United States General Accounting Office

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Report to the Chairman, Subcommittee on Regulation, Business Opportunities, and Energy, Committee on Small Business, House of Representatives

January 1992

NONPRESCRIPTION DRUGS

Over the Counter and Underemphasized

GAO/PEMD-92-9

GAO

United States
General Accounting Office
Washington, D.C. 20548

Program Evaluation and
Methodology Division

B-246187

January 10, 1992

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
Business Opportunities, and Energy
Committee on Small Business
House of Representatives

Dear Mr. Chairman:

In your letter of February 5, 1991, you asked us to examine the Food and Drug Administration's (FDA) procedures for approving and monitoring over-the-counter (OTC) drugs in order to identify potential vulnerabilities in these procedures that could result in the approval and marketing of unsafe and ineffective drugs.[1] On July 17, 1991, we provided an oral briefing to your staff on the results of our review. Following the briefing, you asked us to conduct additional analyses to compare the procedures for OTC drugs with those for prescription drugs and to provide the Subcommittee with a written report of our findings. This report responds to your request.

OTC drugs are a common part of our daily lives. Products such as antiperspirant deodorants, mouthwashes, cold remedies, and analgesics are used by millions of people every day. Estimated OTC drug sales in the United States for 1990 were $11.2 billion, or nearly 2 percent of all national health care expenditures.[2] FDA has estimated that there are between 125,000 and 300,000 different OTC products currently being marketed.[3]

In our review of selected epidemiological literature and media accounts, we found numerous examples of the health hazards that can be associated with the use and abuse of widely used OTC drugs. As might be expected, many problems are associated with user abuse or interaction effects of multiple drugs. For example, long-term use of acetylsalicylic

[1] The 1951 Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act of 1938 created two categories of drugs: (1) those restricted to sale by prescription, and (2) those that can be sold without prescription (that is, over the counter). The principal factors that decide the prescription or OTC status of drugs are the margin of safety, method of use and collateral measures necessary to use, benefit-to-risk ratio, and adequacy of labeling for self-medication.

[2] These are the latest statistics available from the Nonprescription Drug Manufacturers Association, an industry trade association.

[3] FDA's inability to provide a precise or even a usable estimate is discussed in the Principal Findings section of this report.

acid, the active ingredient in aspirin, has been linked to bleeding ulcers and hearing loss. Acetaminophen, the active ingredient in other analgesics, has been associated with fatal liver damage when combined with alcohol consumption, and kidney damage when taken over an extended period of time. Ibuprofen, the active ingredient in still other analgesics, has been associated with kidney damage and ulcers when taken for a long period of time or in large dosages.

OTC drug products have also been linked with adverse health consequences not necessarily arising from abuse or misuse. For example, guar gum—which is used in some OTC diet and laxative products—has been associated with several cases of nonfatal choking. Problems caused by product mislabeling and the occurrence of adverse effects that were identified only after the product had been approved for marketing and distributed have also been associated with serious patient injury. Additionally, recent congressional hearings have raised serious concerns about both the safety of certain OTC appetite-suppressant products and their association with bulimia and anorexia.[4] The prevalence of OTC drugs in our society, the absence of trained health care providers acting as intermediaries, and the potential for patient deaths or serious injuries are all factors that underscore the importance of adequate regulation and monitoring of OTC drugs marketed in the United States.

Results in Brief

In our comparison of FDA regulation of OTC and prescription drugs, we found several differences in how FDA ensures the safety and effectiveness of OTC and the safety and effectiveness of prescription drugs. Specifically, we found that (1) unlike prescription drugs, many OTC drugs have not been required to demonstrate their safety and effectiveness before being made available to the public; (2) during FDA inspections for compliance with current good manufacturing practices (CGMP), FDA has statutory authority to inspect records and documents of prescription drug manufacturers but not those of OTC drug manufacturers; and (3) FDA collects less postmarketing surveillance information and conducts fewer product performance analyses for OTC drugs than for prescription drugs. Postmarketing analyses routinely conducted for prescription drugs include patterns of usage, the magnitude of any identified problem and the appropriate level of response, and trends in adverse

[4] U.S. Congress, Juvenile Dieting, Unsafe Over-the-Counter Diet Products, and Recent Enforcement Efforts by the Federal Trade Commission. Hearing before the Subcommittee on Regulation, Business Opportunities, and Energy, House Committee on Small Business (Washington, D.C.: U.S. Government Printing Office, Sept. 24, 1990).

reactions. (See appendix I for a summary comparison of FDA regulatory controls for OTC and prescription drugs.)

