Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

PRESCRIPTION DRUG ADVERTISEMENTS IN MEDICAL JOURNALS

Richard P. Kusserow
INSPECTOR GENERAL

JUNE 1992

OFFICE OF INSPECTOR GENERAL

The mission of the Office of Inspector General (OIG), as mandated by Public Law 95-452, as amended, is to protect the integrity of the Department of Health and Human Services' (HHS) programs as well as the health and welfare of beneficiaries served by those programs. This statutory mission is carried out through a nationwide network of audits, investigations, and inspections conducted by three OIG operating components: the Office of Audit Services, the Office of Investigations, and the Office of Evaluation and Inspections. The OIG also informs the Secretary of HHS of program, and management problems, and recommends courses to correct them.

OFFICE OF AUDIT SERVICES

The OIG's Office of Audit Services (OAS) provides all auditing services for HHS, either by conducting audits with its own audit resources or by overseeing audit work done by others. Audits examine the performance of HHS programs and/or its grantees and contractors in carrying out their respective responsibilities and are intended to provide independent assessments of HHS programs and operations in order to reduce waste, abuse, and mismanagement and to promote economy and efficiency throughout the Department.

OFFICE OF INVESTIGATIONS

The OIG's Office of Investigations (OI) conducts criminal, civil, and administrative investigations of allegations of wrongdoing in HHS programs or to HHS beneficiaries and of unjust enrichment by providers. The investigative efforts of OI lead to criminal convictions, administrative sanctions, or civil money penalties. The OI also oversees State Medicaid fraud control units which investigate and prosecute fraud and patient abuse in the Medicaid program.

OFFICE OF EVALUATION AND INSPECTIONS

The OIG's Office of Evaluation and Inspections (OEI) conducts short-term management and program evaluations (called inspections) that focus on issues of concern to the Department, the Congress, and the public. The findings and recommendations contained in these inspection reports generate rapid, accurate, and up-to-date information on the efficiency, vulnerability, and effectiveness of departmental programs.

This report was prepared in the Boston Regional Office under the direction of Regional Inspector General Mark R. Yessian, Ph.D., and Deputy Regional Inspector General Martha B. Kvaal. Project staff include:

David Veroff, *Project Leader*
David Schrag, *Analyst*
Michael Wilkes, M.D., *Consultant*
Bruce Doblin, M.D., *Consultant*
Martin Shapiro, M.D., *Consultant*
Penny Thompson, *Headquarters*
Mary Beth Clarke, *Headquarters*

To obtain a copy of this report, call the Boston Regional Office at (617) 565-1050.

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

PRESCRIPTION DRUG ADVERTISEMENTS IN MEDICAL JOURNALS

Richard P. Kusserow
INSPECTOR GENERAL

OEI-01-90-00482

EXECUTIVE SUMMARY

PURPOSE

The purpose of this study is to assess the accuracy, truthfulness, educational value, and quality of prescription drug advertisements in leading medical journals. It is intended to assist the Food and Drug Administration in its oversight of prescription drug advertisements.

Many researchers and marketing professionals have noted the substantial influence advertising has on prescribing decisions. Misleading pharmaceutical advertising has serious implications for society because it can lead to inappropriate prescribing.

BACKGROUND

In its obligation to help promote public health and to administer Medicare, Medicaid, and other health care programs, the Department of Health and Human Services has a broad responsibility for promoting the proper prescribing of medications. Through the Food and Drug Administration (FDA), it has a precise statutory mandate to oversee the truthfulness and accuracy of prescription drug advertising.

We focus in this report on evaluating the overall quality of prescription drug advertisements in leading medical journals. We also assess the educational value of the advertisements. Finally, we evaluate them in terms of criteria based on FDA regulations governing truth and accuracy in prescription drug advertising.

Our data were gathered by a group of Robert Wood Johnson clinical scholars at the University of California at Los Angeles. They recruited physicians and pharmacists to review the advertisements. The physicians have acted as peer reviewers for leading medical journals. The pharmacists have worked at medical centers with established and well-respected drug information programs and have been involved in educating physicians about prescription drugs. These expert reviewers were asked to complete a review form for each of two advertisements. The form allowed reviewers: to evaluate the acceptability of the advertisements for publication in leading journals using criteria similar to those used in reviewing scientific articles; to judge the educational value of the advertisements; and to evaluate specific aspects of the advertisements, such as images, claims, balance, and use of statistics, all of which relate to FDA guidelines and regulations. A total of 109 advertisements from early 1990 issues of leading medical journals were reviewed by 108 physician reviewers and 53 pharmacist reviewers.

We report results using advertisements as the unit of analysis, unless otherwise noted. To summarize the two or three reviews we had for each advertisement we use a majority rules criteria. In other words, we report opinions on which at least two reviewers agreed.

We have worked extensively with FDA in developing our findings and conclusions. The FDA has indicated to us its interest and concern in the issues presented in this report.

FINDINGS

The reviewers found many deficiencies with the prescription drug advertisements they reviewed.

- The reviewers noted the following major deficiencies: the advertisements lacked needed references and information on efficacy, appropriate populations, safety, and side effects or contraindications.

- The reviewers rated 60 percent of the advertisements poor or unacceptable in terms of scientific references.

- Using criteria similar to those used for reviewing scientific articles, the reviewers would have rejected for publication 17 percent of the advertisements and would have required major revisions for another 24 percent.

The reviewers rated half of the advertisements as having little or no educational value.

- The reviewers found that 50 percent of the advertisements had little or no educational value.

- The reviewers concluded that 59 percent of the advertisements would not lead to proper prescribing if the physician had no other information.

The reviewers frequently found the advertisements to be lacking in comparison to the principles stated in FDA regulations on prescription drug advertising.

- On average, the reviewers cited 4.3 examples of inadequate, misleading, or inappropriate information per advertisement. These examples indicate potential violations of FDA regulations.

- The reviewers frequently found the advertisements to be inadequate in the areas of presentation of side effect information, referencing, use of headlines, and presentation of comparative claims.

The FDA has used a variety of regulatory responses to remedy violations or correct misleading or false advertising, but it has rarely taken formal action against violators.

- After monitoring over 19,000 prescription drug advertisements in print media in fiscal year 1991, FDA took formal regulatory action against an advertiser 217 times. The FDA's actions consisted of issuing notice of violation and warning

letters and requesting that manufacturers publish corrective advertisements or send letters to pharmacists and physicians correcting advertisements.

- The FDA took formal legal action (injunction) against only two false or misleading advertisers since June 1991.

Although journal review prior to publication can improve the quality of published prescription drug advertising, many medical journals do not review the content of the advertisements they publish.

- Our reviewers rejected no advertisements in the one journal selected for our study that reviewed advertisements prior to publication.

- According to a survey of 221 medical journal editors, 37 percent of medical journals review advertising prior to publication and only 13 percent do any sort of peer review of advertising.

CONCLUSION

While the Public Health Service (PHS), through FDA, is the government agency responsible for oversight of prescription drug advertisements, it cannot alone assure their truthfulness and value. The pharmaceutical industry is first and foremost responsible for the quality of prescription drug advertising. Medical journals also have clear responsibilities in this regard. Below we offer several options to improve pharmaceutical advertising.

Options for improving pharmaceutical advertising:

- The Public Health Service (PHS), through FDA, could conduct periodic review of a sample of prescription drug advertisements in medical journals. It could use pharmacist and physician consultants to conduct the reviews.

