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THE DRUG REGULATION REFORM ACT
(S.2755 - H.R. 11611)

STATUS

On March 16, 1978, the Drug Regulation Reform Act of 1978 (S. 2755 and H.R. 11611), the Carter Administration's proposal for sweeping revisions of the Food, Drug, and Cosmetic Act, was introduced in both the House and the Senate. Since then, the Senate Subcommittee on Health and Scientific Research, chaired by Senator Edward Kennedy (D-Massachusetts), has held five days of hearings. Besides Senator Kennedy, four other members of the seven-man subcommittee are cosponsors of the bill. In the parent Committee on Human Resouces, the entire nine-man majority has lined up to cosponsor the bill. Subcommittee markups are scheduled to begin on June 15. House hearings have begun and will continue through the week of June 19 before the Subcommittee on Health and the Environment of the Committee on Interstate and Foreign Commerce. Subcommittee chairman Paul Rogers (D-Florida) and ranking minority member Tim Lee Carter (R-Kentucky) are cosponsoring H.R. 11611 while an identical bill, H.R. 12980, has been introduced by six other members of the subcommittee majority and Harley O. Staggers (D-West Virginia), chairman of the parent Commerce Committee. Much earlier in the 95th Congress, Congressman Steven Symms (R-Idaho) and Senator Jesse Helms (R-North Carolina), introduced the Medical Freedom of Choice Act (H.R. 54 and S. 1683), a bill designed to curb the regulatory power of the Food and Drug Administration (FDA). To date, Congressman Symms has 115 cosponsors for his bill -- forty-seven Democrats and sixty-eight Republicans.

In his State of the Union Message of January 19, 1978, President Carter said that "We will propose legislation to reform regulation of the drug industry, which will protect the consumer and make regulations fairer and less burdensome." At the same time, the President re-emphasized his commitment "to reduce outdated,

ineffective, and nitpicking regulations." In his March 17 testimony before the Senate Subcommittee on Health and Scientific Research, HEW Secretary Joseph Califano stated that the Drug Regulation Reform Act would "promote competition and help lower prices" and that the bill would "restore an important element of fairness in FDA's relationship to regulated industry." Senator Kennedy, in his opening statement at the Senate hearings, declared that the new bill would "build public accountability into the drug approval process without hurting the pharmaceutical industry's research capabilities and without compromising the physician-to-patient or the pharmacist-to-patient relationship."

THE FOOD AND DRUG ADMINISTRATION

Charged with ensuring that drugs are safe and effective, the FDA regulates a $16 billion-a-year industry that markets about 60,000 prescription and 200,000 over-the-counter products. The agency also oversees food and cosmetic safety, but with 3,800 employees and a $128 million annual budget, the regulation of drugs, biologics, blood, veterinary medicine and medical devices absorbs the greatest part of FDA resources.

Before the twentieth century, most food and drug controls were directed against impure and adulterated foods. Thus, with the passage of the Pure Food and Drug Act in 1906, food abuses were the primary concern of the legislators, not drug safety. The 1906 Act was the child of the rising tide of progressivism and of the legendary muckrakers. It was designed to protect consumers by requiring that a medicine's ingredients be stated on a package label. There was no important restriction on the content or use of drugs. This posture was modified by the Food, Drug, and Cosmetic Act of 1938, passed in reaction to the introduction of a liquid form of the drug sulfanilamide whose solvent was discovered to be lethal poison after commercial distribution began. The 1938 law forbade marketing of any new drug until the Food and Drug Administration approved a New Drug Application (NDA) submitted by the manufacturer. Before approval was given, the NDA had to demonstrate that the drug was "safe" for the use suggested on the label. The law provided for automatic approval of any NDA not rejected within 180 days. In practice the FDA was able to extend this period by requests for further information.

A most important change in regulation of the development of new drugs came with the 1962 amendments to the 1938 law. The 1962 amendments provided that a manufacturer must prove to the FDA's satisfaction that a drug is "effective," that is, that it has the curative powers the manufacturer claims for it.

The initial impetus for changing the 1938 law came from

hearings begun in 1959 by Senator Estes Kefauver's Antitrust and Monopoly Subcommittee. Underlying these hearings was the belief that prevailing regulation permitted the introduction of new drugs of dubious efficacy that were sold at unusually high prices. The 1962 amendments would not have been enacted without the thalidomide episode of 1961-1962. Thalidomide was, in fact, kept from the U.S. market by the FDA under provisions of the 1938 law. However, the manufacturer had distributed the drug to some physicians for experimental purposes. The 1938 law permitted distribution of this sort to those deemed by the manufacturer to be "qualified experts" as long as the drug bore a label warning the expert that it was still under investigation. The American manufacturer of thalidomide ended investigational distribution of the drug and withdrew its NDA after reports that deformed babies had been born to European mothers who had used the drug during pregnancy.

