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January 28, 2000

Protecting the Ignorant, the Unthinking and the Credulous: Are the FDA's Efforts to Acc

Recently, five approved prescription drugs were recalled in a one-year period after the Food and Drug Administration (FDA or the agency) deemed them to be too unsafe for patient use.¹ Notorious among them was fenfluramine (Pondimin), the “fen” half of “fen-phen,” a drug used to promote weight loss in patients. The list also includes Seldane, a popular antihistamine as well as Redux, Posicor, and the pain medication Duract.² All had side effects not detected in clinical trials. This unusually high rate of withdrawals in such a short period of time sparked the most recent round of debate over the ever-controversial topic of the FDA drug approval process.

For decades the FDA has been criticized for its lengthy approval process.³ Patients have demanded faster access to drug treatments and medical products. Recently, however, the debate has shifted to the other extreme. Patients are demanding safer drugs, claiming that the agency is allowing drugs to go to the market before they are proven to be safe and effective.⁴ The FDA, the govern-

¹See Tamar Nordenberg, *When is a Medical Product Too Risky?* FDA CONSUMER MAGAZINE, September – October 1999; See also John Schwartz, *Is FDA too Quick to Clear Drugs? Growing Recalls, Side-Effect Risks Raise Questions*, THE WASHINGTON POST, March 23, 1999.

²See Nordenberg, *supra* note 1.

³See PETER BARTON HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW: CASES AND MATERIALS, SECOND EDITION, at 580-83 (Critics coined the term “drug lag” to describe the lengthy, and what many consider unnecessary, FDA review process).

⁴See Report to the FDA Commissioner from the Task force on Risk Management, *Man-*

ment's guardian of public health and safety, must balance two compelling, yet contradicting ideals. The agency must get drugs out to the public as fast as possible but keep drugs in clinical trials long enough to prove them safe.

The high rate of drug withdrawals in 1999 has brought the debate full circle from 1987, the peak of the AIDS crisis. Then, patients were literally climbing the walls of FDA offices and staging protests across the nation demanding access to drugs as early as possible.⁵ The FDA sped up the approval of AIDS related drugs through legislation that allowed accelerated approval for "investigative new drugs" (INDs).⁶ Since that time the agency has put many more regulations in place that speed up almost every aspect of the approval process. Now, with the recall arm of the FDA working overtime, patients are demanding that the agency slow down and set in place more regulation to insure greater safety. Despite the current attitude that the agency has compromised its standards in the rush to approve untested drugs, the current process of drug approval that allows new drugs to get to the market faster strikes the proper balance between the individual patient's right of access and the overall protection of human health and safety.

aging the Risks From Medical Product Use: Creating a Risk Management Framework, U.S. Department of Health and Human Services, Food and Drug Administration, May 1999, at 17. (The report notes specifically that the Public Citizen's Health Research Group expressed concerns that the agency was compromising its safety standards for shorter review times. Public Citizen conducted a survey of FDA reviewers and determined that 19 out of 53 reviewers had at least one recommendation of disapproval denied by the agency. This statistic, not very telling without more information, nonetheless caused tremendous concern for Public Citizen); see also Rochelle Sharpe, *FDA Tries to Find the Right Balance on Drug Approvals*, THE WALL STREET JOURNAL, April 20, 1999.

⁵See Remarks by David Kessler, IOM 25th Anniversary Lecture, Seattle, Washington, November 7, 1994, <<http://www.fda.gov/oashi/aids/iomkes.html>>; see also Larry Thompson, *Experimental Treatments? Unapproved But Not Always Unavailable*, FDA CONSUMER MAGAZINE, January-February 2000 (1000 gay activists staged a protest outside of the agency's headquarters in Rockville, Maryland, trapping the agency's staff inside).

⁶See *infra* part I.B.

I. A Historical Perspective on Accelerated Approval Mechanisms

A. Pre-1987

The first cornerstone of today's drug legislation was laid in 1938 following the tragedy of Elixir of Sulfanilamide, a calamity that moved Congress to pass the Food Drug and Cosmetic Act (FDCA).⁷ Almost 100 people were poisoned by the elixir, which reached the market without any testing for toxicity.⁸ The legislation required that companies test their products for safety before releasing them to the public. In 1962 yet another tragedy struck. After thalidomide, a morning sickness alleviator, caused more than 1,000 birth defects in Europe,⁹ Congress added the second fundamental consumer protection legislation to the FDA pre-market approval process.¹⁰ Now companies would be required to show that their products were both safe *and effective* in treating what they were marketed to cure. Effectiveness had to be proven through the use of controlled trials.¹¹ The adequacy of the trials was determined according to specific scientific standards for evidence.

