that the drug was “overpromoted and oversold, placing an unnecessarily large number of patients at risk.”56 The excessive media attention raised patient awareness of the drug’s benefits, but not its side effects. Patients demanded the acne “won-

54 Dr. David Graham, quoted in Michael Waldholz, FDA Panel Suggests Strict Limits on Use of Acne Drug That Causes Birth Defects, WALL ST. J., April 27, 1988, at 3. Roche disagreed, setting the figure at 78,000. Id.
55 David Graham, quoted in Popular Anti-Acne Drug Linked to Birth Defects, TRIAL, June 1988, at 90. The FDA estimated in 1988 that 1 in 23 Americans has used the drug, and that 97% of the prescriptions were inappropriate. See Nygaard, supra note 26, at 82.
56 Lewis, supra note 31, at 16. See also Nygaard, supra note 26, at 83.
der drug,” and many physicians were happy to comply. As one researcher admitted, “[i]sotretinoin has been promoted by many physicians as a “cure” for acne, so it was inevitable that infants would be born after being exposed in the first trimester of pregnancy.” The “inevitability” of this tragic result had Accutane been restricted to its approved use is not clear. What is clear, however, is that the mixture of pre-approval testing, legal use of prescription drugs for non-approved purposes, and the media attention common in an information-based market economy can be a dangerous combination.

3. Limits of Pre-Market Approval Mechanisms

In theory, careful pre-market testing is a very good idea. In practice, as the above discussion illustrates, it has many flaws. While some of these flaws may be attributed to the unique American medical economy, there are problems inherent in any system relying on pre-market testing.

The main problem is that many severe adverse reactions are rare enough that they “will not necessarily manifest themselves until a drug has been used by a far greater proportion of the population than is feasible even with extensive pre-market testing.” A fatal reaction that occurs in one out of every 50,000 patients will probably not be discovered in a trial of even 5,000 subjects, but will occur if 500,000 people actually take the drug. The same can be said of reactions that occur only after long-term use; even the most comprehensive clinical trials do not duplicate the conditions of a patient who must remain on therapy for the rest of her life. In addition, it is easy to forget that medications require a trade-off between the dangers of the underlying condition and those of the drug. If a drug is potent enough to work, it will probably have some side effects. Thus, “[t]he public good requires the FDA to make judgments based on necessarily incomplete information.” While pre-approval testing procedures can be improved a great deal, there is a point at which only lifelong testing in the entire patient population would provide perfect data. Since this is not a feasible solution, the logical next step is to create post-market procedures to track and address adverse reactions that pre-approval testing missed. It is to these procedures, both in the U.S. and abroad, that we now turn.

67 Benke, supra note 32, at 3267.
68 Teff, supra note 4, at 579. See also Olli S. Miettinen, Alternatives to Clinical Trials in Post-Marketing Research on Drug Effects, in DRUGs BETWEEN RESEARCH AND REGULATIONS 65 (C. Steichle et al., eds., 1984).
69 See, e.g., Dr. F. Gilbert McMahon, How Safe Should Drugs Be?, 249 JAMA 481 (1983) (Commentary). In many cases, the more serious the disease, the more potent the drug and hence its side effects. There are notable exceptions, however, such as the use of antibiotics to treat many infections.
70 Id. at 482.
B. Adverse Reaction Reporting in the United States

Mindful of some of the shortcomings of clinical trials, the U.S. has a system for tracking post-market adverse reactions. In contrast to other countries, however, the U.S. system is weakly enforced and the information it generates is underutilized. This attitude is somewhat consistent with an overall regulatory philosophy that stresses pre-approval proof of safety over post-approval "clean-up."

The U.S. system depends in large part on cooperation between the FDA and drug companies, who are required by law to report most adverse reactions within a specified period of time;\(^1\) physician reporting is voluntary. To facilitate collection and analysis of this data, the FDA established a Division of Drug and Biological Product Experience and designed a Drug Experience Report form and guidelines for determining the likelihood that a drug caused the adverse event.\(^2\) Once the reports are received, the FDA puts them into a computerized Adverse Drug Reaction ("ADR") system, and analyzes the data for patterns of adverse effects. Once patterns of toxicity emerge, the FDA may take a variety of actions. Although the system is adequate in theory, whether or not it actually works is the subject of some debate. One of the main drawbacks to the U.S. system is that only drug companies, and not physicians, are required to report adverse reactions. The drug companies must rely, in turn, upon reports voluntarily made by physicians and information gathered by drug salespeople during their sales calls with physicians. In fact, the FDA admits that fewer than 10% of physicians report reactions, and those physicians only report a small percentage of the reactions they actually observe.\(^3\) There is some evidence that the voluntary system works; for example, the pain reliever Suprol was suspended by its manufacturer after voluntary physician reports of flank pain and temporary kidney failure in healthy male patients were received.\(^4\) There is also scientific evidence that education can increase the number of voluntary physician reports; in one study, after two years of educational intervention there was more than a 17-fold increase in adverse reports submitted by the physician subjects compared with the yearly average prior to the study.\(^5\) Yet the wisdom of relying on voluntary reports for such important information is still questionable.

