Is the FDA Safe and Effective?

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Medical drugs and devices cannot be marketed in the United States unless the Food and Drug Administration (FDA) grants specific approval. We argue that FDA control over drugs and devices has large and often overlooked costs that almost certainly exceed the benefits. We believe that FDA regulation of the medical industry has suppressed and delayed new drugs and devices, and has increased costs, with a net result of more morbidity and mortality. A large body of academic research has investigated the FDA and with unusual consensus has reached the same conclusion.

Drawing on this body of research, we evaluate the costs and benefits of FDA policy. We also present a detailed history of the FDA, a review of the major plans for FDA reform, a glossary of terms, a collection of quotes from economists who have studied the FDA, and a bibliography with many webbed links. A more detailed table of contents follows. We are happy to receive comments and criticisms.

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Contents

History of Federal Regulation: 1902–Present

Major legislation with regard to drugs and medical devices:

The Nineteenth and Early Twentieth Centuries

At the turn of the twentieth century, pharmacy was a young and immature science. Most drugs were still created by hand in a local pharmacy. Technologies to assess and create uniformity in drugs often did not exist. Indeed, a major task of nineteenth- and early twentieth-century pharmacy was to define what a drug was and to create standards of composition, purity, and strength. Pioneering efforts in this direction had begun in 1820 with the creation of the *U.S. Pharmacopoeia (USP).* A private, voluntary undertaking of physicians, pharmacists and colleges of pharmacy, the USP presented a formulary of compositions and listed chemical compounds, crude drugs, fixed oils, and other substances typically kept by a pharmacist (then called a *pharmaceutist* or an *apothecary*). Later the *USP* listed tests for determining purity. Leading pharmacists regularly revised the *USP* as new and better drugs, compositions, and tests were discovered and created. Medical men interested in advancing their crafts and the dignity of their professions formed themselves into state medical societies and pharmaceutical associations, the American Medical Association (AMA, 1848), and the American Pharmaceutical Association (APA, 1852). The major societies and associations often published journals, collaborated with medical schools, and sometimes maintained committees on drug adulteration to check drug

samples and to publicize information. Pharmacists compiled the *National Formulary,* first published by the APA in 1888. The *Formulary* has since 1896 functioned to provide standards for drugs omitted from the *USP* and to serve as a proving ground for drugs eventually transferred to the *USP*. (On the earlier history of the *USP* and *National Formulary* see Sonnedecker 1970).

But before the twentieth century there was no direct federal regulation of drugs or other consumer products. In 1848, Congress forbade the importation of adulterated drugs, but the law quickly became moribund, as the drug examiners were usually untrained political spoilsmen (Young 1970, 151). The Reconstruction years saw the formation of the U.S. Department of Agriculture Bureau of Chemistry, the predecessor of the FDA. Consisting of only a few men, the bureau did little more than request customs inspections of imported foods and to a lesser extent drugs. In 1883, the bureau got a righteous and rambunctious chief in Harvey Washington Wiley, who campaigned for federal laws.

Biologics Act of 1902

A common pattern in the history of federal drug control has been the shocking event that unleashes new governmental powers. In 1901, contaminated smallpox vaccines and diphtheria antitoxins led to tetanus outbreaks and the death of several children. Vaccines, blood and blood products, extracts of living cells, and other drugs belong to a category called biological drugs. The Biologics Act of 1902 required that federal government grant premarket approval for every biological drug and for the process and facility producing such drugs. Never before had such premarket control existed in the United States. The same premarket authority was enacted for animal biological drugs in the Virus, Serum, and Toxin Act of 1913 (Miller 2000).

Pure Food and Drugs Act of 1906

In 1906, Upton Sinclair's book *The Jungle* described the filthy conditions of a meatpacking plant. In the most shocking incident, a worker collapses into a lard canister and is indiscriminately ground and shipped for sale. At about the same time in the nonfiction world, Chemistry Bureau Chief Harvey Wiley recruited a group of young men into "the Poison Squad." The squad volunteers ingested formaldehyde, boric acid, and other food colorings and preservatives in concentrated form. Eventually their digestive systems showed ill effects. Wiley's dramatic stunts earned him the folkname "the Crusader" and inspired popular songs about his patriotic self-poisoning disciples. The combination of the Poison Squad and *The Jungle* prompted Congress to pass the Pure Food and Drugs Act in 1906.

The 1906 law recognized the privately produced *U.S. Pharmacopoeia* and *National Formulary* as official standards for the strength, quality, and purity of drugs and for the tests to make such determinations. Thus, the 1906 law defined an *adulterated* drug as a drug that was listed in the *USP* but that did not meet *USP* specifications (unless variations from the *USP* were clearly labeled). Practitioners, however, had given the *USP* "official" status long before *USP* specifications were anointed by law. In addition, several states had already made reference to the *USP* in defining adulteration. Thus, the federal law mandated what was already practiced widely, though not universally.

The 1906 law included provisions against "misbranding." A drug was considered misbranded if it contained alcohol, morphine, opium, cocaine, or any of several other potentially

dangerous or addictive drugs, *and* if its label failed to indicate the quantity or proportion of such drugs. (The law pertained only to labeling, not to advertising.)

For consumers, the main result of the 1906 law was not to restrict choices but to provide more information. In addition, the scientists of the Bureau of Chemistry performed useful and important work in developing assays and tests to help identify and purify drugs and to make production uniform. Because the feds could not wield coercive premarket power, the Chemistry Bureau and industry trusted each other and cooperated to improve drug manufacturing.

The clause against "false and misleading" labeling was, however, initially used in an aggressive manner. Under this clause, federal enforcers prosecuted many manufacturers who sold "cures" for headache, baldness, cancer, and other ailments. Prosecutions typically resulted in confiscation and small fines. When the government prosecuted "Dr. Johnson's Mild Combination Treatment for Cancer," Dr. Johnson, the manufacturer, fought back, taking the case to Supreme Court. The Court agreed with Johnson, ruling that any therapeutic claim is a matter of opinion. It follows that there exists no authoritative medical opinion that coercively overrides others, and hence no charges can be brought against therapeutic claims unless the sellers actually intended fraud. Justice Oliver Wendell Holmes affirmed that the FDA was "to regulate commerce in food and drugs with reference to plain matter of fact, so that foods should be what they professed to be[,] . . . [rather] than to distort the uses of its Constitutional power to establishing criteria in regions where opinions are far apart" (quoted in Temin 1980, 33). Seeking to overcome the limitations discovered by the Supreme Court, Congress passed the Sherley Amendment in 1912, but this amendment banned only "false and *fraudulent*" claims i.e. claims that the seller new to be false thus it failed to deliver the sought-for expansion of power. The act moreover, did not extend the police power against "false and fraudulent" claims to advertising.

Following the Supreme Court's ruling and the Sherley Amendment, the FDA's function became fixed to monitoring the identification of a drug. Nonetheless, the developments of this early period set a precedent for federal government activism in medicine.

Meanwhile, in 1927 the regulatory functions of the Bureau of Chemistry were reorganized to become the Food, Drug, and Insecticide Administration, which in 1930 changed its name to the Food and Drug Administration.

Harrison Narcotics Act of 1914

The Harrison Narcotics Act of 1914 placed a tax on the production, sale, and use of opium and required prescriptions for products exceeding the allowable limit of narcotics. This act also mandated increased record keeping for physicians and pharmacists who dispense narcotics. Initially passed to ensure the orderly marketing of narcotics, the act was later interpreted to prohibit the supply of narcotics, even to addicts on a physician's prescription. Under the Harrison Act, thousands of physicians were imprisoned for prescribing narcotics.

Food, Drug, and Cosmetic Act of 1938

Under the new administration of Franklin D. Roosevelt, the FDA immediately began pressing for more regulatory powers, but not much happened with respect to drugs until the next

shocking episode. A well-established pharmaceutical company, Massengill, released a new sulfa drug (an antibacterial) under the name Elixir Sulfanilamide. The drug itself had undergone a variety of quality and safety checks, but in producing a liquid form the company failed to test the solvent. Possessing a pleasant green shade, this solvent, diethylene gycol—better known today as antifreeze—had deadly effects on the kidneys. As a result, 107 people, mostly children, died before the product was quickly recalled.

The Elixir story is often told to lament the meagerness of federal control. The FDA could prosecute Massengill merely for misbranding: the product Elixir Sulfanilamide did not contain alcohol and therefore did not fit the definition of an *elixir.* Nothing could be done about the Elixir deaths, runs the usual lament, because Massengill had not made fraudulent claims for the product. The tragedy is said to have demonstrated that unfettered markets cause reckless injury and that public safety called for additional laws.

That telling of the story, however, entirely overlooks the role of tort law in providing compensation to victims and in promoting deterrence. At the time of the Elixir episode, the common law did provide remedies for harm from misbranded or adulterated drugs, and Massengill was successfully sued in tort for its gross negligence (Krauss 1996). The chemist responsible for creating Elixir Sulfanilamide committed suicide.

Within months of the tragedy, Congress passed the Food, Drugs, and Cosmetic Act of 1938. The Constitution does not give the federal government any power to regulate drugs. As has often been the case, the wedge into federal control was the federal government's power to regulate interstate commerce. The laws regulating drugs were thus written so as to apply only to drugs used or produced in more than one state. Given the broad, sometimes absurdly broad, construction the courts have given to the interstate commerce clause, in practice the law regulates every drug despite the original intent of the framers.

The 1938 Act included several provisions that would prove to be significant wedges for future power expansion. The most salient change was the requirement that manufacturers file a New Drug Application (NDA) with the FDA. The application would indicate the drug's composition, report test results on safety, and describe how the drug was to be manufactured and quality controlled. If a company submitted an NDA, it would be automatically approved in sixty days if the FDA took no action. Thus, the default position was approval; the burden of proof for departure from the default position fell on the FDA, and as a result the costs of the FDA to the public were kept low.

To some extent, the 1938 Act continued the information provision requirements of the 1906 Act. The classification "misbranded" was expanded, for example, and now included any drug whose label failed to identify and quantify the precise ingredients, to list effects and possible side effects, and to give directions and cautionary information that even the least-educated person could understand.

Other provisions did restrict choice and reduce consumer information. Proof of fraud was no longer required to stop "false" claims for drugs. Falsity would, of course, mean "deemed by the FDA to be false." Thus was erected the pedestal of authoritative knowledge regarding truth and falsehood for all users in all situations.

An obscure provision of the Food, Drug, and Cosmetic Act and of a series of subsequent FDA regulatory decisions had the effect of creating a new class of prescription-only drugs. The original labeling laws were meant to provide more information to consumers and thus improve their ability to make good decisions. The intention of Congress in passing the act was to further

the goal of creating informed consumers. Indeed, the House committee reporting out the bill declared explicitly that "[this] bill is not intended to restrict in any way the availability of drugs for self medication. On the contrary, it is intended to make self medication safer and more effective" (quoted in Temin 1992, 351). Yet the FDA decided that some drugs could not be labeled safely. Thus, in some cases, the FDA required that drugs be labeled in such a way that a consumer could *not* understand them or else that they be labeled only with the warning "Caution: To be used only by or on the prescription of a physician." In the latter case, sale without prescription was illegal.

Traditionally the manufacturer decided whether a drug was a prescription or an over-the-counter (OTC) drug, and sometimes some manufacturers sold a drug by prescription only, while others sold the same drug over the counter. Now, however, manufacturers were subject to considerably uncertainty because they had to guess whether the FDA would deem a drug prescription only or OTC. If a manufacturer thought consumers could properly use a drug, and thus labeled it and sold it OTC, the FDA might disagree, remove the product, and sue the manufacturer for misbranding. Indeed, if a patient misused the drug, even deliberately so, the manufacturer bore all resulting legal responsibility. Divided authority began to stifle entrepreneurship. The disarray continued until 1951, when the Congress passed the Durham-Humphrey Amendment (see below).

The 1938 Act also expanded the FDA's powers over medical devices. Although the FDA could not prevent a medical device from coming onto the market, as it could for drugs, it did have the authority to ask the courts to stop the production or sale of devices already entered into interstate commerce. Under this authority, the FDA removed a number of quack devices from the market (Higgs 1995c).

Durham-Humphrey Amendment, 1951

The Durham-Humphrey Amendment drew a clearer legal distinction between prescription-only and OTC drugs, and authorized the FDA to classify drugs accordingly. Many important drugs could be sold only by prescription from a licensed practitioner. Licensed doctors, therefore, became deputies and spoilsmen in the growing system of controls. Consumers had to pay for the drug and a visit to the doctor. These new privileges for doctors were the bounty of the government's regimentation of the drug industry and assault on consumers' freedom to self-medicate. Dependence on doctors was further institutionalized and legitimated by making it difficult for consumers to gain information, in particular by the labeling and advertising controls that prohibited information or mandated unintelligibility. Thus, licensed doctors gained wealth and relative status by stripping others of freedom and by dumbing down consumers. (Under this amendment, manufacturers still had discretion over the classification of already approved, non-habit-forming drugs, which were to come under FDA control in 1962.)

Miller Pesticide Amendments of 1954

These amendments required premarket approval of pesticide residues in or on food.

Food Additives Amendment of 1958

The Food Additives Amendment required premarket approval of food additives. The FDA later used this authority to regulate dietary supplements, but such authority was removed with the Dietary Supplement Health and Education Act (DSHEA) of 1994.

Color Additive Amendments of 1960

The Color Additive Amendments required premarket approval of color additives. The so-called Delaney anticancer clause prohibits the FDA from approving any color additive that has been found to cause cancer in humans or animals regardless of the dosage levels. As a result, substances that cause cancer when rats ingest hundreds or thousands of times the typical human dose have been banned from food products. (See Wildavsky 2000 on the inappropriate use of animal studies in the regulation of carcinogens.)

Kefauver-Harris Amendments of 1962

In the post–World War II era, the field of pharmacology entered a new age. People with bacterial illnesses could now be treated with a host of new antibiotics, and diabetics were likewise given the life-saving invention of insulin. In the 1950s in particular, many new drugs were called "magic bullets" because of their potency and swift defeat of disease. The very success of the new drugs, however, spurred new regulations.

Senator Estes Kefauver, who sat on the Senate Antitrust and Monopoly Subcommittee, decided that in dealing with medications, the government must do more than control their labels, contents, and safety and their marketing and distribution processes. It must also control their prices and enforce "competition." In 1960, Kefauver initiated hearings in an attempt to expose unfair marketing practices. Kefauver's bill called for a scheme of compulsory patent sharing. Each pharmaceutical company would, after three years, be required to share its new patents with competitors, while collecting an annual royalty fee of some 8 percent of the total. Although Kefauver's main concern was pricing, another provision called for NDAs to show proof of both safety *and efficacy*.

Though President Kennedy spoke fondly of the "safety and efficacy" clause, the Kefauver bill lacked popularity and went nowhere. As with the acts of 1902, 1906, and 1938, another tragedy paved the way to passage. The tragedy was so great, so sensitive, and so graphically shocking that it still evokes strong emotions and arrests intellectual discourse.

In 1957, a West German pharmaceutical manufacturer introduced a new sedative, thalidomide, which alleviated the symptoms of morning sickness in women during the first trimester of pregnancy. In 1962, by which time the drug had been sold in forty-six countries, it became clear that thalidomide damaged the fetus, causing stillbirth or, most prevalently, *phocomelia* (Greek for "seal limb"). Thousands of newborn babies were found to have truncated limbs that resemble flippers. By virtue of photojournalism, the horror and sadness were shared throughout the world.

In the United States, an NDA for thalidomide had been submitted to the FDA in 1960, but

approval had been delayed as the FDA investigated adverse neurological reactions. FDA officials had not even suspected that the drug caused birth defects. In 1962, President Kennedy bestowed the Distinguished Federal Civil Service Award on the FDA physician who held up approval, Frances Kelsey, even though her withholding of approval was more a matter of bureaucratic delay than of investigation (Harris 1992).

"Thalidomide babies" became a bludgeon for urging stronger government action. The Kefauver bill was revised so that the pricing and patent-sharing provisions were deleted, and the Kefauver-Harris Amendments were soon law. The amendments authorized the FDA to require drug companies to conduct and submit tests determining safety and efficacy. In addition, the FDA now had to preclear all human trials, drug advertising, and labeling. The FDA also increased its regulatory power over manufacturing.

The 1962 Amendments significantly reduced the choices of doctors and patients, and expanded the power of the FDA, which increased its staff from one thousand members in 1951 to nearly sixty-five hundred two decades later (Temin 1980, 121). In addition to requiring efficacy testing for new drugs, the FDA, with the help of the National Academy of Science Drug Efficacy Study Implementation, launched an investigation of the efficacy of the then current stock of drugs.

The task of proving efficacy is much more difficult, expensive, and time-consuming than the task of proving safety. To a great extent, efficacy, which is sensitive to individual conditions and mediated by market process, had in the past always been judged jointly by doctors and consumers. A drug's efficacy ought to be judged relative to the alternative therapies and is therefore constantly changing, being discovered, and being proven by medical-market experience, with the use of postmarket surveillance and research. Safety, naturally, always calls for strong prior assurance. But the search for improved efficacy had proceeded, to some extent, by people serving as each other's guinea pigs, and the result had been rapid progress. In 1962, however, the FDA began to act on the premise that it could establish authoritative knowledge of efficacy prior to experience and experimentation in actual market processes.

The time spent waiting for FDA approval and the expense and duration of the bureaucratically determined testing procedures combined to cause tremendous delays in drug development and production. Drug development declined significantly after 1962, and the wait for new life-saving drugs increased to more than a decade by the end of the 1970s (see FDA Harm below).

The role of thalidomide in the passage of the 1962 Amendments is riddled with unfortunate ironies. First, the episode aroused great public empathy for human suffering, but no thought was given to the suffering that was bound to result from the ever more confining grip on drug development, availability, and information. Second, people cited thalidomide in claiming that drug approval delay is a blessing, but the pre-1962 FDA had proven to be sufficiently slow to avoid thalidomide harm in the United States. Third, the old law of 1938 already required premarket approval for safety. Nothing about thalidomide even superficially recommended premarket approval for efficacy.

Animal Drug Amendments of 1968

These amendments required premarket approval of new drugs and feed additives for

animals.

Medical Device Amendments of 1976

As with drugs, the field of medical devices entered a new era after World War II. Cardiac pacemakers, renal catheters, replacement joints, and many other innovations were introduced in this period. The FDA first tried to regulate these new products by reclassifying them as drugs, but in the usual story it took a tragedy, this time over the faulty Dalkon Shield IUD, to generate new law.

The 1976 Amendments expanded the definition of a medical device and authorized the FDA to categorize all medical devices into three classes. Class I devices—tongue depressors and gauze, for example—are subject to reporting requirements and Good Manufacturing Practices (GMP) regulations. Class II devices are subject to the same controls as Class I devices and the same product-specific performance standards supposedly developed by the FDA (see further below). Class III devices—artificial hearts and angioplasty catheters, for example—must pass an FDA approval process similar to that required for new drugs; that is, before marketing can begin, Class III devices have to be proven safe and effective in extensive clinical trials, and submit to and pass an FDA premarket approval process.

In an excellent example of FDA thinking, *new* devices are automatically categorized as the most *risky* devices, i.e., Class III devices, regardless of actual risk. (See Some Remarks about Medical Devices for an absurd consequence of this procedure.) A new device can escape going through a premarket approval procedure if it can be shown to be "substantially equivalent" to a preamendment device (and, since the Safe Medical Devices Act [SMDA] of 1990, to any currently marketed non–Class III device). "Substantially equivalent" devices are supposed to be able to go through a simpler premarket notification (as opposed to approval) process known as the 510(k) route, after that section of the 1976 Act.

The neat classification scheme of the Medical Device Amendments does not describe actual FDA practices. The FDA, for example, did not develop *any* performance standards until 1997! Thus, Class II devices have played no role in medical device development up until recent times, and it remains to be seen whether they will become more common in the future (the requirements for a Class II device were loosened in the Safe Medical Devices Act of 1990). Furthermore, the "simple" 510(k) procedure evolved to become what in effect was an extensive and time-consuming premarket approval process. (The reality was recognized in the SMDA, which formally made the 501(k) process into an approval process.)

Munsey (1995) provides a good overview of the medical device regulation.

Toxic Substances Control Act of 1976

This act required premarket notification for chemical substances.