- The PHS could seek congressional approval to strengthen FDA's authority to deal with violators of prescription drug advertising regulations. This could include authority to impose civil monetary penalties and to require violators to publish corrective or educational advertisements to remedy the violations.

- The Pharmaceutical Manufacturers Association could emphasize to its members the importance of accuracy and truthfulness in advertising and could assist them in improving procedures for reviewing advertisements prior to publication.

- Medical journals could identify specific ways to assure the truthfulness and accuracy of the pharmaceutical advertisements they publish.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

INTRODUCTION 1

FINDINGS 4

The reviewers found many deficiencies with the prescription drug advertisements they reviewed 4

The reviewers rated half of the advertisements as having little or no educational value. 5

The reviewers frequently found the advertisements to be lacking in comparison to the principles stated in FDA regulations on prescription drug advertising. 6

The FDA has used a variety of regulatory responses to remedy violations or correct misleading or false advertising, but it has rarely taken formal action against violators. 8

Although journal review can improve the quality of published prescription drug advertising, many medical journals do not review the content of the advertisements they publish. 10

CONCLUSION 11

APPENDIX A
Methodology A-1

APPENDIX B
Deficiencies noted by reviewers in advertisements not acceptable in their published form B-1

APPENDIX C
FDA prescription drug advertisement regulations C-1

APPENDIX D
Reviewers' opinions of prescription drug advertisements: adherence to FDA regulations D-1

APPENDIX E
Notes E-1

INTRODUCTION

PURPOSE

The purpose of this study is to assess the accuracy, truthfulness, educational value, and quality of prescription drug advertisements in leading medical journals. It is intended to assist the Food and Drug Administration in its oversight of prescription drug advertisements.

Many researchers and marketing professionals have noted the substantial influence advertising has on prescribing decisions. Misleading pharmaceutical advertising has serious implications for society because it can lead to inappropriate prescribing.

BACKGROUND

Inappropriate prescribing can cause deaths, illnesses, and injuries, and can add to the overall health care bill of the United States.[1] Physicians frequently learn about medications from information supplied by drug companies. Particularly in the case of new products, journal advertising has become the most readily available and succinct source of information for physicians.[2] In one study, Avorn and Soumerai found that physicians were unable to distinguish between information they received from drug advertising and that obtained from a journal text.[3] Because physicians have limited formal education in pharmacology,[4] their reliance on advertising as an information source is particularly important.

In its obligation to help promote public health and to administer Medicare, Medicaid, and other health care programs, the Department of Health and Human Services has a broad responsibility for promoting the proper prescribing of medications. Through the Food and Drug Administration (FDA), it has a precise statutory mandate to oversee the truthfulness and accuracy of prescription drug advertising.[5]

Many researchers and marketing professionals have noted the influence advertising has on prescribing decisions. In a 1977 article, Smith cited numerous studies that measured the effect of journal advertising on prescribing decisions. The evidence was mixed.[6] However, many studies done since 1977 bolster the evidence that advertising affects prescribing decisions. For example, a 1989 study sponsored by the Association of Independent Medical Publications and five pharmaceutical manufacturers addressed the issue of whether journal advertising increases market shares. The study concluded that an effective sales theme will raise a product's share of new prescriptions in a predictable way.[7] Avorn and colleagues showed that doctors believed in the superiority of two heavily promoted drugs over alternative forms of therapy, despite overwhelming scientific evidence to the contrary. They concluded that these doctors must have been relying on promotional information (such as journal advertising) rather than scientific material in forming their opinions.[8]

The very fact that pharmaceutical companies commit huge sums of money to advertising further speaks to its effectiveness in changing medication use. It is unlikely that given the deep understanding pharmaceutical manufacturers have of the market for prescription drugs, they would spend such large amounts on ineffective advertising.[9]

The Food and Drug Administration (FDA) is charged with regulating promotion of prescription drugs. It has the authority to penalize pharmaceutical manufacturers who sponsor false or misleading advertisements through criminal and civil actions. It can also use its influence to alter or cancel inappropriate advertising. But until recently, FDA's Division of Drug Marketing, Advertising, and Communication[10] had a staff of less than 10 full-time professionals to review tens of thousands of advertisements in medical journals and promotional activities.[11] One FDA official estimated that this scarcity of resources made it possible to act on only about five percent of the advertisements that are false or misleading.[12] In response to these problems, the Commissioner of FDA has focused much attention on prescription drug advertising and promotion, and has doubled the staff for the division.[13]

Our objective is to discover the level of inaccurate, low quality, or otherwise unsuitable prescription drug advertising in medical journals. We evaluate advertisements in three general areas: (1) whether there were major deficiencies with the advertisements; (2) the educational value of the advertisements; and (3) whether the advertisements appear to adhere to FDA regulations concerning false and misleading advertising. In addition, we describe current responses to false or misleading advertising. We conclude with suggestions for the Public Health Service (including FDA) and others on how to improve regulatory and other responses to false and misleading advertising.

We have worked extensively with FDA in developing our findings and conclusions. The FDA has indicated to us its interest and concern in the issues presented in this report.

METHODS

This project was conceptualized and designed by a group of Robert Wood Johnson clinical scholars at the University of California at Los Angeles (UCLA) working under contract for us. They gathered assessments of prescription drug advertising and presented the results to us. They enrolled physicians who had acted as peer reviewers for medical journals as well as pharmacists who had been involved in physician education about pharmaceutical drugs to review the advertisements. A total of 161 reviewers participated in the study, 108 of whom were physicians and 53 of whom were pharmacists. Each reviewer was asked to complete a review form for each of two advertisements. The form allowed reviewers: to evaluate the acceptability of the advertisements for publication in leading journals using criteria similar to those used in reviewing scientific articles; to judge the educational value of the advertisements; and to evaluate specific aspects of the advertisements, such as images, claims, balance, and use of statistics, all of which relate to FDA guidelines and regulations.

Our instrument led each reviewer through 30 specific statements about the advertisement with which they could agree or disagree. It then asked the reviewers to rate the quality of the advertisement on four criteria. The instrument then asked the reviewers to rate how much educational value, rather than promotional value the advertisement had. Each reviewer was then asked what his or her overall suggestion to a journal editor of a leading medical journal would be regarding publication using review criteria similar to those used in reviewing a scientific article. If the reviewer felt the advertisement needed to be revised or rejected the advertisement, he or she was asked what deficiencies the advertisement had.

The UCLA researchers selected all advertisements in early 1990 editions of 10 leading peer-reviewed medical journals for inclusion in the study.[14] After eliminating duplicates, they were able to evaluate 109 pharmaceutical advertisements. In addition to the advertisements themselves, they provided each reviewer with all the available references cited in the advertisements. Their intent was to have two physician-reviewers and one pharmacist-reviewer evaluate each advertisement. They accomplished that goal for 84 percent of the advertisements. For 15 percent, they received 2 reviews and for 1 advertisement, they received 1 review. A total of 309 reviews were conducted.

We report results using advertisements as the unit of analysis, unless otherwise noted. To summarize the two or three reviews we had for each advertisement we use a majority rules criteria. In other words, we report opinions on which at least two reviewers agreed. Appendix A provides detail on the methods used and on the credentials and demographic profiles of the reviewers.