\(^1\) See Records and Reports for Approved Products, supra note 24.
\(^2\) For an outline of the FDA guidelines, as well as a sample of the form, see R. Dorrien Venn, Adverse Reactions and Interactions of Drugs, in NEW DRUG APPROVAL PROCESS: CLINICAL AND REGULATORY MANAGEMENT 223-30 (Richard A. Guarino ed. 1987).
\(^3\) See Samuel Ackerman, Watching for Problems Testing May Have Missed, in FROM TEST TUBE TO PATIENT, supra note 6, at 51-53.
Other criticisms of the system concern what the FDA does with the information once it is received, and how often the agency uses its power to require more stringent surveillance of a particular drug. According to a 1986 GAO report, the ADR computer system misplaced a substantial portion of the reports it received each year. In addition, many of the reports contained inaccurate data, and the information was of little use to the reviewers responsible for assessing the safety of specific drugs. Other commentators have stressed that the FDA has the power to require much more stringent post-marketing surveillance, yet has chosen to apply that power in only a select few cases (such as the heroin substitute methadone).

The present ADR system does have its proponents. For some, Accutane is an example of the system's "success": because the manufacturer and FDA received reports of birth defects, the FDA was able to require much stricter warnings against use during pregnancy. Yet there are those who would undoubtedly say that even one birth defect was too many for a drug that sponsors always knew had teratogenic potential. At the very least, some might question the effectiveness of the stronger warnings in preventing Accutane use during pregnancy, or criticize the delay between the first reports of birth defects and the requirement of much more stringent warnings and procedures. In addition, post-marketing surveillance did not generate the type of information that most researchers find essential, including adequate assessments of exposure rates during pregnancy and a calculated risk of adverse outcomes. If Accutane is an example of how the U.S. ADR system "works," it may raise serious questions about the effectiveness of the overall U.S. regulatory scheme.

C. Post-Approval Controls in the United States

Of course, monitoring reports of adverse drug reactions is only part of the process: for the system to control the safety of marketed drugs, there must be an adequate response to the gathered information. The U.S. approach is extremely flexible in this regard, allowing the FDA many avenues of action before removing a drug from the market. Once again, Accutane tested just how creative the system could be.

66 See PINK SHEET 1986, Oct. 20, 1986, (LEXIS, Genmed library, T&G-8, T&G-9) (estimating that about 10,000 of the 40,000 ADRs received each year are missing because the FDA fails to enter them into the computer system).
67 Id.
69 See Zamula, supra note 1, at 9.
1. The Developing Accutane Warnings

Accutane presented a very compelling scenario for the use of flexible regulatory measures: the only available treatment for a physically and psychologically debilitating disease, it posed major risks only in one specific population. The FDA dealt with this danger through a combination of warnings and education, which became increasingly more stringent and creative as birth defects continued to occur. The perceived failure of these approaches leaves open the question of whether the U.S. system is fundamentally inadequate, or whether Accutane simply presented a combination of features that stretched the system beyond its limits.

The original Accutane labeling included such side effects as severe drying and chapping of lips and elevated cholesterol levels; it referred to evidence of birth defects in animal studies, but stated there was no such evidence for humans (an accurate statement, since pregnant women were excluded from the clinical trials). Statements were included to the effect that women of childbearing age should not be given Accutane unless they used effective contraception, and that counseling should be available to discuss the possible effects on a fetus and the desirability of continuing any pregnancy that occurred during treatment. At least one commentator has put the bulk of the blame on this initial labeling, claiming that “[i]nstead of starting out with rigorous restrictions on Accutane, to be relaxed in the light of experience, the FDA took the opposite approach.”

Knowing that the drug was likely to cause birth defects (as acknowledged by the stringent contraception/voluntary abortion requirements of the clinical trials), the FDA relied on fairly standard labeling and warnings. In the face of widespread media coverage of the “miracle cure,” this was simply not enough.