Scope and Methodology

This study examined FDA's policies and procedures for the regulation of pharmaceuticals produced and marketed in the United States. We limited its scope to the relevant legislation, currently prescribed FDA requirements and procedures for regulating and monitoring OTC and prescription drugs, and implementation mechanisms.[5] Finally, although in our review we found numerous examples of health hazards associated with OTC drugs, we did not attempt to determine the extent of these hazards as they affect public health.

Our methodology combined qualitative and quantitative data to develop a dynamic model and description of FDA's regulation of drugs, as well as to identify the points of divergence between OTC and prescription drugs, gaps in regulations and regulatory authority, and potential consequences. We reviewed and analyzed the legislative history, FDA's policies and procedures documents related to drug regulation, and selected empirical literature. We conducted structured interviews with FDA officials in the Center for Drug Evaluation and Research and knowledgeable persons in the private sector to confirm and clarify the documentary evidence and to identify other issues and perspectives. Finally, we obtained summary statistics for the period of 1985-90 from FDA on the size of the industry, FDA's progress toward completion of the OTC drug regulations, the number of new drugs reviewed, inspections of drug manufacturers, and reported problems with marketed drugs.

We conducted our review between March and June 1991 in accordance with generally accepted government auditing standards.

[5] FDA's regulation of OTC and prescription drugs occurs at three stages that correspond to the life cycle of a drug product: (1) premarket approval, (2) production quality assurance, and (3) postmarketing surveillance. FDA may invoke regulatory sanctions at any stage of the product's life cycle. The sanctions available are warning letters to manufacturers, recommendation of a product recall, injunctions, seizures, and prosecutions. Injunctions, seizures, and prosecutions require judicial review before they can be invoked by FDA. The other options are within FDA's independent regulatory authority and may be exercised without judicial review.

Principal Findings

Premarket Approval

There are four principal routes through which a manufacturer may obtain FDA approval to market a drug product: (1) compliance with an FDA regulatory statement (called a monograph) that specifies the ingredients, dosage, labeling, mode of administration, and the combination of generally recognized safe and effective ingredients permissible in the product;[6] (2) submission of a new drug application (NDA) that includes sufficient data from clinical studies to permit its evaluation from specific technical viewpoints, including chemical, pharmacological, medical, biopharmaceutical, and statistical;[7] (3) submission of an abbreviated new drug application (ANDA) for products with the same or very closely related active ingredients, dosage form, strength, administration route, use, and labeling as a product that has already been approved as safe and effective;[8] and (4) submission of a new drug application supplement for changes in a product that already has an approved NDA.[9] (See figure 1.)