THE DRUG INDUSTRY AND THE INTRODUCTION OF NEW DRUGS

For the last several years, doctors, pharmacists, pharmaceutical manufacturers, and clinical pharmacologists have directed a fusillade of criticism at the "efficacy" requirement of the 1962 amendments. The conclusion of many of them is that regulatory zeal at the FDA and the difficulty of proving a drug uniformly "effective" for all patients has resulted in greatly increased costs to the consumer, has decreased competition and innovation, has restricted research and development in the drug industry, and has caused significant delays in the marketing of new drugs with the result that many Americans are suffering unnecessarily from diseases and infirmities that could be relieved by already perfected drugs that the FDA will not approve for distribution. The United States is the only country in the world that requires its government to determine a new drug to be effective before it can be used. As a result, what many American experts agree are safe drugs are now available in foreign countries but not in the United States. Some patients with serious and persistent conditions have begun traveling abroad in order to get medication.

THE DRUG LAG

Professor Sam Peltzman of the University of Chicago found in his study, Regulation of Pharmaceutical Innovation (American Enterprise Institute, 1974), that the 1962 amendments

> Have reduced the annual flow of new drugs by about 60 percent, have reduced total new drug sales by a comparable amount, and have delayed by two years or more the marketing of those drugs which have been introduced.

In 1973, the doctor's magazine, Medical Times, asked family physicians how FDA regulations implementing the 1962 amendments have affected their practices. It found that 86 percent of the doctors questioned felt that the FDA regulations overprotect their patients and deprive them of important therapeutic drugs. In addition, 81 percent stated that government action had deprived them of drugs which they had found both safe and effective in their practice of medicine.

An analysis of United States drug development involving new chemical entities between 1962 and 1974 by Louis Lasagna and William Wardell of the University of Rochester School of Medicine found that, "The mean time required for clinical study and approval has risen steadily from 2.5 to 6 years."

In 1973, Private Practice magazine reported that during the ten years prior to the adoption of the 1962 amendments, the pharmaceutical industry produced and marketed an average of forty-three new chemical entities per year. Between 1962 and 1970, this figure dropped to seventeen, while the average between 1968 and 1973 dropped to thirteen per year.

A study reported in Barron's Weekly in June of 1975 found that during the years 1958 through 1962, "It generally required about two years and a little over $1 million to develop a new drug in the U.S. Now it takes eight to ten years and up to $20 million: the average probably runs around $12 million."

The 12th International Congress of Diseases of the Chest convened in 1974 by the American College of Chest Physicians concluded that the FDA's implementation of the efficacy clause of the 1962 amendments deprived American physicians and their patients of valuable and safe drugs for an unnecessarily long time.

In a study of the introduction of new drugs in the United States and Great Britain, Professor William M. Wardell of University School of Medicine found that the United States is lagging seriously behind Great Britain in the introduction of new therapeutic drugs. In a comparison of eighty-two drugs which are now available in both countries, Wardell found that only fourteen of these drugs were introduced into both countries during the same year while forty-three were introduced into Britain first, and only twenty-five were introduced into the United States first. In a comparison of ninety-eight drugs which became available in only one of the two countries, Wardell found that seventy-seven of the drugs were exclusively available in Britain while only twenty-one drugs were exclusively available in the United States (Private Practice, November 1973).

In Drug Regulation and Innovation (American Enterprise Insti-

tute, 1976), Professor Henry G. Grabowski of Duke University reviewed a number of studies of the production of beneficial drugs before and after the 1962 amendments, and concluded that the annual rate of introduction of new chemical entities declined from fifty-six a year before adoption to seventeen a year thereafter.

FDA's approval this year of the drug sodium valproate is most illustrative of the drug lag. The most effective drug now known to medical science for the treatment of epilepsy, sodium valproate, has been successfully used in Europe for a decade. There are approximately two million epileptics in the United States, and the Commission for the Control of Epilepsy has long estimated that the availability of the drug in the United States could prevent one million epileptic seizures annually.

Although the drug had been available in France since 1967, no American manufacturer had attempted to win FDA approval because of the high costs and interminable delays. Finally, in 1974, Abbott Laboratories agreed to undertake a study that it hoped would satisfy the FDA. Even though the FDA's Neurologic Drugs Advisory Committee reviewed the application and unanimously recommended approval in 1977, the FDA did not capitulate until a mounting storm of criticism forced them to action. For instance, Professor Wardell pointed out that from 1960 to date all except one of the eleven drugs introduced for epilepsy in the United States had been introduced first into Britain by margins of up to eleven years, and that half of the drugs for epilepsy available in Britain are not yet available in the United States.