⁷Food, Drug and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended in 21 U.S.C. §§301-92 (1994)).

⁸See Richard J. Nelson, *Regulation of Investigational New Drugs: 'Giant Step For the Sick and Dying'?* 77 GEO. L.J. 463, 468-69, (1988); See also Lois K. Perrin, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69 S. CAL. L. REV. 105, 110 (1995); See also Myron L. Marlin, *Treatment INDs: A Faster Route to Drug Approval?* 39 AM. U. L. REV. 171, 176 (1989).

⁹See *Id.*

¹⁰Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. §§301-81 (1994)).

¹¹See Hutt & Merrill, *supra* note 3, at 514-16, for a detailed discussion of the three phases of a drug investigation. (citing the Report of the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology, 96th Congress, 2nd Session (1980)).

The 1962 Drug Amendments, whose mechanisms are largely in tact still today,¹² calls for pre-market testing first on animals. This initial phase lasts on average about two years¹³ and must show evidence of low toxicity to advance to the stage where human testing is allowed. The human testing, known as clinical trials, encompasses three phases.¹⁴ Phase I involves use of the product in a small number of healthy subjects to determine dosage and gather preliminary data. Phase II begins the actual trials of the drug in subjects who have the condition that the drug is intended to treat against. This stage involves a control group. Finally, Phase III involves several thousands of patients in a wide spread investigation of the drug's effectiveness. The average time period for a drug to move through these three phases is around 5 years, but the range encompasses two to ten years.¹⁵ Once the testing is complete, sponsor companies may submit a "new drug application" (NDA) to the FDA and wait for a period of one to two years while the agency administers the approval process.¹⁶ If the NDA is approved, the drug can be prescribed to the public. Post-market use (often called Phase IV) is, however, an important element of the investigation and calls for a careful monitoring of the drug for safety and effectiveness.¹⁷ It is in this stage that the FDA may withdraw its approval and pull a drug off the market if it becomes clear that its use is unsafe or if safer alternatives develop.

Even as early as 1970 the agency recognized the need to decrease the time of

¹²See Nelson, *supra* note 8, at 470.

¹³See Ken Flieger, *Testing Drugs in People*, FDA CONSUMER MAGAZINE, July-August 1994.

¹⁴See *Id.*; see also text accompanying note 11.

¹⁵See Flieger, *supra* note 13.

¹⁶See *Id.*; see also Nordenberg, *supra* note 1.

¹⁷See Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the New Diet Drug Debacle*, 79 B.U. L. Rev. 93, 112 (1999).

the drug approval process for critically ill patients with little or no alternative treatments. In 1977 the FDA introduced a predecessor to today's treatment IND, known as "compassionate IND" which allowed physicians to prescribe an experimental drug to a patient even if the primary purpose was not investigation, but actual treatment.¹⁸ Use of compassionate INDS was informal, ad hoc and not widely publicized.¹⁹

B. AIDS and Treatment INDs

The drug approval process has been widely criticized for its length since its inception in 1962.²⁰ However, never had the agency been so moved to action by its critics until the early 1980s when, in the words of recent FDA commissioner David Kessler, "AIDs activists were literally scaling the walls of the FDA building in Rockport, Maryland demanding access to potential therapies that had barely moved out of the test tube."²¹ These were desperate patients with no alternatives who felt that the agency's policies were denying them of their choice to take the risk of unknown treatments over the near certainty of death. In 1987 the FDA responded to AIDS patients' demands to rush new medication through the approval process.²² Congress passed legislation to allow for investigational

¹⁸ See Ken Fliieger, *FDA Finds New Ways to Speed Treatments to Patients*, FDA CONSUMER MAGAZINE, October 1993; see also Nelson, *supra* note 8, at 471.

¹⁹ See *Id.*

²⁰ See Hutt & Merrill, *supra* note 3, at 581 (quoting Sam Peltzman, Testifying before the Subcommittee on Monopoly of the Senate Small Business Committee, 93rd Congress, 1st Session (1973)).