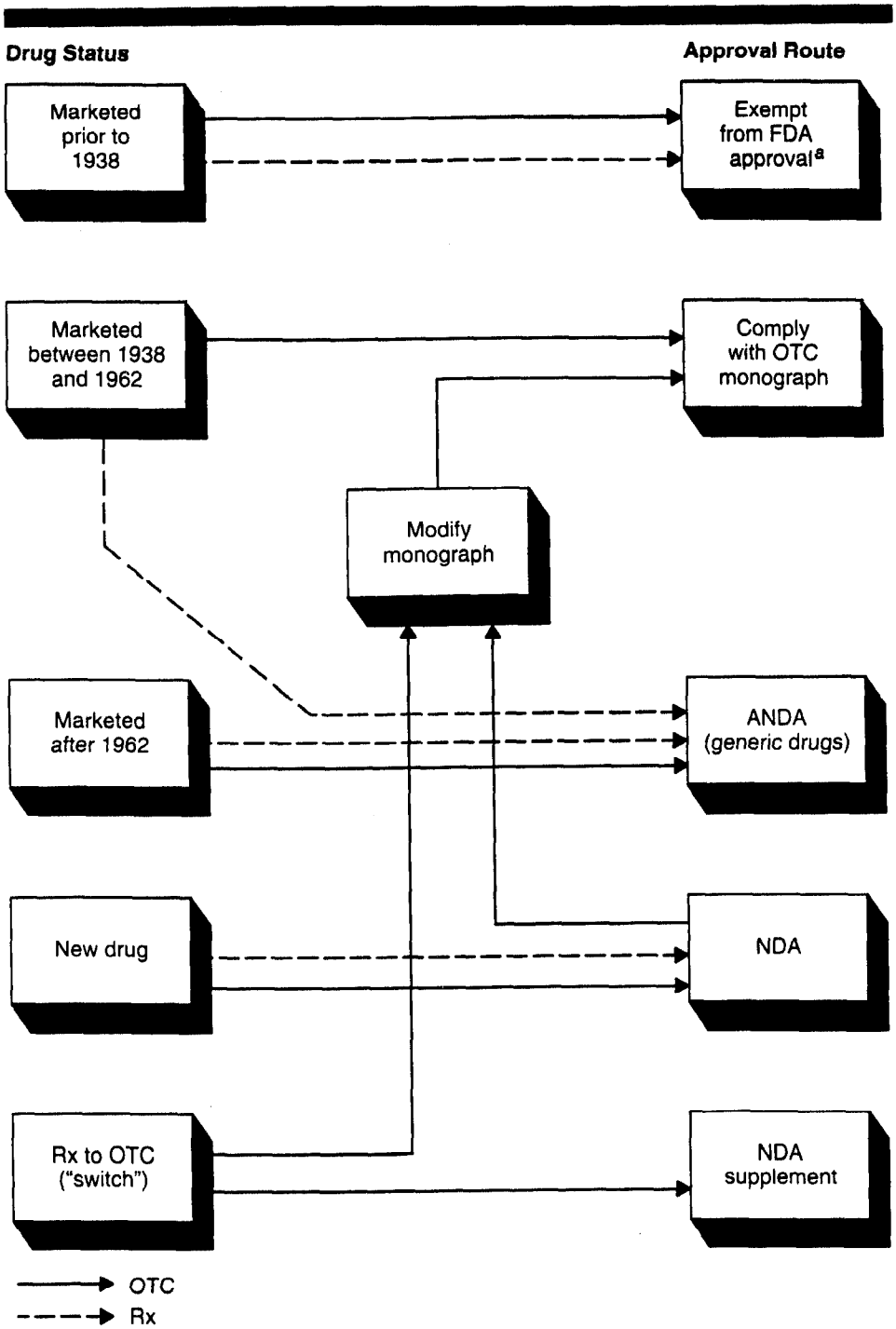
[6] This route is applicable only to OTC drug products.

[7] An approved NDA represents FDA's determination that the specific drug product is safe and effective for its intended use.

[8] This is the principal route to market for drug products that are bioequivalent and identical in formulation to a product currently on the market, and it is applicable to both OTC and prescription drugs. These types of drugs are often referred to as "generic drugs."

[9] Examples of product changes include the introduction of a capsule form of a product that was approved in pill form, or the use of new technology in the manufacturing process.

Figure 1: Requirements and Procedures for Obtaining FDA Approval to Market OTC and Prescription Drugs



[a]To qualify for exemption, the product and labeling must be exactly the same as in 1938.

In 1972, FDA began a review of OTC drugs as part of the 1962 congressional mandate to review drugs approved between 1938 and 1962.[10] The review, also known as the monograph program, is the principal route to market for OTC drugs.[11] Drug products that the manufacturer determines meet the requirements of the relevant monograph may be marketed without any FDA review. For example, since the monograph that prescribes the requirements for aspirin is complete, a manufacturer may produce and market a conforming product without FDA approval.

As of June 1991, however, nearly 30 years after the legislation was enacted, FDA has promulgated only 34 of the 71 proposed monographs into final rules. Additionally, FDA has adopted a policy that extends the coverage of the monograph program to all OTC drugs that were marketed up to 1972. As a result of this extension, FDA has exempted an undetermined number of individual OTC drug products first marketed between 1962 and 1972 from the NDA requirement to show proof of their safety and effectiveness.[12] The monograph program, as it is implemented, makes the adequacy of FDA's regulation and monitoring of production quality assurance and postmarketing surveillance activities critical to protecting the public health.