Infant Formula Act of 1980

This act required premarket notification for infant formulas.

Orphan Drug Act of 1983

By 1983, the research, testing, and development of a new drug could take up to twenty years, seven of which expired in waiting for final FDA approval of the NDA. (For more recent average times, see the Drug Development and Approval Process below). Heightened awareness of patients direly waiting for pending treatment gave rise to reform. Because the costs of obtaining FDA approval were the same whether the projected market was two million patients or twenty thousand patients, companies naturally pursued, all else being equal, the development of large-market therapies and abandoned (or "orphaned") small-market therapies. Thus, FDA regulation had especially negative consequences for people suffering from rare diseases. The Orphan Drug Act was created in an effort to reduce drug loss for "rare" diseases, which were defined as having fewer than two hundred thousand cases in the United States. The Orphan Drug Act gave tax breaks, subsidies, and special exclusivity privileges to sponsors of drugs for rare diseases.

Rather than reducing the FDA barriers to producing orphan drugs, the Orphan Drug Act was meant to stimulate the development of such drugs by granting sponsors new monopoly privileges. The exclusivity granted under the act differs from a patent. A patent protects against competition from a drug with the same chemical structure. Market exclusivity as implemented by the Orphan Drug Act grants protection for seven years against competition from any drug with a *similar effect.* The FDA thereby bars firms from marketing drugs that treat diseases also treated (and perhaps less effectively) by a drug granted exclusivity.

Officials claim that this act has been a success, noting that almost a thousand drugs have been granted orphan status. The number of such drugs is misleading, however, because many would have been produced even without the act. Furthermore, the administering of the act involves several artifices. Cancer patients number in the millions, but a drug may be granted orphan status to treat ovarian cancer or bladder cancer. Thus, a drug used to treat ovarian and bladder cancer could be an orphan in each category even though the total population served by the drug would be well more than two hundred thousand. Even more absurdly, the market for a drug may be divided into a prevention category and a treatment category, and if the number afflicted in either category is less than two hundred thousand, orphan status is granted. Moreover, the same drug can be an orphan for more than one disease, multiplying its monopoly privileges (Arno, Bonuck, and Davis 1995).

The history of the Orphan Drug Act shows an interesting expansion of benefits to drug manufacturers. When originally enacted, the standard for orphan status was "no reasonable expectation that the costs of development will be recouped from U.S. sales." Because worldwide sales often much exceed U.S. sales, even this standard could grant exclusivity, subsidies, and tax breaks to drugs that would still be profitable without such benefits. To prove that there was no reasonable expectation of recouping cost, pharmaceutical firms were supposed to submit financial data to the IRS. The pharmaceutical industry disliked this provision, however, and lobbied to have the requirement weakened. In 1984, the standard for orphan status was weakened to say that there be fewer than two hundred thousand potential U.S. patients at the time of the request for designation of orphan status. In the early years of AIDS, when the disease affected relatively few people, the revised standard allowed many AIDS drugs to gain orphan status despite the fact that the market for these drugs was expected to grow rapidly. AZT was designated an orphan drug despite its having generated billions of dollars of sales. Initially,

Congress had also restricted the exclusivity to drugs that could not be patented; this restriction was dropped in 1985. Thus, over time the Orphan Drug Act has become significantly more beneficial to the established U.S. drug manufacturers.

A sponsor seeking orphan status for a drug need not be the creator of the drug, and the drug need not be new. The drug Oxandrolone had been used to treat wasting in hepatitis patients and had been available by prescription for thirty years. When body builders began to use it illegally to bulk up, the drug received bad publicity and was discontinued. Another company then gained the rights to the drug and presented it to the FDA as a new treatment for HIV-related wasting. Orphan status was granted. AIDS patients now paid a price 1,200 percent higher than when the manufacturer did not have monopoly rights (LeBlanc and Sabados 1996).

On the surface, the Orphan Drug Act seems like one instance in which policymakers recognized some of the problems created by restrictions and moved to rectify matters. The act does not, however, roll back restrictions, but rather grants new powers to the FDA and throws new monkey wrenches into private-sector affairs. FDA proponents of the act claim, without substantial evidence, to be solving the problem. Unfortunately, no major cost-benefit analysis has yet been performed to determine the net effects of the act.

Waxman-Hatch Act of 1984

If the U.S. government grants a patent to a drug, all other manufacturers are barred for a prespecified number of years from producing a product of the same chemical composition (except by franchise from the patent holder). A patent, therefore, grants a degree of monopoly power to the patent holder. The usual term of patent life is seventeen years. When developing a new drug, the company is anxious about the possibility that another company is also working on the drug (or has received news or leaks about the promising incipient drug) and is eager to attain a patent. Companies therefore apply for and receive drug patents in advance of final FDA approval to market the drug.

But some of the seventeen years of patent protection is dissipated waiting for approval. The "effective patent life" of a new drug is the time from approval to the end of the patent. When a patent expires, other producers are permitted to replicate the product and to sell it as a "generic drug." This competition drives down prices.

During the 1970s and 1980s, the duration of FDA requirements continued to grow, reducing the effective patent life. The drug companies therefore experienced not only greater drug development costs and delays, but also shrinking patent protection of products that were eventually emerging from the FDA gauntlet. They were squeezed at both ends.

Commissions established by Presidents Carter and Reagan recommended that patent terms be adjusted to make up for time lost in regulatory review. The generic drug producers, however, opposed the idea. It proved impossible to pass patent term reform over their opposition. Thus was born a bilateral bill, the 1984 Drug Price Competition and Patent Term Restoration Act, known as the Waxman-Hatch Act. This act served the generic drug producers by removing some arbitrary and absurd constraints on generic drug manufacturers. Prior to the act, it was not sufficient for a generic drug manufacturer to prove that its drug was bioequivalent to an approved drug. Instead, the manufacturer had to submit *independent* information on safety and efficacy. Thus, the generic drug manufacturer had to repeat many of the clinical trials performed by the original manufacturer, despite the fact that the drugs could be shown to be bioequivalent. As a

result of the costs of performing clinical trials, many drugs did not face generic competition even after the relevant patents had expired. The act required the FDA to accept bioequivalence as sufficient for approval (something the FDA could have elected to do prior to the act). The procedure for a generic drug approval is called an Abbreviated New Drug Application (ANDA).

The liberalization of generic drug approval was the inducement generic drug companies required in order to support the second part of the act, patent term adjustment. Waxman-Hatch extends patents for time lost during FDA review and for one-half the time lost during FDA-required clinical testing. The extension is capped at a maximum of five years, and the total patent term is capped at fourteen years from the data of FDA approval. Prior to the act, effective patent terms were approximately seven to ten years. Waxman-Hatch has extended patents by two to three years on average for an effective patent life of approximately nine to twelve years (Grabowski and Vernon 1996). Although patent law grants seventeen years of patent life, patent terms much beyond ten years are typically of low value because the advent of new drugs diminishes the value of old drugs, patented or not.

Drug Export Amendment Act of 1986

The FDA had made it illegal for Americans to export drugs that had not been approved in the United States. FDA paternalism was thus not restricted to U.S. citizens, but also impinged on people throughout the world. Some firms moved manufacturing plants abroad to escape the restriction. The export restrictions also contributed to drug loss because they made U.S. drug development less profitable. The 1986 Drug Export Amendment Act liberalized U.S. export of such drugs.

Under the act, export is allowed if the drug (not FDA approved) satisfies three conditions: (1) U.S. approval is actively being sought; (2) the drug is also covered by a U.S. investigational exemption; and (3) the drug is for export to any of twenty-one nations that have approved the drug and have regulatory programs that meet U.S. standards (the standards, that is, of a foreign country's regulatory program, not necessarily the FDA standards for drug control) (Kaplan 1995).

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Nutrition Labeling and Education Act (NLEA) of 1990

The NLEA required food manufacturers to include nutritional labeling on most food products. (Ironically, such labeling had been illegal prior to the early 1970s!) The act added such things as saturated fat, cholesterol, total and subgroups of carbohydrates, and dietary fiber to the list of nutrients that must appear on nutrition labels. Although meat and poultry remain under the control of the U.S. Department of Agriculture, the FDA has authority over the form and content of nutrient descriptors for most foods. The NLEA also codified the FDA's authority to allow health claims on foods and dietary supplements. Although the intent of the NLEA was to increase the amount of information consumers received by broadening the health claims allowed on foods and dietary supplements, the FDA officials took an aggressive stance and announced that they planned to regulate supplements as drugs. The resulting backlash led to the passing of the Dietary Supplement Health and Education Act (DSHEA) of 1994.

Safe Medical Device Act (SMDA) of 1990

The SMDA substantially increased reporting requirements for medical devices, including requiring device users to report adverse events to the FDA and to device manufacturers. The Medical Device Reports require extensive and costly paperwork often with little value. The SMDA also formally changed the 510(k) procedure, which was originally intended to be a notification procedure, to a premarket approval procedure. Up to the time of this act, the FDA had never issued any Class II performance standards, so the SMDA modified the requirements, making it easier for the FDA to establish a standard; it also provided that Class II devices could be issued if accompanied by "special controls." Special controls include postmarket surveillance and other controls the FDA may deem necessary. The SMDA also permitted the assessment of substantial civil penalties for violating the Food, Drug, and Cosmetic Act relating to devices.

Munsey (1995) provides a good overview of the medical device regulation.

Prescription Drug User Fee Act (PDUFA) of 1992

Pre-1992 figures indicated that on average it took the FDA two and a half years to review an NDA and sometimes up to eight years. Often, the cause of delay was not the difficulty of the application but merely backlog. Applications would sit unexamined for months or even years. The FDA concluded that the process of approval could be speeded up if they had better equipment and more workers to review applications. Congress was unwilling to increase FDA appropriations, however. Thus was born the Prescription Drug User Fee Act of 1992, establishing for a five-year period a mandatory fee of roughly $200,000 to be submitted by a pharmaceutical company along with its application. The FDA hired hundreds of new employees and observed that the average processing time fell by half, to eighteen months, as a result of the legislation. Because of this evident success, the Modernization Act of 1997 renewed the practice for another five-year period and increased the user fees. The necessity of renewing the PDUFA every five years has put pressure on the FDA to streamline its processes so that drug manufacturers will support renewal. The possible threat, in other words, of losing the user fees and thus of having to cut back on staff and other perquisites appears to have made the FDA bureaucracy more efficient and amenable to customer needs.

Dietary Supplement Health and Education Act (DSHEA) of 1994

The FDA has for decades tried to regulate the sale and use of vitamins, herbs, and other dietary supplements. By law, any ingested product that is intended by its manufacturer to prevent or treat a disease is a *drug*. Products, other than "food," that are intended to affect the structure or function of the body are also considered drugs. Throughout the 1950s and 1960s, the FDA brought hundreds of court actions against nutrition manufacturers for making health-related claims for their products. Under threat of law, food manufacturers were even prevented from labeling the fat, cholesterol, or other nutritional content of their food! (Later such labeling was allowed, and with the Nutrition Labeling and Education Act of 1990 nutrition labeling became mandatory.)

The FDA actively prosecuted vitamin retailers that sold vitamins and other supplements in conjunction with books or pamphlets that extolled their use. It was illegal, for example, for a

health food store to sell vitamins *and* books extolling the virtues of vitamins. The FDA justified such practices, which many considered to be a violation of the First Amendment, under the theory that literature that was sold near a product was thereby converted into a *product label,* and if health claims were made in the literature, then the product had to be regulated as a drug (and thus had to go through FDA clinical trials before being sold).

In 1973, the FDA published regulations (to take effect in 1975) expanding its control over supplements by declaring that *any dietary supplement that it considered to lack nutritional usefulness* was a drug and thus under the FDA's control. High-potency vitamins, by which the FDA meant vitamins sold in dosages as little as twice the federal recommended daily allowance (RDA) for example, were ipso facto considered a drug (i.e., regardless of manufacturer claims or lack thereof). High-potency vitamins were effectively made illegal by this ruling because they could not be sold without FDA approval, and the FDA would not approve supplements that it considered to be unnecessary. Vitamin manufacturers and consumers fought back, and in response Congress passed the Proxmire Vitamin Mineral Amendment of 1976, which stated that the FDA could not classify a mineral or vitamin as a drug "solely because it exceeds the level of potency which [the FDA] determines is nutritionally rational or useful" (21 USC 350 [1994, originally enacted 1976], [a][1][B]).

It is worth pointing out explicitly, although it will come as no surprise to anyone who follows today's health news, that numerous scientific studies have since validated many of the health claims for vitamins and minerals that the FDA had earlier suppressed. The FDA suppression of information concerning vitamin E and heart attacks, for example, may rank alongside its suppression of information concerning aspirin as one of the most deadly regulations of the post–World War II era.

In 1985, the FDA lost a related turf war with the Federal Trade Commission (FTC) and the National Institutes of Health (NIH). Under recommendation from the National Cancer Institute, a division of the NIH, the FTC permitted Kellogg to claim that a high-fiber diet reduced the probability of certain types of cancer. The FDA wanted to sue Kellogg, but the FTC argued that the ads presented "important public health recommendations in an accurate, useful, and substantiated way" (quoted in Calfee 1997, 25). Under pressure, the FDA backed down, and as a result it was established that food products could advertise a "substantiated" health claim without going through the FDA drug approval process.

Under the protection of the Proxmire Amendment, the dietary and nutritional supplement industry expanded, but the FDA stepped up enforcement again in the early 1990s after thirty-eight deaths were attributed to L-tryptophan, an amino acid widely used for treating depression and building muscle mass. (The Centers for Disease Control later exonerated L-tryptophan in the deaths, which were caused by a contaminant, but the FDA did not lift its ban on OTC sales of L-tryptophan (Beisler 2000). In 1993, the FDA announced that it planned to regulate as drugs all amino acids, herbs, and other supplements including fibers and fish oils. The FDA soon found itself under a furious attack from millions of consumers of nutritional supplements. The DSHEA, passed in 1994 and taking effect in 1996, explicitly required the FDA to revoke its Advance Notice on supplements.

Under the DSHEA, nutritional supplements can make substantiated "statements of nutritional support" that do not thereby invoke FDA control. Supplements, however, cannot make claims regarding disease without becoming regulated as drugs. The distinction between statements of nutritional support and claims regarding disease is vague. Manufacturers of St.

John's Wort, for example, may claim that St. John's Wort "promotes healthy emotional balance and well-being," but they cannot say St. John's Wort "is useful in the treatment of depression." The distinction is mostly for lawyers, not consumers, considering that many consumers do take St. John's Wort for depression. (Such consumers are in fact justified in doing so; a number of studies indicate that not only is St. John's Wort effective at relieving mild cases of depression [e.g., Woelk 2000], but it does so with fewer side effects than many antidepressive pharmaceuticals. In addition, St. John's Wort is considerably cheaper than pharmaceuticals and does not require a prescription.)

Dietary supplements that make nutritional claims must carry the following two disclaimers: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." In the section Reform Options, we suggest that the first disclaimer is useful and that this split-label approach be extended to drugs proper. The second disclaimer is not informative.

Subject to certain conditions, such as that the information presented is not false or misleading and not biased in favor of a particular manufacturer or brand, the DSHEA also restricts the FDA's ability to ban the dissemination of information on dietary supplements (Pinco and Rubin 1996). Health food retailers, for example, can now market books, magazines, and scientific articles describing the uses of dietary supplements. As a result, in recent years consumers have become much better informed about the role of vitamins and other supplements in optimal health.

The full text of the DSHEA can be found here.

FDA Modernization Act of 1997

By the late 1990s, numerous academic studies and government reports had indicted the FDA for drug lag and drug loss. Pressures for reform finally began to be felt in Congress, a portion of which had recently promised deregulation in their "Contract with America." In 1996, the House wrote an FDA reform bill that would have significantly threatened some of the FDA's central powers , but the FDA and its supporters in the Clinton administration "pulled out all the stops to defeat it" (Miller 2000, 55). Facing a veto and adverse spin, Congress abandoned the serious bill. The next year they passed a much watered-down bill, the FDA Modernization Act of 1997 (link to bill) .

Much of the Modernization Act merely codified what was already FDA practice (Miller 2000). For example, it authorizes the FDA to appoint panels of scientific experts to assist the agency in evaluating new drugs, a practice the FDA has followed for decades. Similarly, it codified the rule that only one adequate and well-controlled clinical study and only confirmatory evidence could be the basis of approval. Because the FDA has always had this flexibility but rarely exercised it, the impact of the rule is likely to be negligible. The act also codified restrictive FDA policies on dissemination of information regarding off-label uses of drugs. (Subsequently, *Washington Legal Foundation v. Friedman* found such restrictions unconstitutional and expanded firms' ability to disseminate information.) For medical devices, the Modernization Act exempted most Class I and Class II devices from premarket approval and increased physician authority to use investigational devices. Finally, in a variety of clauses, the FDA was required to provide manufacturers with better and timelier information concerning its procedures.

The most important provisions of this act were the reauthorization of user fees for another five years and new inducements to drug manufacturers to conduct pediatric studies. Following the model established by the Orphan Drug Act, this act rewarded development of pediatric-use information with monopoly privileges. Under the Modernization Act, a sponsor that develops pediatric information is granted six months of exclusive marketing privileges *in addition* to any patent or other nonpatent rights for which the drug may already be eligible. Moreover, the marketing privileges are for all uses of the drug and not just for pediatric uses. As with the Orphan Drug Act, the increased incentive to research and develop new drugs and pediatric uses also brings higher drug prices. The trade-off might be worthwhile, but no studies on the issue have been done.

Today, the FDA is a vast organization of fifteen offices, including the Office of Regulatory Affairs, the National Center for Toxicological Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine. The administration has nine thousand employees, who monitor and process $1 trillion worth of products each year. Obviously, the FDA has grown tremendously since its inception in the Bureau of Chemistry.

Some Remarks about "Approval"

The government extensively controls the system of drug development, production, and usage. In exercising control, the government apparatus develops and institutionalizes a vocabulary. Terms within the "official" vocabulary often mean something more than, or different from, what they mean in ordinary language. Being aware of the complexity of meaning helps us to grasp the workings of the apparatus.

The term *approval* calls for special scrutiny. In ordinary society, if someone approves a product, he or she regards it with favor, affirms its value, and perhaps endorses the product. Once upon a time, adult Americans were free to produce, trade, and use drugs according to the ordinary constraints of property and consent. At that time, if a doctor, pharmacist, or medical association approved a drug, it meant that they affirmed its value. In the case of an organization that rates or certifies quality and safety, *approval* means to endorse or grant certification to a product. Today, Good Housekeeping approves the products to which it grants the Good Housekeeping Seal of Approval, and Underwriters' Laboratories approves the products to which it grants the UL mark of safety.