In addition to the reviews of the advertisements, we used literature, interviews, and other data gathered from research for another Office of Inspector General report. That report was the first of three (of which this is the third) which discuss prescription drug promotion. Entitled "Promotion of Prescription Drugs through Payments and Gifts" (OEI-01-90-00480), it was released in August 1991. The second report, released in draft in March 1992, presents the results of a national survey of physicians on prescription drug promotion practices involving payments and gifts. It is entitled "Promotion of Prescription Drugs through Payments and Gifts: Physicians' Perspectives" (OEI-01-90-00481).

Our review was conducted in accordance with the *Interim Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

FINDINGS

The reviewers found many deficiencies with the prescription drug advertisements they reviewed.

- The reviewers noted the following major deficiencies: the advertisements lacked needed references and information on efficacy, appropriate populations, safety, and side effects or contraindications.

For 53 percent of the 109 advertisements reviewed, two or more of the reviewers agreed[15] that the advertisement lacked information on efficacy; for 50 percent, that the advertisement lacked needed references; for 40 percent, that the advertisement lacked information on appropriate populations; for 38 percent, that the advertisement lacked information on safety; and for 28 percent, that the advertisement lacked information on side effects or contraindications. Table 1 lists all the deficiencies mentioned and the percentage of advertisements in which the reviewers agreed revisions were needed to correct them.

TABLE 1

Deficiencies in Advertisements in Leading Medical Journal

Deficiency Type	Percent of Advertisements on Which Two or More Reviewers Agreed on the Deficiency (N=109 advertisements)[16]
Lacked information on efficacy	53
Lacked needed references	50
Lacked information on appropriate populations	40
Lacked information on safety	38
Lacked information on side effects and contraindications	28
Contained misleading statements in the text	14
Contained misleading images	7
Contained misleading references	5
Contained misleading graphs or tables	5
Other correction needed	4

Source: OIG/UCLA Solicited Assessments of Medical Journal Advertisements, Winter 1991

- The reviewers rated 60 percent of the advertisements poor or unacceptable in terms of scientific references.

In addition to asking our reviewers to decide what deficiencies advertisements had, we asked them to evaluate each advertisement's overall quality in terms of four criteria: factual accuracy, scientific references, clarity, and honesty of claims. The advertisements were generally poorly rated on scientific references, with the reviewers agreeing that 60 percent of the advertisements were poor or unacceptable on this measure. On factual accuracy, clarity, and honesty of claims, the advertisements fared better, but still 18 percent of the advertisements were rated poor or unacceptable on accuracy, 16 percent poor or unacceptable on honesty of claims, and 12 percent poor or unacceptable on clarity.

- Using criteria similar to those used for reviewing scientific articles, the reviewers would have rejected for publication 17 percent of the advertisements and would have required major revisions for another 24 percent.

We asked each reviewer to evaluate whether he or she would have accepted the advertisement for publication, accepted it contingent upon minor revisions, accepted it contingent upon major revisions, or rejected it. The reviewers were asked to use criteria consistent with those they would use for a scientific article. The reviewers agreed that 17 percent of the 109 advertisements would have been rejected, 24 percent would have required major revision, 26 percent would have required minor revision, and only 3 percent would have been accepted without change (figure 1).[17] The reviewers did not agree on 31 percent of the advertisements. For the 34 advertisements on which there was no agreement, we used reviews as the unit of analysis and similar patterns emerged.[18]

These ratings are validated by the deficiencies cited by the reviewers. Deficiencies were proportionally more prevalent when the reviewers judged that the advertisement required major revision or rejected the advertisement. Appendix B shows this in detail.

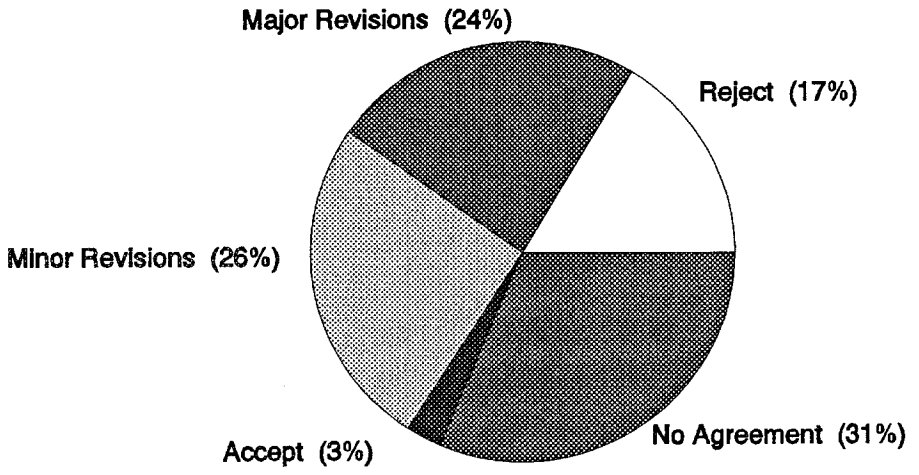
The reviewers rated half of the advertisements as having little or no educational value.

- The reviewers found that 50 percent of the advertisements had little or no educational value.

We asked our reviewers to evaluate each advertisement on the basis of how much educational value, as opposed to promotional value, the advertisement had. For only one advertisement did two or more reviewers agree the advertisement had a great deal of educational value. For 21 percent of the 109 advertisements, the reviewers agreed that the advertisement had some educational value; for 38 percent, the reviewers agreed the advertisement had little educational value, and for 12 percent of the advertisements, the reviewers agreed the advertisement had no educational value (figure 2). The reviewers did not agree on 28 percent of the advertisements.

FIGURE 1

Acceptability of Prescription Drug Advertisments in Medical Journals



Source: OIG/UCLA Solicited Assessments of Medical Journal Advertisements, Winter 1991.

- The reviewers concluded that 59 percent of the advertisements would not lead to proper prescribing if the physician had no other information.

According to several studies, advertisements are a primary source of prescribing information for physicians, particularly for new drugs.[19] As a secondary measure of the educational value of the advertisement, we asked the reviewers whether the advertisement would lead to proper prescribing if a physician had no other information about the medication. The reviewers found that 59 percent of the advertisements would not lead physicians to proper prescribing, while 35 percent would. There was no agreement on six percent of the advertisements.

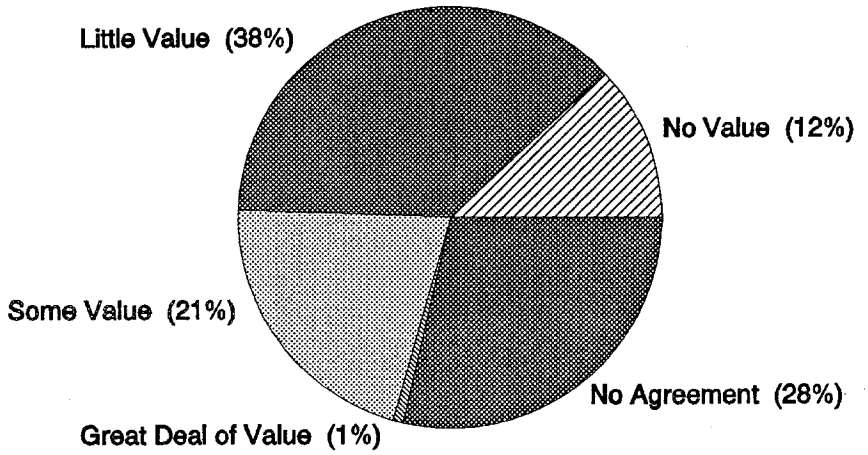
The reviewers frequently found the advertisements to be lacking in comparison to the principles stated in FDA regulations on prescription drug advertising.

