

Stoning a Dead Bird: Advertising Limits on Approved New Drugs

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I. INTRODUCTION

Representative Ron Wyden (D-Ore.) recently questioned the Food and Drug Administration (FDA) on its policy of “censoring” scientifically credible information provided by manufacturers about unapproved uses of approved drugs. As summarized, the FDA responded that

distribution of scientific journal articles on unapproved uses of drugs “goes right to the heart of the efficacy standard.” Journal articles on off-label uses “are about the most powerful tool you can give the drug industry . . . if you allow the detailers to take that journal article into the physician’s office, you will make a major impact on unapproved uses.” Permissible use of such articles would discourage submission of supplements to FDA. And journal articles on unapproved uses “are often wrong.”¹

This article suggests that the FDA’s current policy is incorrect. A policy with controlled, but permitted, distribution of journal articles about approved products, and advertising based on such articles, would not undermine the efficacy standard but would strengthen it. Such a policy would not increase the ill-advised uses of approved new drugs, but rather would decrease them. Finally, new indication supplements would not be discouraged, because supplements rise or fall on whether an expanded market (for which there is adequate exclusivity) is economically sufficient to pay for the performance and submission of new data.

II. THE CURRENT IMPASSE

On November 27, 1992, the FDA published its long-awaited *Draft Policy Statement on Industry-Supported Scientific and Educational Activities*² on continuing medical education (CME) policy. The statement was intended to clarify an established non-enforcement policy that permits financial support for educational activities by a drug manufacturer even if the content goes beyond the approved labeling of the company’s products. Instead, the document became an assertion of the FDA’s jurisdiction over medical education.

In the policy statement, the FDA established the conditions under which industry may provide financial support for information transfers by and among scientists and

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¹*Off-Label Promotion Restrictions Should Focus on Direct Contact with Consumers, Representative Wyden Suggests at House Oversight Subcommittee Hearing*, F-D-C Rep. (“The Pink Sheet”), May 29, 1995 at 9 (reporting on *A Consumer’s Perspective on Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce* (May 25, 1995)).

² 57 Fed. Reg. 56,412 (Nov. 27, 1992).

physicians that discuss the off-label use of approved products. Among other restrictions, these conditions require that financing be at arm's length from the content, the manufacturer play only a passive role in suggesting speakers, support be disclosed, promotional materials are not placed in the same room, and support not include the supply of slides or drafting assistance. Additionally, the manufacturer must ensure that the content of the forum is scientifically sound, accompanied by provisos about accuracy, and fairly balanced. The program's content must be developed independent of the manufacturer's influence and the information provided must be accurate and balanced (two factors that may be mutually incompatible).

Following the submission of a citizen's petition³ on October 13, 1993, the Washington Legal Foundation (WLF) filed suit in early 1994 to contest the legality of the policy statement.⁴ In both the petition and lawsuit, WLF alleged that the FDA had acted beyond its statutory powers. On a motion to dismiss, the court held that the draft policy statement was challengeable as a final agency position.

On June 6, 1995, Representative Wyden introduced legislation that would permit drug advertising to include scientifically-valid reprints of articles about off-label use, provided that balancing information about the scientific basis also is supplied.⁵

III. WHY SHOULD CURRENT POLICY BE CHANGED?

Current FDA policy should be changed for a number of reasons. First, the logical underpinnings of the efficacy standard for product approval do not necessarily apply to approved product advertising. Second, the demand for off-label information ensures that the supply of such information cannot be proscribed effectively. Control rather than proscription provides a better means to ensure the satisfactory usage of such information. Third, significant changes in a large portion of the drug purchasing marketplace since 1962 make the current system of off-label information controls antiquated.

IV. A NEW POLICY

The FDA can simply and effectively bar the transmission of information on unapproved products because there is no demand for information about products that cannot be purchased. The FDA also can effectively exercise editorial control over the label, the package insert, and the brief summary. The Kefauver-Harris Drug Amendments of 1962⁶ intended these documents (which are based on adequate and well-controlled clinical studies) to act as the official and correct information about a drug.

Other forms of information transfer, however, cannot be controlled readily by government. As the agency's CME policy illustrates, when demand for off-label information exists, manufacturers will attempt to supply it. Furthermore, attempted proscription requires the expenditure of significant agency resources and continuous vigilance. As long as the demand for such information exists, and non-manufacturer sponsored speech about drugs is constitutionally protected, it will be impossible to proscribe the distribution of information that does not meet the efficacy standard.

³ See 59 Fed. Reg. 59,820 (Nov. 18, 1994) (public notice requesting comment on citizen's petition filed by the Washington Legal Foundation).