The case of a group of drugs called beta-blockers is still more graphic. These drugs, developed over the past fifteen years, are proving to be very effective in the treatment of high blood pressure, irregular heartbeats, chest pain and other symptoms of heart disease. Although more than twenty beta-blockers have been developed, only the oldest is presently available in the United States, and that one was approved before the effectiveness rule became law. Frederick Roll, in his Of Politics and Drug Regulation (1977), makes the following observation about the introduction of beta-blockers in the United States:

> The modern use of beta-blockers for a variety of important new indications has been pioneered abroad, with the U.S. following ten years behind. Current studies are showing that beta-blockers can prevent heart attacks and sudden death. The estimated potential saving in the U.S. is at least 10,000 lives per year. The use of these drugs for that indication is at least five years away for the U.S. (Emphasis added)

THE DRUG COMPANIES

Aside from increasing the monetary costs of drugs to the American consumer, the 1962 amendments have fostered a monopolistic trend in the drug industry. Since 1962, while the total number of drug innovations has dropped, the proportion of new drugs developed by large corporations has dramatically increased. A study by Frederick Roll, conducted under a grant from the National Science Foundation, showed that before 1962, "The rate of innovation was greatest in those markets where small firms were innovating and taking market shares away from the leading sellers. This was not the case for the period 1963 to 1973 where the data show that innovation occurred most rapidly in markets dominated by a few large producers."

Nevertheless, the stocks of the large drug companies face an uncertain future. A recent article in Fortune (January 30, 1978) reports that although the "per-share earnings at almost all of the drug companies are expected to be about 10 percent for 1977," the average price-earnings ratio of these drug stocks, which was over 40 earlier in this decade, has now sunk to 13. The industry's profitability has been based largely on drugs created in the 1950's and early 1960's. Despite increased research spending by the pharmaceutical companies, only seventeen drugs were introduced in 1977 whereas an average of more than fifty a year were introduced in the late 1950's. In the middle and late 1960's, the drug companies profited from the rapid expansion of medical insurance plans, and the creation of Medicaid and Medicare, which stimulated demand for all types of health care. But now the patents on drugs introduced in the 1960's are expiring rapidly. Thus the drug lag has begun to take on some ominous implications for the future earning power of most companies. David Schwartzman, professor of economics at the New School for Social Research, estimates that the increased cost of bringing new products to the market will reduce the average return on research and development funds to about three percent. In 1960, the expected return was almost 12 percent.

RESPONSE OF THE FDA AND CONSUMER ADVOCATES

The Food and Drug Administration has largely ignored criticisms about overregulation and the unfortunate consequences of the 1962 amendments. In the April 13, 1978 edition of the New England Journal of Medicine, Donald Kennedy, FDA's current Commissioner of Food and Drugs, said that he looks forward to an increased regulatory role for the FDA:

> For its part in the disenthralling process, I think that the FDA has to liberate itself from the notion, with which it more than occasionally comforts itself and its medical constituency, that it regulates drugs and

> devices but not doctors. As much as we might wish otherwise, to regulate technology is to regulate practice. The Agency has never been, and is not now, anxious to exert direct regulatory control over the way in which physicians and other health professionals work. But like other regulatory agencies, FDA has turned an important corner from the policing the health-care system against fraud, quackery and bad manufacturing practices, to functioning as a regulator in the transfer of health technology. We have to be evaluated on the basis of how well we perform that function, and in a comprehensive way that counts loss of innovation as a cost.

In their testimony before the Senate Subcommittee on Health and Scientific Research, Sidney Wolfe and Benjamin Gordon of the Public Citizen Health Research Group, an influential consumers lobby, dismissed all criticisms as "a myth circulated by the drug industry, directly and indirectly, that thousands of Americans are dying each year because therapeutic agents, which are available in certain other countries, are being withheld from the American public and that this is due to the Kefauver amendments in particular and to the regulatory process in general. There is no evidence to support this point of view."

THE CURRENT STATE OF DRUG REGULATION

Under the current Food, Drug and Cosmetic Act, no one can market a new drug or any chemical intended to be used as a component of a new drug without the approval of the FDA. When a drug company's tests on animals show a new drug to be non-toxic and possibly therapeutic, it applies to the FDA for an investigational new drug exemption (IND) in order to conduct tests on human beings. For several years after the 1962 amendments became effective, the filing of an IND form was tantamount to permission to begin human trials. Now, during a thirty-day waiting period, the FDA reviews the work to date on the drug and any other information available about it; it also considers in some detail the manufacturer's plans for further investigation should the drug appear promising in early testing.