Education efforts began soon after the drug entered the U.S. market. Dr. Frank Yoder warned his colleagues of numerous side effects in the January 21, 1983 issue of the Journal of the American Medical Association, the first “Dear Doctor” letters went out in July and August, and the FDA published reports of the first 12 reported “adverse pregnancy outcomes” in the August 27 issue of the Lancet. In September, after the Health Research Group charged that the drug was being oversold, the first labeling changes were made: information was included about “human congenital abnormalities,” and the pregnancy contraindication was put into boldface type. The new label also included information about

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71 Information was also available about other potential side effects, which included conjunctivitis, fatigue, rashes, alopecia (hair loss), skin infection, increased sensitivity to the sun, and chemical abnormalities of the liver. See Chorlton, supra note 27, at A17, col. 5.
73 Yoder, supra note 28, at 350.
74 Rosa, supra note 29, at 513.
serious central nervous system and gastrointestinal side effects, and reminded practitioners that the drug should be reserved for treatment of severe recalcitrant cystic acne unresponsive to conventional therapy.

By early 1984, with 16 major birth defects and 20 spontaneous abortions reported to the FDA, the labeling was again changed. Roche now advised women to use effective forms of contraception for a month before and after Accutane use, requested a pregnancy test two weeks before the start of treatment, and added a boxed warning about a cerebral side effect that mimicked the symptoms of a brain tumor. As a precautionary measure, the FDA asked blood banks not to accept donations from people during and up to a month after Accutane therapy, fearing that the blood might be transfused into pregnant women. Roche prepared educational advertisements detailing proper prescribing procedures, which appeared in "Medical Director's Page" formats in medical and pharmacy journals. As early as May 1984, however, the FDA's Dermatologic Drugs Advisory Committee rejected suggestions that Accutane prescriptions be restricted to dermatologists, that a second opinion be required before initiation of therapy, and that a contraceptive automatically be prescribed in combination with the drug.77

As reports of birth defects continued, minor labeling changes and publicity efforts occurred. It was not until 1988, however, that the FDA publicly concluded that its earlier efforts at education and admonition had failed, estimating that many more than the 62 reported cases of birth defects had occurred in the 16,000 to 24,000 exposures of pregnant women to the drug between 1982 and 1986.78 When the Dermatologic Drugs Advisory Committee met on April 26, its members rejected a ban on the drug but asked for unusually stiff restrictions; in what many called an extraordinary and unprecedented step, the Committee advised that the drug's availability to doctors be curtailed, although it did not specify how.79 Suggestions included limiting prescriptions to certain specialists, limiting the types of patients who could obtain the drug (e.g., by age or severity of acne), or requiring a second opinion before therapy. Although such measures had been taken by individual companies on their own in the past, the FDA had never taken such action against an approved drug, and many observers doubted the agency had the legal right to do so.80 The Public Citizen Litigation Group, a sister organization of Dr. Sidney Wolfe's Health Research Group, soon filed a petition requesting that the FDA invoke imminent hazard provisions to remove Accutane from the market until highly restrictive new approval restrictions could be designed.

76 Accutane Warnings Expanded: Blood Banks Asked Not to Accept Donations from Persons Under Treatment, supra note 35.
77 PINK SHEET, May 21, 1984, at T&G-2.
78 Abramowitz and Hilts, supra note 37, at A1, col. 2.
79 Waldholz, supra note 54, at 3, col. 2.
80 See, e.g., Altman, supra note 70; Popular Anti-Acne Drug Linked to Birth Defects, TRIAL, June 1988, at 89.
Not surprisingly, the FDA chose a middle ground, requiring comprehensive labeling, packaging and marketing changes but declining to restrict physician access to the drug. Revised patient labeling included a statement that the risk of birth defects was one in four or greater, a photograph (later a drawing) of an infant with typical deformities, a "nonpregnancy" symbol on each page, advice that patients obtain an informed consent form, a statement advising prescriptions to begin only on the second or third day of the menstrual cycle, and a phone number to call for further information. The revised physician labeling included stronger contraindications in bigger print, advised that the drug be withheld unless the patient was capable of understanding the risks and complying with the procedures, advised that patients acknowledge the warnings both orally and in writing and have a negative pregnancy test within two weeks of beginning therapy, included the nonpregnancy symbol, and advised that Accutane should be prescribed only by physicians with special competence in treating this form of acne. A detailed informed consent form was developed for mailings to all physicians who might prescribe the drug, and the patient brochure was revised to include the photograph/drawing. Blister packaging was developed, dispensing only ten doses at a time and including a nonpregnancy symbol on the package of each individual dose. Each blister pack included a tear-off, pre-paid postcard for patients to provide identifying information and proof that the informed consent was received.

