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## Testimony

Before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, U. S. House of Representatives

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For Release on Delivery  
Expected at 10:00 a.m.  
September 12, 1996

# PRESCRIPTION DRUGS

## Implications of Drug Labeling and Off-Label Use

Statement of Sarah F. Jagger  
Director of Health Services Quality and Public Health Issues  
Health, Education, and Human Services Division



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Mr. Chairman and Members of the Subcommittee:

We are pleased to appear before you this morning to discuss the general area of off-label drug use and the more specific problem off-label use poses for drug promotion and advertising. This area is critically important in ensuring the quality of health care, controlling expenditures, and maintaining a viable pharmaceutical industry.

My statement will set this important policy issue in context, by covering four points: (1) what “off-label” use is; (2) the existing evidence on the prevalence and nature of off-label use; (3) the dilemmas posed by off-label use, including the question of whether or not to allow promotion for off-label uses; and (4) two general approaches for how these dilemmas may be resolved.

My comments today are based on our study of off-label drug use among physicians who specialize in cancer care that was published in 1991 and on new analyses of FDA performance that we conducted expressly for this hearing.<sup>1</sup>

In sum, we found that off-label use is a prevalent phenomenon that has presented different problems for policy-makers at different times. As it stands now, the problem is that the drug industry feels overly constrained by labels in its ability to promote its products. This problem can be solved either by relying on sources in addition to the label to define appropriate promotion or by making improvements in the process for updating the label. These two options are not necessarily mutually exclusive and both have benefits and drawbacks.

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## Drug Labeling and Off-Label Drug Use

Amendments to the Federal Food, Drug, and Cosmetic (FD&C) Act of 1962 mandated that FDA evaluate the safety and effectiveness of all new drugs. Before marketing a new drug in the United States, the manufacturer (also called the “sponsor”) must obtain approval from FDA by specifying both the medical conditions the drug is effective against and the patients groups for whom the drug has been shown to be effective. This information is contained in the proposed “label” submitted by the sponsor. It is the sponsor’s responsibility to assemble all the evidence that would support the uses proposed in the label.

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<sup>1</sup>U.S. General Accounting Office, *Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies*, GAO/PEMD-91-14 (Washington, D.C.: September 1991).

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When FDA reviews the sponsor's evidence for the drug's safety and efficacy, it does so primarily for the conditions specified in the sponsor's proposed label. Therefore, when FDA "approves" a new drug application, this approval identifies only the uses for which the manufacturer has demonstrated to FDA's satisfaction substantial evidence of safety and effectiveness.

If, after FDA has approved a drug, evidence arises of its safety and effectiveness in treating conditions or patient groups other than those named in the label, then the drug's manufacturer (or any other interested party) can submit a new application to have the label changed. This application, known as an "efficacy supplement," is similar to the original application in that it must contain evidence demonstrating to FDA's satisfaction that the product is both safe and effective for the treatment of the new condition. If FDA agrees with the sponsor's claims in the supplemental application, the agency changes the label to reflect the expanded use that the applicant has requested. Physicians use a drug "off-label" when they prescribe an FDA-approved drug for treatments other than those specified on the label.<sup>2</sup> According to FDA,

"the legislative history of the FD&C Act indicates that the Congress did not intend FDA to interfere with the practice of medicine. Thus, once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed on the FDA-approved labeling."<sup>3</sup>

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## Patterns of Off-Label Drug Use

The evidence on the extent and types of off-label drug use has not been extensive. Almost a decade ago, a University of Washington Family Medicare Center study found that off-label use was relatively rare: only 46 drugs of the 500 that were evaluated were being used in an off-label context. However, assertions by a group representing community cancer care centers presented a very different picture.<sup>4</sup> In 1989, in an effort to document the amount and types of off-label use, we initiated a study of drug-prescribing patterns among cancer specialists. By examining the drugs oncologists prescribed for specific types of cancer, we determined

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<sup>2</sup>Other terms used to describe the use of medical products for conditions other than those specified on the label include "unapproved," "unlabeled," or "extra-label" use.

<sup>3</sup>Statement by William B. Schultz, Deputy Commissioner for Policy, FDA, before the Committee on Labor and Human Resources, United States Senate, February 22, 1996.

<sup>4</sup>Throughout the late 1980s, the Association of Community Cancer Centers issued a series of reports saying that off-label use was prevalent among its participating institutions.

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that one third of all drugs they administered were used off-label. Further, of the 46 approved anticancer drugs and hormonal agents prescribed by oncologists at the time, 44 were prescribed at least once to treat an off-label indication. Perhaps most significant was our finding that more than half of the cancer patients (56 percent) were prescribed at least one drug off-label as part of their chemotherapy regimen.