If the FDA approves an IND, the manufacturer enters the first of three testing phases. Phases I and II are designed to discover what the drug does inside the body. During Phase I additional animal testing is done to justify the longer human exposures that will occur in Phase II. During Phase II, the drug is administered to a small number of patients who have the condition that the drug is supposed to affect. Most of the new chemical entities tested are discarded during Phase I or early Phase II.

Phase III is intended to prove and document effectiveness. This is the phase in which the drug is administered to a few thousand patients as part of well-controlled clinical studies to test efficacy under conditions closely approximating normal clinical use.

After completion of Phase III testing, the manufacturer submits a new drug application (NDA) for FDA's approval. At that point the FDA reviews the work that has been done on the drug during the preceding several years. The FDA can approve or disapprove the drug for marketing or require additional testing. The burden of proof of safety and efficacy is on the manufacturer.

At present, the FDA has six months to review an application. However, it is alleged that not infrequently the manufacturer has failed to receive useful feedback from the FDA until the 180 days are almost over and is then told that the NDA is defective in some regard, whereupon the process begins again. Or the FDA may request a further delay, almost invariably granted by the manufacturer, which may last for months or even years.

After the FDA has approved a drug, it cannot require post-approval surveillance or additional studies. It can advise doctors on how to use a drug but cannot enforce its advice, nor can it restrict the distribution of drugs except to require that they be available only on a doctor's prescription. But it can suspend marketing of a drug if it finds that the drug presents an "imminent hazard."

THE DRUG REGULATION REFORM ACT OF 1978 -- H.R. 11611 AND S.2755

In General

Under the administration's bill, the conduct of clinical research on human beings, now regulated by an IND, would be divided into two stages: an "innovational" or discovery stage of investigation and a "developmental" or documentary stage. The FDA would authorize drug innovation investigations for research that is now conducted in Phase I and Phase II studies. As the bill is written, applications to conduct such research would require significantly less detailed information than is now required and would be issued if the application indicates that investigation would not subject the human subjects participating in the research to significant risks of illness or injury. However, the bill seems to give the FDA unilateral authority to delay approval by demanding information and documentation "as is necessary" from the drug companies. A thirty-day waiting period before commencement of the study would be required.

The new bill would require a second approval process for drug development investigations for what are now generally Phase III tests. Drug development investigations would be designed to gather the data necessary to support a petition for the issuance of a marketing license and would be authorized only if the FDA decided that the benefits from the use of the drug and the conduct of the research clearly outweighed the risks posed to the subjects of the research and to society. For this investigation, the FDA would require a sixty-day waiting period after which it could deny or still delay approval.

If, during the conduct of these investigations, it appears that a major breakthrough drug for a life-threatening or severely debilitating illness has been discovered, the FDA would be able to approve the drug provisionally for general or restricted distribution even before well-controlled, lengthy clinical studies had been completed. However, this provisional authority can be qualified at the discretion of the FDA.

When the drug investigations have been completed, the manufacturer will file two documents with the FDA: (1) a petition to establish a "monograph", a public document covering the drug entity or entities used in the product, and (2) an application for a product license under the monograph. At the time of filing, information concerning the safety and effectiveness of the drug will be made available to the public. During the next several months, FDA will review the petition and application, and the public will have an opportunity to evaluate the safety and effectiveness data. Before FDA decides whether to approve the petition and application, it must hold a public hearing at which interested persons may present views orally or in writing. Thereafter, FDA will determine not merely whether to approve the drug, but also:

whether restricted distribution is necessary to make the drug safe;

whether to require a patient's informed consent;

what post-approval surveillance or investigations are needed;

what the physician labeling and the patient package insert should say.

All of these matters will be open for discussion at the public hearing.

The drug will be approved only through the issuance of a drug monograph. The monograph will identify the drug contained in products licensed under it, the safe uses of those products, the standards to which the products must conform, and related conditions and requirements.

After a drug is approved, FDA will continue to regulate it. Any of the actions that could have been taken upon the drug's initial approval may also be taken after approval if circumstances warrant. The bill also replaces the "imminent hazard" test for summary suspension by language that makes clear that suspension is warranted if a drug presents an unreasonable and substantial risk of harm.

NEW FDA CONTROLS OVER THE DRUG INDUSTRY

Sections 101 and 102

Under findings and declarations, the bill announces that the last vestiges of distinction between interstate and intrastate commerce will be eliminated. The intention is to bring all cures, such as laetrile, manufactured and sold completely within a state, under federal regulations.

The new bill significantly widens the definition of drug components to include any substance that comes into contact with the drug product during manufacture even though that substance is not part of the final drug. Thus the FDA would be given new power to regulate the manufacturing process.