All those forms of approval are voluntary. When it comes to FDA approval, however, the FDA grants not only its own seal of approval but also *permission* for citizens to use the drug. Until the FDA approves the drug, citizens are forbidden by federal law from producing, selling, or using the drug. Anyone who refuses to obey the FDA will eventually face armed federal agents, confiscation, and imprisonment (the FDA has its own armed inspectors, many trained as DEA or Secret Service agents, and it has conducted SWAT-like raids). FDA "approval" therefore means, above all else, federal officials withdrawing certain coercive threats and refraining from certain coercive actions. The language of "approval" connotes the useful work of evaluating

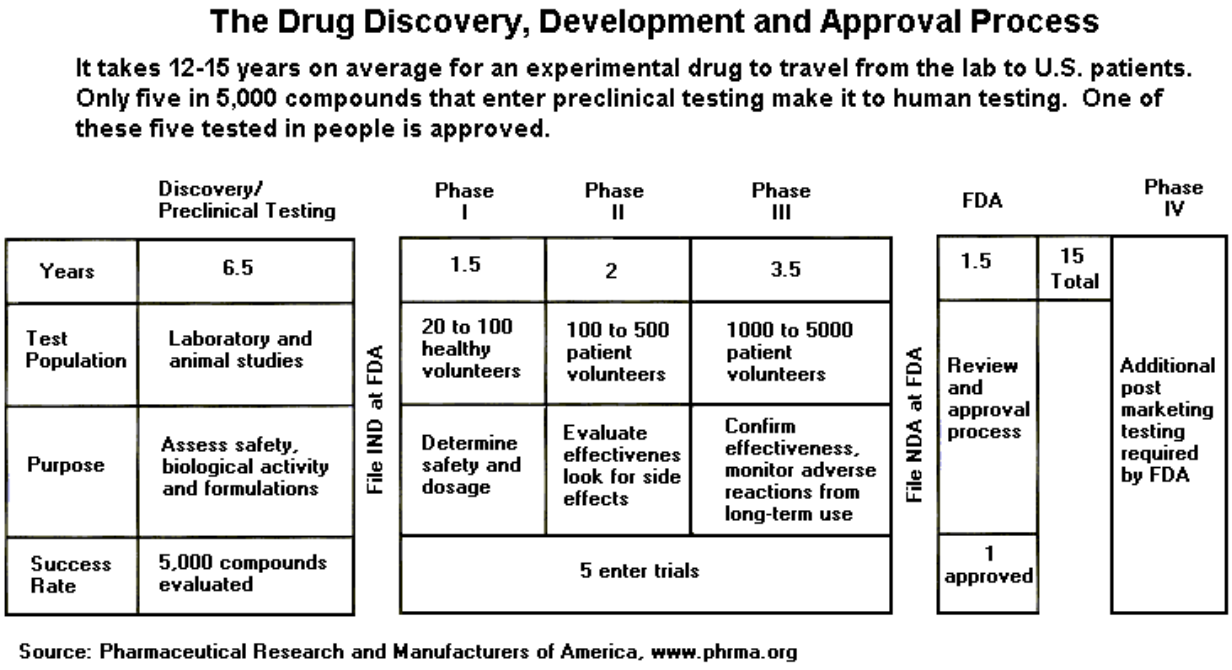
products and granting a seal of approval. Thus, the newspapers report that the "The FDA today approved a drug that will save thousands of lives." It would be more accurate, however, to report that *"The FDA today lifted the ban on a drug that will save thousands of lives."*

It should be noted that, although the FDA might, within the framework of existing legislation, be much more oriented toward letting manufacturers, doctors, and patients engage in consensual transactions and might recommend liberalizing amendments, it cannot rightly ignore the restrictions that legislation places on Americans. The fundamental flaw of federal drug policy lies, therefore, not within the FDA itself but within the enabling legislation.

The Drug Development and Approval Process

The process of getting a drug to market, from first testing to final FDA approval, is summarized in figure 1 and described at greater length below.

Figure 1



Drug companies continuously analyze thousands of compounds, seeking ones of therapeutic value. During the six to seven years of preclinical testing, the manufacturer completes synthesis and purification of the drug and conducts limited animal testing. Of five thousand compounds tested, approximately five will appear promising enough to induce the company to file an Investigational New Drug Application (IND). If the IND is approved by the FDA and by an Institutional Review Board, the manufacturer may begin the first phase of development.

The IND stage consists of three phases. In phase I, clinical trials using healthy individuals are conducted to determine the drug's basic properties and safety profile in humans. Typically the drug remains in this stage for one to two years. In phase II, efficacy trials begin as the drug is

administered to volunteers of the target population. At the end of phase II, the manufacturer meets with FDA officials to discuss the development process, continued human testing, any concerns the FDA may have, and the protocols for phase III, which is usually the most extensive and most expensive part of drug development. During the phases of the IND, the manufacturer can obtain accelerated development/review of the drug. Other accommodations for usage prior to approval include treatment IND and parallel tracking.

Once Phase III is complete, the manufacturer files an NDA. Review of the NDA typically lasts one to two years, bringing total drug development and approval (that is, the IND and NDA stages) to approximately nine years. During the NDA stage, the FDA consults advisory committees made of experts to obtain a broader range of advice on drug safety, effectiveness, and labeling. Once approved, the drug may be marketed with FDA regulated labeling. The FDA also gathers safety information as the drug is used and adverse events are reported, and it will occasionally request changes in a labeling or will submit press releases as new contraindications arise. If adverse events appear to be systematic and serious, the FDA may withdraw a product from the market.

Over time there has been a clear tendency for FDA regulations and requirements to expand and multiply. In 1980, the typical drug underwent thirty clinical trials involving about fifteen hundred patients. By the mid-1990s, the typical drug had to undergo more than sixty clinical trials involving nearly five thousand patients.

Some Remarks about "Safety"

The term *safety* is often used in a simplistic and misleading manner. Safety depends on many particulars of the individual case. For example, one of the authors of this Web site (Klein) ingests ten milligrams of a blood thinner called Warfarin every day. Warfarin is also available in hardware stores as rat poison. When mixed with something tasty, rats gobble it up and die from internal bleeding. Humans with vascular problems reduce risks of thrombosis by ingesting small amounts of rat poison. Large amounts would be deadly. Dosage and condition are just two of the many factors that affect safety.

Is chemotherapy safe? Medicine is often poison. University of Iowa professor of medicine William B. Bean (1970) explained the point as follows:

> [T]he power of a drug [usually] carries with it almost in parallel a potential for dangerous reactions. . . . [E]ach person in the world is biochemically, anthropologically, genetically, and in any other way you wish individual and unique. The postulate that there is a dose, a fixed dose, of a drug which is routine for any person with a specific disease—a standard to be applied by pressing a button in a kind of therapeutic automat—is irrational. Absorption varies. Internal bodily metabolisms are different. At one end of the spectrum there are persons who react idiosyncratically or allergically to a drug. In addition there are sensitivities that exist without harming a person at all until he encounters a biochemical agent to which he may have a violent reaction, even though the majority of people exposed to the same thing do not react in that way. After a while he may learn not to revolt against its administration. . . . [I]n the practice of

> medicine we should remember that [powerful and potent drugs] are two-edged swords that cut back at you if you are not very careful in the way you wield them. With increased potency we have increased danger. (132–33)

In 1994, it is estimated that at least 106,000 people died from adverse reactions to "safe," FDA-approved drugs (Lazarou et al. 1998). (This figure includes only hospitalized patients and does not include those people who died because of medical error such as the prescribing of the wrong drug, which also accounts for some 100,000 deaths every year [Kohn, Corrigan, and Donaldson 1999].) It is inevitable that many people, often in weakened and uncertain condition, will suffer and die from unwanted side effects.

Despite the subtleties involved, the FDA is set up to screen out "unsafe" drugs for all cases of usage, taken in aggregate. But neither the administering of drugs by doctors nor the taking of drugs by patients is done on an aggregate basis. A drug stamped "safe" by the FDA is usually *not* safe for every particular case or individual, and a drug not so stamped is, nonetheless, safe for many particular cases and individuals. As the Warfarin and chemotherapy examples demonstrate, it might be "unsafe" both to take the drug and not to take the drug. But the relevant benchmark is not a state of perfect health. What really matters is whether taking the drug is *safer* than not taking the drug. The people intimately concerned in the situation and intimately informed, not bureaucrats in Rockville, Maryland, should make this determination, however.

The safety of a drug depends on myriad particulars about the patient, including age, sex, physical strength, condition, activities, allergies, diet, dosage, medical attention, and drug regimen. Furthermore and importantly, what is "safe" contains an unalterable subjective component (Higgs 1994). Patients faced with the same diseases will make different treatment decisions depending on how they perceive and evaluate the inherently risky trade-offs among health, pain, and disability. The establishment of a single society-wide standard of safety and efficacy does violence to the reality of myriad individuals with different values and experiences. We see the dilemma most clearly when the FDA withdraws an "unsafe" drug from the market, and *patients complain.* The drug Latronex, for example, was withdrawn from the market in November 2000 under pressure from the FDA. Latronex was prescribed for irritable bowel syndrome, a disease that causes abdominal pain and intense bouts of diarrhea. In the ten months that it had been on the market, some three hundred thousand people used the drug without serious problem, but seventy users developed a serious side effect, and three deaths were possibly linked to the drug (Grady 2001). Latronex is thus not without complications, but it improved the lives of many patients to the extent of allowing them to hold a job and leave their homes without fear of pain or sudden attack of diarrhea. On learning that Latronex might be withdrawn, many of these patients went to great efforts to stockpile the drug, and when it was indeed withdrawn, they complained vociferously to the FDA.

The example of Latronex indicates how the FDA's "one size doesn't fit all" policy can harm many patients. The FDA could better serve *all* patients if, instead of making choices on behalf of patients whom it cannot know or understand, it collected and disseminated information that helped these patients make informed choices in the context of their lives.

It's important to recognize that the Latronex case is unusual because patients knew that the FDA had taken away a drug that was beneficial to them. In the usual case, the FDA fails to approve a drug that could have benefited patients, and the patients never learn of the drug's possible existence. (On the importance of what is seen and unseen in FDA policy, see the

glossary item Types of FDA Error and the section FDA Incentives.)

Theory, Evidence, and Examples of FDA Harm

To obtain permission to market a drug, the manufacturer must satisfy the FDA that the drug is both safe and effective. Additional testing often enhances safety and effectiveness, but requiring a lot of testing has at least two negative effects. First, it delays the arrival of superior drugs. During the delay, some people who would have lived end up dying. Second, additional testing requirements raise the costs of bringing a new drug to market; hence, many drugs that would have been developed are not, and all the people who would have been helped, even saved, are not.

In addition, because FDA approval is mandatory, industry and medicine must heed FDA standards regardless of their relevance, efficiency, and appropriateness. Not all testing is equally beneficial. The FDA apparatus mandates testing that, in some cases, is not useful or not appropriately designed. The case against the FDA is not that premarket testing is unnecessary but that the costs and benefits of premarket testing would be better evaluated and the trade-offs better navigated in a voluntary, competitive system of drug development.

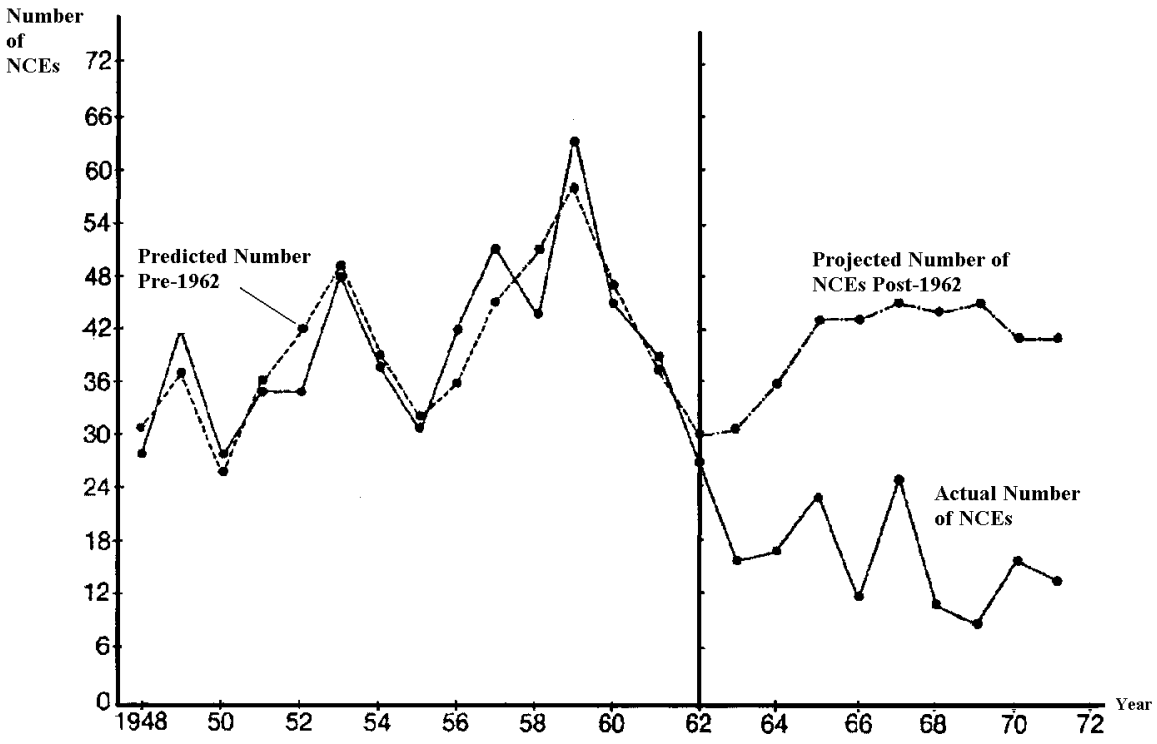
Three bodies of evidence indicate that the costs of FDA requirements exceed the benefits. In other words, three bodies of evidence suggest that the FDA kills and harms, on net. First, we compare pre-1962 drug approval times and rates of drug introduction with post-1962 approval times and rates of introduction. Second, we compare drug availability and safety in the United States with the same in other countries. Third, we compare the relatively unregulated market of off-label drug uses in the United States with the on-label market. In the final section, before turning to reform options, we also discuss the evidence showing that the costs of FDA advertising restrictions exceed the benefits.

Comparison of Pre- and Post-1962

Sam Peltzman (1973) wrote the first serious cost-benefit study of the FDA. He focused his attention on the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetics Act of 1938, which significantly enhanced FDA powers. The amendments added a proof-of-efficacy requirement to the existing proof-of-safety requirement, removed time constraints on the FDA disposition of NDAs, and gave the FDA extensive powers over the clinical testing procedures drug companies used to support their applications.

Using data from 1948 to 1962, Peltzman created a statistical model to predict the yearly number of new drug introductions. The model is based on three variables, the most important of which is the size of the prescription drug market, lagged two years. The idea is that if the prescription drug market were large two years ago, manufacturers would invest more money in research and development, which would pay off two years later in a new drug. (Prior to 1962, it took approximately two years to develop a new drug.) Despite the model's simplicity, it tracks the actual number of new drug introductions quite well, as indicated by figure 2.

Figure 2



Drug Loss Due to 1962 Increase in FDA Powers

Because Peltzman's model tracks the pre-1962 drug market quite well, we have some confidence that *if all else had remained equal,* the model also should have roughly tracked the post-1962 drug market. Peltzman's model, in other words, estimates the number of new drugs that would have been produced if the FDA's powers had not been increased in 1962. Thus, by comparing the model results with the *actual* number of new drugs, we can draw an estimate of the effect of the 1962 amendments. The model predicts a probable post-1962 average of forty-one new chemical entities(NCEs, or new drugs) per year, yet in fact the average was only sixteen. The 1962 Amendments appear to be responsible for a whopping 60 percent reduction in the number of new drugs.

The average number of new drugs introduced pre-1962 (forty) was also much larger than the post-1962 average (sixty). Thus, whether one compares pre- and post-1962 averages or compares the results from a forecast with the actual results, the conclusions are the same: the 1962 Amendments caused a significant drop in the introduction of new drugs. Using data of longer span, Wiggins (1981) also found that increased FDA regulations raised costs and reduced the number of new drugs.

Even if FDA regulations have not improved safety, they might be redeemed if they have reduced the proportion of inefficacious drugs on the market. Using a variety of tests, however, Peltzman (1973) found little evidence to suggest a decline in the proportion of inefficacious drugs reaching the market since 1962. Thus, he concluded, "(the) penalties imposed by the marketplace on sellers of ineffective drugs prior to 1962 seem to have been enough of a deterrent

to have left little room for improvement by a regulatory agency." (1086) Similarly, in their survey of the literature, Grabowski and Vernon (1983) conclude, "In sum, the hypothesis that the observed decline in new product introductions has largely been concentrated in marginal or ineffective drugs is not generally supported by empirical analyses" (34).

The costs of FDA regulations do not vary with the number of potential users of the drug, so the decline in drug development has been especially important in the treatment of rare diseases. By definition, each rare disease afflicts only a small number of people, but there are thousands of rare diseases. In aggregate, rare diseases afflict millions of Americans: according to an AMA estimate (AMA 1995), as many as 10 percent of the population. Thus, millions of Americans have few or no therapies available to treat their diseases because of increased costs of drug development brought about by stringent FDA "safety and efficacy" requirements. In response to this problem, in 1983 the Orphan Drug Act was passed to provide tax relief and exclusive privileges to firms developing drugs for diseases affecting two hundred thousand or fewer Americans (AMA 1995). It would be better to reduce or eliminate FDA regulations for all drugs and patient populations.

The Grisly Comparison. The delay and large reduction in the total number of new drugs has had terrible consequences. It is difficult to estimate how many lives the post-1962 FDA controls have cost, but the number is likely to be substantial; Gieringer (1985) estimates the loss of life *from delay alone* to be in the hundreds of thousands (not to mention millions of patients who endured unnecessary morbidity). When we look back to the pre-1962 period, do we find anything like this tragedy? The historical record—decades of a relatively free market up to 1962—shows that voluntary institutions, the tort system, and the pre-1962 FDA succeeded in keeping unsafe drugs to a low level. The Elixir Sulfanilamide tragedy, in which 107 people died, was the worst of those decades. Every life lost is important, but the grisly comparison is necessary. *The number of victims of Elixir Sulfanilamide tragedy and of all other drug tragedies prior to 1962 is very small compared to the death toll of the post-1962 FDA.*

Comparison with Other Countries

The second source of evidence comes from comparing drug availability and safety in the United States with the same in other countries. Prior to the Kefauver-Harris Bill of 1962, the average time from the filing of an IND to approval was seven months. By 1967, however, the average time to approval had increased to thirty months. Time to approval continued to rise through the late 1970s, when on average a successful drug took more than ten years to get approved. In the late 1980s and 1990s, times to approval decreased somewhat, but are still eight years on average, far higher than in the 1960s (Peltzman 1974; Thomas 1990; Tufts Center for the Study of Drug Development 1998).

Time to approval has historically been shorter by years in Europe than in the United States. Drugs are usually available in Europe before they are available in the United States. The difference between the time of a drug's availability in Europe and that in the United States has come to be called the *drug lag* (Grabowski 1980; Kaitin et al. 1989; Wardell 1973, 1978a,1978b; Wardell and Lasagna 1975). In recent years, however, the FDA has improved. In the latest data, covering 1996–98, the average time from filing the IND to submitting the NDA was 5.9 years

and average NDA approval time was 1.4 years, for a total of 7.3 years, the quickest approval times in decades (Kaitin and Healy 2000). Researchers have suggested that the drug lag may be disappearing (Healy and Kaitin 1999).

What is significant for our purposes is that from approximately 1970 to 1993 the FDA clearly lagged significantly behind its counterparts in the United Kingdom, France, Spain, and Germany (Kaitin and Brown 1995). This fact gives us a basis for comparison: During the period of consistent drug lag, did the delay correspond to greater safety? Put another way: Did speedier drug approval in Europe lead to a scourge of unsafe drugs?

If the U.S. system resulted in appreciably safer drugs, we would expect to see far fewer postmarket safety withdrawals in the United States than in other countries. Bakke et al. (1995) compared safety withdrawals in the United States with those in Great Britain and Spain, each of which approved more drugs than the United States during the same time period. Yet, approximately 3 percent of all drug approvals were withdrawn for safety reasons in the United States, approximately 3 percent in Spain, and approximately 4 percent in Great Britain. There is no evidence that the U.S. drug lag brings greater safety. Wardell and Lasagna (1975) concluded their comparison of drug approvals in the United States and Great Britain by noting: "In view of the clear benefits demonstratable [*sic*] from some of the drugs introduced into Britain, it appears that the United States has lost more than it has gained from adopting a more conservative approach" (105).

Deaths owing to drug lag have been numbered in the hundreds of thousands. Wardell (1978a) estimated that practolol, a drug in the beta-blocking family, could save ten thousand lives a year if allowed in the United States. Although the FDA allowed a first beta-blocker, propranolol, in 1968, three years after that drug had been available in Europe, it waited until 1978 to allow the use of propranolol for the treatment of hypertension and angina pectoris, its most important indications. Despite clinical evidence as early as 1974, only in 1981 did the FDA allow a second beta-blocker, timolo, for prevention of a second heart attack. The agency's withholding of beta-blockers was alone responsible for probably tens of thousands of deaths (on this general issue see Gieringer 1985; Kazman 1990).

A chief source of information about drug delay is the Tufts Center for the Study of Drug Development, a scholarly, not too outspoken research center funded chiefly by pharmaceutical companies. Their information is often mined by researchers at the Competitive Enterprise Institute (CEI). The CEI has noted that in recent years thousands of patients have died because the FDA has delayed the arrival of new drugs and devices, including Interleukin-2, Taxotere, Vasoseal, Ancrod, Glucophage, Navelbine, Lamictal, Ethyol, Photofrin, Rilutek, Citicoline, Panorex, Femara, Prostar, Omnicath, and Transform. Prior to FDA approval, most of these drugs and devices had already been available in other countries for a year or longer.