The extent to which off-label use is prevalent in all areas of medicine is not clear. However, there is evidence that it is even more common within AIDS care than for cancer. In a study published earlier this year, researchers from California reported that more than 80 percent of AIDS patients received at least one drug off-label as part of their treatment and that 40 percent of all drugs that were given were provided off-label.<sup>5</sup> Further, it is generally acknowledged that off-label use is also extensive for pediatric populations.<sup>6</sup> This may well stem from a hesitancy to conduct medical experiments on children. Even if these were the only areas where off-label use was common, the number of patients affected would be considerable.<sup>7</sup>

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## Problems Posed by Off-Label Drug Use

While it may appear to be problematic that many physicians prescribe medications for conditions for which there has been no official determination of safety and benefit, off-label use is not necessarily inappropriate. In fact, a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease. This seemingly anomalous situation can arise when research conducted subsequent to FDA approval shows the drug's effectiveness in treating other conditions, yet the label remains unrevised.<sup>8</sup> For example, this occurred with some frequency in the cancer area where drugs that had been approved for one form of cancer were subsequently shown to have efficacy against other cancers, yet the label remained unchanged.

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<sup>5</sup>Carol L. Brosgart et al., "Off-Label Use in Human Immunodeficiency Virus Disease," *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 12:1 (May 1, 1996), 56-62.

<sup>6</sup>The American Academy of Pediatrics claims that 80 percent of drugs administered to children are given off-label. The latest evidence supporting this claim was recently published: Leona Cuttler et al., "Short Stature and Growth Hormone Therapy," *Journal of the American Medical Association*, 276:7 (August 21, 1996), 531-37.

<sup>7</sup>For example, more than 1 million patients are diagnosed with cancer each year.

<sup>8</sup>Efficacious uses of the drug can remain off the label for a variety of reasons: (1) a supplemental application was not submitted; (2) FDA did not feel the evidence in the application was sufficient to warrant a change in the label; and (3) FDA is still reviewing the supplemental application.

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FDA acknowledges the potential benefits of off-label use. The agency has stated that “under certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice.”<sup>9</sup> FDA also recognizes that there are important off-label uses of approved drugs and that physicians need to have access to accurate information about these drugs. This being so, why does evidence of extensive off-label use present a problem?

Our analysis shows that the nature of potential problems associated with the drug label have changed. At the time we collected the data on off-label drug use (spring 1990), the primary concern was with reimbursement denials associated with off-label use. We found that denials made because the FDA label did not include the specific drug were certainly prevalent. More than half of all the cancer physicians we surveyed reported problems with reimbursement for off-label use, and most indicated that the problems had gotten worse in recent years. Most troubling was that many respondents said they altered what they believed to be optimal therapy in response to these reimbursement denials. In fact, 62 percent of physicians responding to our survey said that they had admitted to hospitals patients who did not require hospitalization solely as a way to circumvent problems with reimbursement denials.<sup>10</sup>

While reimbursement concerns were the primary ones associated with the drug label in the earlier part of this decade, this issue seems to have declined significantly since that time. This decline has been attributed to legislation in 1993 that required Medicare carriers to rely on sources in addition to the FDA-approved label in making reimbursement decisions for cancer therapy. Subsequently, the insurance industry generally followed suit. This is to say not that there are no longer any reimbursement problems with off-label drug use—just that they seem to be more isolated.

In recent years concern about the off-label use of drugs has resurfaced. This time the focus is on the limiting role the label plays in defining

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<sup>9</sup>Schultz, cited above.

<sup>10</sup>Reimbursement for a hospital stay is based on the condition for which the patient is admitted and not on the basis of which drugs are given.

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appropriate boundaries for drug promotion and advertising.<sup>11</sup> Although definitive evidence of a cause-and-effect relationship is difficult to obtain, the concern with promotion seems to have grown in direct relation to the increasing competitiveness of the market for pharmaceuticals. As changes in health care brought on by managed care and other attempts at cost containment have accelerated, pharmaceutical manufacturers have faced a more competitive environment. With increasing competition, it is in the interest of manufacturers to demonstrate as many benefits for their products as possible. The need to impress prospective clients of the value of drugs may be especially true with respect to pharmacoeconomic benefits, in which formulary managers are understandably interested.<sup>12</sup>

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## General Approaches to Address the Promotion Dilemma

Two approaches exist for resolving the dilemma of whether and how widely to allow promotion of off-label uses. One is to rely less on the label as the determinant of what can and cannot be said about a product. The other is to improve the process for updating drug labels.

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## Change Restrictions Associated With the Label

Under one approach, promotion could be based partially or entirely on any of a variety of other sources of information that are commonly accepted as reputable, such as the drug compendia and refereed journals. The Congress used this strategy for dealing with the previous off-label “crisis,” that of reimbursement denials. In the Omnibus Budget Reconciliation Act of 1993, the Congress defined the term “medically accepted indication” to include not only the conditions incorporated in the FDA-approved label but also uses

“supported by one or more citations which are included (or approved for inclusion) in one or more of the following compendia: the American Hospital Formulary Service—Drug Information, the American Medical Associations—Drug Evaluation, the United States Pharmacopeia—Drug Information, and other authoritative compendia as identified by the Secretary.”