The word "person" would be redefined to include all government agencies besides individuals and corporations. This would give the FDA the power to regulate all drug-related activities of all government agencies: federal, state, and local.

"Drug entity" is redefined to be the therapeutic substance (as distinct from the product that is used to deliver this substance into the patient's body). In addition, the definition provides that injury and other health conditions are targets for drug therapy. Because the existing statute refers only to "diseases," it has been interpreted to exclude conditions which are considered natural but which are attended by medical needs often fulfilled by use of drugs. These conditions include puberty, pregnancy, and menopause. Drugs used in conjunction with such conditions would be brought under the definition and the regulatory control of drug entities.

Section 105

Current law states that no one may "introduce or deliver for introduction into interstate commerce" any drug without FDA approval. The new bill states that "no drug entity may be manufactured, imported, distributed or held for distribution" without FDA approval. Thus, it would be a crime to possess or distribute drug entities even non-commercially.

Sections 125-133

As stated before, the FDA currently requires one regulatory approval, the investigational new drug exemption (IND), in order for a manufacturer to bring a new drug from conception to the point where a license to market is requested. In place of this single process, the new bill would create two regulatory approvals, the drug innovation investigation and the drug development investigation. The FDA would retain its discretionary authority to amend, cancel, or require a new beginning for research on any drug.

The Monograph System

Monographs are currently used under the law for insulin, antibiotic drug products, for certain biological drug products and for non-prescription drug products. The new bill would bring all drugs, including those that previously were outside the drug law's premarketing approval procedures, under the monograph system. The monographs for the above mentioned drugs would be changed to conform to the standards of the new monographs. Monographs for all drugs already on the market, no matter for what length of time, would have to be drawn up.

Research

Under Section 128, the FDA would have substantial authority to hold up new drug research if it determines that "the proposed plan for the development of the drug product is not adequate to meet its stated objectives" or "the proposed investigations are inadequate to meet their stated objectives." Such a provision seems to be a kind of prior restraint since it will move the debate about the approvability of a prospective new drug to near the beginning of scientific research and investigation whereas it is now done at the time that a drug company seeks a license to market a drug. The FDA could "review" the progress and results of the ongoing and completed investigations. In effect, the FDA would become the arbiter of scientific methods and experimental techniques. In addition, the FDA would have the authority to "evaluate the risks and effectiveness of the drug product" while research is going on instead of at the end.

Section 110 is intended to encourage work on the "breakthrough drugs", namely, those which show great promise for serious medical conditions but for which proof of substantial efficacy is not yet available. But the requirements for approval of such drugs seem so stringent as to make it questionable whether many breakthrough drugs will reach the market except by the ordinary monograph procedure. The drug company must satisfy the FDA that a "significant portion of the patient population" would be benefitted by the drug; that the drug would be a "major advantage to patients" compared to alternative methods of treatment; that no other effective method

of "diagnosis, cure, prevention" or even "mitigation" exists; and that the drug is "effective", a determination made at the discretion of the FDA. All of these conditions seem impossible to meet except through long, elaborate research, the time spent for which would make the word "breakthrough" seem academic.

Section 166 gives the FDA the authority to suspend or terminate clinical investigations if it decides that the rights of the participants are being violated or the validity of the study is questionable. A drug firm that conducted a single research study in violation of this section could be barred from doing any and all drug research "until such person demonstrates to the Secretary that the person will comply with the applicable requirements."

The bill would give the Secretary of HEW the authority to conduct, or contract for, drug research, testing and clinical investigations. Section 179 simply grants this authority to the Secretary and seemingly empowers him to conduct drug research in any of the agencies of the Department of HEW, not just in the Food and Drug Administration. Section 201 provides for the establishment of a new HEW agency, the Center for Clinical Pharmacology, whose purpose it would be to "conduct and support research in clinical pharmacology and clinical pharmacy." Under these two sections, the Secretary of HEW, unburdened by the research and development decisions of the competitive marketplace, could develop his own drugs and conceivably use the drugs in the numerous HEW health programs without having to contract with private drug companies at all. HEW could also conduct its own drug investigations as a means of double-checking data of drug investigations being carried on by private drug and research firms. Such studies would delay approval of new drugs even longer. The Center would also oversee "the consequences of State and Federal regulation of the manufacture, importation, export, and distribution of drug products; public and private research activities and practices involving drug products; and practices of the pharmaceutical industry and health professionals respecting drug products." Thus, government money would be in competition with private money in the field of drug research.

MONOGRAPHS

The monograph would become the basic document for the marketing of any drug product. As stated before, the monograph would become a public document of record. Approval for the manufacture of a drug product by a drug firm would be granted by individual licenses under the monograph. All the data contained in a monograph would be the fruits of a pioneer firm's years of research and millions of dollars of investments about the safety and efficacy of a drug entity. In general, the bill will permit

a second manufacturer of any drug to rely on a pioneer's data. It does not require that the second manufacturer duplicate the pioneer's tests.