²¹ Kessler, *supra* note 5.

²² See *How the AIDS Crisis Made Drug Regulators Speed Up*, NEW YORK TIMES, Sept. 24, 1989, p.E5.

new drugs, known as “IND”s, to have an accelerated clinical trial period.²³

The FDA did, however, impose restrictions on treatment INDs. While the initiative makes drugs available in the Phase 2 stage, it applies to drugs intended only for the treatment of “immediately life threatening” and “serious” diseases, for which no satisfactory therapy is available at that stage of the disease.²⁴ In addition, the agency imposes restrictions on the sponsor company. The sponsor must exercise due diligence in completing the clinical trials and investigation of the new drug.²⁵ In addition, the sponsor may charge for the drug to recover costs, but it may not commercialize its product.²⁶ This legislation marked the first formal procedure that allowed patients to decide for themselves whether they would rather bear the risk of unproven treatment or struggle with an untreatable disease.

C. More Recent Acceleration Mechanisms

Since the 1987 treatment IND program, the agency has instituted more policies designed to speed up many aspects of the drug approval process. While the treatment IND program made drugs available to a certain class of people sooner, the fast track program expedited widespread approval.²⁷ The fast track approach allows drugs to enter the market after two, rather than three, phases of testing. This would usually mean that two or three years would be cut off

²³21 C.F.R. § 312.34(b)(1)(i)-(iv) (1988), (promulgating new regulations that allow greater access to promising new drugs not yet available on the market).

²⁴See *Id.*

²⁵See *Id.*

²⁶See Flieger, *supra* note 18.

²⁷21 C.F.R. §§312.80-312.82 (1988)

the standard approval time for the product.²⁸ In 1992 the FDA instituted the parallel track program that offers patients who cannot participate in a clinical trial either for geographic reasons or for lacking entry criteria to receive the same promising therapies from their physicians.²⁹

That same year the FDA initiated the Prescription Drug User Fee Act (PDUFA).³⁰ This program enabled sponsors to pay fees to the agency in exchange for priority review. The fees allowed the FDA to obtain more resources and staff, which greatly increased the agency's ability to process NDAs faster. The PDUFA program was instituted for a five-year trial period but it was so successful that the FDA reauthorized PDUFA in the FDA Modernization Act of 1997 (FDAMA).³¹ The Modernization Act also formalized approval based on surrogate marker data.³² This program allows for drug effectiveness to be proved from sources not traditionally relied on. While the sources of evidence may vary from traditional clinical studies, the FDA claims that its standards of effectiveness have not changed.

II. Right to Access versus Right to Answers

A. The Necessity of Patient Choice.

²⁸See Salbu, *supra* note 17, at 114.

²⁹Expanded Availability of Investigational New Drugs Through Parallel Track Mechanism for People with AIDS and Other HIV-Related Disease, 57 Fed. Reg., 13,250, 13,250 (1992).

³⁰Prescription Drug User Fee Act, Pub. L. No. 102-571, §101, 106 Stat. 4491 (1992).

³¹Modernization Act, Pub. L. No. 105-115, §101, 111 Stat. 2296, 2296-2305

³²New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942, 58,942 (1992) (For example, if a new product claims that it reduces the likelihood of death, then the meaningful endpoint of an investigation into that drug is death of the subjects. However, the FDA allows a surrogate endpoint, such as a decrease in a symptom of the disease, to substitute for the intended endpoint).

The Supreme Court has upheld the FDA's right to withhold experimental drugs from patients in *United States v. Rutherford*.³³ The Court held that the agency has the authority to require a showing of safety and effectiveness in every drug, including those used to treat the terminally ill. The Court concluded that Congress intended to shield even those patients from fraudulent products. This case established that the agency may constitutionally prevent patients from having a choice in their drug therapy.