Gieringer (1985) used data on drug disasters in countries with less-stringent drug regulations than the United States to create a ballpark estimate of the number of lives saved by the extra scrutiny induced by FDA requirements. He then computed a similar ballpark figure for the number of lives lost owing to drug delay:

> [T]he benefits of FDA regulation relative to that in foreign countries could reasonably be put at some 5,000 casualties per decade or 10,000 per decade for worst-case scenarios. In comparison, it has been argued above that the cost of FDA delay can be estimated at anywhere from 21,000 to 120,000 lives per decade.

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

Note three things about the foregoing passage. (1) The comparison is between the FDA and the foreign systems of drug control. (2) The relative benefits of the FDA are expressed in number of *casualties,* whereas the relative costs are in number of *lives.* (3) In addressing the costs, Gieringer estimated the costs only from drug delay; he does not attempt to quantify the costs associated with drug *loss*. Nevertheless, his conclusion is clear: the FDA is responsible for more lives lost than lives saved.

FDA Incentives

Even if the FDA required only the most relevant clinical trials and worked at peak efficiency to evaluate new drugs, the trade-off between more testing and delayed drugs would still exist. We cannot escape this trade-off. The only question is whether a centralized bureaucracy should decide on these trade-offs for everyone or patients and doctors should make such decisions. Much of the FDA's delay, however, is not owing to useful—albeit not necessarily optimal—testing. Much of the delay is pure waste. The cause is not laziness but incentives. (Read the sidebar Why the FDA Has an Incentive to Delay the Introduction of New Drugs for an explanation.)

Comparison of On-Label and Off-Label Usage

The third sort of evidence on the costs of FDA regulations comes from comparing the utilization of drugs for their on-label uses with their utilization for off-label uses. The hidden lesson of off-label usage is that, even in today's highly regimented setting, there functions a realm of efficacy testing and assurance quite apart from the FDA.

When the FDA evaluates the safety and efficacy of a drug, the evaluation is made with respect to a specified use of the drug. Once a drug has been approved for some use, however, doctors may legally prescribe the drug for other uses. Approved uses are known as *on-label* uses, and other uses are considered *off-label* uses. Amoxicillin, for example, has an on-label use for treating respiratory tract infections and an off-label use for treating stomach ulcers.

For the on-label treatment of respiratory tract infections, amoxicillin has been tested and passed muster in all three phases of the IND clinical study; phase I trials for basic safety and phase II and phase III trials for efficacy. For the treatment of stomach ulcers, however, amoxicillin has not gone through FDA-mandated phase II and phase III trials and thus is not FDA approved for this use. Indeed, amoxicillin will probably never go through FDA efficacy trials for the treatment of stomach ulcers because the basic formulation is no longer under patent. Yet any textbook or medical guide discussing stomach ulcers will mention amoxicillin as a potential treatment, and a doctor who did not consider prescribing amoxicillin or other antibiotic for the treatment of stomach ulcers would today be considered highly negligent. Off-label uses are in effect regulated according to the FDA's pre-1962 rules (which required only safety, not efficacy), whereas on-label uses are regulated according to the post-1962 rules.

FDA defenders suggest that an unregulated market for drugs would be a medical disaster.

Do patients and doctors shrink in fear from uses not certified by the FDA?

Not at all! Most hospital patients are given drugs that are not FDA approved for prescribed use. In a large number of fields, a majority of patients are prescribed at least one drug off-label. Off-label prescriptions are especially common for AIDS, cancer, and pediatric patients, but are also common throughout medicine.

Doctors learn of off-label uses from extensive medical research, testing, peer-reviewed publications, newsletters, lecture presentations, conferences, advertising, Internet sources, and trusted colleagues. Scientists and doctors, working through professional associations and organizations, make official determinations of "best practice" and certify off-label uses in standard reference compendia such as *AMA Drug Evaluations, American Hospital Formulary Service Drug Information,* and *U.S. Pharmacopoeia Drug Indications.* Doctors use this information to try to make the best decisions for their patients. Medical decisions are most often made under uncertainty and partial ignorance, so there is rarely a single best decision, and different doctors and different patients choose different treatments. New information constantly flows into this system as outcomes accumulate, epidemiological studies reveal new correlations, scientists propose theoretical explanations, researchers design and embark on new clinical studies, scientific institutions arrive at new judgments, and pharmaceutical companies create new drugs. As this medical knowledge grows and develops, information flows in a decentralized fashion, and doctors adjust their decisions accordingly. (See the section The Sensible Alternative on how the institutions work without government intervention.)

Economist J. Howard Beales (1996) found that off-label uses appeared in the *Pharmacopoeia* on average 2.5 years earlier than the FDA recognized those uses. The difference between the on-label and off-label markets is not that the off-label market is "unregulated" but that it is unregulated by the FDA, a centralized and coercive authority. In approving or rejecting a new drug, the FDA makes a decision everyone must obey. It's as if the Department of Transport unilaterally decided what vehicles Americans could and could not purchase. Heterogeneity among patients in both preferences and circumstances is great. A drug that can save the life of A may be dangerous to B even if A and B have the same disease. An athlete and a college professor with the same disease may choose different courses of treatment. The FDA's "one size fits all" policy is not appropriate for every patient.

The off-label market is regulated by thousands of doctors and patients acting in a decentralized manner. Compared to the FDA, this market adjusts quickly to new information, shows less sign of biased incentives, and allows a more precise adjusting of treatment decisions to preferences and the conditions of time and place. The evidence indicates that these benefits are not offset by significantly greater risk (Tabarrok 2000). The off-label market operates with much less government intervention than the on-label market and provides a good idea of the benefits to be had from reducing FDA control over approval decisions.

By their actions, doctors tell us that they believe in off-label prescribing. Getting the FDA to approve a new use for an old drug requires an expensive and lengthy process. In many cases, the costs to the sponsor of the required testing exceed the benefits of approval. It is clear that if the FDA prohibited off-label prescribing, current practices would have to change significantly. No one would be foolish enough to suggest that the FDA prohibit off-label prescribing.

But there is a logical inconsistency in allowing off-label prescribing and requiring proof of efficacy for the drug's initial use (Tabarrok 2000). Logical consistency would require us *either* (1) to oppose off-label prescribing and favor initial proof of efficacy, *or* (2) to favor off-label

prescribing and oppose initial proof of efficacy. Experience recommends the second option. Efficacy requirements should be dropped altogether!

Summary of the Three Bodies of Evidence: FDA-Caused Mortality and Morbidity Are Unredeemed

Evidence from the pre-1962 market shows that FDA restrictions have greatly reduced the number of new drugs, and because there was little or no corresponding gain in drug quality, the concomitant mortality and morbidity were unredeemed. The international evidence shows that there has long been a drug lag in the United States, and because Americans have not benefited from the extra "precaution," the concomitant mortality and morbidity are unredeemed. Finally, the off-label evidence indicates that the network of doctors, patients, pharmaceutical firms, hospitals, universities, rating organizations, and so forth is really in charge of defining and judging efficacy and that it functions smoothly and successfully in the realm of uses not approved by the FDA; hence, the mortality and morbidity that result from proof-of-efficacy requirements are unredeemed. All the systematic evidence goes against the coercive FDA apparatus.

FDA Advertising Restrictions: Ignorance Is Death

In addition to permitting drugs on the market, the FDA controls advertising and promotion. The costs of such control parallel the costs of restricting drugs. They include (1) reducing the speed at which consumers learn of and adopt important new therapies; (2) reducing the size of the market for drugs, thereby reducing the incentive to research and develop new drugs; and (3) reducing the number of treatment options, making it more difficult for physicians to provide therapies tailored to each individual patient (Rubin 1995; Tabarrok 2000).

In numerous instances, the FDA has reduced the speed at which patients and their agents have learned of and adopted new drugs or new uses of old drugs.. The most important example is aspirin.

The FDA prevented aspirin manufacturers from advertising that clinical studies had shown that the use of aspirin during and after heart attacks might prevent death. When, years after the clinical studies had been completed, the FDA finally sanctioned aspirin for heart-attack patients, Dr. Carl Pepine, codirector of cardiovascular medicine at the University of Florida College of Medicine, estimated that as many as ten thousand lives annually could be saved. In other words, Dr. Pepine thought that the FDA restrictions preventing the advertising and promotion of aspirin for heart attack patients were responsible for the deaths of tens of thousands of people. Noting that the decision should have come years earlier, Dr. Pepine said, "I'm disappointed that something that has such potential to save so many lives took so long. But it's better late than never." (quoted in Ross 1996). Paul Rubin (1995), whose paper on FDA advertising restrictions provides the title for this section, wrote that "the banning of advertising of aspirin for first heart attack prevention, may be the single most harmful regulatory policy currently pursued by any agency of the U.S. government." (48) (Keith [1995] reaches a similar, though less pointed, conclusion). Despite studies showing benefits, the FDA still does not allow aspirin manufacturers to advertise the benefits of aspirin as a preventive measure for people at

high risk for a first heart attack.

Another example: In 1992, the federal Centers for Disease Control and Prevention (CDC) recommended that women of childbearing age take folic acid supplements. Studies showed that taking folic acid reduced risks of babies suffering neural-tube birth defects such as anencephaly and spina bifida. The FDA immediately announced, however, that it would prosecute any food or vitamin manufacturer that placed the CDC recommendation in its advertising or product labeling (Calfee 1997). The public did not learn of the importance of folic acid until Congress passed the Dietary Supplement Health and Education Act of 1994, which loosened the FDA's vise on the advertising of vitamins and other dietary supplements. Within only a few years of its ban on publicizing the CDC recommendation, the FDA made a complete turnabout. Since 1998, the agency *has required* manufacturers to fortify a variety of grain products with folic acid—that which is not prohibited is mandatory!

The FDA has also restricted how manufacturers can promote the off-label uses of drugs (these restrictions were in part ruled unconstitutional in *Washington Legal Foundation v. Friedman*). Such restrictions make it more difficult for doctors to best match patient with treatment. In a survey, 79 percent of neurologists and neurosurgeons, 67 percent of cardiologists, and 76 percent of oncologists said that the FDA should not restrict information about off-label uses. In response to a follow-up question, similar numbers indicated that the FDA policy of limiting information had made it more difficult for them to learn about new uses of drugs and devices (Conko 1998).

(On government control of advertising more generally, see Calfee 1997; Kaplar 1993; Masson and Rubin 1985; Rubin 1991a, 1991b, 1994; and Tabarrok 2000; they evaluate FDA restrictions on advertising and promotion in more detail.)

Some Remarks about Medical Devices

Medical devices came under official FDA control in 1976 with the Medical Device Amendments. The definition of medical devices encompasses everything from tongue depressors to artificial hearts, all of which must go through some FDA approval procedure. Although the regulation of devices has not been as well studied as the regulation of drugs, it is clear that FDA control of such devices has led to similar costs, especially *device lag* and *device loss* (Campbell 1999; Higgs 1995c).

An especially absurd example of device delay occurred to the Sensor Pad. The Sensor Pad is so simple it hardly justifies the term *device:* it is two sheets of sealed plastic that sandwich a silicon lubricant. With the Sensor Pad, a woman can more easily detect unusual breast lumps in a self-examination. Although the product is simple, it is quite useful and can save lives through early detection of breast cancer. The Sensor Pad was invented in 1986 by Earl Wright of Inventive Products and was submitted to the FDA for approval. The FDA, however, could find no other substantially equivalent product on the market and thus *automatically* classified the Sensor Pad as a high-risk, Class III device. Before being allowed to sell the Sensor Pad, Inventive Products had to submit a premarket approval application to the FDA.

Inventive Products submitted hundreds of pages documenting the safety and effectiveness of the Sensor Pad (both of which were evident to anyone who used the product for sixty seconds), yet *years* went by, and still the FDA wanted more documents. As it turned out, the

FDA decided that in order for the device to be approved, Inventive Products needed to show not simply that the Sensor Pad helped women to detect breast lumps but that it reduced the mortality of breast cancer. Proof of this kind would require extensive clinical trials involving thousands of women tracked over many years—all this in order to get permission to sell a device substantially less complicated and less dangerous than a toaster oven.

Canada, western Europe, Japan, and other countries quickly approved the Sensor Pad. In Canada, a country that is hardly known as the Wild West of medical devices, the Sensor Pad was approved in thirty days with approximately half a dozen pages of documentation. Frustrated at the delay, Inventive Products defied the FDA and in 1988 began selling the Sensor Pad to hospitals.

Hospitals bought several hundred thousand Sensor Pads and gave them to women, *some of whom would later testify in Congress that the product had saved their lives.* Doctors too began to use the device and reported positive results. In 1989, however, the FDA raided Inventive Products and a number of hospitals (!) and "on behalf of American women" confiscated the Sensor Pads. Several lawsuits and several years later the product was still not available in the United States.

In April 1994, the situation began to change when the *Wall Street Journal* ran a story on the Sensor Pad that was later discussed in Congress by Representative John Duncan of Tennessee (the Congressional Record contains Duncan's remarks and the *Wall Street Journal* story). Later that same year, ABC's *20/20* did an investigative report on the FDA highlighting the Sensor Pad fiasco as well as other examples of device delay (see, for example, the Baby Ventilator Incident). The next year, Congress held hearings at which a number of women and doctors testified in favor of the Sensor Pad. Finally, after nearly ten years of delay and several million dollars in legal and other costs, the Sensor Pad was approved in December 1995. But the mandarins at the FDA had the last word: they decreed that the Sensor Pad was to be used only with a doctor's prescription!

The lesson of the Sensor Pad is not simply one of FDA intransigence. The larger lesson reveals itself when we consider that *if Inventive Products had not defied the FDA, there would have been no women ready and able to testify in Congress that the Sensor Pad saved their lives.* The media paid attention because it could place a human face on the Sensor Pad story. If Inventive Products had not defied the FDA, knowledge of the Sensor Pad would not have leaked out from behind the FDA's wall of silence. (It's noteworthy that, since the Safe Medical Devices Act of 1990, the FDA can fine companies up to $1 million for an alleged violation of the Food, Drug, and Cosmetic of 1938 related to medical devices. Inventive Products probably could not afford to challenge the FDA today.) Tragically, the usual situation is for information to remain locked behind FDA doors. We rarely get to try products that the FDA fails to approve, and we never get to try products that are never brought into existence because FDA rules and regulations have made research and development uneconomic. As a result, the public remains ignorant of the true costs of FDA power. (The section FDA Incentives discusses this problem at greater length) It is only in rare cases, when the FDA withdraws approval from a product (recall the Lartronex example) or bans an already existing product, that the true costs become clearer.

The Question of Software

According to the FDA, software is a medical device and is regulated accordingly.

Because medical software is often new, it can, like the Sensor Pad, be classified as a high-risk Class III device even if it is not involved in high-risk procedures. As with the regulation of other devices and drugs, FDA regulation of software can (and does) often result in less safety. Volokh (1997), for example, noted that

> In X-ray therapy for breast cancer, the affected tissue can be irradiated from three different directions, and to avoid overdosing or underdosing the patient, the doctor has to be sure that there are no gaps or overlaps of the X-ray beams. Once the doctor knows which treatment machine is to be used, and what the patient's measurements are, he can figure out where the patient should be positioned and how the beams should be directed. But this calculation, when performed manually on a calculator, is tedious, error-prone, and time-consuming, taking up to half an hour.

A radiologist developed some software to simplify the calculations. Initially, the software even received FDA clearance. Dr. Martin Weinhous, chief medical physicist in the radiation oncology department at the Cleveland Clinic in Ohio, noted, however, that as the software evolved, "the FDA began to require more of its creator. Eventually, the FDA required that [the developer] test his software tool against every possible PC and Macintosh configuration, even though the inherent risk is small. Faced with unrealistic GMP requirements, he ceased manufacturing of the device. So we in radiation oncology have no choice but to continue to use a less sophisticated and more error-prone method" (quoted in Volokh 1997).

The most serious problem with software regulation is the potential for the FDA to use software regulation as a means of regulating medical practice. Congress has always insisted that the FDA cannot regulate doctors. As a result, once a drug or device has been approved for some use it can be used off-label for any use. As is discussed above and at greater length in Tabarrok (2000), the off-label use of drugs has been a tremendous boon to patients. The FDA has always been uncomfortable with off-label use, however, and has tried to suppress such use whenever possible. With the growing use of software as a component in devices and drug delivery systems, the FDA believes it has found a way to limit off-label uses. Essentially, it is demanding that the software in any device be written so that the device can be operated only for FDA-approved uses. Excimer lasers, for example, have many different uses in eye surgery, but when the FDA approved excimer lasers, they physically and legally tied use of the laser to software that was limited to FDA-approved procedures (Volokh 1997).

The FDA claims, though, that it has not regulated medical practice in the laser case, and this claim has a certain logic. Approved devices may be used for unapproved uses, but unapproved devices cannot be used at all. In tying the excimer laser to restrictive software, the FDA simply approved a narrowly defined product; technically it did not regulate medical practice. The argument illustrates that freedom of choice has survived in the medical arena only because it has hidden itself in the interstices of policy that the FDA once found too costly to fill.

John Calfee explained how this practice could greatly expand:

> Imagine that the oncologist using a combination drug therapy uses a computer-controlled device to administer the drugs. Suppose the computer software determines all dosages, and does so according to settings provided by the physician. Now suppose that

> when the FDA approves the drug-administration device for marketing, it also approves the software in every detail. If the FDA forbids physicians or others from reprogramming the device, it could effectively tell doctors how to administer the drug and could even exercise considerable control over which kinds of patients receive the drug and even which illnesses are treated. (quoted in Volokh 1997)

Third-Party Certification and Review

The European Union (EU) maintains strict quality-control standards for medical devices, including extensive reporting requirements, but does so with very little government involvement. Low risk products can be marketed under a self-certification system. Higher-risk products can be marketed after being certified by "notified bodies" that test products and certify that EU standards have been met. Notified bodies are themselves certified by governments. Approval of a product by a notified body is essentially equivalent to government approval.

In 1996, under pressure from Congress, which was considering much stronger legislation, the FDA introduced a third-party certification system that was later extended by the 1997 Modernization Act. Manufacturers have not extensively used the third-party certification program, however, because the FDA has limited its use to relatively simple Class I products. The program and the larger European experience on which it is based does, however, suggest a model for FDA reform based on the creation of drug-certifying bodies. We take up reform options in the next section.

Reform Options

In recent years, some welcome FDA reform has occurred, particularly with the PDUFA of 1992 and the 1997 Modernization Act. The significant component of these reforms is the partial shifting of FDA funding from general appropriation to "user fees" for FDA services. FDA funding is now tied to NDAs, so the FDA has managed to approve drugs more rapidly because such promptness induces more NDAs and more "user fee" revenues for the FDA.

We believe, however, that the health and well-being of Americans and others worldwide would be best served by more significant reductions in FDA powers. In these matters, we favor adult freedom and hence the repeal of all forms of premarket approval. We believe that nongovernmental parties and tort law should generate and administer all of the rules, standards, institutions, and practices that make up drug affairs. We describe how such a system would work in the section below called The Sensible Alternative.

Freedom may be the North Star, but in the American system decontrol comes slowly and gradually, when it comes at all. Drug affairs are now fettered by numerous restrictions. Relaxing or removing any of the significant restrictions would help. The following subsections suggest reforms that fall short of the full freedom of what we consider the sensible alternative but nevertheless would substantially improve on current policy.

- Improve Consumer Information and Control
- Create a Field of Drug-Certifying Bodies
- Implement International Reciprocity
- Drop the Proof-of-Efficacy Requirement

- Make FDA "Approval" Voluntary

Improve Consumer Information and Control

Traditionally, patients have been expected to be patient while doctors and other elites make treatment decisions on their behalf. FDA paternalism, therefore, has been part and parcel of the paternalism of American medicine. The latter paternalism has a number of social and historical roots but is also tied up with the professionalization and regulation of American medicine (see, e.g., Starr 1982). In recent years, as competition in the market for health services has increased, consumers have become more informed about health matters and more willing to question their doctors and participate closely in their treatments. Yet consumers remain uninformed in many respects, and, unfortunately, the FDA has tended to resist the trend toward greater consumer information and control. The FDA, for example, tried for decades to suppress the use and sale of vitamins and other dietary supplements such as St. John's Wort (for more, see the history section).