At the time that a manufacturer files a petition for the issuance of a drug monograph, a summary of the manufacturer's safety and efficacy data will be released to the public. The summary will contain scientific papers relating to the studies of the drug, including all critical tables, compilations, and analyses of data. However, detailed compilations of the data -- --virtually every datum used in research on the new drug -- will be made available for inspection on individual request between sixty and ninety days prior to the hearing on the petition.

Since monographs would have to be drawn up for all drugs already on the market, such data as contained in the monographs, now still the private property of the innovative firms, would be available to competing firms. Second or third manufacturers could receive all data in order to prepare a competitive drug for the market as soon as the patent protection for the original drug expires.

Release of such detailed data could become a powerful disincentive to research. Some domestic manufacturers would be able to discontinue costly research activities and simply wait to capitalize on the labor of others. Under this situation, it can be wondered whether many manufacturers will take the initiative to conduct new research. In foreign countries, the results could be equally devastating. Virtually all countries of the world will accept U.S. clinical data as a basis for registration of a drug. Assuming the U.S. innovator chose to market first in the U.S., copies in a foreign country, upon release of data at a time before the product can even reach the U.S. market, could certainly make fruitful and profitable use of it.

The bill provides that a pioneer firm shall have five years of exclusive use of its own research information before a second manufacturer could use the same information. This exclusive use period is in addition to, and independent of, any protection the pioneer may derive from a patent (a drug patent runs for seventeen years). The period of exclusive use runs concurrently with the patent period and does not extend it. The five year period does notbegin to run until the monograph becomes effective. Thereafter, normal patent rights, if any remain, are applicable. The drug companies contend that reliance on patent rights is not enough to protect the valuable property rights over the detailed monograph data. Many countries, including almost all Latin American and Iron Curtain countries, have no effective patent systems. Of the top ten drug markets in the world, six do not have effective drug patent protection. Release of safety and efficacy data

as proposed by the bill would benefit competitors in those countries both in instituting clinical trials and in applying for registration. Many other countries, France for instance, have patent systems that govern manufacturing processes but not products. Release of research data would enable manufacturers in these countries to market the innovative products as long as they were able to develop a new manufacturing process, so the five year ban will offer no protection from manufacturing pirates in foreign countries.

Under Section 111, the innovative drug company is required to supply not only data to demonstrate that the candidate drug meets the efficacy and safety standards but "any other data and information that the Secretary may request." Thus, the FDA could order the expenditure of drug company funds for an unlimited number of tests of an unspecified kind.

Under Section 109, in determining whether to issue a monograph, the FDA would be required to consider not only the safety and efficacy data and any known adverse effect, but also any "suspected" adverse effect on patients and health personnel when used as directed and any "suspected" or "potential" adverse effects upon the health of individuals or the public health even when used for the purposes other than that for which it is recommended or when abused. In other words, any "suspicion" by the FDA of consequences for non-indicated use or abuse could block the market entry of a valuable drug. In this case as in numerous places in the bill, it seems that drug companies who must commit millions to drug research and manufacture are faced with an extensive and unknown discretionary governmental authority.

Under Section 108, the FDA could require a company to conduct clinical studies at vast expense to pursue an indication for a drug which the company does not believe is appropriate and for which it does not wish to market the drug. Under the wording of the section, this authority seems not to be discretionary but mandatory. Again, the FDA could direct the expenditures of private drug firm monies for its own purposes.

Under Section 109, the FDA could require a company to conduct clinical trials at vast expense if it thinks that the drug "might" be improperly used. In addition, the FDA could make a firm demonstrate that its product's effectiveness "clearly outweighs" the risk of injury or illness even if it were misused.

Section 108 provides that the FDA will normally require a drug company to establish and maintain for at least five years a system of post-marketing surveillance. The monograph shall require that reports be periodically submitted to the FDA. An adverse drug reaction program is already being developed by the

Joint Commission on Prescription Drug Use, and some clinical pharmacologists maintain that a program that would provide reliable data has not yet been developed. Nevertheless, the new bill would mandate these surveillance programs as soon as the bill is passed.

Under the same section, the FDA would be empowered to summarily remove any drug from the market without any prior notice to the company and without a hearing if it finds "an unreasonable and substantial risk of illness or injury." The FDA would not be required to show the imminence of a serious hazard as under existing law. A drug company's only redress would be through time-consuming court action which, even if won, would probably permanently ruin the profitability of the drug under question because of the resulting publicity.