Since the AIDS crisis in the eighties, the FDA's efforts to increase accelerated approval mechanisms have been driven by the philosophy that patients deserve more of a say in their treatment, and thus warrant greater access to experimental drugs.³⁴ The paternalism of the eighties seems to have given way to a regime in which patients are freer to judge for themselves the marginal benefits of unknown therapies. But now, in light of the recent withdrawals, people are concerned that patient access is too excessive. Even seriously ill patients should not have access to truly unsafe drugs. Deciphering this dilemma requires the determination of whether or not a patient can make a rational choice based on very little information. The government may provide physicians with all known information and possible risks, but it may not be enough to insure that the patient understands the choice in front of her. Despite these concerns, however,

³³442 U.S. 544 (1979). (This case arose when a group of terminally ill cancer patients filed a class action suit to enjoin the government from prohibiting the movement in interstate commerce of Laetrile, a cancer drug not approved by the FDA. Although the plaintiffs raised both the modification and privacy issues, the Court left the privacy issue aside, and held that the FDA regulations were to be applied without exception even to terminally ill patients).

³⁴See Thompson, *supra* note 5. ("Over the last decade, FDA's institutional philosophy has evolved to be more supportive of risk-taking by patients who have run out of options.").

current accelerated approval mechanisms strike an appropriate balance between these two difficult options.

One example of criticism has focused on the drug Viagra, prescription medicine that combats male impotence. The drug took just six months for its NDA to be approved.³⁵ Soon after the drug became available to the public, evidence trickled in to the FDA that the drug might be associated with heart attacks and high blood pressure.³⁶ However, patients continuously choose to use the drug despite warnings about the risks involved. Doctors are finding that men lie about their heart conditions and about other medications they are currently taking in order to obtain a prescription for Viagra.³⁷ A similar story surrounds the acne medicine known as Accutane. Accutane is a wonder drug for those who feel debilitated by their bad skin. However, it is also a powerful teratogen, causing horrible birth defects if taken by pregnant women.³⁸ The FDA found that, despite explicit package warnings,³⁹ patients still chose to take the medication even at the risk of such harm. Even though critics feel that the patients' choices are not rational, the FDA has taken the correct position in allowing patients access to this kind of treatment. Protestors argue that impotence and acne are not terrible enough problems to warrant the risks associated with these drugs.

³⁵ See Shanon Brownlee, *Dying for Sex: The FDA approved Viagra Quickly – Perhaps Too Quickly*, US NEWS AND WORLD REPORT, January 11, 1999.

³⁶ See *Id.*

³⁷ See *Id.* (“Georgia Medical College’s Dr. Lewis says he prescribed Viagra to a man who swore up and down that he wasn’t on nitrates. Then, in a chance meeting with the man’s regular physician, Lewis learned that the man was in fact on the drugs. ‘You can’t imagine the patients who are asking for Viagra. . . they have multiple heart attacks. I have warned patients time and again, and nevertheless they get Viagra.’”).

³⁸ See Hutt & Merrill, *supra* note 3, at 436.

³⁹ Every single pill has a picture of a pregnant woman encircled with a slash. In addition, the packaging contains pictures of deformed babies and has printing in bold “NOT TO BE TAKEN IF YOU ARE PREGNANT.”

However, patients, not the government, are the only ones who can decide if the benefits of treating their conditions are worth the known or possible risks.⁴⁰

The IND program also comes under frequent attack for providing too much patient access in the pre-approval stage. However, within the IND regime, drugs are available only to treat patients with “serious” or life-threatening” illnesses.⁴¹ Drugs may come under consideration only if there are few or no alternatives available. Patients with this category of illness must play a very active role in their health care, especially if they have a disease that requires them to see different physicians, keep track of their medications, and monitor their own development.⁴² Patient choice and access is especially critical in a pressing disease, since only the individual herself can elect how much she is willing to sacrifice in return for only small possibilities of benefit. More importantly, access is limited to drugs that have a reasonable chance of being successful in the marketplace. Because a company must pursue a clinical trial investigation with “due diligence” it will not release a drug under IND status unless it intends to market it eventually.⁴³ Competition, financial resources, and projected demand for a drug will influence its distribution and labeling as an IND.⁴⁴

⁴⁰See Sheila Anne Feeney, *The Battle with Acne*, NEW YORK DAILY NEWS, January, 10, 2000. (The article interviews one patient who testifies that her life with acne as a teenager contributed to her current alcoholism. The article also quotes a statistic that people with acne are twice as likely to be unemployed as those with normal skin. Many of these patients feel that a drug that could eliminate their acne may well be worth the risk of harm).

⁴¹See *supra* part I.B.

⁴²See Nordenberg, *supra* note 1.

⁴³See Perrin, *supra* note 8, at 140-41.