In the tradition of American medical paternalism, drug information has tended to flow hierarchically from the FDA to the physician and then (perhaps) to the consumer. Physicians have supported this hierarchical information structure because it places them in control of the highly profitable information gateway (Benham and Benham 1975). The FDA has, for the most part, supported or acquiesced to this hierarchy. It has used its power over labeling, for example, to create the class of prescription-only drugs (see the history section). Prescription-only drugs did not need to carry *any* consumer labeling except for the warning "Caution: to be used by or on the prescription of . . . " (3 *Federal Register* 3168, Dec. 28, 1938). Thus, product labeling evolved so that it became common for consumers to be given potentially dangerous drugs with no written information other than the doctor's instructions.

Even today, consumer's typically do not receive a copy of the product label with their prescription. If they are lucky, their pharmacist may give them a computer-generated synopsis of warnings and contraindications. Consumers can and should ask for product labels with their prescriptions. The FDA should also pay more attention to designing labels that can be easily read and understood. At present, product labels are difficult to read, badly organized, and poorly formatted. Gieringer (1984) argues that "the organization of warnings and risk analysis would seem to deserve a sophisticated effort at risk analysis . . . this could be done through some form of dedicated labeling agency" (121).

Aside: Questioning prescription-only restrictions.

Restrictions on direct-to-consumer advertising is another example of the ways in which the FDA has supported the hierarchical transmission of information. Drug advertising on television has only recently been allowed, a good fifty years after the invention of that medium.

A minor reform in the direction of improving the transmission of information would be to return control over drug promotion and advertising to the FTC (which had it until 1962). The FDA often acts unreasonably in regulating promotional literature and advertising. Drug companies fear the FDA and refrain from challenging its edicts because the it has a stranglehold on the whole industry, and no company wants to get on the its bad side (Volokh 1995).

Separating NDA approval from advertising approval would increase the willingness of firms to stand up to unreasonableness. In addition, since at least the 1980s, the FTC has been more respectful than the FDA of the consumer's ability to filter and grade information from advertising claims. The FTC, for example, was instrumental in allowing food manufacturers to make substantiated health claims regarding food, with notable improvements in the health of consumer food products as a result (Ippolito and Mathios 1990).

A large improvement would be to allow "Not FDA Approved" claims. Under a split-label regime, the product label would consist of a part for FDA-approved health and nutrition claims and a part for "Not FDA Approved" claims. Although retaining FDA certification for those who want assurance from the FDA, the split-label approach increases the amount of information available to the consumer. Recall that many patients are prescribed drugs for off-label uses. By definition, FDA labeling contains no information specific to off-label uses, and thus many patients are not well served by the FDA label. (In addition, the well-known *Physician's Desk Reference [PDR]* is only a compilation of FDA labeling; the *U.S. Pharmacopoeia Drug Information (USPDI)* and its consumer version, *Complete Drug Reference,* are better sources of information than the *PDR*). A split-label approach would mean that all of a drug's common uses were described on the label. Manufacturers of aspirin, for example, would be allowed to state its uses as a prophylactic for first heart attacks on the "Not FDA Approved" portion of the label. The same idea could also be applied to advertising claims.

A split-label approach now exists, following the 1994 passage of the DSHEA, for claims made on behalf of vitamins, minerals, and other dietary supplements. Dietary supplements can now make "nutritional support" claims but not "drug" claims so long as they carry the warning, "These statements have not been evaluated by the Food and Drug Administration." The split-label approach would extend the idea of a split label to all drugs and medical devices.

Create a Field of Drug-Certifying Bodies (the Miller Plan)

Henry Miller recently developed an intermediate reform proposal in which drug development and application would be overseen by nongovernmental *drug-certifying bodies.* They would compete with one another for hire by companies developing a new drug. The hired drug-certifying body would oversee investigation, help develop the NDA, and then make an initial decision on the application—that is, decide whether to certify the drug. The European agencies would also be permitted to serve as drug-certifying bodies. The company and its certifying body would then go together to the FDA for final approval of the new drug. The FDA, therefore, would retain final authority, but would rely on a set of trusted drug-certifying bodies, which would compete to get it right, do it quickly, and keep fees low. Unlike the FDA, the certifying bodies would be liable to litigation for negligence. Under such a regime, according to Miller (2000), the FDA "becomes primarily a *certifier of certifiers*, rather than a *certifier of products*" (106).

Once the FDA receives the NDA with the certifying body's recommendation for approval, it will have ninety days to respond. The FDA would not be able to extend the ninety-day review period, and failure to act will constitute automatic approval at the close of the ninety-day period (a feature reminiscent of the pre-1962 FDA). If the FDA rejects the application, it must provide an explanation that rebuts the presumption given to the recommendation (Miller 2000, 94).

Rejection would be open to appeal to "an independent standing advisory committee of experts, located organizationally in the Department of Health and Human Services (DHHS), where the FDA is located, at the level of the office of the secretary (therefore, not reporting to the FDA commissioner). [The committee would] advise the secretary of DHHS, who, it is expected, [would] accept their advice and instruct the FDA commissioner to implement the committee's decision" (100).

Miller thoughtfully seeks to design a new set of institutions to sustain in the United States a cooperativeness that is more natural to the countries of western Europe. Miller's plan might vastly improve the situation in the United States. But Miller's plan gives the FDA final authority over new drugs and devices as well as hegemony over the setting of drug quality and safety standards and the recognition of drug-certifying bodies.

In addition, Miller is explicit in seeking reforms that would lower type 2 errors without increasing type 1 errors. Although all such reforms should be pursued, there is little reason to believe that the current level of type 1 error is best. Indeed, an understanding of FDA incentives suggests that at present type 1 errors are too high relative to type 2 errors, and some trade-off is thus warranted.

Implement International Reciprocity

If the United States and, say, Great Britain had drug-approval reciprocity, then drugs approved in Britain would gain immediate approval in the United States, and drugs approved in the United States would gain immediate approval in Great Britain. Some countries such as Australia and New Zealand already take into account U.S. approvals when making their own approval decisions. The U.S. government should establish reciprocity with countries that have a proven record of approving safe drugs—including most west European countries, Canada, Japan, and Australia. Such an arrangement would reduce delay and eliminate duplication and wasted resources. By relieving itself of having to review drugs already approved in partner countries, the FDA could review and investigate NDAs more quickly and thoroughly.

EU countries established a limited reciprocity system in 1983. Over time, however, the European system has evolved in a somewhat different direction. The reciprocity principle has two virtues, competition and elimination of duplication. Unfortunately, the EU has begun to subvert the first virtue (Hansen 2000). Today many products *must be* reviewed by the European Agency for the Evaluation of Medicinal Products (EMEA), headquartered in London. EMEA approval opens the market to all EU countries. Still, the EMEA regime is better than the FDA. For most drugs, the EMEA is not the sole source of authorization (hence, there is competition among the EU drug agencies); it contracts most of its reviews to outside experts; it takes a less adversarial posture; and it places more confidence in the sponsors' summary reports (rather than reanalyzing the raw data) (Miller 2000). Nevertheless, there is little guarantee that the system will maintain its current performance, and, besides, being better than the FDA is nothing to brag about. If the EU centralizes authority, the vestiges of competitive governance might give way to monopoly governance.

International reciprocity would eliminate the FDA's monopoly on drug approval. Under such a system, U.S. drug companies could submit the NDA equivalent to the authorities in partner countries and thereby gain approval in the United States. Thus, the FDA would have to compete for business. It would have to shape up or lose out on the fees that come with NDAs.

Drop the Proof-of-Efficacy Requirement

Prior to 1962, the FDA screened drugs only for safety. NDAs did not have to demonstrate efficacy. As we have seen, the pre-1962 years were a time of great pharmaceutical advance. Also, we know from the current practice of off-label prescriptions that a panoply of nongovernmental institutions research, mediate, and certify efficacy of drugs, quite apart from FDA efficacy evaluation. Hence, there is strong evidence that private enterprise and tort law takes care of efficacy and that the costs, delays, and drug loss from FDA efficacy requirements are unredeemed. A splendid reform, therefore, would be to drop the proof-of-efficacy requirements in drug approval and return to the pre-1962 principle of requiring only proof of safety. That simple reform would greatly expand the range of drugs developed (in particular for rare diseases), increase the speed with which they get to market, and significantly reduce costs and drug prices.

Make FDA "Approval" Voluntary: FDA Certification That Would Mean Something Other Than Permission

FDA drug testing and certification might be made optional. Drug companies would be welcome to submit applications for *voluntary certification* by the FDA. If doctors and patients were assured of quality and safety apart from FDA certification (as they are now with respect to off-label drug uses), they would be free to purchase the drug clearly labeled "Not FDA Approved." On the other hand, if FDA certification is as valuable as the FDA claims, patients and doctors would avoid non-FDA-certified drugs and rely on FDA certification. Under this plan, the FDA would become a genuinely voluntary institution, much like Underwriters' Laboratories.

Under such a regime, the image of the FDA would change. Today, when a drug company applies for FDA "approval," there is an ambiguity about whether the company actually sees value in the FDA's seal of approval or merely seeks legal permission. Under the proposed regime, the meaning of FDA approval would be unambiguous. Approval would be sought because the company believes the FDA seal of approval to be valuable. The relationship between the company and the agency would be one of integrity, appreciation, and cooperation because the agency would not exercise coercive power over the company.

Voluntary certification would make the FDA one among a set of many certification agencies, a set that might include governmental drug agencies in other countries, the American Medical Association, the Mayo Clinic, the *U.S. Pharmacopoeia*, and private for-profit or nonprofit firms such as Underwriters' Laboratories, which would specialize in testing drugs and medical devices. In the section below, The Sensible Alternative, we discuss in greater detail how a voluntary system would provide safe and efficacious drugs.

Aside: Understanding the FDA's Opposition to Liberalization

The Sensible Alternative: The Voluntary Provision of Assurance

We believe that it would be desirable to move toward a voluntary system in which private firms, organizations, and perhaps also other governments and a voluntary FDA assured consumers of drug safety and efficacy. The desirability of a voluntary system, however, depends not just on how poorly the FDA performs but also on how well such a system would perform in its stead. In this section, therefore, we provide further information on how voluntary practices assure drug safety and efficacy.

Consumers want quality and safety in their drugs and devices. Moreover, consumers—prior to purchase and use—want *assurance* of quality and safety (see Klein 1997, 2000a). Society has three broad approaches to quality and safety assurance:

1. Voluntary practices and institutions, such as reputation, knowers, and middlemen, which assure quality and safety because it is profitable to satisfy the consumer and live up to one's promises

2. Tort remedy, by which consumers who are harmed or cheated may sue under the rubrics of fraud, false representation, breach of warranty, negligence, malpractice, and so on

3. Governmentally imposed restrictions on voluntary exchange, whereby government attempts to determine the quality and safety of goods and services, and prohibits exchange until it has given permission

Careful reflection will show that the combination of voluntary practices and the tort system are well able to meet the demand for quality and safety assurance.

Reputation

In any industry, trade or profession, a seller's trading partners, associates, and customers develop opinions of his trustworthiness. They develop a sense of whether the seller's products and services live up to the quality and safety that he promises. A good *reputation* is one of the most important keys to success because a good reputation will bring satisfied customers calling again and will bring others who hear of the seller's good reputation. If the seller sells an unsafe product, he will not only pay tort penalties, but also lose his reputation and business. Reputation is generated by word of mouth and by other informal means, but also by various services and organizations that evaluate, rate, and report on the quality and safety of the seller's products.

Ultimately, the whole enterprise of medical science and pharmacology is about safety and efficacy. Historians of private professional regulation have shown that professional men and women built institutions to research, test, certify, and monitor drug purity, safety, and efficacy even before the FDA existed (see Burrow 1970; Dowling 1970; Sonnedecker 1970). Such efforts often led, rather than followed, government efforts to assure safety and efficacy. The 1906 Pure Food and Drugs Act, for example, made certain privately produced drug compendia the official

standards for purity. Glenn Sonnedecker (1970) described the era prior to federal government intervention: "Having relied on voluntary work and democratic decision-making for the creation of the *Pharmacopoeia,* organized medicine, and later organized pharmacy, also relied on voluntary compliance. It thus seemed a characteristic American venture of free and independent professions" (103).

The Role of "Knower" Organizations

A private organization that knows more than the consumer about a seller's reputation or about the quality and safety of the seller's products is called a *knower organization.* When paid by the seller, knower organizations often inspect quality and safety, and grant a certification mark or *seal of approval.* This is what Underwriters' Laboratories does for electronic safety, Good Housekeeping does for many consumer products, Orthodox Union does for kosher foods, Moody's does for securities, medical schools do for newly graduated practitioners, and the American Dental Association does for dental products (see Campbell 1999; Tollison 1996).

Alternatively, knower organizations may investigate quality and safety, and sell their reports directly to consumers (which includes hospitals, clinics, and HMOs as well as individuals). ECRI, for example, compares and evaluates a variety of medical products for hospitals, HMOs, and government agencies around the world. *Consumer Reports,* credit bureaus, and doctors and pharmacists who recommend which drugs to take also act as knower organizations. For many years, for example, the AMA ran a drug certification program for products advertised in its journals much as Good Housekeeping does for products in its magazine (Dowling 1970). Other types of seals of approval are a doctor's membership in a medical group, affiliation with an HMO or hospital, and medical degrees from medical school. These seals of approval assure consumers that they can trust the doctor who recommends a drug. In the drug field, the growth and development of knowers and knower organizations is severely stunted by FDA command of the drug and device industries. Nonetheless, numerous knower organizations exist today. There are major reference compendia such as the *AMA Drug Evaluations, American Hospital Formulary Service Drug Information,* and *U.S. Pharmacopoeia's Drug Information for Healthcare Providers.* There are newsletters such as *Clinica, Health Devices Alert,* and the *Medical Letter*. There are many specialized scholarly journals and volumes of conference proceedings, and there are a number of medical Web sites (for encyclopedic drug databases, go to WebMD or Medscape) and specialized sites for particular diseases.

Today, these kinds of knower services are relatively undeveloped because FDA "approval" is mandatory regardless of any other seals of approval; there is, for example, little reason to study and report on a drug that no one intends to sponsor. The FDA's role as a permission granter is often conflated with its role as a knower organization. Because of its monopoly as permission granter, it has also gained hegemony in the realm of seal-of-approval services. Private organizations would surely expand and mature if drug affairs were depoliticized and decontrolled.

The Role of Middlemen

A retail drug store or pharmacy—such as Rite Aid, Long's Drugs, or Safeway—is an example of a *middleman.* The middleman purchases goods from suppliers and then sells to

consumers. Middlemen have repeated dealings with customers and wish to induce the customer to continue buying from them. Not only would a pharmacy that sold a customer an unsafe drug be subject to tort penalty; it would probably lose the customer's business and perhaps the business of those who learned of the wrong. Seeking to build and preserve a good reputation, pharmacies have a strong incentive to keep unsafe and ineffective drugs from their shelves. They have strong incentives to know about drug safety.

Writing of pharmacists in the era prior to any federal control of drugs, Glenn Sonnedecker (1970) noted: "[T]he pharmacist exercised a scientific sense of responsibility as the last link in a chain of medicopharmacal services and the guarantor that the patient would receive exactly what was intended, in the form and quality intended. [A] pharmacist whose living depended upon his knowledge of drugs, and upon his reputation for providing unwavering quality in pharmaceutical service, could best appreciate the significance of reliable and impartial standards" (106, 108).

Another form of middleman is the pharmaceutical company. The company's profits depend on confidence in its brand name (such as Merck, Johnson & Johnson, Upjohn, Eli Lilly). The company purchases the inventions and discoveries of researchers, develops them into brand-name products, and then sells them to the public. To preserve the reputation of the brand name and to avoid law suits, it thinks carefully before putting a new drug on the market.

Another example of the middleman is the health care organization, which employs staff and purchases supplies and equipment. Consumers have repeated dealings with the hospital or HMO, and it has repeated dealings with its suppliers and staff. The HMO has strong incentives to give its members safe and effective drugs because it pays their medical bills. Miller (2000) described this development:

> [P]rofound changes have resulted from the evolution of various nongovernmental entities into de facto drug-vetting, standard-setting organizations. The newest and most potent of these are managed-care organizations, which exercise their influence through large-scale purchasing, monitoring, formularies, and drug utilization reviews. [Computerized systems] perform overall integration of the medical record for case management. A physician can be prevented from prescribing medication if, for example, according to computerized monitoring of his decisions, the drug is inconsistent with a patient's listed diagnosis; excessive in dose, frequency, or length of administration; or likely to interact dangerously with another medication the patient is taking. . . . In a sense the HMO has become a second gatekeeper between the manufacturer and the patient. (29)

A Thought Experiment

How is safety assured in other industries? In electronics, manufacturers submit products to Underwriters' Laboratories, a private organization that grants its safety mark to products that pass. The process is voluntary: manufacturers may sell without the UL mark , but retailers and distributors prefer the UL mark. Private-sector institutions and the tort system assure safety in electronics.

Suppose someone proposed that the system in electronics were replaced by a regime that forbade manufacturers from making a product until it was specifically tested and permitted by a

central government agency (the "Federal Electronics Administration"). What would you think of the proposal? Probably you would think it is crazy. There is no apparent problem with the current free-enterprise approach to safety assurance in the electronics industry. The twentieth century supposedly taught humanity that command and control suck.

But the command-and-control approach is the system we have in drugs. It is inconsistent to favor the free-enterprise approach in electronics but the command-and-control approach in drugs.

Sometimes people rejoin: "But drugs have larger effects on physical well-being. They are too important to be left to free enterprise." The point, however, cuts both ways. As we have seen, the harms of government control also are great. Drugs are too important to be controlled by politicians and bureaucrats.

Do the math. The historical record—decades of relatively free enterprise up to 1962—shows that free institutions and the tort system succeeded in keeping unsafe drugs to a minimum. The Elixir Sulfanilamide tragedy was the worst of those decades and far exceeded any other of the kind. (The thalidomide tragedy happened in Europe, not in the United States) The comparison is a grisly one, but we must face harsh realities: The 107 people killed by Elixir Sulfanilamide is a drop in the bucket compared to the yearly—or even weekly—death toll of the post-1962 FDA era. (Peltzman 1973 thoroughly "did the math" on this comparison and reached the same conclusion.)

A nexus of assurance is readily available without the FDA. A drug company suffers devastating losses when it harms consumers with an unsafe drug. Its reputation suffers, and it pays hefty tort damages to victims. Drug safety is assured by brand names, by merchant middlemen, by seals of approval, by newsletters, by medical testing and publishing (the *New England Journal of Medicine,* etc.), by consumer research (extensive drug information on the Internet), and by the consumer's questions to the doctor about which drug to take. And the tort system further discourages negligence or fraud (Krauss 1996).

Quotations: Economists' Judgments about the FDA

Many economists have studied and written on the FDA. It seems that all economists who pass judgment on the FDA find it to be overly restrictive and favor freer markets. Some propose specific and piecemeal decontrol; others favor creating a free market by abolishing the agency. We have not been able to find a single economist who defends or supports the contemporary FDA or advocates tighter regulation. Thus, informed economists agree that government should make the drug market freer.

The authorities quoted here are economists (they have received advanced degrees in economics). We do not mean to suggest that only the thoughts of economists are worth paying attention to; rather, we suggest that anyone who studies the issue in a systematic way, as economists are trained to do and are compelled to do to some extent by the standards of their profession, and publishes a judgment invariably favors reform in the libertarian direction.

J. Howard Beales III (1997, 15): "[My study] suggests that there is considerable room for improvement in the existing process. Changes to accelerate approval of new drugs would offer

significant health benefits to patients."

John E. Calfee (1996, 318): "[Where an examination of the effects of the FDA's pharmaceutical advertising policies is possible,] the evidence is very strong that the FDA suppresses a great deal of useful information. Experience from related markets in this nation and abroad also strongly indicates that informational competition involving drugs and devices is likely to work well, and that the pharmaceutical market does not pose unique problems that make it unsuitable for traditional competitive dynamics."