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<sup>11</sup>The issue has alternatively been discussed as the desire to promote products more broadly and the need to inform physicians more fully about drugs. Physicians currently gain access to information about off-label uses through compendia, journal articles, continuing medical education programs, symposia, and professional meetings. They also have access to a number of databases that provide information about off-label uses. None of these sources of information is limited by what is contained on the FDA-approved label. Further, a manufacturer can supply physicians with information about off-label uses if the physician specifically requests such information. However, the manufacturer cannot provide information on off-label uses without such a request.

<sup>12</sup>A formulary is a list of drug products. The basic types are “open” formularies, which list the drugs that are recommended but do not restrict physicians in their prescribing behavior, and “closed” formularies, which specify the drugs that physicians can prescribe and, by omission, drugs that they cannot provide to patients.

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Further, reimbursement could also be based on supportive clinical evidence in peer-reviewed medical literature appearing in publications that have been identified by the Secretary of Health and Human Services. Legislation currently being considered (H.R. 3199) proposes a conceptually similar approach with respect to promotion of off-label drug uses.

This strategy has both benefits and limitations. The benefits are that (1) it avoids many of the costs needed to assemble a supplemental application for FDA approval and (2) it allows promotion earlier than would be likely if companies had to wait for FDA to approve an efficacy supplement.

However, relying on sources other than the label for defining appropriate promotion also has its drawbacks. Most importantly, in instances in the past, drugs that had been shown to be effective in research that was published in respected peer-reviewed journals were later found to be either ineffective or, in some cases, actually harmful for patients.

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## Change the Process for Updating the Label

Another approach to reducing the barriers to promotion faced by pharmaceutical companies is to encourage changes in the process for updating labels so that it is more timely and more reasonable in its demands for information. Expediting the review process for efficacy supplements would make the information on labels more reflective of the most current understanding of a drug's benefits, while modifying the information needed to obtain a supplemental approval, could well reduce the costs and disincentives of submitting an application for approval. A process that produced an up-to-date label would benefit all who sell, buy, prescribe, and use drugs.

Although there are benefits to changing the process, the Congress did not choose to do so in response to the problems created when insurers refused to reimburse for off-label uses. This may be the result of the perception that FDA takes an inordinate amount of time to process applications and is unwilling to adapt to an increasingly dynamic environment. Also, any demands that FDA reduce the amount of time it takes to make decisions might result in increased resources for the agency in an era of growing sensitivity about the costs of government.

However, since the time of our work on off-label drugs, much has changed at FDA. One change is that the agency has improved its performance in processing drug applications. In October 1995, we reported that the time

to reach decisions on new drug applications had declined by more than 40 percent.<sup>13</sup> In preparing for this hearing, we also looked at FDA's timeliness in responding to efficacy supplements. Our findings are shown in table 1.

**Table 1: Approval Times for Efficacy Supplements in Months, Fiscal Years 1993-95**

Year of submission	Number of submissions	Percent approved	Median approval time	Average approval time
1993	69	57%	18	19
1994	67	63	14	14
1995	48	71	12	12

As can be seen from the table, how long it takes for FDA to approve efficacy supplements has been reduced considerably. This improvement is consistent with that found for new drug applications and with the goals established under the Prescription Drug User Fee Act of 1992. Under this act, FDA is held accountable for rapid action on efficacy supplements in the same way that it is accountable for processing new drug applications. The user fee legislation has the added dimension of providing FDA with additional resources so that shorter action times become more realistic goals.

FDA has also made changes in the evidence necessary to obtain approval since the time of our off-label drug study. Largely in response to pressures from patient groups eager to have potentially life-saving drugs available as quickly as possible, FDA has instituted "accelerated approval," a means by which drugs can receive approval with considerably less evidence than was traditionally necessary. FDA has already made some changes in the evidence required for certain efficacy supplements and is considering more far-reaching changes.

Although the changes in FDA review time and in the evidence requested by the agency are promising indicators that labels will become more reflective of a drug's true benefit, the process of updating a label is a collaborative one that involves the sponsor of the application as well as FDA. Therefore, a major limitation of relying on changes in the way FDA reviews efficacy supplements as the solution to the off-label promotion problem is that the agency cannot act on drugs for which supplemental applications are not submitted. If companies remain hesitant to submit

<sup>13</sup>U.S. General Accounting Office, FDA Drug Approval: Review Time Has Decreased in Recent Years, GAO/PEMD-96-1 (Washington, D.C.: October 1996).

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supplemental applications, changes in the process at FDA would have little effect on the utility of the label.<sup>14</sup>

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Mr. Chairman, this concludes my statement. I would be happy to answer any questions that the Subcommittee might have.

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**For more information about this testimony, please call George Silberman, Assistant Director, at 202-512-9226. Other major contributors include Michele J. Orza and Thomas J. Laetz.**

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<sup>14</sup>For example, the expiration of a patent on a drug may well remove much of the incentive that a sponsor might have for incurring the costs of the research necessary to support an efficacy supplement for that drug.

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