- On average, the reviewers cited 4.3 examples of inadequate, misleading, or inappropriate information per advertisement. These examples indicate potential violations of FDA regulations.

The FDA regulations specify that prescription drug advertisements must make a "true statement" of information. The FDA has two basic criteria for this statement: 1) the advertisement must present a fair balance between information on side effects and

FIGURE 2

Educational Value of Prescription Drug Advertisements



Source: OIG/UCLA Solicited Assessments of Medical Journal Advertisements, Winter 1991

contraindications and information on the effectiveness of the drug, and 2) the advertisement must not be false or misleading with respect to side effects, contraindications, or effectiveness. The FDA regulations specify 33 criteria for judging whether an advertisement makes a "true statement." Twenty of these criteria indicate that an advertisement **is** false, lacking in fair balance, or otherwise misleading, while 13 criteria indicate that an advertisement **may** be false, unbalanced, or misleading. These 33 criteria are summarized in appendix C. Our questions walked the reviewers through statements related to these guidelines, asking them to evaluate the advertisements based on the statements. While our reviewers made determinations based on their own scientific knowledge and not on FDA law or FDA-approved labeling, the questions allowed our reviewers to cite specific examples of *potential* violations of FDA regulations. The FDA bases its determinations of *actual* violations only on comparisons to approved labeling.[20]

On average, the reviewers cited 4.3 specific examples of potential violations of FDA regulations per advertisement.[21] For 92 percent of the advertisements, two or more reviewers answered in agreement on at least one of our questions indicating a potential violation of FDA's guidelines. For 38 percent, our reviewers cited five or more examples of potential violations. For 7 of the 109 advertisements, our reviewers cited more than ten examples.

- The reviewers frequently found the advertisements to be inadequate in the areas of presentation of side effect information, referencing, use of headlines, and presentation of comparative claims.

We asked reviewers to respond to a series of statements about each advertisement they were reviewing. For each question, we analyzed data only for advertisements on which at least two reviewers responded.

For 58 percent of the 85 advertisements for which at least two reviewers responded to the question, the reviewers agreed that images minimized concerns about, or awareness of, side effects or adverse drug reactions. For 57 percent of the 95 applicable[22] advertisements, the reviewers agreed that information presented on side effects and contraindications was not comparable in prominence and readability to information presented on effectiveness. The reviewers agreed that the headlines were not adequately supported by the references given for 48 percent of the 64 applicable advertisements. For 47 percent of the 49 applicable advertisements, the reviewers found that the advertisement did not appropriately highlight side effects and contraindications in special patient populations. The reviewers found that the headlines were not supported by the written text for 42 percent of the 92 applicable advertisements. For 40 percent of the 104 applicable advertisements, the reviewers agreed that the advertisement did not present a fair balance between information on efficacy and on side effects and contraindications. The reviewers disagreed with a claim about the drug being more effective than another for 39 percent of the 23 applicable advertisements. Appendix D summarizes reviewers' opinions relating to FDA guidelines.

The FDA has used a variety of regulatory responses to remedy violations or correct misleading or false advertising, but it has rarely taken formal action against violators.

- After monitoring over 19,000 prescription drug advertisements in print media in fiscal year 1991, FDA took formal regulatory action against an advertiser 217 times. The FDA's actions consisted of issuing notice of violation and warning letters and requesting that manufacturers publish corrective advertisements or send letters to pharmacists and physicians correcting advertisements.

The FDA Division of Drug Marketing, Advertising, and Communication's small staff monitored 19,161 advertisements in print media in FY 1991 (October 1990-September 1991).[23] The division chose to review 227 advertisements in more depth.[24] The FDA identified most of the advertisements to review through complaints from outside parties, including physicians, consumer groups, and other pharmaceutical manufacturers.[25]

The FDA's formal regulatory action takes several forms. The FDA can issue two levels of letters. One is a notice of violation letter, which specifies how an advertisement is in violation of FDA guidelines and proposes or demands a remedy.[26] This is usually sent if more informal means fail to induce the

manufacturer to withdraw or alter the advertisement. A more severe step is a warning letter,[27] which notifies the advertiser it should take remedial or corrective action and warns of impending legal action if the advertisement is not revoked. This letter is more strongly worded than the other and is released publicly. The FDA can request two types of remedial or corrective action. It can ask the manufacturer (1) to send a letter to physicians and pharmacists explaining how the advertisement was false, unbalanced, or misleading, or (2) to publish advertisements in the publications in which the original advertisements appeared that correct the faulty information. Manufacturers almost always comply because they wish to maintain positive relationships with FDA. Recently FDA has requested repeat offenders to submit advertising and promotional material prior to public release.[28]

The FDA sent 215 letters in FY 1991 -- 211 notices of violation and 4 warning letters. It requested corrective or remedial action twice -- both times with "Dear Doctor" letters.

The FDA's efforts resulted in 39 advertisements being canceled by the manufacturers in FY 1991.

- The FDA took formal legal action (injunction) against only two false or misleading advertisers since June 1991.

The FDA can take a range of civil and criminal actions against violative advertisers. Possible criminal penalties include prison terms of up to three years and fines of up to $10,000. In addition, FDA can seize the firm's products or file an injunction against the manufacturer to force it to stop the violative action.

The FDA did not begin the process of taking legal action against any violator in FY 1989 or 1990.[29] It had not successfully prosecuted a violative drug advertiser in 23 years.[30] However, in June 1991, FDA successfully filed an injunction against ICN Corporation, prohibiting promotion of its drugs for unapproved uses.[31] In October 1991, FDA also successfully filed an injunction against Syntex Laboratories in reaction to misleading promotion of Naprosyn® (naproxen). Syntex signed a decree of permanent injunction agreeing to a massive remedial campaign to correct the misleading claims the company made in promotional material and print advertising.[32]

The FDA's reluctance to prosecute a drug company may have to do with the difficulty of proving criminal intent. If criminal intent is not proven, there is only a slim chance that a conviction will result in imprisonment, especially if no injury or death is linked to the advertisement. Seizure is not pursued apparently because FDA is concerned it might seize a medically useful product.[33]

Personnel at FDA, however, have indicated an intent to pursue legal action more actively against violators. Last year, the acting Director of FDA's Division of Drug Marketing, Advertising, and Communications told pharmaceutical executives, "Prepare

yourselves for much more serious penalties. All traditional methods--seizures, injunctions, prosecutions--as well as preclearance" will be considered.[34]

Although journal review prior to publication can improve the quality of published prescription drug advertising, many medical journals do not review the content of the advertisements they publish.

- Our reviewers rejected no advertisements in the one journal selected for our study that reviewed advertisements prior to publication.

Only one of the 10 journals selected for our study reviewed the advertisements prior to publication.[35] None of the advertisements in this journal on which reviewers' judgements agreed were rejected. In comparison, the other journals had an average rejection rate of 19 percent.[36]

- According to a survey of 221 medical journal editors, 37 percent of medical journals review advertising prior to publication and only 13 percent do any sort of peer review of advertising.