Noel D. Campbell (1999, 242): "There is an alternative to reform: abandon the current regulatory process and embrace the free market that has worked so well for so long in other fields. Free market third-party certification promises safe and effective devices—quickly and efficiently—and gives consumers the freedom to choose the amount of risk that best suits them. The market provides consumers with the full remedies and protections of our legal system, and it frees businesses from the crippling costs of undue regulation."

Milton Friedman (quoted in Pearson and Shaw 1993, 39): "'The FDA has already done enormous harm to the health of the American public by greatly increasing the costs of pharmaceutical research, thereby reducing the supply of new and effective drugs, and by delaying the approval of such drugs as survive the tortuous FDA process.' When asked, If you could do anything to improve health in America, what would you do? Friedman replied: 'No more licensing of doctors. No more regulation of drugs. Not of any kind. Period.'"

D. H. Gieringer (1985, 196): "[T]he benefits of FDA regulation *relative to that in foreign countries* could reasonably be put at some 5,000 casualties [not lives] per decade or 10,000 per decade for worst-case scenarios. In comparison, it has been argued above that the cost of FDA delay can be estimated at anywhere from 21,000 to 120,000 lives per decade. . . . Given the uncertainties of the data, these results must be interpreted with caution, although it seems clear that the costs of regulation are substantial when compared to benefits" (italics added).

Henry G. Grabowski and John M. Vernon (1983, 71): "A more fundamental kind of regulatory reform could be accomplished through congressional change in the FDA's regulatory mandate. It is possible to envision an FDA regulatory structure that would operate more as a certifier and disseminator of information for the vast majority of new products introduced. . . . Manufacturers would have the option to market a new drug even if it failed to be certified by the FDA."

Robert Higgs (1995b, 2): "Americans would be better off with drastic curtailment—ideally the complete abolition—of the current regulatory regime, which imposes major costs while providing little if any genuine protection of the public health."

Alison Keith (1995, 99): "A more widespread consumer understanding of the benefits and risks of routine aspirin use could produce substantial medical benefits. Suppose that most of the 1.5 million Americans expected to have heart attacks in 1994—and the one-third of those who

were expected to die—had taken aspirin routinely. Surely the number of people avoiding heart attacks and staying alive would have been large. On the other side, the medical risk associated with a less restrictive information policy toward consumers is an increase in serious side effects, but for a substantially smaller number of people, since both baseline and aspirin-caused increase[s] in risk of serious side effects are apparently small. The current policy appears to put a much greater weight on the side-effect risk of allowing more information to consumers, relative to the expected benefits."

Daniel B. Klein (2000b, 95–96): "Even without the government approval systems, voluntary institutions and the tort system would utilize testing and professional certification to screen out unsafe drugs. The government approval process here and abroad is a set of bureaucratic hoops and hurdles often inappropriate or unnecessary for the drug in question. . . . [T]he harms of the FDA are unredeemed."

Sam Peltzman (1973, 207–8): "If the Food, Drug and Cosmetic Act [of 1938] was intended to benefit consumers, the inescapable conclusion to which this study points is that the intent is better served by reversion to the status quo ante 1962. This conclusion follows fairly directly from the size of the 'problem' with which the 1962 Amendments sought to cope. Consumer losses from purchases of ineffective drugs or hastily-marketed unsafe drugs appear to have been trivial compared to their gains from innovation. In this context, any perceptible deterrent to innovation was bound to impose net losses on consumers and the Amendments seem clearly to have provided such a deterrent. Indeed, the conclusion can be put more strongly. If our estimates of the gains and losses due to exceptionally beneficial and unsafe drugs respectively are at all reasonable, there was already a bias costly to consumers contained in the pre-1962 proof-of-safety requirement of the [1938] Act. . . . [T]he [1962] Amendments have simply exaggerated this bias."

Paul Rubin (1995, 48): "When we think of the FDA and overregulation, we tend to think of the inexcusable delays in approval of new drugs. Scholars have long been aware that the agency causes unnecessary deaths and suffering by this policy. Nothing in this chapter is to be interpreted as minimizing this cause of needless suffering. But this is only part of the problem with the FDA. . . . [The] FDA's policies greatly retard the spread of [drug] information. . . . The FDA should allow manufacturers to advertise any claim for which reliable scientific evidence exists, whether or not this claim has been approved for the label, and this advertising should be allowed for both consumers and physicians. No policy requiring prior approval of advertisements would be mandated, by Congress or by the FDA. With respect to ads to consumers, the requirement of the "brief summary" should be abolished. The FDA should allow free and unrestricted advertising of pharmaceuticals on TV and in print, subject only to regulation for 'falsity' but not for 'deception' as currently defined. The results will be greatly improved health of consumers and reduced prices of pharmaceuticals."

Meir Statman (1983, 62): "A number of alternatives have been suggested to counter the trend of decreasing incentives for pharmaceutical R&D caused by FDA regulations. The more modest of these alternatives involve increasing the efficiency of the regulatory process, thereby reducing some of the regulatory costs. More radical alternatives involve the abandonment of the

requirement for FDA approval of drugs in favor of a new role for the FDA as a provider of information on drugs. Since consumers can sue for damages the manufacturers of drugs that are not safe or effective, there may be sufficient incentives for drug firms to introduce only safe and effective drugs even without FDA regulations."

Alexander Tabarrok (2000, 48): "I find that the largely unregulated system of off-label prescribing has large benefits and few costs. Off-label prescribing speeds medical innovations to patients, it increases the number of drugs available to doctors, and it lowers the costs of medical innovation. Consistent with these benefits, off-label prescribing is widespread and common in the United States today. The largely unregulated system of off-label prescribing is thus working well *and should be extended.* . . . [A]n analysis of off-label prescribing strongly suggests that the FDA's authority over new drugs, particularly the requirement that new drugs be tested for efficacy[,] appears to be detrimental to the health and welfare of U.S. health consumers and thus should be ended."

Peter Temin (1980, 206, 213): "Current drug policy ignores [the trade-off between a therapy's effectiveness and its painfulness]. By denying this choice [a less-effective but less-painful therapy], the policy restricts people more than it should. I would favor allowing people to choose this intermediate treatment position, although I would try to make sure that their choice was an informed one. But whether or not people are capable of understanding the relevant information, I still would favor giving people more choice for their own well-being than the current system allows. . . . The [program] I have in mind combines less surveillance at the premarket level and more surveillance, of a particular kind, at the prescription level."

Murray Weidenbaum (1993, 89): "The first [lesson of this article] is that while some drugs are very profitable, many more are not. The second is that price controls would be a mistake. The third is that what's needed is more competition. Warts and all, the competitive marketplace is the best protector of consumers."

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Links

Many of the references above are linked to online documents. What follows below are links to other organizations that have significant information on FDA-related issues.

The FDA: The FDA has an excellent Web site with many documents available by search.

The Food and Drug Law Journal: The *FDLJ* has many authoritative papers on FDA law, a number of which are cited in this Web page. Although these papers provide valuable descriptions of FDA-related law, most do not investigate actual FDA practice, which often differs substantially from what the law requires. The papers in the *FDLJ* are written primarily for an audience interested in getting along with the FDA rather than in evaluating the FDA. Back

issues of the journal are available online.

The Drug Information Journal: Similar in scope to the *FDLJ,* the *DIJ* contains authoritative papers by industry experts and insiders on the workings of the pharmaceutical industry, including the FDA. Some of the same caveats apply to the *DIJ* as to the *FDLJ,* although more papers in the *DIJ* evaluate the FDA. Back issues of the journal are available online.

Tufts Center for the Study of Drug Development: The Tufts Center is the primary collector of data on drug development and FDA review times. A critical resource that everyone in the field uses.

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Drs. Klein and Tabarrok have independently published research on numerous public policy topics.

Dr. Klein's work has focused on toll roads, urban transit, auto emissions, credit reporting, the FDA, quality and safety assurance, discovery of opportunity, and spontaneous order. He is the coauthor of *Curb Rights: A Foundation for Free Enterprise in Urban Transit* (Brookings Institution, 1997), editor of *Reputation: Studies in the Voluntary Elicitation of Good Conduct* (University of Michigan Press, 1997), and editor of *What Do Economists Contribute?* (New York University Press and Macmillan/Palgrave, 1999). He has published articles in *Economic Inquiry, Journal of Economic History, Economics and Politics, Economics and Philosophy, Law and Society Review, Constitutional Political Economy, Journal of Economic Behavior and Organization, History of Political Economy, Journal of Transport Economics and Policy,* the *Independent Review,* and numerous other academic journals.

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Appendix One :Why the FDA Has an Incentive to Delay the Introduction of New Drugs

FDA drug reviewers are immune from legal liability, but they may be reproached and humiliated by congressional hearings, television exposés, and newspaper condemnations. Why don't congressional representatives, television reporters, and newspaper columnists bring the deadly consequences of FDA delay to light? Answer: When the side effects of a new drug cause little Tommy of 236 Elm Street, Saginaw, Michigan, to become gravely ill, television reporters show the poor lad languishing in a hospital bed, and viewers respond emotionally. When little Tommy dies, reporters interview the grieving parents. Blame falls on the drug company, on the FDA officials who approved an unsafe drug, and maybe on the doctor. FDA reviewers are anxious to avoid such censure, which might damage their careers and reputations.

The consequences of error in the other direction, however, are not symmetric. If little Tommy suffered from a disease that would be cured by a drug not yet allowed by the FDA, it is unlikely that Tommy's parents or doctors would even be aware of that fact. If they heard about the not yet allowed drug and inquired into its availability, the FDA may simply say that it "must

hold the unproved drug until safety questions and risks to the public health are resolved." No one who could counter such claims would be in a position to do so. Thus, the bad consequences of disallowing the drug would not be identifiable and would not revisit the FDA. In consequence, FDA officials are much less concerned about such consequences. Only in rare cases in which suffering patients have been well organized and vocal, in particular in AIDS cases, have FDA officials taken much heat for withholding approval. Even then the heat is not extreme because the FDA officials can always claim that they are simply doing their job in delaying the approval of experimental drugs. Researchers have long noted that in anxiously seeking to avoid risk of approving an unsafe drug, FDA officials often fall deeply into the inverse error: *disallowing valuable drugs*. Figure 3 shows the two types of error and indicates the reason for systematic bias toward type 2 errors.

Figure 3.
Two Types of Error in FDA Approval Decision

The FDA Reviewers	Drug Is Beneficial	Drug Is Harmful
Allow the Drug	Correct Decision	Type 1 Error: Allowing a harmful drug. Victims are identifiable and traceable, and might appear on Oprah.
Do Not Allow the Drug	Type 2 Error: Disallowing a beneficial drug. Victims are not identifiable and scarcely even acknowledged in the abstract.	Correct Decision

Thus, in addition to the error of approving a bad drug, there is the error of withholding a good drug. It would be foolish to minimize the first type without minding the effects on the incidence of the second type. Attention to the two types of error reminds us that FDA policy can be very harmful overall even if reducing the FDA's power would *increase* type 1 errors. Reducing FDA delay in approving drugs, for example, could result in perhaps hundreds of additional mortalities, but if the benefit is thousand of lives saved (fewer type 2 errors), then consumers are on net better off. This analysis shows the danger of comparing two situations based solely on the type 1 error. Willman (2000), for example, has excoriated the FDA for speeding up the approval of new drugs in the 1990s , but he looks only at type 1 errors and not at all at type 2 errors. The current level of type 1 errors should not be made sacrosanct. It is possible to have too few type 1 errors when this means a high rate of type 2 error.

It should go without saying that any reform that reduces one type of error without increasing the other is to be applauded. The FDA reforms of the 1990s, in particular with regard to user fees, have reduced the number of type 2 errors without increasing the number of type 1 errors. Although more drugs have been withdrawn in recent years, it is solely because more drugs have been accepted; the rate of drug withdrawals has not increased. Sadly, Willman (2000) misses even this elementary point. See FDA Reform for a further discussion of reforms.

Type 2 errors should be not only acknowledged but perhaps regarded as even more pernicious than type 1. Economists Friedrich Hayek, Armen Alchian, and Israel Kirzner have stressed that the strength and flexibility of an economic system lies in *its propensities to correct its own errors.* In the medical system, an error involving a bad drug tends to be corrected: it leads to bad outcomes, suffering, complaint, loss of reputation, legal penalties, and serious medical review. An error involving a good drug, on the other hand, does not lead to any specific or readily identifiable problem. Even after years of delaying important new drugs, there may be little public pressure to get the FDA to grant permission. This type of error is not inherently self-correcting. The difference in propensity for error *correction* gives a good reason for concerned parties, in managing the trade-offs between the two types of error, to be especially vigilant against policies and procedures that will introduce type 2 errors.

One of the most active current critics of the FDA is physician and Hoover Institution fellow Henry I. Miller. Miller's most significant qualification, however, is that he worked in the FDA from 1979 to 1994 serving its regulatory apparatus. Speaking from personal experience, He described (in Miller 2000) the incentives inside the FDA:

> In the early 1980s, when I headed the team at the FDA that was reviewing the NDA for recombinant human insulin, . . . we were ready to recommend approval a mere four months after the application was submitted (at a time when the average time for NDA review was more than two and a half years). With quintessential bureaucratic reasoning, my supervisor refused to sign off on the approval—even though he agreed that the data provided compelling evidence of the drug's safety and effectiveness. "If anything goes wrong," he argued, "think how bad it will look that we approved the drug so quickly." (41)

Miller explains that the anecdote is representative of FDA behavior:

> A classic type 1 error . . . was the FDA's approval in 1976 of the swine flu vaccine. Although the vaccine was effective at preventing influenza[,] it had a major side effect that was unknown at the time of approval: temporary paralysis from Guillain-Barré Syndrome in a small number of patients. This kind of mistake is highly visible and has immediate consequences—the media pounces, the public denounces, and Congress pronounces. Both the developers of the product and the regulators who allowed it to be marketed are excoriated and punished in modern-day pillories: congressional hearings, television news magzines, and newspaper editorials. Because a regulatory official's career might be damaged irreparably by his good faith but mistaken approval of a high-profile product, decisions are often made defensively—in other words, to avoid type 1 errors at any cost. . . . This predilection, or pressure, toward commission of type 2 errors is not the way the

> system is supposed to operate. Lifetime tenure for civil servants—which itself extracts costs—is supposed to free regulators to consider only the public interest as they render decisions. Instead, it has given us the worst of both worlds. (42–43)

Miller is not the first whistle-blower, and virtually all economists who study the FDA are critical (see Quotes Section). When enlightened criticism hits at the exterior walls of the FDA, how do those inside respond? Typically they do not respond at all.

American citizens have been led to think that agencies such as the FDA protect and benefit them. The official interpretation is propagated by America's most powerful cultural institutions: the major media, the schools and colleges, and the government itself. To dissent publicly and seriously from the official interpretation is to confuse and upset the Americans who passively accept it. To dissent is also to court the enmity of the agency itself. Drug companies, although in the best position to know the sins of the FDA, are especially not inclined to vex or challenge their masters. FDA officials enjoy a respected "consumer protection" status and operate in a world of informational imperviousness and legal immunity (NDA reviewers are immune from legal liability for negligence).

Vincent Kleinfeld (1970), a Washington, D.C., attorney who worked on drug approval affairs, wrote, "the courts in this area of the law tend to equate the Food and Drug Administration with God, motherhood, and country." He describes how the situation goes down in court when someone challenges the FDA for disallowing a drug:

> If the Food and Drug Administration yells "hazard" or "danger," you are not going to get one judge out of a hundred to hold against the Food and Drug Administration; this I can testify to from very bitter experience since I have been in private practice and with the government. When you are before a judge, it makes practically no difference whether the government is right or wrong. The government attorney looks up gravely at the judge and says, "Your Honor, the Food and Drug Administration . . ."—there is a pause right there—"takes the position that this product is dangerous; it may cause death either directly or because it keeps the patient away from the knife, the X-ray machine, radium. If Your Honor wishes to take the grave responsibility of substituting your judgment for that of the Food and Drug Administration . . ."—another pause. That is it. (180, 191)

Thus, the official interpretation of the FDA remains hegemonic.

When response does occasionally become necessary, Miller (2000) explains the consequences: "boxes on the organizational chart are arranged and rearranged, added and eliminated; names of entities are changed (and then changed back); and various pilot programs come and go. FDA managers avidly craft and meet new performance milestones, but there is little impact on the bottom line of timely patients' access to new therapies." He notes that more than one hundred studies and inquiries have documented the negative impacts of the existing system. "The reports of these studies, however, just seem to get filed away and forgotten" (49, 45-46).

Appendix Two: Prescription-Only Requirements

Prior to 1938, a consumer could buy any nonnarcotic drug without first obtaining a doctor's prescription. Consumers often obtained prescriptions or at least sought the advice of physicians before self-medicating, but were under no legal compulsion to do so. The situation may seem remarkable, but why? Today car owners may use the services of a certified auto mechanic to fix their cars but are not required to obtain a mechanic's prescription before working on the car (despite the fact that improper maintenance can be dangerous). As noted in the text, the creation of the prescription-only class of drugs was a regulatory decision made by the FDA and seemingly at odds with congressional intent.

If there were no prescription requirements today, many consumers would continue to seek a doctor's advice or prescription for some conditions, just as they did prior to 1938. It follows that the main effect of a prescription requirement is to make it more difficult to obtain those drugs that consumers previously obtained without a prescription. Consumer rationality implies that these drugs are the ones that least require a prescription (Peltzman 1987). By raising the costs of obtaining drugs, prescription requirements raise the cost of health care and thereby reduce treatment and injure health.

Some will contend that prescription-only requirements protect consumers from their own ignorance and haste. Peltzman (1987) compares accidental poisonings in the United States before and after the 1938 law and across countries today. He concludes that "enforcement of prescription-only regulation does not significantly improve the health of drug consumers. . . . Apparently, consumers are able to understand the value of a doctor's advice even if they are not required to seek it" (235–36).

One legitimate concern with relaxing prescription-only requirements is the possibility of excerbating already serious problems with antibiotic resistance. When antibiotics are used indiscriminately for nonbacterial infections or when they are not taken in a full course, bacteria can become resistant, and such resistance can rapidly spread throughout an entire population. Prescription-only requirements for antibiotics might, therefore, be a wise measure on the grounds that improper use can cause external effects (i.e., can negatively affect other people.) Unfortunately, prescription-only requirements have not kept the problem of antibiotic resistance under control.

Temin (1992) examines the costs and benefits of switching from a prescription-only status to an over-the-counter status for drugs and finds that the benefits have been large. Peltzman's and Temin's results suggest that, with the exception perhaps of antibiotics, prescription requirements should be abandoned or at least loosened.

Appendix Three: Understanding the FDA's Opposition to Liberalization

By granting people more freedom while maintaining the option of FDA seals of approval and certifications, many of the foregoing reform proposals expand options without taking away anything beneficial. These proposals might strike the reader as remarkably simple and sensible, so why does the FDA resist them? The answer is provided by basic economics. Government enterprise, lacking the fusion of motivation and decisive authority in private ownership, simply

cannot compete in a field of open competition. To survive, government enterprise needs to receive either tax dollars (e.g., government schools) or privileges against competition (e.g., the U.S. Postal Service). The FDA currently receives both, but especially the latter. If privileges against competition (in permitting new drugs or in granting seals of approval) were removed, the FDA would probably sink like a stone, and FDA officials know it. Liberalizations such as allowing Not FDA Approved claims, international reciprocity, or voluntary certification would probably be tantamount to killing the FDA altogether because people would simply say, "No, thank you" to its services.

Our point is captured by the description in Miller (2000) of the FDA's attitude toward reciprocity: "the FDA has been consistently recalcitrant on the pivotal issue of reciprocity of approvals. . . . [W]hen asked by the author how negotiations were progressing, a high-ranking European regulator . . . quipped, 'Discussing reciprocity with FDA is like discussing the Thanksgiving menu with the turkeys'" (57).

Glossary

Abbreviated New Drug Application (ANDA)

The ANDA was established by the Waxman-Hatch Act. Under an ANDA, proof of bioequivalence is enough to satisfy FDA safety and efficacy requirements for a generic drug. In addition, the manufacturer of the generic must certify that the original drug is either *(a)* not patented, *(b)* has an expired patent, *(c)* has a patent expiry date before which the generic will not be sold, or *(d)* has an invalid patent or a patent that the generic does not infringe. If the manufacturer claims the original patent is invalid or not infringed, there is a thirty-month litigation period during which the FDA cannot approve the generic.