The distribution of these unique "Pregnancy Prevention Kits" began on September 19, 1988. Although some observers thought the plan was "a bold example of what can be accomplished when a manufacturer, professional organizations, and FDA cooperate in finding ways to minimize the risks of a drug while preserving its availability to those who can greatly benefit from it," others thought the FDA had not gone far enough. By October 1989, over 12,000 women were enrolled in Roche's survey, and the company had begun a dermatologist-targeted advertising campaign with an untraditional focus on drug contraindications, rather than drug uses. There were some indications of the programs' success: there were 12 reported cases of birth defects in 1986, 10 in 1987, 3 in 1988, and 4 in 1989. By May 1990, however, some FDA officials concluded that the campaign had failed: an estimated 65,000 women of childbearing age had received new prescriptions for the drug in 1989, despite beliefs that only about 4,300 women had the severe form of acne for which

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81 See sources cited supra, note 38.
82 Judith Willis, New Warnings About Accutane and Birth Defects, FDA CONSUMER, October 1988, at 26, 29.
84 Charles Marwick, Additional Steps Proposed to Ensure Antiacne Drug Used Only in Appropriate Patient Population, 263 JAMA 3125-26 (1990). However, critics argued that the expected rate of contraceptive failures suggested that from 33 to 227 birth defects actually occur each year; Dr. Graham estimated 112-130 birth defects for 1989. Id.
the drug was indicated.\textsuperscript{85} Roche took additional steps, including preparation of a videocassette about the risks of the drug (for patients to view in the doctor's office), and expansion of referrals to obstetrician/gynecologists for pre-therapy pregnancy testing. The FDA agreed to wait until the end of 1990 before assessing the effects of the company's educational efforts. On May 20, 1991, the Dermatologics Drugs and Fertility and Maternal Health Drugs Advisory Committee concluded that the campaign was succeeding and unanimously rejected restrictions on the distribution of Accutane, but suggested further tightening of the label warnings.\textsuperscript{86}

2. Assessing the Accutane Efforts

It is extremely difficult to assess the effectiveness of the warnings and educational campaigns used to try to decrease the number of Accutane-induced birth defects. A large part of the problem is the lack of adequate statistics; proponents claim the rate of birth defects has fallen as the education campaign and stringent warnings took effect, but others claim the number of unreported cases is, and has always been, much higher. The deficiencies in our ADR system contribute to the lack of knowledge of how many birth defects, spontaneous abortions, and even voluntary abortions occurred in exposed women. Yet some of this may be due to the way in which Accutane exerts its teratogenic effects. Since damage to the fetus occurs before day 40\textsuperscript{87} (before many women realize they are pregnant), and may result from even limited exposure, a woman may be unaware that she has exposed her fetus to the drug. Similarly, it is difficult to count spontaneous abortion rates in a population that may not know it is pregnant.


\textsuperscript{86} The committees recommended that doctors wait for negative pregnancy test results before filling Accutane prescriptions, that women be warned not to start Accutane therapy until the second day of their menstrual cycles, that the acceptable types of pregnancy tests be expanded, and that the drug indication be changed to reflect changing dermatological definitions of acne. The committees relied in part on Roche's preliminary data from an ongoing study of Accutane use in women of childbearing age, conducted by Boston University's Slone Epidemiology Unit. \textit{See Roche Accutane Labeling Should Reflect “Broader Definitions” of Severe Acne}, PINK SHEET, May 27, 1991, at 7 (available in LEXIS, Genmed Library); \textit{Expert Panels Reject Restrictions on Acne Drug Distribution}, Reuters, May 20, 1991 (available in LEXIS, Nexis Library). Roche later reported that the number of new Accutane patients who were women of childbearing age had declined from 95,000 in 1985 to 57,000 in 1990. \textit{Roche Reports Progress in Accutane Warning Program}, FDA CONSUMER, September, 1991, at 4.

\textsuperscript{87} \textit{Popular Anti-Acne Drug Linked to Birth Defects}, supra note 80, at 91.
Even in the beginning, it was clear that the primary task was to keep this drug away from pregnant women. If anything, the difficulties posed by Accutane's early teratogenic activity, as well as the well-known fact that even the most effective contraceptives do fail, could have argued for more stringent controls from the start. While the FDA should be lauded for its creative and flexible efforts at regulation and education after the drug entered the market, some blame can certainly be put on the original, lax warnings.

Another unanswered question is whether the warnings effectively reached their intended audiences. As one doctor noted, patient illiteracy and lack of fluency in English makes the literature-based warnings/education approach less attractive. The massive media attention also compounded the problem, and probably led to exposure of more pregnant women to the drug. If deformed babies were "inevitable" given the media promotion, it was likely that "high-visibility publicity was necessary to counteract the positive media attention Accutane received when it first appeared on the market." The educational efforts adopted by Roche at the FDA's request were largely targeted to physician prescribers (e.g., "Dear Doctor" letters or advertisements in medical journals). Efforts to warn the public, which had read again and again of the "miracle cure," were limited. Ideally, a well-informed and ethical physician would not prescribe the drug if asked by a patient with mild acne. However, more than most drugs, Accutane requires a level of care and responsibility on the part of some patients (i.e., women of childbearing age) that the media failed to stress. Perhaps the FDA could have targeted the general media more, but it still might not have been enough.