In a recent study, researchers found from a survey of 221 medical journal editors that only 37 percent of journals use editorial staff to review prescription drug advertisements. In addition, peer review of advertising is conducted by 13 percent of the journals.[37]

Only 32 percent of the journal editors in the survey agreed with a statement that medical journals should be responsible for the truthfulness of prescription drug advertisements in their journals.

CONCLUSION

Our review looks at the overall quality, truthfulness, accuracy, and educational value of prescription drug advertisements in leading medical journals from the perspective of highly respected clinical reviewers. The sharp criticisms these reviewers made, based on criteria relevant to prescribers' interpretations of advertisements, indicate significant problems with prescription drug advertisements and their potential effects on prescribing. While the Public Health Service (PHS), through FDA, is the government agency responsible for oversight of prescription drug advertisements, it cannot alone assure their truthfulness and value. The pharmaceutical industry is first and foremost responsible for the quality of prescription drug advertising. Medical journals also have clear responsibilities in this regard. Below we offer several options to strengthen pharmaceutical advertising.

OPTIONS

The Public Health Service (PHS), through FDA, could conduct periodic review of a sample of prescription drug advertisements in medical journals. It could use pharmacist and physician consultants to conduct the reviews.

Although FDA has recently increased the staff allocated to review prescription drug advertising, it is still not likely to be able to review prescription drug advertisements adequately. The volume of advertisements is simply too large. But if FDA were able to solicit the expertise of physician and pharmacist reviewers, it could at the very least identify advertisements needing more detailed review.

Furthermore, this group of reviewers would give FDA the advantage of having prescribers' perspectives on drug advertisements. This unique viewpoint would be helpful in validating claims of impropriety and would certainly bolster legal efforts.

Finally, educating physicians and pharmacists who act as reviewers in FDA regulations and having them carefully evaluate prescription drug advertisements would make them much more aware of the potential problems with advertisements. Since physician and pharmacist reviewers could potentially be important and respected leaders in the clinical community, their increased awareness could encourage others to be more attentive to the limitations of advertising.

The PHS could seek congressional approval to strengthen FDA's authority to deal with violators of prescription drug advertising regulations. This could include authority to impose civil monetary penalties and to require violators to publish corrective or educational advertisements to remedy the violations.

Civil Monetary Penalties. Although FDA has used regulatory means to change and cancel advertisements they have found to be in violation, these means are effective only after advertisements have been published. These means do not appear to have

acted as significant deterrents to keep some pharmaceutical companies from publishing false or misleading advertising. Currently available legal and civil actions have rarely been taken and thus likely are not seen as a deterrent. Many violators of FDA regulations who are cited by FDA are not penalized.

The PHS might benefit from having a new tool to deter and punish violative advertisers. The currently available legal actions can be either too difficult to pursue or inappropriately matched to the violations. The possibility of proving criminal intent in the case of false or misleading advertising seems remote. On the other hand, seizure of a company's product seems ill matched to the offense. A company may have a fine product which has been inappropriately advertised; if FDA seized the product, it could negatively affect the public health.

Civil monetary penalty (CMP) authority would allow PHS to pursue financial damages suits against violative pharmaceutical manufacturers without having to prove criminal intent. Substantial CMPs could help deter pharmaceutical companies from producing false and misleading advertising.

Authority to Require Corrective or Educational Advertisements. Although FDA has occasionally requested that advertisers publish corrective or educational advertisements to remedy violations, pharmaceutical companies do not have to comply with the requests. The authority to **require** publication of corrective or educational advertisements would allow FDA to assure that violators of their regulations, at the very least, produce information that corrects false or misleading advertisements. It could also deter advertisers from producing improper advertisements.

The Pharmaceutical Manufacturers Association (PMA) could emphasize to its members the importance of accuracy and truthfulness in advertising and could assist them in improving procedures for review of advertisements prior to publication.

As we stated earlier, the pharmaceutical industry is first and foremost responsible for the quality of prescription drug advertising. It is important for the PMA to make clear to its members how vital the quality of advertisements is to the medical community and to the credibility of pharmaceutical manufacturers.

Individual manufacturers' procedures for reviewing advertisements prior to publication may vary significantly. The PMA could help coordinate information about how best to conduct pre-publication review. For example, they could foster communication among companies through panels, seminars, and newsletters.

Medical journals could identify specific ways to assure the truthfulness and accuracy of the pharmaceutical advertisements they publish.

Studies have shown that prescription drug advertisements have some influence on physicians' prescribing decisions. In this study, our expert reviewers found that advertisements in leading medical journals are often misleading, inaccurate, and

incomplete. It is, therefore, possible that prescription drug advertising in medical journals is responsible for some inappropriate prescribing of medications.

Medical journals, which play important roles in informing and educating physicians, should guard against this possibility. These journals, which devote considerable effort to scrutinizing the adequacy of articles submitted for publication, could similarly review the content of advertisements.

Assuming responsibility for advertising content raises some difficulties for medical journals.[38] Yet this role is one that some journals already are performing and that many others can perform without an extensive commitment of resources.[39] We suggest that the leadership of medical journals address the issue and identify specific ways in which their journals can best review the prescription drug advertisements they receive.

APPENDIX A

Methodology

Selection of Advertisements

We selected advertisements from 10 peer-reviewed medical journals. Nine were specialty medical journals and one was a general medical journal. The specialty journals were *American Journal of Psychiatry, Annals of Emergency Medicine, Annals of Internal Medicine, Annals of Surgery, Archives of Neurology, Archives of Surgery, Journal of Family Practice, Obstetrics and Gynecology,* and *Pediatrics*. The general medical journal was the *New England Journal of Medicine*. For each journal, we used the first issue of 1990 (with the exception of the *Annals of Surgery* for which copies of the second issue were obtained, because original copies of the first issue were unavailable).

From each journal, we selected all pharmaceutical drug advertisements of at least one page length. If identical advertisements appeared more than once in the 10 journal issues, duplicate advertisements were eliminated. If a drug product had two different advertisements, then both remained in the study. We finally selected 109 unique advertisements as our sample. We then attempted to obtain all material referenced in each advertisement. When references were not available in the Regional National Library of Medicine Reference Library, we contacted the pharmaceutical manufacturer and requested reprints. Of the 149 references cited in the advertisements, we were able to obtain copies of 64 percent. The process by which we attempted to obtain references was thorough and exhaustive, but many of the references were made to unpublished papers, confidential reports, or studies from journals that could not be obtained. Requests to the manufacturers were returned with written comments claiming that the reference was confidential or that they could not find it in their files.[40]

Physician Reviewers

The editors of three specialty journals provided us with lists of experienced peer reviewers who covered the range of medical expertise required for this study. These journals were the *Archives of General Psychiatry, Annals of Internal Medicine*, and *Obstetrics and Gynecology*. We sent the nominated peer reviewers a cover letter describing the study and asking whether they wished to participate. We enclosed a letter from the editor of the journal for which they were the reviewer, encouraging them to participate. We then systematically telephoned the nominated until 125 agreed to act as reviewers. Only about 15 percent of those contacted declined to participate. We sent 113 of these physicians (91 percent) advertisements to review, basing their selection on areas of expertise. For example, infectious disease specialists reviewed only antibiotic advertisements, and psychiatrists reviewed only psychiatric medicines. This constituted a sample large enough to send each advertisement to two

physician reviewers, while sending each reviewer two advertisements. Of the 113 physicians we asked to act as reviewers, 96 percent or 108 returned reviews. Table A-1 lists the characteristics of the physician reviewers.