⁴⁴See *Id.*

B. Structural Limitations on Patient Access

The concern about widespread patient access is disproportionate to the actual access available to patients. In fact, the drug pre-approval stage has structural limitations built into the system that serve to protect patients in the absence of approval. For one thing, the FDA cannot give out the name of drugs in experimental trials.⁴⁵ Only in consult with a physician may a patient obtain information about experimental treatment. Therefore, patients must have met with a professional doctor, a step that brings them much closer to making a truly informed decision.

Patients cannot receive an experimental drug from the FDA alone. The responsibility, as well as the desire, to participate in these accelerated approval programs rests solely in the hands of the sponsor company.⁴⁶ The FDA cannot force a company to distribute its products, even at the patient's request. Patients must petition the sponsor directly for access to the experimental treatment. Companies weigh many factors in deciding whether or not to distribute drugs to qualifying participants in the programs, and may choose to withhold a drug that it feels does not show enough promise, or if there is not sufficient information on dosage. Since all use of the product must be reported to the FDA even outside of the structured clinical investigation, if the patients has

⁴⁵ See Thompson, *supra* note 5.

⁴⁶ See *Id.*; see also Statement by Michael A. Friedman, M.D., Lead Deputy Commissioner of the Food and Drug Administration, Department of Health and Human Services, before the Committee on Government Reform and Oversight, United States House of Representatives, April 22, 1998, <<http://www.fda.gov/ola/1998/therapy.htm>>.

qualifications that may skew the data and delay approval for more general use, the company may wish to decline distribution of an experimental drug, even at the patient's request with informed consent.

Finally, the FDA does not advise patients.⁴⁷ The agency does not influence patients one way or the other in deciding on treatment. This neutrality is important for the patient to make her own choice in weighing the risks against the benefits.

III. Faster Approval Times Do Not Mean Lower Drug Safety

The story of INDs and other acceleration methods has been one of true success. Over the past five years, pharmaceutical firms have been able to introduce 172 new medical products into the market, a substantial increase over prior decades.⁴⁸ Since PDUFA in 1992, the average number of new products approved per year has increased by 40%, and in 1998 alone 75% of worldwide molecular entities were first launched in the United States.⁴⁹ In prior decades Americans complained of the “drug lag,” the idea that drugs were available much earlier abroad.⁵⁰ However, today's environment is such that drugs are

⁴⁷ See Thompson, *supra* note 5.

⁴⁸ See Statement by Jane E. Henney, M.D., Commissioner of Food and Drugs, Food and Drug Administration, before the Committee on Health, Education, Labor and Pensions, United States Senate, October 21, 1999, <<http://www.fda.gov/ola/modernization.html>>.

⁴⁹ See *Id.*; see also Risk Management Report, *supra* note 4, at 17.

⁵⁰ See Perrin, *supra* note 7, at 115-16. (Actually, the term “drug lag” has been used in two different contexts. The first context describes the time difference between approval abroad and

now being reviewed in the United States as fast or faster than anywhere else in the world.⁵¹ Nevertheless, the FDA faces a justifiably fickle public. For decades patients have demanded greater choice and access, and now, when the FDA can prove success at meeting the public demand, patients insist they deserve more insurance of drug safety. In response to recent concerns, the agency issued a report studying the drug approval process and reexamining whether the new procedures do enough to protect public health and safety.⁵²

The FDA's Risk Management Report, published in May 1999, showed that the current withdrawal rate in the United States is actually *lower* than it has been for the past few decades.⁵³ The drug approval process is proving more effective in weeding out unsafe drugs. The rate was about 3% in the 1980s, lower in the 90s and only slightly greater than 1% today.⁵⁴ So, while new mechanisms provide for faster approvals, the drugs that are eventually approved are proving to be safer than those of a decade ago.

The report shows that while the NDA review process is halved, the overall length of clinical trials has not decreased.⁵⁵ In fact, the trial period is increasingly expanding with greater scientific knowledge.⁵⁶ The trial period is also

lengthened, as the FDA has increasingly required more studies of different pop-
approval in the United States, but the second usage describes the time between the completion of the clinical trials and FDA approval. Critics claim that the agency creates a "drug lag" with its lengthy review process. See text accompanying note 3; see also Risk Management Report, *supra* note 4 at 16).