What alternatives were available to the FDA and Roche for preventing further exposure of pregnant women to Accutane? In severe cases, as with the anti-arthritis pain-killers in the early 1980's, the FDA has taken drugs off the market or pressured the manufacturers to do so. But as the Dermatologic Committee realized, removing Accutane from the market (whether by FDA command or at Roche's own initiative) would have deprived thousands of people who were not at risk of the only available treatment for a disfiguring disease; it might also have had the effect of slowing development of new drugs with similar profiles. Although the FDA might have imposed stricter limitations on dispensing the drug at the time of approval, as it recently attempted to do with the anti-schizophrenic drug Clozaril, imposing restrictions after approval would have

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88 The Needless Tragedies of Accutane, supra note 72, at A34.
89 Altman, supra note 70.
90 Lewis, supra note 31, at 19.
92 Wary of a fatal but detectable blood disorder associated with the use of the uniquely effective drug clozapine (marketed by Sandoz as Clozaril), the FDA originally required that distribution be "bundled" to an expensive national drug-distribution and side-effect monitoring system. See, e.g., Carl Salzman, Mandatory Monitoring for Side Effects: The 'Bundling' of Clozapine, 323 NEW ENG. J. MED. 827 (1990).
created a host of political and legal battles. In dealing with Accutane, the FDA used a creative variety of approaches permitted by the U.S. drug regulatory system. Although it can be seen as a failure of the system to live up to its potential, the Accutane story may also show us the natural limits of the U.S. system.

IV. ALTERNATIVE METHODS OF DRUG REGULATION: THE BRITISH APPROACH

The U.S. approach to drug regulation is by no means the only one. In each country, regulatory controls and procedures reflect a careful consideration of the basic dilemmas, combined with the values and traditions of that particular culture. For these purposes, a good counterexample to the U.S. approach is that of the United Kingdom.

A. The United Kingdom Approach

In many respects, drug regulation in the U.K. is quite similar to the U.S. Both countries have a licensing process, both require approval before a drug enters the market, and both maintain control over marketed products. The key difference, however, is that

in the U.K. . . . regulatory practice has more readily accommodated to the unpalatable truth that the research process continues even after a licensed drug has been made available for general prescription, and that serious, rare side effects will not necessarily manifest themselves until a drug has been used by a far greater proportion of the population than is feasible even with extensive pre-market testing.93

This contrast in regulatory philosophy shifts the emphasis on safety to post-marketing surveillance mechanisms.

Drug regulation in the U.K. is governed by the Medicines Act 1968.94 Prior to the Act, there were no safety or efficacy requirements for drugs; it was in this atmosphere that the thalidomide disaster occurred. A temporary, voluntary system of controls, with which most manufacturers complied, was instituted after the disaster; it was replaced by the Medicines Act 1968, which imposed safety and efficacy requirements and required companies to submit new drug applications to the Committee on Safety and Medicines ("CSM") for approval.95

93 Teff, supra note 4, at 579.
94 See generally Teff, supra note 4, for a comprehensive look at the history of drug regulation in England.
95 The British system strives to be “scientific,” rather than “political.” To this end, safety decisions are made directly by the CSM, while efficacy decisions are made by committees of medical advisors. In the U.S., the FDA has responsibility for both. See Rosemary Pierce Wall, Note, International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation, 10 RutgerS Computer & Tech. L.J. 317, 326 (1984) (written before the new IND and NDA changes were announced).
Very briefly: In England, a clinical trial certificate ("CTC") will be issued if the animal and volunteer studies satisfy safety, quality and efficacy criteria; no authorization is needed before this point. Trials similar to Phases II and III are then conducted under CSM guidelines, and the licensing authority must be "satisfied" as to safety, efficacy, and quality before final approval. The differences are most apparent, however, once the drug has gained approval. Systematic, mandatory reporting of adverse reactions and ineffective treatments through formalized procedures is the rule. Moreover,

[i]n the U.K., not only is there more stress on monitoring post-market adverse reaction, but limiting the right to prescribe certain drugs to hospital pharmacies, or to particular categories of medical specialists, is an accepted method of identifying and minimizing potential harm.\(^9\)

The British regulation of Accutane illustrates some of these approaches.\(^9\) Like thalidomide and certain chemotherapy agents, Accutane is in a special, stringently controlled category. A woman with acne must receive a referral from her own doctor to one of the select 350 dermatologists who can prescribe the drug. If the drug is indicated, the dermatologist must warn the woman of the risks of becoming pregnant, provide a written warning, obtain two copies of a signed informed consent form (one of which the woman keeps), and obtain her agreement that she will obtain an immediate abortion should she become pregnant.