Clinical Pharmacist Reviewers

We contacted seven university medical centers with established and well-respected drug information programs (two from Connecticut and five from California). The director of each program was informed about the research project and asked to participate in the study by providing a list of experienced clinical pharmacists at their institution who were involved in physician education concerning pharmaceuticals. All seven programs agreed to participate and supplied the names of 54 clinical pharmacists. Of those contacted, 100 percent agreed to participate in this study. Each clinical pharmacist was asked to review two advertisements. Of the 54 clinical pharmacists we asked to act as reviewers, 98 percent or 53 returned reviews. Table A-1 lists the characteristics of the pharmacist reviewers.

Instrument

Our instrument lead the reviewers through 30 specific statements regarding the advertisements. Twenty-eight of these related to FDA regulations, while one related to whether or not the advertisement was offensive and one asked whether the advertisement would lead to proper prescribing if it were the only source of information about the drug. Reviewers were asked whether they strongly agreed, somewhat agreed, somewhat disagreed, or strongly disagreed with the statement. Depending on the statement, agreement either meant the reviewer thought the advertisement was in violation with an aspect of the FDA regulations or it was not. For example, one statement was "This advertisement presents a fair balance between information relating to efficacy and to side effects/contraindications." If the reviewer agreed with the statement, he or she was saying that the advertisement was not in violation of an FDA regulation on fair balance. However, another statement was, "This advertisement uses statistics derived from inconclusive, dissimilar, or poorly designed studies." If the reviewer agreed with this statement, he or she was citing an example of a violation of an FDA regulation. While our reviewers made determinations based on their own scientific knowledge and not on FDA law or FDA-approved labeling, the questions allowed our reviewers to cite specific examples of *potential* violations of FDA regulations. The FDA bases its determinations of *actual* violations only on comparisons to approved labeling. Appendix C summarizes all of the statements relating to FDA regulations, as well as the reviewers' assessments about these statements.

In addition to these statements, reviewers were asked to rate the overall quality of advertisements regarding several criteria: factual accuracy, scientific references, clarity, and honesty of claims. They were asked to use a scale of 1 to 5 with one being unacceptable and 5 being excellent to make these ratings.

They were also asked to rate how much educational value, rather than promotional value, the advertisement has on a scale of 1 to 4 with 1 being none and 4 being a great deal.

Finally, each reviewer was asked what his or her overall suggestion to a journal editor of a leading medical journal would be regarding publication using review criteria for a scientific article. The reviewer was asked whether he or she would accept the advertisement in its present form, accept it contingent upon minor revisions, accept it contingent upon major revisions or reject it. He or she was then asked what revisions were necessary.

Analysis of Data

Most of the analyses are presented in terms of percentage of advertisements. We usually reported only about advertisements which at least two reviewers evaluated. Except when noted, we reported only opinions agreed on by at least two reviewers. When there were three reviews for the advertisement, it was possible that we reported an opinion that only two of the three reviewers agreed on. When there were only two reviews for the advertisement, both of the reviewers had to agree. We call this technique the majority rules criteria. In some cases, the percentage of advertisements on which no agreement was reached is a relevant statistic. In these cases, we report this also.

When summarizing the questions on FDA regulations, we grouped the strongly agree and somewhat agree categories into an agree category and the strongly disagree and somewhat disagree categories into a disagree category.

To evaluate the pattern of responses, we assessed agreement within one category on the question about acceptability. For each group of reviewers, we compared agreement with one category on the four category reject/major revisions/minor revisions/accept scale (e.g. if one reviewer recommended rejection, the other reviewer agreed within one category if he or she recommended rejection or major revision). The concordance rates among reviewers, using pairwise kappas were fair to good: 0.68, 0.56 and 0.52 for each of the 3 reviewer pairs in advertisements with three reviewers.

TABLE A-1

Characteristics of Physician and Pharmacist Reviewers

Characteristic	Physicians (n=108)	Pharmacists (n=53)
Age (mean ± standard deviation)	52 ± 10	34 ± 6
Sex (percent male)	98%	51%
Academic rank (physicians only):		
Lecturer	2%	-
Assistant Professor	10%	-
Associate Professor	19%	-
Professor	56%	-
Other Academic	12%	-
Highest degree in pharmacy:		
Doctorate	-	75%
Masters	-	6%
Bachelor	-	19%
Articles authored in peer-reviewed journal in past three years (mean ± standard deviation)	15 ± 16	2 ± 3
Articles peer-reviewed in past three years (mean ± standard deviation)	11 ± 4	0
Percentage who received payments from pharmaceutical manufacturers in the past two years	71%	26%
Less than $200	3%	23%
More than $5000	53%	0%

Source: OIG/UCLA Records on Physician and Pharmacist Reviewers, Winter 1991

APPENDIX B

Deficiencies Noted by Reviewers in Advertisements
Not Acceptable in Their Published Form

Deficiency Type	Advertisements for Which at Least One Reviewer Recommended Minor Revisions, Major Revisions, or Rejection (N=104 advertisements)	Advertisements for Which at Least One Reviewer Recommended Major Revisions or Rejection (N=59 advertisements)	Advertisements for Which at Least One Reviewer Recommended Rejection (N=24 advertisements)
Lacked information on efficacy	60%	75%	71%
Lacked needed references	54%	56%	71%
Lacked information on appropriate populations	43%	59%	87%
Lacked information on safety	38%	47%	71%
Lacked information on side effects and contraindications	28%	36%	42%
Contained misleading statements in the text	14%	24%	33%
Contained misleading images	7%	12%	12%
Contained misleading references	5%	8%	4%
Contained misleading graphs or tables	4%	7%	8%
Other correction needed	4%	2%	0%

Note: Figures are percent of advertisements on which two or more reviewers cited the listed deficiency

Source: OIG/UCLA Solicited Assessments of Medical Journal Advertisements, Winter 1991

APPENDIX C

FDA Prescription Drug Advertisement Regulations

Advertisements that are false, lacking in fair balance, or otherwise misleading:

1. contain statements of being "better, more effective, useful in a broader range of conditions, safer, having fewer side effects" that have not been demonstrated adequately;

2. contain claims comparing to another drug that have not been demonstrated adequately;

3. contain information or opinions that are not in agreement with current scientific knowledge;

4. contain claims of safety that have not been demonstrated adequately;

5. present information from a study in a way that implies the study is more representative than it really is;

6. use references that do not adequately control for concomitant therapy or placebo effect;

7. contain information from nonclinical studies in a way that suggests the information is from clinical studies;

8. contain a statement from a recognized authority that has been superseded by other statements or information from the same authority;

9. use a quote or paraphrase out of context to convey a false or misleading idea;

10. use information that purports to support a claim, but in fact does not;

11. promote the drug for an unapproved use;

12. offer a combination of drugs as treatment when one of the drugs in the combination adequately treats the condition;

13. use a study based on healthy subjects when the treatment is not for healthy individuals;

14. use statistics based on pooled data from inconclusive studies;

15. use "no statistically significant difference" to demonstrate that two therapies are similarly effective;

16. use statements that the drug differs from or does not contain another drug to misleadingly represent that the advertised drug is safer or more effective than another drug;

17. use data from studies that provide subjects with dosages of the drug that are different than those recommended in labeling;

18. use headline, subheadline, or pictorial or other graphic matter in a way that is misleading;

19. represent that because drug dosages are proper for certain types of patients they are safe for other types of patients; and

20. lump together specific side effects into one general condition.