Accelerated Development

After the IND has been filed, a drug that can be used by patients who are suffering from life-threatening or seriously debilitating conditions, for which no other drug treatment exists, can qualify for accelerated development. Approval can be based on surrogate endpoints or on an FDA determination that the drug can be used safely if distribution is limited.

Aspirin

Aspirin has been called the wonder drug of the twentieth century. It is used extensively in the treatment of mild to moderate pain, fever, and inflammation, and has also been discovered to be useful in the management and prevention of heart attacks and strokes (which are off-label uses) and perhaps also of colon cancer and other maladies. For many years, the FDA prohibited manufacturers from advertising or promoting the use of aspirin for heart attack victims, a decision that was responsible for thousands of needless deaths (see the section Advertising Restrictions). The FDA continues to prevent manufactures from advertising and promoting some of aspirin's many uses.

Luckily for Americans, aspirin was available in the United States long before the modern FDA (aspirin was known to Hippocrates, although that knowledge was lost and not rediscovered until the late eighteenth century). Given the FDA's dangerously risk-averse attitude and its reliance on animal studies, *many people have speculated that aspirin would not be approved by the FDA if it were discovered today* (see, for example, Wardell and Lasagna 1975, 137–39). Although aspirin is in general a very safe drug, it can cause stomach bleeding and is responsible for some seven thousand deaths and seventy-six thousand hospitalizations per year in the United States (Grinspoon 1997). In addition, aspirin, along with a number of other familiar drugs such as penicillin, produces very negative effects in some laboratory animals. All of this leads us to the question, How many wonder drugs have we lost because of the FDA's deadly overcaution?

Assurance of Quality and Safety

Consumers want quality and safety in their drugs and devices. Moreover, consumers, prior to purchase and use, want *assurance* of quality and safety. Society has three broad approaches to quality and safety assurance. The first is voluntary practices and institutions—such as reputation, knowers, and middlemen—which assure quality and safety because it is almost always unprofitable to harm or cheat the customer. The second is tort remedy, by which consumers who are harmed or cheated may litigate under the tort doctrines of fraud, negligence,

breach of contract, and so on. The third is governmentally imposed restrictions on voluntary exchange, whereby government attempts to determine the quality and safety of goods and services, and prohibits exchange until it has given permission. The FDA represents the third approach, which is the only approach that entails coercion against innocent parties. The theme of this Web page is that the best way to meet the demand for assurance is the combination of voluntary means and the tort system. We argue that the third approach, government restriction, does not achieve anything beyond what would be achieved by the other two approaches, yet prevents people from consummating many important and legitimate activities and exchanges. We argue, essentially, that the demand for assurance, like the demand for clothing, is best met by the free-enterprise system working within a sensible tort system.

Baby Ventilator Incident

Krauss (1996) explains: "[In the early 1990s, the FDA] ordered hospitals to stop using specialized baby ventilators, which are irreplaceable in saving sick infants because they provide uniquely tiny breaths of air, because hospitals refused to 'blind-test' them and thereby condemn[ed] fifty percent of air-deprived infants. Dr. Martin Kessler of Georgetown University Medical Center estimates that scores of babies died as a result. Subsequent to the FDA decision, protest from doctors who pointed to named infants' deaths were aired on the [ABC] television show '20/20' ["So Safe You Could Die—Overregulation by the FDA," broadcast 12 August 1994]. Only then did the agency again allow use of the ventilators" (468–69).

This incident (see also Some Remarks about Medical Devices) illustrate what it takes to pry permission from the FDA stranglehold. The special circumstances that made the public-information campaign successful in this case are, tragically, extremely rare. Usually, doctors are not able to identify the victims of the FDA's withholding of new therapies.

Biological Drugs

Biological drugs (or biologics) such as insulin, penicillin, blood and blood products, vaccines, derivatives of natural substances, and extracts of living cells are grown or cultured in separate batches. Just as with beer or wine, the quality can vary considerably by batch depending on small differences in inputs. Thus, in addition to obtaining marketing approval, a biologics manufacturer previously also had to have its production methods and facilities FDA licensed. Moreover, every batch of biologics had to be FDA tested. Recent advances in biotechnology, however, have diminished the variation and made production more like that of nonbiological (or chemically synthesized) drugs. In 1995, the FDA announced simplified rules on "well-characterized" biologics, dropping manufacturing-facility licensing and batch certification in such cases. Today many biologics are treated in the same fashion as nonbiological drugs. The FDA's rules on biologics were codified in the 1997 Modernization Act.

Breast Implants

In 1992, journalists highlighted claims by women that their silicone breast implants caused connective tissue diseases. Without clinical tests or clear scientific evidence, the FDA banned most implants and crusaded against the industry, leading to a $3.2 billion court settlement that drove manufacturer Dow Corning into bankruptcy. Studies by the University of Michigan,

the University of Maryland, the Mayo Clinic, the Harvard Medical School, the American Medical Association, and others, however, have found no causal link between implants and connective tissue diseases. An independent panel of experts commissioned by the British government concluded that "Silicone gel breast implants are not associated with any greater health risk than other surgical implants." And "In particular, there is no evidence of an association with an abnormal immune response or typical or atypical connective tissue diseases or syndromes." The British study (*Silicone Gel Breast Implants: The Report of the Independent Review Group* [London: Department of Health, 1998]) references previous reviews and the voluminous scientific literature. Angell (1997) is an accessible yet scientifically accurate account of the breast implants controversy.

Brief Summary

The brief summary is a technical document written for physicians and other health care professionals that the FDA requires to accompany an advertisement for a drug. It is typically a page in length, written in small, often illegible print and is so technical that it is virtually incomprehensible to consumers. The brief summary is not required if the advertisement mentions the name of the drug but not the use or if the remedy is mentioned without the name of the drug. Because the brief summary typically requires an additional page in a printed ad or additional airtime in a TV or radio ad, many pharmaceutical companies have less incentive to inform consumers of useful information.

Dietary Supplement Health and Education Act of 1994 (DSHEA)

The DSHEA rejected the FDA's attempt to regulate vitamins, minerals, oils, fibers, and other dietary supplements as drugs. Under the DSHEA, manufacturers can make statements of nutritional support but not drug claims. Manufacturer's of St. John's Wort, for example, may claim that St. John's Wort "promotes healthy emotional balance and well-being," but they cannot say St. John's Wort "is useful in the treatment of depression." The distinction is mostly one for lawyers, not consumers, considering that many consumers do take St. John's Wort for depression. (Such consumers are in fact justified in doing so: a number of studies indicate that not only is St. John's Wort effective at relieving mild cases of depression (e.g., Woelk 2000), but does so with fewer side effects than many antidepressive pharmaceuticals. In addition, St. John's Wort is considerably cheaper than pharmaceuticals and does not require a prescription.) As another example, a manufacturer of cranberry juice might claim that "cranberry juice helps to maintain a healthy urinary tract" but could not maintain that cranberry juice is "useful in preventing a urinary tract infection (UTI)" despite the fact that millions of women do drink cranberry juice for that reason (although there is some scientific evidence that cranberry juice can prevent UTIs, it is, as of 2001, very preliminary).

The DSHEA also allowed manufacturers and retailers of dietary supplements to disseminate scientific information on the value and use of supplements.

More information can be found in the history section. The full text of the DSHEA can be found here. Pinco and Rubin (1996) offer a useful review of the legislation.

Drug Efficacy Study Implementation

The 1962 amendments authorized the FDA to test old as well as new drugs for efficacy. The FDA lacked the personnel to do these tests, so the National Academy of Sciences appointed

a special committee to perform efficacy investigations on some four thousand pharmaceuticals. The committee, the Drug Efficacy Study Implementation (DESI), was composed of 160 physicians, who relied on their pharmacological knowledge, literature reviews, clinical experience, and intuition. The appointment of this group was somewhat paradoxical: instead of drawing on the knowledge of all doctors, which included knowledge about specific patients and what treatments had and had not worked on *those* patients, 160 doctors were empowered to decide for the nation in the absence of much relevant information.

Drug Lag and Drug Loss

Europe's more efficient regulatory structure typically allows new drugs to be approved sooner in Europe than in the United States. The difference between the date of European adoption and that of U.S. adoption is known as *drug lag.* Drug lag has been important in the debate about the FDA because it is measurable and because U.S. legislators do not like to think that Europe does things better than the United States. Drug lag, however, is far from an ideal measure of the costs of the FDA. Note that drug lag will be reduced the more inefficient the European system becomes, but this is scant comfort for patients in the United States who die from lack of access to new drugs. Moreover, it is far from obvious that Europe has the best system of drug approval, even if it is faster than the system in the United States. More generally, as a result of the FDA's long review times and extensive regulations, new drugs take longer to reach the marketplace than they would in a voluntary certification system. Because a voluntary certification system doesn't presently exist, we cannot measure drug lag with respect to such a system, but such lag is almost certainly considerably longer than drug lag with respect to Europe.

The FDA does more than delay the introduction of new drugs; it also reduces the total number of new drugs created. This is known as *drug loss.* Drug loss is difficult to measure, although Peltzman's (1973) results (see also the discussion in the text) suggest that it is very extensive.

Durham-Humphrey Amendment

The Durham-Humphrey Amendment codified the distinction between prescription and OTC drugs. A drug was to be an OTC drug unless (1) it was habit forming, (2) had potentially harmful effects or potentially harmful effects when used by a lay person, or (3) was limited to prescription use by a New Drug Application. Prior to this amendment, manufacturers decided whether a drug was to be sold OTC or by prescription only, but the company could be sued for misbranding if the FDA believed that the drug could not be properly labeled for consumer use.

More information on this amendment can be found in the history section.

Elixir Sulfanilamide

Elixir Sulfanilamide is a sulfa drug (antibiotic) released by Massengil in1937 in liquid form without prior toxicity testing of its solvent. The solvent diethylene glycol, used today as automotive antifreeze, caused the death of 107 people, mostly children. The chemist who created the elixir committed suicide. The "Elixir Sulfanilamide tragedy" prompted the passage of the Food, Drug, and Cosmetic Act of 1938. Although the deaths of 107 people were tragic, many more people have died because of FDA regulation. Deaths caused by drugs are seen, however, whereas deaths caused by a lack of drugs are unseen.

Ethical Drugs

The old term *ethical drugs* signified drugs advertised only to doctors. The expression refers to the original 1847 code of ethics of the AMA, which deemed advertising directly to the public to be unethical. Over time, the term came to mean legal drugs.

FDA Modernization Act of 1997

The 1997 Modernization Act moved in the direction of "reform"; thus, most of its requirements were in the direction of reducing FDA bureaucracy and speeding drugs and devices to patients. The act was, however, at best a modest reform package. Specifically, the Modernization Act reauthorized user fees for another five years, codified rules for fast-track approval, codified the rule that only one adequate and well-controlled clinical study and confirmatory evidence could be the basis of approval, and codified restrictive FDA policies on dissemination of information regarding off-label uses of drugs. (*Washington Legal Foundation v. Friedman* found such restrictions unconstitutional and further opened up the ability of firms to disseminate off-label information.) Concerning medical devices, the Modernization Act exempted most Class I and some Class II devices from premarket approval, and it increased physician authority to use investigational devices. Finally, in a variety of clauses, the FDA was required to provide manufacturers with better and more timely information concerning its procedures.

More information is available in the history section. The bill can be found online here.

Federal Trade Commission (FTC)

Set up in 1915 to restrain monopoly, the FTC monitored drug advertising from its inception until 1962, when the regulation of advertising of prescription drugs matter was transferred to the FDA. The FTC still regulates the advertising of OTC drugs, with a few exceptions, notably aspirin. On food products, the FDA and the FTC have split responsibilities, with the FDA regulating food labeling and the FTC regulating food advertising.

Form 510(k)

Manufacturers of a new medical device need not file a premarket approval form if the device is "substantially similar" to an already approved device that did not require a premarket approval form. Instead manufacturers may file the simpler form 510(k). The 510(k) was supposed to be a premarket *notification* that did not require approval. In the years following 1976, the FDA began to require that more and more information be included with the 510(k) notification. Now the industry considers the 510(k) to be the first in a series of premarket approval hurdles, rather than a notification. With the passage of the SMDA in 1990, the 510(k) officially became a premarket approval regulation.

Food, Drug, and Cosmetic Act of 1938

Passed after the Elixir Sulfanilamide tragedy, the Food, Drug, and Cosmetic Act required pharmaceutical manufacturers to submit a New Drug Application to prove the drugs safety. The act also provided the basis for the distinction between prescription and nonprescription drugs that was further developed in the Durham-Humphrey Amendment.

Generic Drugs

After a drug goes off-patent, any manufacturer who finds it profitable may produce an equivalent drug and sell it under the drug's chemical or "generic" name. The original version is then called the brand-name drug, and the new competitive versions generic drugs. The Waxman-Hatch Act made it much easier for generic drugs to compete against their originals.

Good Manufacturing, Laboratory, and Clinical Practices (GMP, GLP, GCP)

The various Good Practices are lengthy FDA rules and regulations governing manufacturing, laboratory, and clinical facilities. Most of the rules are obvious and include such things as, "Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas," and "Personnel shall practice good sanitation and health habits." Many rules require the keeping of extensive written records. The current GMPs can be found here. Although the rules and accompanying inspections are not without utility, manufacturers rarely challenge the FDA, in part because they fear retaliation through arbitrary and capricious interpretation of the various standards and regulations (see, for example, the cases discussed by Volokh 1995).

The private sector also offers quality-control certification through such services as ISO 9000 Certification. The ISO 9000 standards are a series of standards for quality management that are produced by the Swiss organization International Organization for Standardization. The standards involve repeated audits and inspections. A useful explanation of ISO 9000 from two certified companies can be found here and here.

Institutional Review Board (IRB)

IRBs review, approve, and monitor research involving human subjects in order to evaluating the ethical acceptability and the scientific validity of any such studies. An IRB is formally designated by an institution in which research takes places, such as a hospital or university. FDA regulations on IRB membership are quite strict. The IRB must be composed of at least five members including at least one scientific member, one nonscientific member, at least one person not affiliated with the research institution, no members with conflicts of interests, both genders if at all possible, and so forth. Research cannot begin until the IRB approves.

Investigational Device Exemption (IDE)

Medical devices must receive FDA approval before being marketed (since the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act). Similar to an IND, an IDE allows companies to sell and use a limited number of devices for investigation purposes and clinical trials. The IDE exempts the device not only from the premarket approval regulation but also from a host of other reporting and recording regulations.

Investigational New Drug Application (IND)

Before testing a new drug on human subjects, the company must file an IND. Prior to filing an IND, the sponsor develops information on the chemistry of the drug so that it can be produced in batches of known strength and purity. In addition, the sponsor must conduct a number of animal studies to produce information on the pharmacology and toxicology of the drug.

Information, for example, must be produced on the absorption, distribution, metabolism, and excretion properties of the drug. Finally, detailed protocols for testing on human subjects must be submitted. In addition, since 1971, the FDA has required that all proposed clinical studies be reviewed by an institutional review board. Technically, unless otherwise notified, the sponsor can begin clinical studies within thirty days (if the IRB approves). The FDA can, however, terminate an IND at any time; thus in practice the FDA must approve the IND proposal. The IND stage of drug approval is broken into three phases. The FDA exerts considerable control over all phases of the clinical trial process, and at any stage the FDA can and often does request additional clinical trials and changes in trial protocols.

Phase I

This phase consists of short-term clinical tests of the drug on twenty to eighty healthy volunteers to determine basic pharmacological and toxicological information in humans especially as regards safety. The FDA can stop clinical testing if they deem the drug unsafe.

Phase II

This phase consists of small-scale, longer-term tests for efficacy and safety. Typically the drug is tested in one hundred to three hundred patients. In phase II trials, dosage levels are experimented with to find optimal dosage levels, and further information on safety is collected.

Phase III

Large-scale testing for safety and effectiveness is conducted in phase III. Typically one thousand to three thousand patient volunteers are used in this phase. The primary information the FDA will use to decide whether the drug satisfies its (often arbitrary) benefit-risk relationship is developed in phase III trials. The trials are tightly controlled, may involve a large number of patients, and can take several months to several years for completion.

Kefauver-Harris Bill of 1962

Also known as the 1962 Amendments to the Food, Drug, and Cosmetic Act of 1938, the Kefauver-Harris bill required pharmaceutical firms to wait for FDA approval prior to marketing their product. By law, the FDA is supposed to review an NDA within 180 days, but no penalties for failure exist, and the FDA has never come close to meeting this requirement. Additionally, the 1962 Amendments required the firm to show that a drug is efficacious in addition to safe for all labeled uses. The 1962 Amendments also brought clinical research and development under the authority of the FDA. Drug sponsors henceforth had to file an Investigational New Drug Application and obtain FDA approval for all investigational studies involving humans. Laboratories and clinics engaged in research also become subject to Good Laboratory Practice and Good Clinical Practice regulations that required extensive paperwork.

More information can be found in the history section.

Knower Organization

An organization that knows more than the consumer about a seller's reputation or about the quality and safety of the seller's products is called a *knower organization.* The term usually refers to private, voluntary organizations. Knower organizations, when paid by the seller, often inspect quality and safety, and grant a seal of approval or certification mark, just as Underwriters' Laboratories does for electronic safety, Orthodox Union does for kosher foods, Moody's does for securities, medical schools do for newly graduated practitioners, and the American Dental Association does for dental products. Alternatively, knower organizations may investigate quality and safety, and sell their reports directly to consumers, as do *Consumer Reports,* credit bureaus, and doctors and pharmacists who recommend which drugs to take. Medical groups, hospital affiliations, and medical degrees are types of seals of approval that assure consumers that they can trust the doctor who recommends a drug. In the drug field, the growth and development of knowers and knower organizations are severely stunted by FDA command of the drug and device industries. Nonetheless, such organizations would surely expand and mature if people were freer in making their own drug choices.

Medical Device Amendments of 1976

These amendments greatly increased the FDA's control over medical devices. The amendments divided medical devices into three classes. Class I devices are subject to general control requirements (certain records and reports provided to the FDA by the manufacturer); Class II devices are subject to general control and specific performance-based standards; and Class III devices are subject to a premarket approval process that is much like the approval process for new drugs. In addition, the amendments gave the FDA power to ban medical devices, to require manufacturers to inform consumers of potential hazards, and to force manufacturers to give refunds.

See the history section for more information.

Medical Device Reports

This law requires hospitals, ambulance services, surgical facilities, nursing homes, and outpatient facilities to file a report to the FDA if a device is "associated with" any death, injury, or illness. With respect to sick individuals, however, it's often difficult to say whether a device is "associated with" an adverse event in any meaningful way. Medical device reports have thus involved extensive paperwork, a large fraction of which the FDA never reads (Higgs 1995c). Adverse events reports involving devices and patient death must be sent directly to the FDA, whereas reports of events that have caused injury or illness are sent to the manufacturer.

Middlemen

A retail drug store or pharmacy is an example of a middleman. The middleman purchases goods from suppliers and then sells to consumers. Middlemen are very important in providing assurance of quality and safety because they have repeated dealings with customers and wish to induce the customer to continue buying from them. A pharmacy that sold someone an unsafe drug not only would be subject to suit, but would probably lose that person’s business and perhaps the business of those who learned of the mishap. Seeking to build and preserve a good

reputation, pharmacies have a strong incentive to exclude unsafe or ineffective drugs from their shelves. They have strong incentives to know which drugs are safe and which dangerous. Another form of middleman is the pharmaceutical company. The company purchases the inventions and discoveries of researchers, develops them into brand-name products, and then sells them to the public. To preserve the reputation of the brand name and to avoid law suits, the company thinks carefully before putting a new drug on the market. Another example of a middleman is a hospital or clinic that purchases supplies and equipment, and employs staff. Consumers have repeat dealings with the hospital, and the hospital has repeat dealings with its suppliers and staff; in this way, the middleman creates a bridge of reputation and trust from consumers to the suppliers and the staff.