Thus, the British system regularly relies on precisely the types of physician and patient restrictions that the FDA refused to adopt for Accutane. From a legal perspective, this is perhaps not surprising. The British system was designed to include such restrictive measures; since the U.S. system was not, it is no wonder that people questioned the FDA's authority to do so. In addition, the later development of the British system (1968 compared to 1938), and its response to the special circumstances of the thalidomide tragedy, may have influenced the drafting process. Yet the real differences are deeper, and reflect each culture's attitudes towards regulation and health care in general.

The distribution, price, and control of pharmaceuticals in Britain (and many other European nations) is strongly influenced by the existence of a nationalized health care system.\(^9\) Under the National Health Service ("NHS"), created in 1948, primary care is provided by government-employed general practitioners; referrals are then made to specialists (called "consultants"), most of whom are employed by regional health authorities. Although a growing private medical care sector also exists, the predominance of NHS makes post-marketing control of pharmaceuticals easier.

\(^9\) Teff, supra note 4, at 579.
\(^9\) See Kolata, supra note 2, at A25, col. 3-4.
In particular, such a centralized system is much more efficient at collecting and processing reports of adverse reactions from patient records.99 The British government is the employer of most physicians, as well as the single major purchaser of drugs. NHS directly bears the costs of many drug prescriptions.100 Recently, a rising national drug bill led the government to distribute a list that limited the drugs for which NHS would pay; the introduction of strict drug budgets for practitioners (with financial penalties for overprescribing) has also been suggested.101 The power exercised by the British government as the major drug purchaser, combined with a referral-based system of consultants, makes it easier for the distribution of drugs to be closely limited and monitored.102 A national system of health care also allows the government to exercise control over drug prices, and sometimes over drug development as well.103 Although the U.S. government is also one of its country’s largest drug purchasers (through Medicare and Medicaid), it has not used its position to exact the same measure of formal or informal control on drug distribution as its British counterpart.

To a certain extent, this may be due to deeper cultural value differences between the nations that contribute to very different regulatory atmospheres. Harvey Teff has noted the British preference for administrative secrecy, compared to the American reverence of official accountability and public access to information.104 Teff traces the British attitude to an historical “notion that the government somehow owns rather than holds in trust information of public interest.”105 By contrast, the American po-

99 See Wall, supra note 94, at 325-26; Teff, supra note 4, at 579. However, many analysts agree that the lack of a centralized health care system does not create insurmountable barriers to the development of such a monitoring system. See, e.g., Wall, supra.

100 There are some limits on the possible overprescription of such drugs, however. See Aaron and Schwartz, supra note 97, at 17 (claiming that “in practice the power to prescribe has little financial reach because GPs provide patients no care more sophisticated (or costly) than that which can be dispensed from the office.”). In addition, “prescription-happy doctors may come under review by other physicians and be warned.” Id.


102 In fact, one reason that the voluntary regulatory scheme in place from 1964 to 1971 was successful had to do with the government’s role as a major purchaser. “[I]n practice all the major manufacturers complied with it, not least because the vast bulk of their domestic trade was with the National Health Service, and doctors could be informed that a drug had not received the committee [on Safety of Drugs] approval.” Teff, supra note 4, at 575.

103 For a discussion of price controls in Britain, see Teff, supra note 4, at 602-06. Restrictive attitudes towards new drug development are illustrated by the policies of the Swedish National Board of Health and Welfare (“NBHW”). By severely restricting “me-too” drugs, “much like a hospital formulary which selectively includes drugs from therapeutic categories, these NBHW regulations have the effect of limiting available drugs in Sweden to those with significant therapeutic differences.” Wall, supra note 94, at 327.

104 Teff, supra note 4, at 578-81.

105 Id. at 580.
political system demands public accountability. Thus the British regulatory system is characterized by secrecy, while that in America involves "substantial Congressional oversight, constant media exposure and the influence of the consumer lobby." Different political histories and cultural values in Britain and the United States have thus created very different atmospheres in which drug regulation evolved.