CIVIL AND CRIMINAL PENALTIES

Sections 161-170 provide for sweeping new criminal and civil penalties for violators of the act. Section 162 would increase the maximum fine for a misdemeanor from $1000 for both individuals and business firms to $25,000 for individuals and $50,000 for business firms. The same section would increase the maximum fine for felonies from $10,000 for both individuals and business firms to $50,000 for individuals and $1,000,000 for businesses.

Civil penalties would be imposed by the Secretary of HEW directly without court proceedings. The power to impose civil penalties is becoming a common legislative provision in the 1970's. Civil penalty provisions appear in a number of other public health regulatory statutes, including the Consumer Product Safety Act, the Water Pollution Prevention And Control Act, the Occupational Safety and Health Act, the Controlled Substances Act, and the Federal Trade Commission Act. Under this bill, the Secretary of HEW could, on his own, levy heavy fines against individuals and manufacturers for actions that he finds are in violation either of the law or of his regulations issued under the law. These fines may be levied whether or not the persons charged participated in the conduct complained of or even knew that it took place so long as such persons held positions of responsibility in the company or were in charge generally of company operations. The Secretary could impose a maximum penalty of $10,000 for an individual and $25,000 for businesses. Section 168 provides that both criminal and civil penalties can be imposed for the same violation of the act and that the imposition of any penalty shall not disqualify the violator from prosecution for further penalty.

NEW REGULATORY CONTROL OVER PHYSICIANS

The bill provides sweeping and summary authority for direct federal government intervention into medical practice and therapeutic decisions. The Secretary could establish, under Section 108, special dispensing and distribution conditions if he found that a drug monograph would not be issued or that an existing monograph would be revoked because the drug posed a significant risk to patients or the public health unless such special conditions were to be imposed. The Secretary could limit a drug's use to physicians with certain training and experience, to certain patients, to certain facilities, and for use only in "approved" dosages. In addition, the Secretary would be authorized to control the amount of a drug that could be dispensed at one time pursuant to a prescription, to dictate whether the prescription could be refilled, to mandate the total amount of a drug that could be made available to a particular patient, and to limit the use of drugs to "treatment programs" that would provide the type of medical services that the FDA deemed appropriate for patient care.

The same section would authorize the FDA to require, as a condition of dispensing certain drugs, that the treating physician obtain the formal informed consent of the patient if the FDA found that the risk posed from the use of a drug for a particular indication would be substantial but that the health benefits from such use would outweigh the risk. Presumably, the form to be filled out by the patient would be a federal form. The bill does not state whether one form would be used for all drugs or whether the FDA would develop unique forms for each drug. The exact procedures and specific requirements for the informed consent would be subject to regulations issued by the FDA under the bill.

The above mentioned authority of the FDA to require drug companies to conduct post-marketing surveillance of drugs would necessarily involve physicians and their medical files. Because of this, the bill would seem to grant power to the FDA to deny physicians access to a marketed drug if they do not submit use and adverse-effect information.

Section 151, interposes another federal regulation between a physician and his patient. The bill would require the Secretary to mandate patient information labeling, also called patient package inserts, for all drugs unless the FDA found that such labeling is not necessary "to protect the public health or to promote the safe and effective use of the drug product by the patient." The labeling developed by the FDA would then become part of the monograph for the drug. The labeling would contain information that the FDA deemed necessary to promote the safe and efficacious use of the product. For most drugs, the physician would be authorized to determine that distribution not

be made to particular patients. However, if the FDA found that patient labeling was "necessary to assure the opportunity for an informed decision by the patient regarding whether to use the drug product," the insert would then be provided to all patients regardless of the physician's determination.

Concerning this provision, Dr. Louis Lasagna made the following comment to the Senate Subcommittee on Health and Scientific Research:

> Patient package inserts (PPI) are to be devised for all drugs despite our lack of knowledge as to how best to do this. As someone, who has surveyed the expressed needs of patients in this regard, I can only shudder at the notion of anything but the most careful, thoughtful, and scientific approach to this important issue, including a candid appraisal of the inadequacies inherent in a PPI procedure that is bound to the glacier-like immobility of FDA evaluations. It can be guaranteed, if the government devises such PPI's, that they will inevitably be out of date even as they are written. The recently issued estrogen PPI is understandable by people with a 9th or 10th grade reading level ability, which means that the millions of U.S. women known to be without such ability are poorly served by this PPI.

Section 175 would authorize searches and inspections by FDA personnel of "regulated premises," a term which includes not only drug manufacturers but also physicians' offices. The latter's offices would be considered regulated premises when records relating to dispensing and distribution conditions were maintained by the physicians or when clinical research was conducted in the physician's office.

