Drugs That Don't Work

Ralph Nader's Health Research Group is waging a campaign to see that ineffective drugs are withdrawn from the nation's medicine cabinets

BY JANET RALOFF

In 1962, Congress passed a law stipulating that in addition to being proved safe, all prescription drugs had to be proved effective if they were to be sold in the United States. It may come as some surprise, then, to learn that one out of every eight prescriptions filled in 1979 — some 169 million prescriptions, representing more than $1.1 billion in retail sales — went for drugs that did not meet the government's 1962 efficacy standards.

Since the 1962 law was enacted, new drugs have met the efficacy requirement — two or more well-controlled scientific studies demonstrating "substantially" that the drug lives up to claims — or been barred entry to the marketplace. But hundreds of drugs that entered the commercial market prior to 1962 remain on the market today even though their efficacy has been questioned since at least 1969. Officially, they are in regulatory limbo awaiting the completion of new scientific studies, the outcome of bureaucratic reviews or adjudication by civil courts.

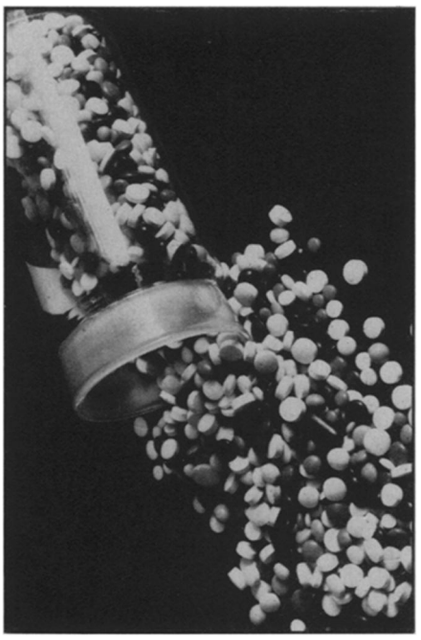
Pills That Don't Work, a book listing 610 of these drugs, was published last December by the Public Citizen Health Research Group in Washington. "All drugs have side effects," points out Sidney Wolfe, who heads the group and who together with Christopher M. Coley directed the team that put together the book.

"If the drugs are effective, their benefits can outweigh the risks," he explains. "But for the 610 drugs listed in our book, the benefits are either zero or close to zero, so side effects here never outweigh the risks." His book states emphatically, "[W]e do not recommend using the drugs."

But with sales of these drugs totaling more than $1 billion annually, clearly many physicians do recommend them. Why? Wolfe, himself a physician, says that even though most drugs considered "less than effective" by the Food and Drug Administration carry a warning label to that effect on their packaging and advertising material, physicians tend to pay as much attention to these warnings as smokers do to the Surgeon General's warning on a pack of cigarettes.

What's more, he says, "All these drugs have been on the market for at least 18 years — some, 25 years or more — and many doctors simply got in the habit of prescribing them before they were found to lack evidence of effectiveness."

Wolfe and members of the Public Citizen Health Research Group add, in their book, that "many doctors think that if they judge a drug to work, even if scientific studies



show it doesn't, they have the right to prescribe it."

By way of example, they point to DES (diethylstilbestrol). Well-controlled studies conducted during the 1950s established that the drug did not protect women from miscarriage.

"Nevertheless," Wolfe's book explains, "it was prescribed *after* this time to prevent miscarriages in millions of women because some doctors 'believed' the drug worked. Each had seen a woman with a miscarriage in a previous pregnancy take DES and then avoid a miscarriage during a subsequent pregnancy. Blinded to the notion that it was not DES, but just the natural variation from one pregnancy to the next, doctors rejected scientific studies in deference to their own personal 'experience' and therefore exposed millions of DES mothers, sons and daughters to cancer, birth defects and problems with pregnancies. In other words, DES (for preventing miscarriage) and many of the drugs in this book are no more effective, but much more dangerous, than a placebo (sugar pill)."

But such practices may change. Later this month, FDA will mail to the nation's physicians a list of about 400 drugs that have so far failed to meet the agency's efficacy requirements. It is the latest phase of an out-of-court settlement reached between FDA and Ralph Nader's Public Citizen attorneys last September. And like publication of *Pills That Don't Work*, it is another step in the campaign being waged by Nader's Health Research Group to see that consumers and physicians alike know enough to be able to steer clear of these drugs until they are either demonstrated effective or withdrawn from pharmacists' shelves.