⁵¹See Statement of Janet E. Henney, *supra* note 48; see also Statement by David Kessler, M.D., Commissioner, Food and Drug Administration, Department of Health and Human Services, before the Committee on Labor and Human Resources, United States senate, February 21, 1996, <<http://www.fda.gov/ola/1996/nktest.html>>.

⁵²See Risk Management Report, *supra* note 4.

⁵³See *Id.* at 34-35.

⁵⁴See *Id.* at 34.

⁵⁵See *Id.* at 17.

⁵⁶See Nordenberg, *supra* note 1.

ulations, women, minorities, elderly, and so forth. Companies are also using that time period to study the marketing effects of the drugs.⁵⁷ This lengthened clinical trial allows for a fuller safety database for the drug.

The criticism aimed specifically at the IND process is additionally unwarranted. Criticism of IND practice centers on the practical reality of the program. Some critics claim that accelerated approval of a drug will discourage the completion of clinical trials and the investigation of the drug's safety.⁵⁸ While the regulation requires that the trials be completed post-approval, the ability of patients to procure experimental drugs without participating in a clinical trial will delay the investigation and completion of safety testing. Protesters emphasize that there is no standard definition of what defines "due diligence" and companies may not direct as many resources to investigate a drug already approved under the treatment IND program. However, very often IND status is granted only when approval is imminent.⁵⁹ In fact, those who support the program frequently fault the FDA for waiting until much after Phase II has been completed to grant IND status.⁶⁰ Typically, drugs allowed under treatment IND status have already shown promise and proven safety.⁶¹ Since the final treatment IND rule was published more than a decade ago, FDA has made more than 40 drug or biological investigational products available to patients early and has approved 36 of them.⁶²

⁵⁷ See *Id.*

⁵⁸ See Nelson, *supra* note 8 at 484.

⁵⁹ See Perrin, *supra* note 8, at 141.

⁶⁰ See *Id.*

⁶¹ See Thompson, *supra* note 5.

⁶² See *Id.*

The agency attributes a lot of this success to PDUFA.⁶³ As the FDA is provided with more resources it can speed up the administrative aspect of the approval process. More importantly, the agency attributes the success of acceleration to greater cooperation between the FDA and sponsor companies. In conducting clinical trials, companies will often fashion their investigations in a manner in which the FDA is not likely to consider proper evidence of the drug's effectiveness. Early correspondence between the agency and the companies has led to a faster trial and review process. In fact, if the FDA had more resources and staff that could spend more time with each sponsor, it could speed up every drug approval process.⁶⁴

IV. Longer Clinical Trials Will Not Result in Safer Drugs

A. Clinical Trials Do Not Mirror Real World Use of the Drug

A major flaw in the critics call for slowing down the approval process by expanding the scope or length of the clinical trial period is the misconception that longer clinical trials mean safer drugs. Congress places great emphasis on carrying out clinical trials:

There is general agreement among all interested groups that maintaining the ability to carry out adequate and well-controlled trials expeditiously is essential because without such trials it is not possible to determine whether the drug is safe and effective. If the evidence for such a determination is never developed,

⁶³ See Nordenberg, *supra* note 1; see also Statement of Janet Henney, *supra* note 48.

⁶⁴ See *Id.*

or it is not developed expeditiously, individuals with the disease for which the drug is intended may suffer needlessly.⁶⁵

Unfortunately, while clinical trials are the most scientific way by which to prove drug safety and effectiveness, expanding the trial length or even using resources to insure that IND trials are completed would probably not unearth the risks that the critics are most concerned about.

Clinical trials test for both safety and effectiveness in a very *small* population of subjects.⁶⁶ Trials are kept small in order to minimize the number of people exposed to possible unknown risks. In addition, the trials require that the subjects have certain entry criteria that enable the researchers to factor for certain variables and to keep the “control” aspect of the tests. The goal of minimizing exposure makes it a good idea to keep the trials small. The goal of controlling the investigation through entry criteria makes it impossible to expand the population of subjects. It simply is too difficult to find many subjects that meet the criteria. In fact, it could take decades or centuries to find a larger group. Thus, clinical trials can only test for risks that have an extremely high chance of occurring.⁶⁷ Risks that have a low or even medium chance of occurring cannot be uncovered in a small population. That must wait until the product is released to the public and tested on a large population.

⁶⁵55 Fed. Reg. 20,802 – 03 (1990) (proposed May 21, 1990).