In contrast to the OTC monograph program, the NDA, ANDA, and NDA supplement routes are applicable to all requests to market a prescription drug or OTC product first introduced into commercial distribution after 1972.[13] All of these programs require a review by FDA of the safety and effectiveness data for each drug product before it is approved for marketing. This premarket review includes the results of clinical trials on humans.

[10] The OTC monograph program is FDA's response to the 1962 Harris-Kefauver Amendments to the Federal Food, Drug, and Cosmetic Act of 1938 (P. L. 87-781).

[11] The OTC review is a three-phase rule-making process that includes an advance notice of proposed rule-making (advisory panel recommendation on the safety and effectiveness of active ingredients and on labeling), proposed rule-making (tentative conclusions based on advisory panel's findings, public comment, available data, and tentative final monograph), and a final rule that identifies those active ingredients that are generally recognized as safe and effective for specified uses and that may be marketed in OTC drug products for each therapeutic class (for example, antacid and analgesic).

[12] FDA's lack of an accurate listing of the OTC products being marketed is discussed in the Postmarketing Surveillance section of this report.

[13] Insulin and antibiotic drugs are exceptions in that they follow a procedure that combines parts of the NDA and monograph programs.

In addition to the routes for initial marketing approval for prescription and OTC drugs, there are several options available to FDA or a drug manufacturer to change the marketing status of a product from prescription to OTC.[14] Ibuprofen (200 milligram tablets) and topical hydrocortisone are recent examples of drugs that were initially available to the public only by prescription and are now OTC products. Since 1972, about 46 prescription drug ingredients, many of them in cough or cold remedies, have been switched to OTC status. As of March 13, 1991, there were 10 prescription drugs with pending NDA "switches" to OTC status.[15]

For the public, the change of a drug's marketing status carries both benefits and risks. Historically, a switch from prescription to OTC status for a drug has generally meant an increase in the availability of more effective drugs for consumer self-medication and a reduction in overall health care expenses. However, when the drug becomes available over the counter, reduced intervention by trained health care professionals and reduced FDA monitoring increase the potential for overuse and misuse of the drug.[16] As the possibility of adverse occurrences increases with the widespread public availability of OTC products, so again does the criticality of production quality assurance and postmarketing surveillance activities.

Production Quality Assurance

The CGMP requires manufacturers of both OTC and prescription drugs to maintain customer complaint files, equipment maintenance logs, and other manufacturing records. However, FDA does not have the statutory authority to inspect the records of OTC drug manufacturers as it does of prescription drug manufacturers. The agency is only able to inspect records that are on display at the time of the inspection or that are voluntarily provided by the manufacturer. FDA officials said that drug manufacturers will generally provide access to their records upon request.

[14] FDA can switch a drug's marketing status under its own initiative, which may include incorporating that drug into the development of an OTC monograph. Manufacturers may obtain an approved NDA supplement from FDA or petition FDA to modify an existing OTC monograph to include the prescription drug.

[15] On rare occasions, some drugs go from OTC availability to prescription status. The most notable case occurred in the 1970's when hexachlorophene was widely available as an antibacterial agent in soaps and powders. However, it was reclassified when it was discovered that infants dusted with powder containing the drug suffered brain damage.

[16] For example, ibuprofen was prescribed for chronic arthritis in 400 milligram doses. When it was designated for OTC usage in 1985, it was marketed as a general pain reliever in smaller dosages. The switch can result in an increased risk that people will use the OTC products at prescription strength for conditions that require trained health care professionals to diagnose.

According to FDA, large manufacturers are more likely than small ones to provide limited access or no access to CGMP-related documents. Small manufacturers will almost always provide access to the requested documents, perhaps through ignorance of their option not to provide them. When access is denied, FDA inspectors interpret this as an indication of a potential problem situation. In an effort to compensate for the manufacturer's failure to provide access to records, FDA may use such techniques as increasing the scope and depth of their observational inspection of the production facility.

Although an individual manufacturer of OTC drugs may receive information about adverse effects associated with its products, may record that information in its complaint files, and may take remedial action, the efforts of a single manufacturer may not be sufficient to protect the public health against a problem that is industrywide. Similarly, problems in the manufacturing process, such as with equipment calibration or sterilization, may be recorded. But because it lacks the authority to inspect OTC records, FDA may be unable to fully protect public safety and health or to validate compliance with the CGMP regulation and, thus, an OTC company's ability to produce a quality product.