Drug regulation began in 1906 when the first Food and Drugs Act was passed by Congress. It prohibited interstate trade in drugs that had been adulterated or fraudulently labeled. In 1938, the Food, Drug and Cosmetic Act added a requirement that studies demonstrating the safety of a proposed drug had to accompany a firm's request to market it.

But a drug could be relatively safe, accurately labeled and still not work. So in 1962 Congress remedied the loophole with amendments to the 1938 law requiring manufacturers to prove that drugs they sold or proposed selling lived up to therapeutic claims. But what to do about prescription drugs that were already on the market when the 1962 amendments passed has proved to be a regulatory nightmare.

Roughly 3,000 drugs carrying FDA's approval were being sold. All had entered the market between 1938 and 1962. (Drugs that entered the market prior to 1938 — such as barbiturates — were exempted from efficacy requirements under a "grandfather" clause.)

Manufacturers sent data hoping to substantiate their drugs' efficacy to FDA. FDA recruited the National Academy of Sciences and its National Research Council to review that data. Thirty panels of six experts each were charged with reviewing the specific class of drugs for which a given panel's members were considered expert (for example, antibiotics).

Their task was staggering. Each of the 3,000 FDA approved drugs being marketed carried an average of five different therapeutic claims. The NAS-NRC panels were asked to validate them all. Complicating matters was a class of "me too" drugs — chemically identical copies of previously approved drugs or combinations of approved drugs. In all, the panels reviewed claims for 3,000 approved drugs and 15,000 "me toos."

As the review panels' findings began trickling in to FDA, the agency initiated what is now known as the DESI — Drug

Efficacy Study Implementation — program. Paul A. Bryan, who has headed the program since its inception in January 1968, describes DESI as "one of the most important projects — perhaps the most important one — ever undertaken to improve the quality of prescription drugs in the U.S."

In the October 1972 FDA CONSUMER, Bryan said: "As a result of the DESI project, the American patient will ... be assured that doctors have more reliable and more objective labeling information on which to select their prescription drugs. ... [A]lso because of the DESI project, FDA has developed a new method for getting a handle on the thousands of unapproved [me too] drugs that had been marketed without FDA knowledge....[A] doctor soon will be able to prescribe any drug with assurance that it is safe and effective."

But Bryan's optimism that existing ineffective drugs would be eliminated "soon" has met with the harsh realities of the U.S. legal system. "It's taken a great deal longer than we'd expected," Bryan now admits. "Much of that has been because of all the legal challenges we've had. We've even gone to the Supreme Court a couple of times" — and won.

Since FDA proposed the first removal of drugs whose efficacy was in doubt more than a decade ago, numerous firms have requested hearings or filed lawsuits disputing the less-than-effective rating FDA ascribed to their products. Others have asked for hearings to air results of new medical studies that might shore up therapeutic claims made for their drugs. Some companies went so far as to challenge the legality of procedures used to categorize their drugs as less than effective. Legal tactics have even been enlisted to stall the final decision on an obviously doomed drug. "And it's perfectly legal," Bryan notes. "While I'm not sure it's perfectly ethical, it sure is legal."

"But we're not worried about the safety of those products that stay on the market legally [pending FDA's final determination of their efficacy]," Bryan adds, because in compliance with the 1938 drug law, all DESI drugs have been approved for safety.

Wolfe's attitude about the established safety of many apparently less-than-effective drugs is less sanguine, however. His book points out, for instance, that a group of 55 vasodilators — drug products to improve circulation by dilating blood vessels — containing papaverine or ethaverine "are not only ineffective; they are clearly dangerous .... In 1969, 20 percent of patients receiving a moderate dose of papaverine (160 milligrams a day) for more than one month were found to have liver damage caused by the drug. The authors of this study, remarking at how surprising it was that this had not been seen earlier, concluded that it was probably because papaverine 'has long been considered a non-toxic drug.'" The book goes on to add that, "in an...editorial, world expert on drug-induced liver damage Dr. Hyman Zimmerman said, 'If the therapeutic role of papaverine were important, the apparent hepatotoxicity might be acceptable.'" But according to the Health Research Group's research, several studies — and even an FDA Advisory Committee in 1979 — found "there is no body of evidence that will support the effectiveness of papaverine and ethaverine for any of the claimed indications."