⁶⁶See Risk Management Report, *supra* note 4, at 43 (The number of patients exposed to the product increases 1000-fold or more when the new product moves to the marketplace. Thus, if the trials include 1,500 patients, then the chances of seeing an adverse reaction that occurs only once in 1500 uses (considered rare) go from 50-50 in the trial setting to greater than 1000 cases in the public market.).

⁶⁷See Nordenberg, *supra* note 1. (“For a risk, say, that would occur in 1 in 50,000 patients, you would have to study 150,000 people before the drug was approved to give you a good chance of that risk even showing up – although you still aren’t guaranteed to find it. To study 150,000 people with each disease would be a prohibitive barrier to getting drugs on the market.”).

Clinical trials alone could never uncover most risks associated with real-world use of a drug, even if they were decades long. The FDA only requires clinical testing for the intended use of the drug. Investigation of drug safety for combination or “off-label” use is not a prerequisite for FDA approval.⁶⁸ One of the drugs pulled from the market in the recall debacle was fenfluramine, a drug used for years for short-term weight reduction. Only when physicians began prescribing it in combination with other drugs did the lethal problems occur. There is no feasible way for the FDA to test in combinations since there are millions of permutations and sample patient populations are not big enough. It would take centuries to procure subjects and run tests and no drug would ever be released to the market. But while the FDA approves of drugs for intended uses alone, most physicians prescribe drugs in combination with another therapy or for other off-label uses. In fact, most drugs are used for purposes that were not tested in FDA approval trials.⁶⁹ This “off label” use is so prevalent and so important to our system that it cannot be eliminated. The FDA has no authority to regulate the practice of medicine, and physicians may use legally marketed drugs however their professional judgment dictates it may best serve the patient.⁷⁰ The FDA itself recognizes the value and necessity of off-label uses.

⁶⁸As a matter of fact, until recently, the FDA had severe restrictions on advertising off-label uses of drugs or disseminating even truthful information about non-approved uses. Patients are now demanding permanent injunctions that bar the enforcement of these restrictions on the flow of information about off-label uses of FDA approved drugs. See WASHINGTON LEGAL FOUNDATION NEW RELEASE, January 4, 2000 (discussing the case of *Washington Legal Foundation v. Henney* that will appear before the U.S. Court of Appeals for the District of Columbia on January 10, 2000).

⁶⁹See Salbu, *supra* note 17, at 122; see also James M. Beck and Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71,

⁷⁰See *In re Orthopedic Bone Screw Products Liability Litigation*, MDL No. 1014, 1996 WL 107556, at *3 (E.D.Pa. Mar. 8, 1996) (“The decision whether or not to use a drug for off-label purposes is a matter of medical judgment, not of regulatory approval”).

A 1982 FDA Drug Bulletin stated that unlabeled uses of a drug are appropriate and rational in certain circumstances and in fact may reflect a therapy that is well reported and approved of in the medical literature.⁷¹

One of the most significant factors that differentiate clinical trial use of a product from real world use is that patients in experimental trial are closely monitored. Clinical trial patients are seen by their physicians for reevaluation on a regular basis.⁷² The physicians monitor the patients' progress and perform regular laboratory tests for early evidence of toxicity.⁷³ Real world use of the product could result in higher incidence and severer consequences of adverse reactions simply because patients are not monitored closely or seen by their physicians on a regular basis for early evidence of problems.

Lengthy review processes will not result in safer drugs. The consequences will simply be less patient access to alternative therapies. Testing greater populations and in various combinations will result in costs so high that no drugs would ever get to the market. Banning off-label use will result in a loss of a myriad of beneficial drug therapies. These are important mechanisms that provide physicians and patients more options by which to fight diseases. Most injuries and deaths associated with the use of medical products, in fact result from known side effects.⁷⁴ More than half of these injuries are avoidable using the information physicians and patients *already* possess.⁷⁵ Sadly, the risks asso-

⁷¹12 FDA DRUG BULLETIN 4-5 (1982) (cited in 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994)).

⁷²See Risk Management Report, *supra* note 4, at 46.