⁴ Washington Legal Foundation v. Kessler, Civ. No. 94-1306, mem. op. (D.D.C. Mar. 9, 1995).

⁵ FDA Modernization Act of 1995, H.R. 1742, 104th Cong., 1st Sess. (1995) (referred to House Comm., 141 CONG. REC. E1157 (June 6, 1995)).

⁶ Pub. L. No. 87-781, 76 Stat. 780 (1962).

The agency, therefore, could divide the information media that manufacturers use into two groups: those that are readily controllable (official media or labeling)⁷ and those that are less amenable to oversight (advertising). By distinguishing between the standards of evidence used for information presented in each of these two forms, and by requiring balancing information that directly informs the user of the lesser worth of off-label information, the FDA could create a distinction between labeling and advertising that would use the market system to ensure better utilization of off-label information.

The original purpose behind the creation of an “official” labeling document by Senator Kefauver was not to impose the same standard of evidence for all information conveyed by manufacturers.⁸ A policy that enunciates a clear distinction between labeling and advertising, and requires off-label advertising to contain warnings about underlying data quality and quantity, will serve to educate the physician community, reduce ill-advised off-label use, improve the clinical evaluation and use of off-label clinical data, and encourage the filing of supplements for new indications. Such a system would empower emerging intermediaries that oversee physician prescribing, (including formulary committees, managed care organizations (MCOs), pharmacy benefit management companies (PBMs), and pharmacy and therapeutics (P&T) committees) to become critical evaluators of off-label data.

Under this policy, advertising could use off-label information only when published in peer-reviewed journals and accompanied by a reference citation and balancing information. Balancing information would discuss critically the data quality or quantity. The worse the study design or the greater the poverty of data, the more critical the balancing information would be. In this case, control over advertising is self-enforcing. The worst information cannot be published in peer-reviewed journals. Furthermore, as data support decreases, the balancing critique becomes increasingly negative, and the manufacturer’s incentive to use the information decreases.

Medical journals could choose to peer review the articles that they receive. Peer review would be defined as the publication of articles only after examination and approval by a panel of appropriate medical experts and an independent biostatistician. The medical and biostatistical review would be directed to whether the study is scien-

⁷ Labeling refers to any written, graphic, or printed material that may be used by the purchaser or prescriber to understand the manufacturer’s intended use of the product.

⁸ See S. 1552, 87th Cong., 2d Sess. § 4(a)(7) (1960) (providing that manufacturers include in all advertising and labeling a “full, true, and correct statement of all findings of fact and determinations made by the Secretary” during product approval to serve as a brake on any unjustified claims); 107 CONG. REC. 5584, 5638-42 (Apr. 12, 1961). The companion bill was H.R. 6245. H.R. 6245, 87th Cong., 2d Sess. (1960). See also summary of S. 1552, reprinted in *Drug Industry Antitrust Act: Hearings on S. 1552 Before the Subcomm. on Antitrust and Monopolies of the Senate Comm. on the Judiciary*, 87th Cong., 1st Sess. 31 (July 5, 1961) (“It is only commonsense that the printed matter in the package may, and frequently does, contain essential cautionary information which is not shown in advertising material”). This “official summary” proposal was supported by the clinical and academic medical communities as well as by former Department of Health, Education, and Welfare Secretary Flemming. See *Hearings Before the Subcomm. on Antitrust and Monopoly of the Comm. on Judiciary Pursuant to S. 57*, 86th Cong., 1st Sess. 12,093 (1960) (statement of Secretary Flemming), 9321 (testimony of Dr. Kline), 12,042 (testimony of Dr. Moulton, FDA), 12,068 (testimony of Dr. King). Similar recommendations had resulted from oversight hearings of the House Committee on Governmental Operations in 1958. See H. REP. No. 2668, 86th Cong., 2d Sess. 4 (1958). This provision now is codified in the Federal Food, Drug, and Cosmetic Act at section 502(n), which provides that “all advertisements and other descriptive matter” contain a “brief summary relating to side effects, contraindications, and effectiveness” as required by the Secretary of Health and Human Services. 21 U.S.C. § 352(n) (1988). A provision requiring a short official summary of the basis for approval and expected side effects in all advertising makes little sense if the advertising may not make any statements that go beyond approved labeling.

tifically reasonable and appropriate, and whether the study design, data collection, selected patient entry and endpoint criteria, controls, and statistical analysis confirm that the article's conclusions are well-founded. The journal could require further documentation for suspicious data. Some journals might consider these controls overly burdensome or costly, but those that adopt these peer review requirements would benefit by being known as a source of quality information that could be used by drug advertisers. A definition of the substance of peer review ensures that published information meets a minimum standard.⁹

V. UNDERGROUND INFORMATION

Information is a commodity. Drug information can be acquired from three different sources: the manufacturer directly via promotion and labeling (currently limited to labeled information), academics not associated with the manufacturer, who can publish or make any statement, and manufacturers that succeed in facilitating the transfer of off-label information by concealing the source and using an underground information market. Neither of the latter two pathways is an economically efficient means of information transfer. The academic pathway is restricted in distribution, clarity of message, and intensity, which, in turn, depend on adequate financing and economic incentives. The underground pathway must be inefficient to remain undiscovered.