FDA's lack of full access to OTC drug manufacturers' records and files denies the agency a critical source of information on the nature and scope of postmarketing problems associated with OTC drug products. In addition, this lack of full access limits FDA's ability to evaluate the effectiveness of the manufacturers' efforts to analyze complaints, remedy problems, and generally produce a safe and effective product. In effect, the current situation hinders FDA from fully carrying out its mandate to protect the public health and to provide reasonable assurance of the safety and effectiveness of OTC drugs.

Postmarketing Surveillance

Our research indicates that FDA obtains only limited information on the postmarketing performance of OTC drugs in comparison with that available on prescription drugs. This lack of postmarketing information is exacerbated in the case of OTC drugs subject to the monograph process. Monograph-controlled OTC drugs represent the majority of all OTC drugs, yet they are the category of drugs for which FDA's postmarketing surveillance system provides the least amount of information. (See appendix I.) FDA does not require manufacturers of OTC monograph drugs to report adverse reactions experienced by their customers.

Additionally, FDA does not know, and is unable to determine, the number of OTC products currently being marketed in the United States.[17] FDA requires manufacturing firms to notify FDA of the products it markets.[18] However, in 1986, FDA assigned a low priority to maintenance of the OTC product listing files.[19] Without information on the number of OTC products marketed, FDA is unable to evaluate the relative magnitude of any identified problem with an OTC product and, in addition, does not know how many OTC products are being marketed in therapeutic categories that still lack finalized monographs. The net effect is that FDA is unaware of (1) the number of individual OTC products currently being marketed and (2) whether these products are safe and effective as determined by any type of FDA review.

Agency Comments

As requested by your office, we did not obtain formal agency comments. However, we received and incorporated as we deemed appropriate comments by responsible agency officials on earlier versions of this report.

As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its date of issue. At that time, we will make copies available to interested organizations, as appropriate, and to others upon request.

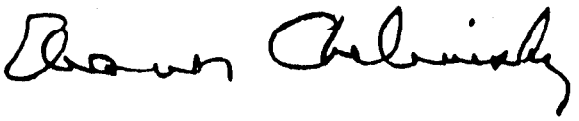
[17] We found the same problem in April 1982 and recommended that the Secretary of Health and Human Services "...establish for each category of drug product a complete master list of firms manufacturing the drug and a list of the products as they are identified for each monograph." See FDA's Approach to Reviewing Over-the-Counter Drugs Is Reasonable, But Progress Is Slow, GAO/HRD-82-41 (Washington, D.C.: April 1982), p. iv.

[18] A drug product is more specific than the brand. For example, 100-count bottles of 250 milligram tablets and 100-count bottles of 500 milligram tablets of aspirin made by one manufacturer would be considered by FDA as two products. Likewise, a manufacturer's 100-count bottles of 250 milligram capsules and 100-count bottles of 250 milligram tablets of aspirin would be considered two products.

[19] According to an FDA official, the agency has since changed that policy. However, OTC manufacturers have been slow to comply with the listing requirement.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Kwai-Cheung Chan, Director of Program Evaluation in Physical Systems Areas, at (202) 275-3092. Other major contributors to this report are listed in appendix II.

Sincerely yours,



Eleanor Chelimsky
Assistant Comptroller General

Application of FDA Regulatory Component by Marketing Status

Regulatory component	Marketing status		
	Prescription	OTC NDA	Monograph
Premarket approval			
Clinical trials	Yes	Yes	No
FDA review	Yes	Yes	No
FDA approval	Yes	Yes	No
Product quality assurance			
CGMP	Yes	Yes	Yes
Access to complaint files	Yes	No	No
Postmarketing surveillance			
Listing file	Yes	Yes	Yes
Registration file	Yes	Yes	Yes
National drug code	Yes	Yes	Yes
Manufacturer drug distribution reports	Yes	No	No
Prescription reports	Yes	No	No
Drug Quality Reporting System	Yes	Yes	Yes
Adverse Drug Reaction reports	Yes	Yes	No
Consumer complaints	Yes	Yes	Yes
Pharmaceutical literature	Yes	Yes	No
NDA field alerts	Yes	Yes	No
Advertising	Yes	No	No
Label review	Yes	Yes	Yes
Product changes	Yes	Yes	No

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