Advertisements that may be false, lacking in fair balance, or otherwise misleading:

21. contain information from an inadequate study;

22. use statistical significance to support a statement that is not clinically relevant or significant;

23. use analyses of data to cite findings not supported by the study;

24. use graphs or tables to distort relationships, trends, and so on;

25. use reports claiming to be using sound scientific methods but do not;

26. contain claims related to the mechanism or site of drug action that are contrary to established scientific evidence;

27. fail to give sufficient emphasis to information on side effects and contraindications in comparison to claims of effectiveness;

28. fail to present information on side effects and contraindications with a prominence and readability comparable to information on effectiveness;

29. fail to provide adequate emphasis for the fact that two facing pages are part of the same advertisement;

30. in promotion directed to a certain class of patients, fail to adequately emphasize specific side effects for that class of patients;

31. fail to present on a page facing another page (or on another full page) of an advertisement on more than one page, information relating to side effects and contraindications when such information is in a distinct part of the advertisement;

32. fail to provide information or at least a reference that information is on another page on side effects and contraindications; and

33. contain information from reports or opinions falsely or misleadingly represented or suggested to be authentic or authoritative.

Source: FDA Regulation, Part 202-Prescription Drug Advertisements - CFR 202.1(e)(6) and CFR 202.1(e)(7)

APPENDIX D

Reviewers' Opinions of Prescription Drug Advertisements:
Adherence to FDA Regulations

Statement	Number of Advertisements for Which At Least Two Reviewers Answered the Question	Number of Advertisements in Which At Least Two Reviewers Cited a Violation	Percentage of Advertisements in Which At Least Two Reviewers Cited a Violation
Claims:			
Drug is useful in a broad range of conditions or diseases	20	3	15%
Drug is effective in a broad range of patients	44	6	14%
Drug is "the drug of choice" for at least one condition	51	16	31%
Drug is more effective than another drug	23	9	39%
Drug is safe	59	4	7%
Use of Headlines:			
Promotes appropriate use of the drug	90	23	26%
Misleads the reader about efficacy	94	30	32%
Are supported by the written text of the advertisement	92	39	42%
Are adequately supported by the references given	64	31	48%
Misleads the reader about side effects and contraindications	95	18	19%
Use of Graphs and Tables:			
Misrepresent the conclusions of clinical studies	23	2	9%

Statement	Number of Advertisements for Which At Least Two Reviewers Answered the Question	Number of Advertisements in Which At Least Two Reviewers Cited a Violation	Percentage of Advertisements in Which At Least Two Reviewers Cited a Violation
Not adequately referenced	23	7	30%
Likely to lead the reader to a misleading conclusion	23	7	30%
Misleads the reader about efficacy	16	6	37%
Promotes appropriate use of the drug	16	4	25%
Supported by written text	16	1	6%
Citation of Studies and Use of Statistics:			
Statistics are derived from inconclusive, dissimilar, or poorly designed studies	27	8	30%
Uses "statistical significance" to support a claim that has not been demonstrated to have clinical relevance or validity	26	1	4%
Contains favorable information or conclusions from a study or studies that is/are adequate in design, scope, or methodology to justify its application in practice	39	11	28%
Makes claims based on studies whose subjects are substantially different from the population of patients for whom this advertisement is directed	55	7	13%

Statement	Number of Advertisements for Which At Least Two Reviewers Answered the Question	Number of Advertisements in Which At Least Two Reviewers Cited a Violation	Percentage of Advertisements in Which At Least Two Reviewers Cited a Violation
Images:			
Promote use in the appropriate populations	87	27	31%
Promote drug use in a manner consistent with the written text	90	19	21%
Minimize concerns about, or awareness of, side effects or adverse drug reactions	85	27	32%
Are used in a manner that misleads the reader about the efficacy of the drug	90	22	24%
Medical illustration is in agreement with current scientific knowledge	24	4	17%
Overall:			
Presents a fair balance between information on efficacy and on side effects/ contraindications	104	42	40%
Presents information on side effects and contraindications with a prominence and readability that is reasonably comparable to the presentation of information on effectiveness	95	54	57%
Appropriately highlights side effects and contraindications in special patient populations	49	23	47%

Source: OIG/UCLA Solicited Assessments of Medical Journal Advertisements, Winter 1991.

APPENDIX E

Notes

1. An October 1990 report by the majority staff of the U.S. Senate Special Committee on Aging presented evidence on the extent and sources of mismedication as well as the effects mismedication has on health care and its costs. The report listed physicians' prescribing errors as one of three major reasons for adverse drug reactions and cited studies that have estimated that up to 7.3 percent of prescriptions have potentially serious errors. The report noted that adverse drug reactions account for three to eight percent of all hospital admissions in the United States and may have accounted for $5 billion to $13 billion in hospital expenses in 1987.

2. See D. Christensen and A. Wertheimer, "Sources of Information and Influence on New Drug Prescribing among Physicians in an HMO," *Social Science and Medicine* 13A (1979): 313-322, and M. Peay and E. Peay, "Differences among Practitioners in Patterns of Preference for Information Sources in the Adoption of New Drugs," *Social Science and Medicine* 18, no. 12 (1984): 1019-1025. Both articles detail research that shows that physicians often receive the first news of a drug from advertising.

3. J. Avorn, and S.B. Soumerai, "Improving Drug-Therapy Decisions through Education Outreach: A Randomized Controlled Trial of Academically Based Detailing," *New England Journal of Medicine* 16, no. 308 (1983): 1457-1463.

4. B.R. Meyer and the Health and Public Policy Committee of the American College of Physicians, "Improving Medical Education in Therapeutics," *Annals of Internal Medicine* 108 (1988): 145-147.

5. Food, Drug, and Cosmetic Act, 21 U.S.C. 331, 352.

6. M.C. Smith, "Drug Product Advertising and Prescribing: A Review of the Evidence," *American Journal of Hospital Pharmacy* 34 (November 1977): 1208-1224.

7. Healthcare Communications, Inc., "The Effect of Journal Advertising on Market Shares of New Prescriptions," 1989.

8. J. Avorn, M. Chen, and R. Hartley, "Scientific versus Commercial Sources of Influence on the Prescribing Behavior of Physicians," *American Journal of Medicine* 73 (1982): 4-8.

9. It should be noted that some observers of the pharmaceutical industry have held a much more cynical view of why pharmaceutical manufacturers spend so much money on journal advertising, namely, that advertising dollars buy influence on the editorial content of medical journals. See M. Silverman and P.R. Lee, *Pills, Profits and Politics* (Berkeley: University of California Press, 1974), p. 56, and M. Wilkes and M. Shuchman, "Pitching Doctors," *New York Times Magazine*, November 5, 1989, p. 88.

10. Formerly known as the Division of Drug Advertising and Labeling.

11. The current acting Director of the division estimated that at the time the advertisements reviewed in our study were published, the division had only four full-time professionals reviewing advertisements.