The underground market exists because a manufacturer has economic imperatives to provide any information about a product that will influence purchasing decisions favorably.¹⁰ This market for off-label information cannot be checked unless physicians make prescribing decisions based only on information that is of the same quality as required for approval in labeling. Numerous studies, however, have demonstrated that physicians make prescribing decisions on data that does not rise to the level of controlled clinical trials.¹¹ The underground information marketplace exists through CME meetings, symposiums, meetings at scientific assemblies, specially published journal supplements, articles published after company-sponsored research, newspapers that report on the latest journal publication, and Grand Rounds presentations. Physicians also independently disseminate information acquired through reading or technical discussions to their colleagues.

VI. MARKETPLACE CHANGES

There have been two basic developments in the marketplace. Neither is complete. They include a sharp shift in control over prescribing practices from individual physicians to the formularies and P&T committees of health insurers, MCOs, or hospitals; and the increasing vertical integration of drug manufacturer, distributor, and retail pharmacy.

⁹ See *contra* Draft Pharmaceutical Research & Manufacturers Association Legislative Proposal, reprinted in FDA WEEK, June 16, 1995, at 10-11.

¹⁰ G.J. Stigler, *The Economics of Information*, 69 J. POL. ECON. 213 (1961).

¹¹ See, e.g., F.A.A. Rogers et al., *Treatment of Myocardial Infarction in the United States (1990-1993): Observations from the National Registry of Myocardial Infarction*, 90 CIRCULATION 2103 (1994); 57 Fed. Reg. at 56,412 ("Two important sources of information on therapeutic products (human and animal drugs, biological products, and medical devices) for health professionals are (1) activities (programs and materials) produced by the companies that market the products [which are limited to approved labeling and based on controlled clinical trials] and (2) independent scientific and educational activities, such as continuing medical education."); Appendix I.

A. *Physician Consolidation*

Before 1962, most physicians' practices were financially-independent and unsupervised. In contrast, most physicians today have some form of ongoing, prospective supervision, if only because they admit patients to a Medicare-eligible hospital. Through both statutory changes and gradual changes in credentialing criteria established by the Joint Commission on Accreditation of Healthcare Organizations, Medicare has evolved to require chart review by outside physicians, hospital oversight of physicians, and quality assurance for physician services.¹²

Many physicians practice in even more highly constrained environments. These include university or research hospital faculty practices with an essentially merged clinical practice overseen by department or section heads; interdisciplinary group practices with a similar structure; physician managed hospital chains; multistate management companies that provide physician and management for such services as emergency medicine, anesthesia, or critical care; closed-shop MCOs; or prescribing restrictions from Medicaid formularies.

Formularies account for over fifty percent of what is prescribed today.¹³ When there are choices to make within a class of drugs with the same or similar indications, those choices frequently are not within the discretion of the individual physician.

B. *Vertical Integration in Drug Delivery*

The second development is the growth of PBMs and their subsequent purchase by drug manufacturers. PBMs develop formularies, sell those formularies to health insurers or MCOs, and then manage delivery of the covered drugs. Over fifty percent of prescriptions are covered now by health insurance.¹⁴ Incentives to comply with the formulary are managed through computerized systems located in virtually every pharmacy in the country. Patients or their physicians can be re-directed to generic or formulary products by the point-of-sale pharmacist twenty-four hours per day. Individual physicians can be targeted for education about the formulary.

Pharmaceutical manufacturers have purchased PBMs. This allows for formulary development and drug marketing within the same legal entity. Manufacturers that own PBMs may gain better or more sophisticated access to formulary P&T committees. The FDA recently advised the Federal Trade Commission (FTC) that it is concerned that vertical integration may permit "pharmaceutical companies [to] find new ways to circumvent . . . legal requirements."¹⁵ The FDA requested that the FTC consider means "to safeguard and clarify the marketing and communications aspect of these mergers."¹⁶

C. *Impact on Off-Label Drug Information Transfer*

¹² See, e.g., JOINT COMMISSION ON ACCREDITATION OF HEALTHCARE ORGANIZATIONS (JCAHO), ACCREDITATION MANUAL FOR HOSPITALS (1990) (Medical Staff Standards (MS.4, MS.5, MS.6) (concerning privilege delineation, reappointment and reappraisal, and monitoring and evaluation of practices) and Quality Assurance Standards (QA.3) (monitoring and evaluation)). The Medicare program functionally requires JCAHO accreditation first by defining hospitals eligible to receive Medicare funds (42 U.S.C. § 1395x(e)) and then by permitting any hospital to meet that definition through JCAHO accreditation (42 U.S.C. § 1395bb(a)).