B. The Approaches in Perspective

Is the British approach truly more effective than the American one? The less stringent pre-approval requirements of the U.K. system do generate less paper and lead to quicker review of drugs. One study found the mean licensing time in 1980 for new chemical entities in the U.K. to be 17.4 months, compared to 34.5 in the U.S.; the U.K. median was 12.7 months, compared to 32.5 for the U.S. However, the data on drug safety are not as clear. Between 1970 and 1989, the U.K. approved 55 more drugs than the U.S., but also discontinued the production of more (33 compared to 19); from 1963 to 1969, when the U.K. did not require proof of efficacy, 77% of the "extra" 48 drugs that made it onto the U.K. market were discontinued. The recent data suggest that the two systems, although they may give different results for particular drugs, are of almost equal overall effectiveness.

What is clear, however, is that the European experience with Accutane has been vastly different from that of the U.S. By 1988, only 9 babies with severe birth defects linked to Accutane were reported outside the U.S.; six of those occurred in Canada, where the drug is regulated in the same manner as in the U.S. What this may suggest is not that the British approach is superior as an overall system, but that it may be better equipped to deal with the rather unusual case of Accutane. For a system designed to avoid the dangers of a drug like thalidomide, perhaps that is not surprising.

C. Changing the U.S. System

What, then, are the chances of adopting the British attitude toward post-marketing surveillance which appears to have spared the Europeans

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106 Id. at 579-80.
109 Kolata, supra note 2, at A25. Other European countries have taken different but also stringent approaches to the drug. In Spain, the drug is only prescribed by dermatologists and only through hospital formularies. Sweden, which did not approve the drug, will provide it if doctors make special, documented requests for it. And in France, the drug is restricted because the national health insurance will not cover it, and patients must pay for it themselves. Id. at col. 3-6.
the tragedy of Accutane? The calls for expanded post-marketing surveillance in the U.S. have come from many quarters. Some proposals target a particular type of drug, such as contraceptives or generics, and some propose sweeping changes in the regulatory system itself. One particularly interesting proposal, emanating from the then-chairman of the Department of Medicine at Stanford University School of Medicine, suggested using the record-keeping systems developed for Medicaid and Medicare, and would finance the system by a $.01 tax on each prescription sold.110

There is some evidence of more concrete changes in FDA surveillance practices, however. The Drug Regulation Reform Act of 1979, which was passed by the Senate but never made it through the House, would have provided explicit authorization for the FDA to require surveillance in many cases.111 The 1980's revisions of the IND and NDA procedures were much more explicit in their requirements for the reporting of adverse reactions by pharmaceutical companies.112 And, in perhaps the most promising development, the FDA has recently established an internal task force to study the possibility of “conditional” approval for drugs for life-threatening illnesses, combined with careful post-market scrutiny.113 What all these plans suggest is a piece-by-piece adoption of post-market orientation for certain drugs only, rather than a full-scale revision of the system. Perhaps this is exactly what is needed; after all, it is in “special” cases, such as Accutane, that the British system appears to be superior.

V. CONCLUSION

A. Future Regulation in the United States

The Accutane story can be viewed in many ways. It can be seen as a failure of the U.S. drug regulatory system, of the clinical trials, ADR reports, and warnings-based approach to regulating a dangerous drug. It

110 See Regional News section, New Hampshire edition, Proprietary to the United Press International, May 9, 1982. Unfortunately, the specific procedures by which such a system would operate were not identified at that time. For other proposals, see, e.g., Contraceptive Post-Marketing Surveillance System Should be Established, Two FDA Panels Concur, THE BLUE SHEET, June 20, 1990, at 4; FDA Actions Against Drug Manufacturers Should be Available to Providers Under FD&C Act, AphA Tells Dingell; Mandatory Two Year Post-Marketing Studies Urged, THE PINK SHEET, Mar. 19, 1990, at 6; Richard Know, New Data to Force Change in Heart Drug Use: Broader Issues Arise as FDA Speeds Approvals and Seeks to Detect Drug Problems After They Reach the Market, BOSTON GLOBE, Jan. 30, 1989, at 25; THE GRAY SHEET, June 30, 1986, at I&W-7.


112 Marlene Cimons, Plan Would Hasten OK for Certain New Drugs, L.A. TIMES, Jan. 12, 1991, at A2. However, this proposal appears to be driven more by the need to “fast-track” drugs for particularly severe illnesses than by a perceived need to improve post-market safety controls in general.
can be seen as a failure of specific parts of the system, such as the original package labeling, which the other stages were unable to cover. But it can also be seen as a successful example of how the U.S. system is flexible enough to address these problems, a "success" story of sorts that simply illustrates that some drugs require restrictions that our system cannot accommodate easily.