POWER FOR CONSUMER ADVOCATES

Section 184 of the Drug Regulatory Reform Act would authorize government compensation for attorney's fees, witness fees and "other costs of participating" in all FDA proceedings dealing with the issuance, amendment, suspension, or revocation of monographs. No restrictions are placed on the number of people who may be compensated under this provision or on the amount of money that may be expended for such services, except that no one may receive more than 75 percent of the annual salary of a GS 13. On their own initiative, several agencies have already created consumer offices, including the Federal Trade Commission, the Environmental Protection Agency, the Consumer Product Safety Commission, and the FDA itself, in order to subsidize consumer interest groups.

It would be at the discretion of the FDA to decide what citizens are to represent the public in agency proceedings. However, if the FDA refused to listen to a citizen's petition, the citizen would be granted, as a matter of right, access to any district court of his choosing in order to require the FDA to commence proceedings on the action sought. Court and attorney's fees could be awarded the citizen. With all these statutory powers available to consumer advocates, it seems that the bill affords many new opportunities to cause innumerable new delays in the drug approval process. Furthermore, citizens' groups seem to have more rights in court than pharmaceutical companies. They would have access to any federal court of their choosing as compared to very limited appeal rights of the innovative pharmaceutical company that petitions for a monograph but has access only to the Court of Appeals, and then on an extremely restricted basis. Section 182 directs courts not to consider an objection to an FDA directive unless "the objection was urged at the appropriate time during the administrative proceedings or unless there were reasonable grounds for failure to so urge it," unless the FDA's findings are "arbitrary or capricious," or if there is "substantial evidence" to support an objection.

CONCLUSION

Interested parties on all sides agree that the 1962 Amendments need reform. Pharmaceutical manufacturers argue that time-consuming and expensive pre-market testing requirements severely cut their incentives for developing new drugs. Associations formed to promote the cure and treatment of specific diseases, such as the Epilepsy Foundation, claim that important drugs are not available for use because of excessive regulatory zeal. The government argues for the necessity of standardizing the regulation of all drugs including drugs, such as laetrile, that have escaped federal control because they have not been manufactured and sold nationally. Consumer activists contend that reform is needed in order to make information on drug hazards more widely available and to counter the spiraling costs of drugs.

The Drug Regulation Reform Act was drafted by a joint task force representing the FDA and the staffs of the concerned Senate and House committees. After releasing a first draft last fall, the FDA heard public testimony from representatives of the pharmaceutical industry, consumer activist groups, labor unions and associations of the elderly. Senator Kennedy has advertised the legislation as "a consensus bill."

Nevertheless, there is still wide disagreement about the intent and implications of the bill. The primary supporters of the bill seem to be the Department of HEW and the sponsors of the bill

in the Congress. Thus, the government maintains that major new legislation is needed because the increase in the manufacture and sale of drugs has outstripped the government's ability to regulate them effectively. Since the 1938 statute establishing the proof of safety as a requirement, drug therapy as the primary means of therapy for an extraordinarily broad range of afflictions has increased in an unforeseen manner. In addition, the supporters contend that the present law is deficient because it regulates drugs differently depending on when they were developed; it closes the scientific review of drug safety and effectiveness to public scrutiny; it allows no effective mechanisms for limiting the distribution of drugs that cannot be marketed in an unrestricted way; it allows no means for quickly removing drugs that present new and unexpected dangers. Finally, the administration has maintained that the new bill would help pharmaceutical manufacturers by removing some of the restrictions on drug testing on human subjects.

But the drug companies deny this categorically, maintaining that even though some restrictions would be removed at the beginning of experimentation, the provisions of the monograph system that mandate public disclosure of research data would be catastrophic to the industry and a powerful disincentive for research and development. The bill provides for some protection of this data, but the manufacturers contend that the protection would prove unworkable. And many opponents perceive the entire bill as tending to reinforce and strengthen the 1962 amendments, and therefore the FDA also, when the evidence is that those amendments are an unnecessary impediment to the introduction of safe and effective new drugs. Thus, Dr. Louis Lasagna, an independent clinical pharmacologist, testified at the Senate hearings that under the new bill, "There is no cognizance taken of, or remedies proposed for, the greatest hindrance to speedy drug approval -- federal regulatory demands for more and more data on safety and efficacy, long after international experts have agreed on the utility and safety of a new drug."

Consumer advocates are not altogether satisfied with the bill as presently written. Although they generally applaud the provisions that allow for more public participation in FDA proceedings and the inclusion of post-marketing surveillance for new drugs, they seem worried that the provision designed to allow for the speedy introduction of breakthrough drugs could be abused with the result that dangerous drugs could be cleared for marketing. But the consumer advocates seem pleased with the new powers given to the FDA to demand informed consent, limited distribution, and package patient inserts.

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