Differences in the Number of Drug Safety Withdrawals

United States
United Kingdom
Germany
France
1970 - 1992

Sidney M. Wolfe, M.D.
Public Citizen's Health Research Group
February 2, 1995

Differences in the Number of Drug Safety Withdrawals United States, United Kingdom, Germany and France 1970-1992

Introduction

There is no question that the laws and regulations concerning drug safety and efficacy in the United States are more stringent than those in any other country. Periodically, there are claims that important, life-saving drugs which have been marketed in other countries are not available here because we are too "cautious." As will be discussed later (see **Discussion**), these claims are almost always unfounded. But the related issue raised by the drug industry is that for all our caution here, there is no evidence that Americans are being more protected from unsafe drugs than people in countries with less stringent approval processes. Previous studies which have examined this issue have always included earlier periods of time when the United States was not as careful in regulating the entry of drugs onto the market and, as a consequence, these studies did not show important differences between countries.

In order to evaluate the more current situation, especially after the 1962 U.S. law -- requiring, for the first time, proof of efficacy from well-controlled trials -- was fully implemented, our study looks only at drugs first introduced in the four-country market of the United States, the United Kingdom, Germany or France in 1970 or later and, subsequently, withdrawn for safety reasons in one or more of these countries. The primary source of data is a 1994 British report, *Drug Withdrawal from Sale*, by Drs. Claude Spriet-Pourra and Michel Auriche, published by the British company, Scrip. This report looked at all drugs, approved at any time in one of the four countries and later withdrawn for safety reasons in one or more of these countries.

The data in the British report were somewhat incomplete: many of the dates of original marketing were missing; some countries in which the drugs had been marketed were omitted; and one drug, cinepazide, was entirely omitted. In order to obtain more complete data, we obtained information from the FDA which keeps extensive records on the marketing and withdrawal of drugs in most countries. Arthur E. Hass of FDA's Office of Planning and Evaluation provided these data. Additional information on several drugs was obtained from sources in foreign countries.

Results

Of drugs first introduced in the four-country market in 1970 or later, 56 had been withdrawn in one or more countries by the end of 1992. Of these 56, 31 were withdrawn in France, 30 in Germany, 23 in the United Kingdom, and 9 in the United States.

Country to Country Comparisons

United States and the United Kingdom

* There were 16 drugs marketed in the United Kingdom and later withdrawn because of safety problems which were not marketed and withdrawn in the United States (one of these, Halcion, was approved and marketed but never withdrawn here). The other 15 were never marketed in the United States.

* There were 2 drugs marketed in the United States and later withdrawn because of safety problems which were never marketed in the United Kingdom.

United States and Germany

* There were 24 drugs marketed in Germany and later withdrawn because of safety problems which were not marketed in the United States.

* There were 3 drugs marketed in the United States and later withdrawn because of safety problems which were never marketed in Germany.

United States and France

* There were 28 drugs marketed in France and later withdrawn because of safety problems which were not marketed in the United States. (One additional drug, etretinate, was withdrawn in France but marketed and not withdrawn in the U.S.)

* There were 6 drugs marketed in the United States and later withdrawn because of safety problems which were never marketed in France.

Complete List of the 56 Drugs Marketed and Withdrawn by 1992

The table on the following pages lists all of the 56 drugs first introduced in the four-country market in 1970 or later and subsequently withdrawn by the end of 1992 because of safety problems in one or more of these countries. The first column lists the year in which the drug was first withdrawn. The second column gives the generic name of the drug and, for the U.S. drugs, the brand name. The third column lists the therapeutic purpose of the drug and the fourth, in which countries the drugs were withdrawn. The last column lists the drug's toxicity or reasons for which it was withdrawn.

Public Citizen's Health Research Group
Analysis of All Drug Product Safety Withdrawals: 1970-1992
(For Drugs First Marketed in 1970 or Later in US, UK, GER, FR)

Year Withdrawn	Drug (U.S. Brand Name)	Therapeutic Use	Country Withdrawn				Safety Problem
			US	UK	GER	FR	
1972	Suprifen + Tussilax	Antitussive			X	X	Hepatic
1975	Alclofenac	NSAID		X[1]	X		Dermatological (Skin); Nephrological (Kidney); Experimental Toxicity
1975	Polidexide	Antihyperlipidemic		X			Experimental Toxicity (Impurities)
1975	Practolol	Beta-blocker		X[2]	X	X	Oculo-mucocut. Synd.
1976	Pifoxime-Pixifenide	NSAID				X	Neuropsychiatric
1979	Pyrovalerone	Psychostimulant				X	Abuse
1980	Podophyllin (Internal Use)	Laxative				X	Animal Teratogenicity
1980	Potassium Nitrate	Potassium Supplement				X	Animal Carcinogenicity
1980	Ticrynafen (Selacryn)	Diuretic	X		X	X[3]	Hepatic; Renal
1982	Benoxaprofen (Oraflex)	NSAID	X	X	X		Hepatic; Multiple
1982	Catechic Extract	Vasoactive Drug				X	Hematological
1983	Indomethacin-R (Slow-Release)	NSAID		X	X		Small Intestinal Perforation; Gastrointestinal; Multiple
1983	Indoprofen	NSAID		X	X[4]		Gastrointestinal