National Formulary

Published by the *U.S. Pharmacopoeia* (USP), a private nonprofit organization, the *National Formulary* is the official compendium of standards for drugs, excipients, dietary supplements, and vitamins and minerals. The *USPNF* defines standards of strength, quality, purity, identity, packaging, labeling, and storage, and describes and defines the appropriate tests, assays, and analytical methods that are used to measure strength, purity, and so forth. The USP also publishes the *USPDI,* a compendium of drug information that is also officially recognized in the United States and in many other countries worldwide.

New Chemical Entities

In the early stages of research, a new substance is called a new chemical entity, a chemical entity that has never been used by humans and has been tested only on animals.

New Drug Application (NDA)

Under the Food, Drug, and Cosmetic Act of 1938, the NDA was submitted to the FDA enumerating the uses of the drug and providing evidence of its safety. If the FDA found no reason to object, the NDA was automatically approved within sixty days. But since 1962 the FDA evaluates proof of efficacy as well as proof of safety, and the company must wait for FDA approval no matter how long that takes. On average, the NDA review process lasts for two years (as of the mid-1990s, some evidence suggests times have shortened). The NDA review is handled by the FDA's Center for Drug Evaluation and Research (CDER). Once the CDER deems the NDA fileable, the medical, biopharmaceutical, pharmacology, statistical, chemistry, and microbiology departments of the CDER review it. The length of an NDA application can reach one hundred thousand pages of material. If the departments pass the NDA, an advisory committee meets. If the advisory committee is satisfied with all of the findings, a labeling review takes place. Once the labeling review is complete, the NDA is approved, and the drug is ready to be marketed.

Nutrition Labeling and Education Act

The NLEA required food manufacturers to include nutritional labeling on most food products. The NLEA also codified the FDA's authority to allow health claims on foods and dietary supplements. Although the intent of the NLEA was to increase the amount of information consumers received by broadening the health claims allowed on foods and dietary supplements,

the FDA officials took an aggressive stance and announced that they planned to regulate supplements as drugs. The resulting backlash led to the passing of the Dietary Supplement Health and Education Act (DSHEA) of 1994.

On-Label Uses and Off-Label Uses

Many drugs that have gained FDA approval have uses other than those for which the drug was officially evaluated and approved. Once a drug has been approved for some use, however, it can be legally prescribed for any use. Approved uses are known as *on-label uses,* whereas other uses are *off-label uses.* Manufacturers may disseminate information, either in literature to doctors or in advertisements to the public, about on-label uses, subject to restrictions such as the brief summary. But disseminating information about off-label uses was prohibited between 1962 (the Kefauver Amendments) and 1997 (the Modernization Act). Off-label uses are often very important and common. Amoxicillin and tetracycline are today routinely used to treat stomach ulcers following Barry Marshall's revolutionary discovery that ulcers are caused by *Helicobacter pylori,* but they are not approved for such uses (as of the late 1990s). Aspirin is also routinely used to prevent heart attack, even though it is not an approved use (as of 2000). Restriction on advertising and information dissemination have limited the information available to doctors and have thus sometimes prevented patients from receiving needed medication. Many of the FDA's restrictions on dissemination of information related to off-label prescriptions were declared unconstitutional in *Washington Legal Foundation v. Friedman D.D.C.* See also the discussion in the text and Tabarrok (2000).

Orphan Drug Act (ODA) of 1983

The market for some drugs is small because the disease treated is rare or because only a small number of people do not respond satisfactorily to the existing therapies. Nevertheless, because there are many diseases that affect only a small number of people, the total number of Americans with an orphan disease has been estimated to be twenty to thirty million (Meyers 1991). Because the costs of getting through the FDA process are the same whether the intended market for the drug is fifty thousand patients or five million patients, drug loss has been especially prevalent for orphan diseases. The 1983 Orphan Drug Act, amended in 1984, recognized this problem, but rather than reducing review times or directly lowering the burden of FDA required trials, it created more government programs to try to counter the effect of the FDA. In particular, the ODA provided for grants to defray the costs of testing products for rare diseases and gave sponsors of orphan products tax credits on their development costs. Most importantly, the FDA agreed that once it approved one sponsor's drug, it would not approve any other similar drug for the same indication for a period of seven years. In effect, sponsors were given monopoly rights. Thus, the number of drugs for orphan indications was increased but at the cost of higher-priced drugs. A notable example of how the ODA has been abused is that the AIDS drug AZT was granted orphan status and has since earned many billions in sales revenue.

More information is available in the history section. See also Arno, Bonuck, and Davis (1995).

Over-the-Counter Drug

A drug that is available to the consumer without a prescription. As recently as 1940, all

nonnarcotic drugs were available over the counter.

Parallel Tracking

Initially designed to help AIDS patients, parallel tracking makes drugs showing promising results in phase III of the IND process available to patients whose condition prevents them from participating in controlled clinical trials. Parallel tracking is similar to the treatment IND, a program started several years earlier.

Patent Medicine

Patent medicine is a term from the pre-1938 era signifying *not* that the drug was patented, but that it was advertised directly to the public and that its ingredients were not being fully disclosed. Patent medicines often contained alcohol, opiates, or cocaine, providing relief rather than cure.

Placebo

A *placebo* is a substance that has no alleged medicinal merit and that is often used as a control in clinical research (i.e., a sugar pill). Uninformed users may be convinced that their condition is improving as a direct response to a placebo, which is one reason why weak or fraudulent medicines could sometimes find a market prior to the more potent drug development of the twentieth century. Confounding the situation is that sometimes the placebo effect is real; in other words, the conviction that a medicine works can result, through pathways that are not well understood, in real and measurable improvement that would not occur without the placebo. As a result, whether doctors may ethically prescribe placebos is a subject of some current concern.

Poison Squad

Early in the twentieth century, Harvey Wiley, chief of the Bureau of Chemistry, was intent on showing the dangers of an uncontrolled food industry. He recruited a volunteer group of young men and had them ingest large quantities of foods with additives and preservatives, such as formaldehyde and boric acid. The consequent ailments of the Poison Squad (1902–6) were well publicized and helped to pave the way for the Pure Food and Drugs Act of 1906.

Preclinical Research

The first stage in drug development, *preclinical research,* involves synthesis and purification testing in the lab and animal testing. Thousands of compounds are tested in preclinical research before a handful are chosen to enter the second stage, which requires filing of an IND.

Premarket Approval

Premarket approval means that regulators must authorize a product, process, batch, or facility before it is allowed to serve the market. That which is not specifically permitted is forbidden. Aaron Wildavsky (1988) has distinguished the hubristic *anticipatory* approach of premarket approval from the humble *resilience* approach of the freedom of contract plus postmarket inspection and recourse (through tort, legal, or recall procedures). Wildavsky argues

that the resilience approach allows for flexibility, differentiation, experimentation, and entrepreneurship. Beginning with the 1902 Biologics Act, however, government control has consistently enacted the anticipation approach by expanding premarket approval requirements. Today, drugs and medical devices must obtain premarket approval by the FDA before the product is allowed on the market. Devices categorized as Class III require premarket approval. According to the 1976 Amendments, all new devices were automatically placed in Class III even if they were low-risk devices. Since the FDA Modernization Act of 1997, new low-risk devices can go through an abbreviated process.

Prescription Drugs

Drugs that consumers may purchase only if they have a doctor's prescription, in contrast to OTC drugs, are called *prescription drugs.* Prescription requirements induce consumers to call on doctors; hence, they raise doctors' income. Prescription requirements may also be viewed in relation to drug prohibition. Prescription laws give doctors the privilege of authorizing the sale of FDA-approved narcotics that are substitutes for illegal "recreational" drugs. To prevent doctors from becoming authorized "drug dealers," the DEA and other authorities monitor and enforce against doctors who "overprescribe" narcotics (known as "script doctors").

See also the subsection Prescription-Only Requirements.

Prescription Drug User Fee Act of 1992 (PDUFA)

Traditionally, the FDA, like other bureaucracies, obtained its funding from general tax revenues according to congressional appropriations. In addition to having biased incentives, the FDA has at times been slow to approve new drugs because it lacked adequate resources to hire enough competent investigators to examine NDAs. Thus, many people died as NDAs sat unexamined on reviewers' desks. In 1992, Congress authorized the FDA to tax drug companies; this tax is euphemistically called a *user fee.* (The term *fee* is dubious because *fee* usually means payment for services rendered, but the FDA does not perform a service; rather, it decides whether to grant permission.) The FDA collects approximately $100 million in "user fees" each year and has hired some seven hundred new employees with those funds (the FDA must report these figures every year in a PDUFA financial report; the link is to the 1998 report). Initially authorized for five years, the fee act was extended for another five years in the FDA Modernization Act of 1997.

User fees have reduced the FDA's average review times, but total time to bring a drug to market was not changed appreciably because of increases in the clinical development time (Kaitin and DiMasi 2000).

More information is available in the history section.

Proof of Efficacy

Part of the 1962 Amendments, the proof-of-efficacy standard requires firms to produce evidence demonstrating that their product is efficacious for claimed uses. The proof-of-efficacy standard creates the distinction between on-label and off-label uses. The FDA reasons that because off-label uses have not passed proof of efficacy, the company is banned from disseminating information about such uses.

Pure Food and Drugs Act of 1906

This act banned the adulteration and mislabeling of food and drugs. It required that products specify the quantity of certain substances (alcohol, morphine, opium, cocaine, heroin, alpha- or beta-eucaine, chloroform, cannabis indicia, chloral hydrate, and acetanilide). It declared the *U.S. Pharmacopoeia* and the *National Formulary* to be the official documents determining standards. If a drug differed from these standards, the difference had to be stated on the package. The act did not address advertisements. Regarding therapeutic claims for a drug, in 1911 the Supreme Court ruled that the act did not prohibit claims that were false but not fraudulent. Along similar lines, the Sherley Amendment of 1912 decisively banned fraudulent claims. In other words, drug sellers could make therapeutic claims, even false claims, as long as they could plausibly show that they believed their own claims.

Rare Diseases

Rare diseases, as define by the Orphan Drug Act, are those diseases or conditions affecting less than two hundred thousand persons in the United States at the time of designation. Or they may be diseases or conditions that affect more than two hundred thousand persons but for which the costs of developing a drug cannot be recouped within seven years from sales in the United States.

Reciprocity

If the United States and, say, Britain had drug approval reciprocity, then drugs approved in Britain would automatically and immediately gain approval in the United States as well. The logic of such a proposal suggests that the U.S. government ought to establish reciprocity with countries that have a proven record of approving safe drugs. Such an arrangement would eliminate the delay with which drugs approved abroad become available to Americans. The FDA opposes the proposal, presumably because the reform would introduce competition. American drug companies would apply to, say, the British authority for approval because it is more efficient and reasonable in reviewing applications.

Reputation

In any industry, trade, or profession, a seller's trading partners, associates, and customers develop opinions of his trustworthiness. They develop a sense of whether the seller's products and services live up to the quality and safety that he promises. A good reputation is one of the most important keys to success because a good reputation will bring satisfied customers calling again and will bring others who hear of the seller's good reputation. If the seller sells an unsafe product, he not only will pay tort penalties, but will lose reputation and business. Reputation is generated by word of mouth and by other informal means, but also by various knower organizations that evaluate, rate, and report on the seller's quality and safety.

Safe Medical Devices Act of 1990 (SMDA)

Passed in 1990, the SMDA has greatly broadened FDA authority over the medical devices industry. The act requires Medical Device Reports; not filing the reports can result in fines. The SMDA also formally changed the 510(k) procedure, which was originally intended to be a notification procedure, to a premarket approval procedure. The SMDA also permitted the

assessment of substantial civil penalties for violating the Food, Drug, and Cosmetic Act relating to devices.

More information is available in the history section.

Seal of Approval

When a knower organization evaluates a product or service, it often grants a seal of approval such as a certification mark, a degree, or a rating, which helps to determine the seller's reputation and provides assurance to consumers.

Sherley Amendment of 1912

See Pure Food and Drugs Act of 1906.

Sinclair, Upton

Socialist muckraker who wrote *The Jungle* in 1906.

Split-Label Proposal

The *split-label proposal* is a reform proposal that would reduce the FDA suppression of information. The product label would consist of a part for FDA-approved health and nutrition claims and a part for non-FDA-approved claims. (A larger stride toward medical freedom would be to permit the marketing of products not approved by the FDA, provided that the label clearly indicates that the product is not FDA approved.) Although retaining FDA certification for those who want assurance from the FDA, the split-label approach would increase the amount of information available to the consumer and evoke market mechanisms, such as knowers and middlemen, to provide nongovernmental assurance of quality and safety.

Supplemental New Drug Application (SNDA)

The off-label uses of a drug may become additional on-label uses if the company submits a Supplemental New Drug Application and the FDA approves the application. SNDAs may take years to process and can be expensive. When a drug is off-patent or if the off-label use is for only a small population, there is little incentive (except that it is easier to advertise on-label uses) for a firm to obtain an SNDA.

Surrogate Endpoints and Postmarketing Studies

t's often very expensive or time-consuming to measure the effect of a drug on an ultimate goal such as mortality. Drugs to reduce cholesterol, for example, are intended ultimately to reduce the number of heart attacks and thus to lengthen life expectancy. It could take twenty or more years to test this hypothesis adequately, however. A surrogate endpoint, such as a reduction in cholesterol counts, is a more easily measured endpoint. A drug may be approved based on clinical trials showing a positive surrogate endpoint if there is evidence from other studies that the surrogate endpoint accurately predicts an ultimate benefit (we know, for example, that men with high cholesterol are at greater risk of a heart attack, but this is not the same as knowing that a reduction in cholesterol will reduce heart attacks, although it is suggestive.) Postmarketing studies can continue to tract the effectiveness of drugs that were approved using surrogate

endpoint methodology.

The use of surrogate endpoints is controversial because a positive surrogate endpoint does not necessarily predict a positive ultimate endpoint. Encainide and flecainide were widely prescribed because they prevented premature beats of the heart on the theory that such prevention would reduce heart attacks. The Cardiac Arryhythmia Suppression Trial later showed that not only was this claim false but that encainide and flecainide could actually increase the number of heart attacks. See Moore (1995) and the brief discussion in Tabarrok (2000).

Thalidomide

The sedative thalidomide was released in Europe in 1957 and taken by pregnant women to relieve morning sickness. Tragically, the drug caused severe birth defects in more than ten thousand children. When the horrible side effects were discovered, the drug was still pending approval by the FDA, which held up the drug for reasons unrelated to its danger to fetuses. Hence, the old, pre-1962 FDA was adequate in screening out thalidomide. Nonetheless, supporters of FDA power used the thalidomide tragedy to secure the 1962 Amendments, which vastly enhanced FDA power. Since that time, *thalidomide* has been a terrifying word. Yet as early as 1965 the drug was discovered to be effective in treating leprosy and in places other than the United States has long been the standard treatment for that disease. Thalidomide has also been used to treat other diseases, including lupus, some cancers, and Kaposi's sarcoma. Yet only in 1998 did the FDA finally permit Americans to use thalidomide. Special rules require that doctors and their patients register with the drug manufacturer and the FDA before thalidomide can be prescribed; women who take the drug must agree to use two forms of contraception and to submit to biweekly pregnancy tests.

The Jungle

Upton Sinclair's famous muckraking novel about the Chicago meatpacking industry contained outlandish, graphic images of Durham's Pure Leaf Lard being made out of the remains of workmen who had fallen into the cooking vats. When this 1906 novel upset the public, regulation advocates used the public's reaction to secure passage of the Pure Food and Drug Act of 1906 (as well as the Meat Inspection Act of 1906).

Treatment IND

This application allows drugs that are at the end of phase III clinical testing to be made available to patients who are suffering from a serious or immediately life-threatening condition when there is no other treatment available. An "immediately life-threatening" condition is defined as one that will result in death within a few months. Instituted in the late 1980s in response to the AIDS crisis, this practice is similar in effect to parallel tracking.

Types of Error in FDA Decisions

Even after extensive testing, the safety and effectiveness of a new drug are always somewhat uncertain. The FDA can thus never be certain that a new drug, device, use, or claim will be a net good or a net bad for society. Type 1 errors occur when the FDA approves a drug that ends up being a net bad for society. Type 2 errors occur when the FDA rejects a drug that

would be a net good for society. Type 1 errors produce identifiable victims. Such errors are very visible and often result in major media attention, public concern, and congressional action against the FDA. Hence, the FDA has a strong incentive to avoid type 1 errors. The FDA makes sure that type 1 errors are rare by increasing the length of the drug approval process and by requiring more extensive clinical trials. Such overcaution is deadly, however, because it leads to more type 2 errors: not permitting a drug, device, use, or claim that would be a net good to society. Type 2 errors are less visible because patients, doctors, and journalists are usually unaware that a drug has been delayed or suppressed and that it would have saved individuals. The victims of type 2 errors, the people who would have lived if the FDA had not delayed the legal use of a new drug, are just as real as those who die because the FDA approved a bad drug, but they are known only in a statistical sense and are much less salient. Intelligent drug policy should aim to minimize the harm associated with the both types of error. Although AIDS and cancer patients have sometimes been vocal in protesting FDA drug suppression, for the most part there is no informed, organized constituency to represent those who suffer as the consequences of type 2 errors. Thus, instead of minimizing total harm, the FDA focuses excessively on avoiding type 1 errors, resulting in many type 2 victims, invisible to the public eye but no less real.

For further discussion, see FDA Incentives.

Underwriters Laboratories Inc. (UL)

Underwriters Laboratories Inc. (UL) is a private, not-for-profit, product safety testing and certification organization. Founded in 1894, UL tests more than eighteen thousand different products for more than fifty thousand customers. It operates testing centers and has customers throughout the world. On a voluntary basis, manufacturers submit products to UL for testing and safety certification. There are no laws specifying that a UL mark must be used. (In the United States, many municipalities have laws, codes, or regulations that require a product to be tested by a nationally recognized testing laboratory before it can be sold in the area, but not necessarily by UL, so UL does not have a monopoly.)

UL successfully ensures high-quality standards in the fields of electrical products, fire suppression devices, automotive equipment, and much more. UL even certifies the electrical and mechanical aspects of medical devices. The success of UL in these fields suggests that UL and similar organizations might also ensure safe and high-quality drugs (Campbell 1999).

U.S. Pharmacopoeia and *USP-DI*

Published by *U.S. Pharmacopoeia* (USP), a private nonprofit organization, the *USP-DI* is a compendium of drug uses, covering both on-label and off-label uses. Using panels of expert physicians who evaluate the literature and clinical practice, the *USP-DI* presents information on which drugs are recommended for which uses, warnings, contraindications, dosages, etc. To keep up with best practices, it is updated regularly. The *USPDI* is the best known of several such compendia. The USP also publishes the *National Formulary*.

The *Complete Drug Reference,* published jointly with *Consumer Reports,* is the consumer version of the *USP-DI.* The *Complete Drug Reference* contains more information than the *Physicians Desk Reference (PDR),* which is useful but compiles product label information only and thus does not deal with off-label usages.

***Washington Legal Foundation v. Friedman D.D.C.* (July 20, 1998)**

Prior to this ruling, the FDA had maintained that manufacturers could not disseminate information about off-label uses to physicians, even photocopies of peer-reviewed journal articles, except under strict conditions (mainly that the manufacturer had to be in the process of submitting an SNDA for the off-label use). In *WLF v. Friedman,* the court ruled that many of the FDA's restrictions violated the commercial free-speech rights of manufacturers. The FDA's policies had in the meantime been codified by Congress in Section 401 of the FDA Modernization Act of 1997 (which did not become effective until late 1998). This aspect of the 1997 statute was subsequently struck down as unconstitutional by the same district court. On appeal, in *Washington Legal Foundation v. Henney* 202 F.3d 331 (D.C. Cir. 2000), the FDA backed down from its earlier position and reinterpreted section 401 of the Modernization Act in a way consistent with the district court's ruling in *WLF v. Friedman.* Hence, the court decisions have broadened manufacturers' freedom to disseminate information about off-label uses, though such freedom remains restricted.

Waxman-Hatch Act (1984 Drug Price Competition and Patent Term Restoration Act)

The 1984 Drug Price Act extended patent terms to account for the time it took a drug to receive FDA approval, and it reduced the barriers to entry for generic drug producers by allowing them to assert safety and efficacy based on information in the original NDA and on a proof that the original drug and generic drug are bioequivalent. The submission procedure for a generic drug is called an Abbreviated New Drug Application (ANDA).

More information is available in the history section.