12. P. Mansfield, "Drug Advertising," *Lancet,* May 20, 1989, p. 1137.

13. For examples of the commissioner's interest, see "Drug Advertising Regulatory Action by FDA Appears Likely: FDA Collecting Records on Repeat Offenders in Preparation for Setting Object Lesson," *F-D-C Reports*, February 18, 1991; p. 6, D.A. Kessler and W.L. Pines, "The Federal Regulation of Prescription Drug Advertising and Promotion," *Journal of the American Medical Association* 264, no. 18 (November 14, 1990): 2409-2415; and "FDA Must Clarify Promotion Rules--And Soon, Kessler Tells Kennedy," *PMA Newsletter* 33, no. 10 (March 11, 1991): 1.

14. *American Journal of Psychiatry, Annals of Emergency Medicine, Annals of Internal Medicine, Annals of Surgery, Archives of Neurology, Archives of Surgery, Journal of Family Practice, New England Journal of Medicine, Obstetrics and Gynecology*, and *Pediatrics*.

15. We used a majority rules criterion. If the advertisement was reviewed by three people and two agreed, that was the judgment we used. If the advertisement was reviewed by only two people, both had to agree on the judgment.

16. These figures represent conservative estimates of percent of advertisements with deficiencies, since for many advertisements there was not agreement. For example, for only 10 percent of the advertisements was there agreement that there was **not** a deficiency in the information presented on efficacy. For over 36 percent of the advertisements, two reviewers had different opinions about the advertisement on this point.

17. Some observers of the peer review process have noted the propensity of reviewers to find at least minor problems with almost all articles. It therefore may be wise to focus less on the minor revisions category as being meaningful. However, the large number of advertisements that would have required major revisions or would have been rejected should raise a great deal of concern.

18. In 28 percent of the reviews for these 34 advertisements, our experts favored rejecting the advertisement; in 32 percent of the reviews, major revisions were called for; in 28 percent, minor revisions were recommended; and in 12 percent, the experts favored acceptance without change.

19. Christensen and Wertheimer, "Sources of Information" and Peay and Peay "Differences among Practitioners".

20. Because our reviewers are not experts in FDA regulations, we do not know with certainty that the examples they cite are indeed violations. Furthermore, FDA, in practice, compares the claims and statements made in advertisements to approved labeling (package inserts). The criteria our reviewers were asked to use was often "current scientific knowledge." Although, in theory, approved labeling should be in agreement with current scientific knowledge, FDA officials assure us that labeling occasionally lags behind scientific knowledge. The FDA regulations specify that "advertisements cannot contain favorable information or opinions about a drug previously regarded as valid but which have been rendered invalid by contrary and more credible recent information" among other things. Our interpretation was that this implied advertisements should agree with current scientific knowledge, but examples of this type may not be cited by FDA as violations.

21. For each violation, at least two reviewers cited the example.

22. "Applicable" means that at least two reviewers responded to the question.

23. The FDA monitored 19,161 advertisements, but many of these were duplicates of one another (i.e. printed in more than one journal or more than one publication date of the same journal). The FDA actions are based on unique advertisements. We were not able to ascertain how many unique advertisements FDA monitored.

    The FDA has a number of methods it uses, both prior to and after a drug advertisement is published, to improve advertisements. These methods are informal efforts that usually require the cooperation of the sponsor of the advertisement. For example, it often sends letters to manufacturers giving them advisory opinions in response to a request to prescreen a proposed promotion; it did this 417 times in FY 1991. It also rendered advisory opinions in meetings and telephone conferences 158 times. The FDA reviewed introductory campaign materials 62 times in FY 1991. Occasionally (77 times in FY 1991), FDA will deliver informal ad critiques to manufacturers in response to complaints or a problem noted in an in-house review.

24. FDA files: FY 1991 Annual, Quarterly, and Monthly Report of Activities of the Division of Drug Marketing, Advertising, and Communication.

25. Conversation on September 5, 1990, with the acting director of the FDA's Division of Drug Advertising and Labeling.

26. D.A. Kessler and W.L. Pines, "The Federal Regulation of Prescription Drug Advertising and Promotion," *Journal of the American Medical Association* 264, no. 18 (November 14, 1990): 2409-2415.

27. Formerly, there were two stages of letters instead of warning letters. One was a notice of adverse findings letter, the other was a more severe measure, known as a regulatory letter.

28. Kessler and Pines, "Federal Regulation." In addition, FDA usually requires that manufacturers submit introductory campaign material prior to publication. The FDA believes that advertising is a prime source of information about new products and therefore new product advertising is more important to review than established product advertising.

29. Ibid. The authors note that "in recent years criminal cases have been pursued, though none to completion, and none has been disclosed publicly." It is also important to note that legal action generally requires the cooperation of the Department of Justice. Initiation of cases is not, therefore, the sole responsibility of FDA.

30. D.L. Breo, "Sidney Wolfe, MD--Healing the System or Just Raising Hell?" *Journal of the American Medical Association*, 266, no. 8 (August 28, 1991): 1133.

31. Personal communication with the Acting Director of FDA's Division of Drug Marketing, Advertising and Communications, October 16, 1991.

32. M. Gladwell, "Firm to Recant Drug Claims," *Washington Post*, October 11, 1991, A1, A4.

33. We conducted interviews with several lawyers specializing in FDA law for our report on "Prescription Drug Promotion Involving Payments and Gifts" (OEI-01-90-00480). At that time, we asked several questions about FDA enforcement activity. In addition, we conducted interviews with FDA officials who did not refute these statements.

34. "Tough Talk from Ann Witt, New FDA Drug Advertising Chief," *PMA Newsletter* 33, no. 19 (May 13, 1991): 1.

35. At the time our reviews were conducted only one journal (*Obstetrics and Gynecology*) reviewed advertisements according to the editors of the journals. At least one additional journal now conducts reviews of advertisements.

36. In addition, Wade et. al. (V.A. Wade, P.R. Mansfield, and P.J. McDonald, "Drug Marketing: Drug Companies' Evidence to Justify Advertising," *Lancet*

(November 25, 1989): 1261-1264.) have noted the positive effects physician review and interaction with pharmaceutical manufacturers can have on improving the quality of advertising. The Australian Medical Lobby for Appropriate Marketing reviews marketing material of pharmaceutical manufacturers and uses the influence of physicians to improve its quality.

37. Unpublished data from a study entitled, "Journal Editors and the News Media," conducted by M. Wilkes from UCLA.

38. Journal editors argue that reviewing editorial content of prescription drug advertising could lead to the perception of collusion between the editor and the advertiser. One writer has said that it would require "setting up an FDA for each journal." (D. Rennie, "Editors and Advertisements: What Responsibility Do Editors Have for the Advertisements in Their Journals?" *Journal of the American Medical Association* 265, no. 18 (May 8, 1991): 2394-2395.)

39. Our consultants conducted thorough peer reviews of advertising within a quick timeframe without many of the resources journal editors have (such as editorial staff, working procedures for handling peer review, and a peer review panel used to working with the journal). Although there was variability, the reviews in our study were conducted in an average of 20 minutes. Medical journals, unlike our consultants, have a ready source of experienced peer reviewers who could screen advertisements.

40. The written comments we received from manufacturers we sought references from include: "we have not been able to locate the study as yet. However, we believe it is a worthwhile study ... if you come across it please let us know," "The information is part of confidential research report of a study commissioned by us," and "unfortunately, the department which maintains these documents has been unable to locate the document."