Year Withdrawn	Drug (U.S. Brand Name)	Therapeutic Use	Country Withdrawn				Safety Problem
			US	UK	GER	FR	
1983	Proglumide	Stress Ulcer; Preventive Drug			X[5]	X	Pneumologic
1983	Zimeldine	Antidepressant		X	X		Neurological; Paralysis
1983	Zomepirac (Zomax)	Analgesic	X	X	X		Allergic Anaphylaxis
1984	Alphaxalone + Alphadolone	Anesthetic		X	X	X	Allergic Anaphylaxis
1984	Anti-Herpes Vaccine	Vaccine			X		Manufacture Problem
1984	Antrafenine	Analgesic				X	Experimental Colon Toxicity
1984	Fenclofenac	NSAID		X			Gastrointestinal; Skin Toxicity; Animal Carcinogenicity
1984	Feprazone	NSAID		X	X		Multiple: Skin; Hematological
1984	Isaxonine (Phosphate)	Neurotrophic				X	Hepatic
1984	Nitrefazole	Alcohol Deterrent			X		Hepatic; Hematological
1985	Canthaxanthin	Dermatological			X	X	Ophthalmological
1985	Cianidanol	Liver Protecting Agent			X	X	Hematological
1985	Growth Hormone (Natural) (Crescormon)	Hormone	X	X	X	X	Manufacture Problem; Neurological
1985	Indalpine	Antidepressant				X	Hematological
1985	Isoxicam	NSAID			X	X	Dermatological
1985	Suloctidil	Vasoactive Drug			X	X	Hepatic
1986	Beta-Ethoxylace-tanilanide	Analgesic			X		Nephrological; Animal Carcinogenicity
1986	Bucetin	Analgesic			X		Nephrological

Year Withdrawn	Drug (U.S. Brand Name)	Therapeutic Use	Country Withdrawn				Safety Problem
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1986	Domperidone (Inject. Form)	Antiemetic		X	X	X	Cardiovascular
1986	Factor VIII	Coagulation Factor		X			Manufacture Problem; AIDS Contamination
1986	Guanethidine	Anti-Glaucoma Eyedrop		X			Ophthalmological
1986	Hydrochloro-thiazide + Sotalol	Antihypertensive				X	Cardiovascular
1986	Nomifensine (Merital)	Antidepressant	X	X	X	X	Hematological
1987	Clometacin	NSAID				X	Hepatic
1987	Cyclofenil	LH Production Stimulant				X	Hepatic
1987	Muzolimine	Diuretic			X	X	Neurological
1987	Suprofen (Oral) (Suprol)	NSAID	X	X			Nephrological
1988	Cells (Fresh Animal)	Cell Therapy			X		Multiple; Dermatological
1989	Desensitizing Vaccines	Vaccine		X			Allergic
1989	Etretinate	Anti-Psoriatic				X	Teratogenicity
1989	Exifone	Aging Brain Stimulant				X	Hepatic
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1991	Encainide (Enkaid)	Antiarrythmic	X				Cardiovascular; Arrhythmias
1991	Fipexide	Psychostimulant				X	Hepatic; Allergic

Year Withdrawn	Drug (U.S. Brand Name)	Therapeutic Use	Country Withdrawn US	UK	GER	FR	Safety Problem
1991	Terodiline	Urinary Incontinence Therapy		X	X		Cardiovascular; Arrhythmias
1991	Triazolam	Hypnotic		X			Neuropsychiatric
1992	Cinepazide	Peripheral Vasodilator				X	Hematological; No Efficacy
1992	Factor XIII (Placental Extract)	Coagulation Factor			X	X	Manufacture Problem
1992	Germander Extracts (Teucrium Chamaedrys)	Slimming Diet Adjunct.				X	Hepatic
1992	Mumps Vaccine	Vaccine	X	X			Neuropsychiatric
1992	Temafloxacin (Omniflox)	Anti-Infective	X	X	X		Hematological; Other
	Totals		**9**	**23**	**30**	**31**	

1. Alclofenac was withdrawn in 1975 in Germany but in 1979 in the United Kingdom.
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Specific Examples of Drugs Withdrawn in Other Countries but Never Marketed in the United States