Accutane does teach us that the parts of the U.S. system are closely interrelated, and that improvements must be made in all areas simultaneously. Speeding drugs through approval is dangerous if we have inadequate post-marketing controls. Carefully designed clinical trials will not be of use unless the labeling accurately reflects their results. A careful system of reviewing ADR reports with an eye towards immediate labeling changes is only good if the ADR reports are collected, tabulated, and made accessible to the reviewers. In essence, isolated changes adopted from other regulatory systems may not work if the overall U.S. philosophy and organization is not taken into account.

For these reasons, I do not read the lesson of Accutane to be that the United States should completely revise its drug regulatory system along the lines of the British scheme. It is doubtful that a system of strict post-approval governmental controls would be politically acceptable in this country, nor has such a system demonstrated substantial advantages for the vast majority of drugs. At the very least, however, we must improve our existing procedures in the areas of clinical trial design, package labeling, and the collection and assessment of post-market adverse reaction information. The tremendous flexibility of the current system, which was demonstrated by the Accutane story, should lead to many more "success" stories. However, we must be willing to recognize that some drugs, like Accutane, may simply exceed the limits of our system of pre-approval testing. For these drugs, which I believe will be few, we must use post-market information much more efficiently, and be willing to contemplate stricter post-market controls on distribution and use.

B. Broader Ethical Implications

In one sense, calling for stricter governmental controls over Accutane only begins the debate. Apart from the dilemmas inherent in any attempt to regulate drugs, these policies involve our ideas about personal liberty, autonomy, and responsibility. Although the media, the FDA, Roche Pharmaceuticals, and prescribing physicians bear some responsibility for the mistakes of Accutane, the women who took the drug must also share the burden. It is easy to view these women simply as victims: bombarded by media reports of the "wonder drug" but not its side effects, they requested the drug from physicians who either neglected to warn their patients or, following the drug labeling, saw little need for worry. However, some women did take the drug without following the recommended contraceptive procedures, and some gave birth. If we accept the ideal of individual autonomy, we must acknowledge that even with the best possible warn-
ings (which admittedly were lacking here), some patients receiving a drug will still choose to engage in behaviors that they have been counseled against. To what extent are we willing to let the government prevent these abuses, at the cost of individual choice?

Accutane is an especially sensitive example because it implicates not only a woman's right to take risks for herself, but her right to put her potential fetus at risk also. Are we willing to allow the government, through stricter drug controls, to make this choice impossible? Even many of the less coercive reforms discussed in this Article would make it difficult, if not impossible, for certain groups to receive such a drug. What of the woman with severe recalcitrant cystic acne who does not believe in birth control? Or the woman whose contraceptive device has failed (as all methods besides abstinence do), but who does not believe in abortion? Are we comfortable allowing the government to make these decisions for us? These issues are certainly not new; we have dealt with such problems on occasion, as in the case of lithium, a treatment for manic-depression. But the widespread use of Accutane has brought the problem home to us in a dramatic way.

It may be argued that some needed improvements in the current drug regulatory system make these questions less critical. For example, if we could truly limit the use of Accutane to its single indicated condition, the number of women who fall into the above categories would be small. But we must still acknowledge how closely any such discussion is linked to broader issues of individual choice and freedom, as well as to current debates over maternal responsibilities and "fetal abuse." Unfortunately, a closer examination of these issues is beyond the scope of this Article.

C. A Final Note: Accutane v. Thalidomide

Why hasn't Accutane generated the same sort of emotionally charged demands for drug reform as thalidomide? The victims of thalidomide made a compelling picture: since many were of normal intelligence, the public saw competent individuals "coping with life as best as anyone can when they lack arms or legs or suffer from other serious deficiencies." Perhaps the Accutane victims are simply too disabled, too easily hidden from view, to generate this amount of public sentiment. Perhaps it is the fact that the reported numbers of Accutane-induced birth defects are smaller. Perhaps we are satisfied that the cost of Accutane is low compared to its

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114 See generally Zamula, supra note 1.
115 Phillip Knightley, et al., Suffer the Children: The Story of Thalidomide (1980). Lest we believe that thalidomide was a great tragedy that became a fairy-tale regulatory "success" story, however, the authors of this book trace the "universal neglect" of the victims and the "near-universal abandonment of families after their afflictions." Id. at 2.
benefits, and satisfied with the cost-benefit analyses institutionalized in the U.S. system. Perhaps we have simply accepted the U.S. system as an embodiment of our political and philosophical ideals. Or perhaps change will come slowly, in the form of tightened procedures and an evolving regulatory philosophy. Perhaps one day these words, written about thalidomide, will apply equally well to Accutane:

As statutory gaps in consumer protection came to be interpreted in terms of deformed babies, public clamor arose for strengthening the law in every respect necessary to close those gaps.\textsuperscript{116}

\textsuperscript{116} Janssen, supra note 6, at 437.