These findings notwithstanding, 5.2 million prescriptions for drug products containing papaverine and ethaverine were written in 1979, accounting for sales in excess of $30 million.

Interestingly, for reasons no one (even Bryan) can explain, these pre-1962 vasodilators are not even included in the DESI review program. They are, however, being studied by another FDA department, Bryan assured SCIENCE NEWS.

It's the speed with which FDA is acting on drugs suspected of being ineffective, though, that Wolfe's group finds most vexing. And others share their frustration. In 1970, for example, the American Public Health Association and National Council of Senior Citizens brought suit against FDA, asking that DESI — undermanned and strangled in litigation as it was — move faster. The court order that resulted two years later criticized DESI's pace and set a 1976 deadline for removing the last of the drugs for which proof of efficacy was lacking. ("We never say anything's ineffective," Bryan says, "we just say we don't have evidence to show they're effective.")

When that 1976 deadline passed and the status of a substantial number of DESI drugs was still far from being resolved, APHA and NCSC again brought suit. The case, settled out of court by Public Citizen's attorneys last fall, won the public interest groups a promise that FDA would: add more staff to expedite the DESI efficacy review, place highest priority on tackling the biggest selling drugs, notify all doctors which drugs still lack evidence of effectiveness and aim to complete final DESI-drug determinations within five years.

As the next phase in its campaign to protect the health and pocketbooks of drug consumers, Wolfe's Health Research Group is compiling a book on ineffective nonprescription drugs. It is due out some time next year. □

Top 30 Less Than Effective Drugs in 1979

Rank	Product	Manufacturer	# Rx	Retail Sales
1	Dimetapp (two forms)	Robins	14,800,000	$67,000,000
2	Actifed	Burroughs Wellcome	12,900,000	49,000,000
3	Donnatal (two forms)	Robins	8,970,000	31,700,000
4	Isordil (three forms)	Ives	7,100,000	61,400,000
5	Mycolog	Squibb	6,300,000	51,000,000
6	Butazolidin Alka	Geigy	5,700,000	34,800,000
7	Librax	Roche	5,600,000	46,000,000
8	Ornade Spansules	Smith Kline & French	4,800,000	27,000,000
9	Phenergan Expectorant w/Codeine	Wyeth	4,000,000	19,500,000
10	Parafon Forte	McNeil	3,800,000	28,400,000
11	Persantine	Boehringer-Ingelheim	3,600,000	53,000,000
12	Pavabid Plateau	Marion	3,300,000	31,300,000
13	Synalgos-DC	Ives	3,100,000	16,100,000
14	Tuss-Ornade	Smith Kline & French	3,000,000	16,400,000
15	Phenergan VC Expectorant w/Codeine	Wyeth	2,900,000	15,200,000
	Equagesic	Wyeth	2,900,000	21,100,000
17	Actifed-C Expectorant	Burroughs Wellcome	2,700,000	12,700,000
	Combid Spansules	Smith Kline & French	2,700,000	22,000,000
19	Nitrobid Plateau Caps	Marion	2,600,000	22,800,000
20	Bentyl	Merrell-National	2,500,000	15,500,000
21	Phenergan Expectorant Plain	Wyeth	2,400,000	9,900,000
22	Benylin Cough Syrup	Parke-Davis	2,300,000	8,900,000
23	Marax and Marax DF	Roerig	2,100,000	13,900,000
	Vasodilan	Mead-Johnson	2,100,000	29,000,000
25	Dimetane Expectorant	Robins	2,000,000	8,700,000
26	Ambenyl Expectorant	Parke-Davis	1,800,000	9,800,000
27	Phenergan VC Expectorant Plain	Wyeth	1,700,000	7,700,000
	Chlor-Trimeton Repetabs	Schering	1,700,000	9,600,000
29	Dimetane Expectorant-DC	Robins	1,600,000	8,500,000
	AVC Cream	Merrell-National	1,600,000	12,000,000

All drugs listed above were among the 200 most frequently prescribed in 1979. To be effective, a drug's therapeutic claims must be validated in two or more scientific studies. For combination-drug products, each active ingredient must enhance the product's effectiveness, safety or chance it will not be misused.

Pills That Don't Work, Public Citizen Health Research Group