Cianidanol

This drug, a "liver-protecting" agent, was marketed and withdrawn in Germany and France because of reports of five patients with hemolytic anemia.[1]

Clometacin

This drug, a nonsteroidal antiinflammatory (NSAID) drug, was marketed and later withdrawn in France because of 130 reports of hepatitis including 9 (7%) deaths from hepatitis.[2]

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This drug, a psychostimulant, was marketed and later withdrawn in France because of fulminant hepatic failure caused by the drug.[4]

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This time-release NSAID was marketed and later withdrawn in the United Kingdom and Germany because of 717 adverse reaction reports including 36 fatalities. Included were 24 reports (3 fatal) of perforated duodenal ulcer, 13 reports (4 fatal) of perforated gastric ulcer, and 8 reports (5 fatal) of intestinal perforation.[5]

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This antidepressant was marketed and later withdrawn in the United Kingdom and Germany because of liver toxicity and some reported cases of Guillain Barre paralysis.[8]

Drugs Marketed and Later Withdrawn in the United States

Of the 9 drugs first marketed in the United States in 1970 or later and subsequently withdrawn by the end of 1992 because of safety problems, 3 were drugs whose manufacturers later pleaded guilty to criminal charges of withholding critical data concerning deaths or serious injuries from the FDA. The companies and their drugs are Lilly (benoxaprofen/ Oraflex), SmithKline (ticrynafen/Selacryn) and Hoechst (nomifensine/ Merital). In the case of Selacryn, for example, by the time the drug was taken off the market, 500 people had suffered liver and/or kidney damage including at least 36 deaths. It is clear that none of these three drugs would have been approved here had the companies not engaged in criminal activity in withholding information about deaths and serious injuries which had occurred prior to U.S. approval.

Drugs First Introduced in the Four-Country Market before 1970

Whereas for the drugs first marketed in 1970 or later and subsequently withdrawn, the United States had far fewer safety withdrawals than the other countries, in the earlier period of time, there was little difference between the number of safety withdrawals among the four countries. Of the 74 drugs marketed in one or more of the countries before 1970 and subsequently withdrawn because of safety reasons, there were 32 in the United States, 26 in the United Kingdom, 30 in Germany and 35 in France. Thus, the advent of the more

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stringent drug efficacy laws in the United States, has been accompanied by a sharp differentiation between this country and the other three in terms of dangerous drugs getting on and, later, taken off the market.

Discussion

As mentioned above, the evidence for a lag in important drugs getting marketed here later than in other countries is extremely weak. In 1994, for example, according to the major international publication on the pharmaceutical industry, the London-based *SCRIP*, there were 47 new chemical entity drugs (as opposed to new dosage forms or salts) approved in the world through December 8, 1994, when the January issue of *SCRIP* magazine, which contains this analysis, went to press. Of these, only 2 were thought to be important therapeutic advances over existing therapy. One is dornase alfa (Pulmozyme, Genentech) for cystic fibrosis and the other, imiglucerase (Cerezyme, Genzyme) for Gaucher's Disease. Not only were both made by American companies but both were approved here before approval in any other country in the world.

Our more stringent regulatory system seems to work quite well for the small number of drugs which are actually important therapeutic advances over existing therapy while keeping many questionable drugs off the market. By more rigorous standards for efficacy, applied even more so when the drug is not a breakthrough drug, the public benefits if and when the drug turns out to have an unexpected safety hazard. It is worth noting that none of the drugs approved in other countries and later withdrawn for safety reasons, but not approved here, were important therapeutic advances over existing therapy.

Summary

It is clear from this study that the more stringent drug safety and efficacy laws and regulations in the United States have saved many lives. The number of reported cases of deaths and injuries which led to the withdrawals in other countries of drugs never approved here is only the tip of the iceberg of damage that would have been done here if the drugs had been approved, for two reasons. First, it is generally agreed that only 1 in 10 adverse reactions which actually occur are reported in this country. It is likely that even a smaller fraction of adverse reactions in some of these other countries would have been reported. Second, the United States is much larger than any of the other three countries and with the usually aggressive marketing campaigns which accompany the introductions of new drugs here, the toll of lives lost or people seriously injured would have been much greater.

There is little question, therefore, that tens of thousands of deaths or serious injuries of Americans would have occurred had the drugs approved in the other countries but not here been approved here. This grim scenario would be a predictable consequence if our

drug laws and regulatory policies were weakened as proposed by many of the FDA-bashing organizations such as the Progress and Freedom Foundation, Citizens for a Sound Economy, the Competitive Enterprise Institute or the Washington Legal Foundation.