⁷³See *Id.*

⁷⁴See *Id.* at 8

⁷⁵See *Id.* (citing Bates, D.W., L.L. Leape, and S. Petrycki, *Incidence and Preventability of Adverse Drug Events in Hospitalized Adults*, J. GEN. INTERN. MED., 8:289-294, (1993)).

ciated with medicines on the market are never zero. A safe drug is one in which the risks are reasonable, not eliminated. Expanded clinical trials cannot reduce those risks. Risk reduction is most effective by means of the dissemination of accurate information on managing those risks.

B. Testing on Women and Minorities

When there is a true need to slow the approval process in the interest of safety, the FDA has been willing to do so. The FDA approval process has always been lacking in its protection of women and minorities, and the accelerated pace at which it proceeds only makes matters worse in this regard. The gender gap is wider than most would anticipate, and extends well beyond reproductive organs. For one thing, women have different saliva and digestive systems than men, and may metabolize some medications differently as well.⁷⁶ Women make more antibodies than men, are more prone to diseases like lupus, and suffer much more from migraine headaches and depression.⁷⁷ Long thought to be a male problem, heart disease has become a much more important issue for women as studies show that just as many women die from heart attacks as men do, although they get them about ten years later in life.⁷⁸ One example of the gender gap is Seldane, one of the five drugs recently pulled from the market. Doctors found that it caused heart arrhythmias in women twice as often than it did in men.⁷⁹ Since the FDA's decision to approve the drug depends on

⁷⁶See Colleen Dunn, *Medicine's Gender Gap Research on Women Picks Up Steam*, CHICAGO TRIBUNE, January 12, 2000.

⁷⁷See *Id.*

⁷⁸See *Id.*

⁷⁹See *Id.*; see also Marlene Cimon, *Genders respond Differently to Drugs: Researchers Trying to Solve Scientific Mystery*, THE FLORIDA TIMES-UNION, June 7, 1999; see also Lauren

a cost/benefit analysis of the known risks, women are at much greater risk than men every time a drug gets approved on the basis of male subjects in clinical trials. Therefore, in 1993, the agency passed legislation requiring that clinical trials include the testing of women as well.⁸⁰ Before 1993, drug testing was conducted primarily on men. This new legislation slowed the clinical trial period, raising the costs of investigation tremendously. However, despite the fact that this is a reversal of the philosophy of patient access, the costs are justified in light of the significant differences in adverse reactions between men and women in many drugs.

Minority testing remains non-existent today. However, some population-specific testing should be required when significant differences in adverse reactions occur in various populations. Researchers have found, for example, that asthma occurs in the African-American community 26% more than in Caucasians.⁸¹ 70% more African-Americans suffer from diabetes than do Caucasians.⁸² Yet no legislation requires testing in this community. The cost of testing *all* drugs on minority communities may be prohibitive to getting most new drugs approved, but certainly drugs intended for use in treating asthma and diabetes should be required to be tested on African-Americans prior to approval. If similar disparities exist in other communities as well, then the same

Neergaard, *Drugs May be Prescribed by Sex*, AP ONLINE, May 15, 1999.

⁸⁰See Executive Summary – Gender Studies in Product Development, *Policy Changes: The 1993 FDA Gender Guideline and NIH Initiatives*, <<http://fda.gov/womens/gender/Exec4.htm>>.

⁸¹See Closing the Gap, Multiethnic Healthcare: Asthma, <<http://www.closing-the-gap.com/Departments/Centers/asthma.html>>.

⁸²See Closing the Gap, Multiethnic Healthcare: Diabetes, <<http://www.closing-the-gap.com/Departments/Centers/diabetes.html>>.

rules should apply.

V. Conclusion

With regard to the drug approval process, the FDA faces an extremely vocal opposition. As one critic put it, “the person who thought of accelerated approval should be shot.”⁸³ However, the FDA’s recent efforts at quickening the drug approval process should be commended. The agency strikes a fitting balance between providing patients with access to alternative therapies while insuring safety to the best of science’s ability. The agency’s current method of requiring clinical trials is sufficient in showing safety and effectiveness, without creating a prohibitive barrier to the marketing of any drug. Recent withdrawal rates remain fairly constant with previous decades, even as more drugs reach the public faster than ever. Yet the FDA is not afraid to intervene in the interest of safety, as is evident by its requirement of testing women in clinical trials. Because the FDA holds such a powerful position in making new drugs available to those who need them, the ability to delicately balance patient access against patient safety is vital.

⁸³See Kessler, *supra* note 5.