Lest we be accused of being uncritical allies of the FDA and its regulatory policies, in the 23 years since I started Public Citizen's Health Research Group, we have filed more than 50 petitions for warning labels or bans of prescription or over-the-counter drugs. Included were successful petitions to ban 2 of the 9 drugs on the U.S. list, Oraflex and Suprol.

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Country to Country Comparisons

United States and the United Kingdom

* There were 16 drugs marketed in the United Kingdom and later withdrawn because of safety problems which were not marketed and withdrawn in the United States (one of these, Halcion, was approved and marketed but never withdrawn here). The other 15 were never marketed in the United States.

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The table on the following pages lists all of the 56 drugs first introduced in the four-country market in 1970 or later and subsequently withdrawn by the end of 1992 because of safety problems in one or more of these countries. The first column lists the year in which the drug was first withdrawn. The second column gives the generic name of the drug and, for the U.S. drugs, the brand name. The third column lists the therapeutic purpose of the drug and the fourth, in which countries the drugs were withdrawn. The last column lists the drug's toxicity or reasons for which it was withdrawn.

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1980	Ticrynafen (Selacryn)	Diuretic	X		X	X[3]	Hepatic; Renal
1982	Benoxaprofen (Oraflex)	NSAID	X	X	X		Hepatic; Multiple
1982	Catechic Extract	Vasoactive Drug				X	Hematological
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1983	Zimeldine	Antidepressant		X	X		Neurological; Paralysis
1983	Zomepirac (Zomax)	Analgesic	X	X	X		Allergic Anaphylaxis
1984	Alphaxalone + Alphadolone	Anesthetic		X	X	X	Allergic Anaphylaxis
1984	Anti-Herpes Vaccine	Vaccine			X		Manufacture Problem
1984	Antrafenine	Analgesic				X	Experimental Colon Toxicity
1984	Fenclofenac	NSAID		X			Gastrointestinal; Skin Toxicity; Animal Carcinogenicity
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1985	Canthaxanthin	Dermatological			X	X	Ophthalmological
1985	Cianidanol	Liver Protecting Agent			X	X	Hematological
1985	Growth Hormone (Natural) (Crescormon)	Hormone	X	X	X	X	Manufacture Problem; Neurological
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Discussion

As mentioned above, the evidence for a lag in important drugs getting marketed here later than in other countries is extremely weak. In 1994, for example, according to the major international publication on the pharmaceutical industry, the London-based *SCRIP*, there were 47 new chemical entity drugs (as opposed to new dosage forms or salts) approved in the world through December 8, 1994, when the January issue of *SCRIP* magazine, which contains this analysis, went to press. Of these, only 2 were thought to be important therapeutic advances over existing therapy. One is dornase alfa (Pulmozyme, Genentech) for cystic fibrosis and the other, imiglucerase (Cerezyme, Genzyme) for Gaucher's Disease. Not only were both made by American companies but both were approved here before approval in any other country in the world.

Our more stringent regulatory system seems to work quite well for the small number of drugs which are actually important therapeutic advances over existing therapy while keeping many questionable drugs off the market. By more rigorous standards for efficacy, applied even more so when the drug is not a breakthrough drug, the public benefits if and when the drug turns out to have an unexpected safety hazard. It is worth noting that none of the drugs approved in other countries and later withdrawn for safety reasons, but not approved here, were important therapeutic advances over existing therapy.

Summary

It is clear from this study that the more stringent drug safety and efficacy laws and regulations in the United States have saved many lives. The number of reported cases of deaths and injuries which led to the withdrawals in other countries of drugs never approved here is only the tip of the iceberg of damage that would have been done here if the drugs had been approved, for two reasons. First, it is generally agreed that only 1 in 10 adverse reactions which actually occur are reported in this country. It is likely that even a smaller fraction of adverse reactions in some of these other countries would have been reported. Second, the United States is much larger than any of the other three countries and with the usually aggressive marketing campaigns which accompany the introductions of new drugs here, the toll of lives lost or people seriously injured would have been much greater.

There is little question, therefore, that tens of thousands of deaths or serious injuries of Americans would have occurred had the drugs approved in the other countries but not here been approved here. This grim scenario would be a predictable consequence if our

drug laws and regulatory policies were weakened as proposed by many of the FDA-bashing organizations such as the Progress and Freedom Foundation, Citizens for a Sound Economy, the Competitive Enterprise Institute or the Washington Legal Foundation.

Lest we be accused of being uncritical allies of the FDA and its regulatory policies, in the 23 years since I started Public Citizen's Health Research Group, we have filed more than 50 petitions for warning labels or bans of prescription or over-the-counter drugs. Included were successful petitions to ban 2 of the 9 drugs on the U.S. list, Oraflex and Suprol.