¹³ Communication with Office of the Actuary, Health Care Financing Admin., Dep't of Health and Human Servs.

¹⁴ *Id.*

¹⁵ Letter from Mary Pendegast, Deputy Comm'r, FDA, to Donald Clark, Sec'y, FTC (Jan. 26, 1995).

¹⁶ *Id.*

Information transfers through the underground market has been made economically easier because both the seller and prescriber now are controlled by a small group of individuals who are sophisticated about drugs. Furthermore, information regarding the economic benefits to capitated insurance systems of using one product over another is readily available. The addition of off-label information, at request of the formulary or through discussions within the control group, is a simple next step. As a result, off-label drug information transfer is even less amenable to oversight than it was in the past. The ease with which information transfer can occur and that it can take place within a single corporate entity makes oversight impossible.

VII. A NEW ROLE FOR THE FDA

Since 1962, the FDA has been charged with ensuring that all information disseminated about drug products provided by the manufacturer is based on scientifically-sound data (adequate and well-controlled clinical trials). All information must be sufficiently balanced so that physicians are not misled about the significance of isolated pieces of data.

Harmful and misleading information still can be conveyed even with the protections afforded by a sophisticated purchasing community. It remains sound policy to have an impartial third party, the FDA, to review the content of the label and labeling for consistency with the underlying science, to audit the data submitted, and to approve the indications for use. Individual physicians often are not trained in the design and analysis of experiments, or do not have the time to perform such an evaluation, and thus can be misled by summaries of complex scientific information. A cursory review of almost any new or supplemental drug application demonstrates that claims are routinely submitted that are not adequately supported by the underlying data. Many initially suggested uses are found later to be useless or harmful.

There still is a need for data audit and review by an impartial scientific body. Not all persons who control prescribing practices are able to understand the clinical importance of relying on well-performed studies that have had their data audited. P&T and formulary committees also may be misled by unreliable data. Most continue to rely on the FDA's audit of data, and biostatistical and medical review of scientific data. Without sophisticated analysis, the raw data do not express clinical impact. Time, work, independence, and specialized training are required to interpret the data. The FDA remains the repository of functions that must be independent of manufacturer control to ensure the safe and effective use of drugs.

Careful data review also imparts a necessary delay between the time that useful and sound scientific data are available and the time that the information becomes directly useable in labeling. This delay, inherent in a system of burden-shifting, is made necessary by the difficulty of ascertaining whether statements are supported truthfully by scientific data.

The potential for rapid information transfer does not diminish the need for careful, time-consuming review. The partial marketplace development of integrated drug and information delivery systems, as well as more sophisticated purchaser intermediaries, does not make obsolete the impartial assessment of clinical data quality. The existence of an underground market in off-label information does not abjure the market from ensuring that there exists a body of information, found on the label, that has been vetted carefully. These developments do call, however, for a re-assessment of formulary and P&T committees' access to information, and the formal mechanisms by which manu-

facturers' safely could convey off-label information.

VIII. WHY THE PARADE OF HORRIBLES WILL NOT OCCUR

A. *Two Stones to Kill the Same Bird*

The efficacy standard, which limits acceptable scientific evidence to that based on adequate and well-controlled clinical trials, was part of the Drug Amendments of 1962.¹⁷ There is abundant scientific and economic evidence that decisions about the effectiveness of drug products based on a lesser data set frequently are erroneous. The testimony on poor utilization of scientific information about drugs presented at the Kefauver hearings makes cogent and compelling reading (*see* Appendix I).

The inability to discern errors in claims of effectiveness without the use of good clinical studies should be the enduring lesson of the Kefauver hearings (*see* Appendix I). As most recently stated by the Committee on Clinical Review established by FDA Commissioner David Kessler to evaluate device clinical data requirements:

In order to conclude that a change in a patient's status after an intervention is the result of that intervention, it must be presumed that the change would not have happened without the intervention. That presumption of what the patient would have experienced without intervention is, in fact, a control, albeit one not usually explicitly identified, and, as described later, one whose use is treacherous. . . . Implicit controls can be treacherous (the natural history of the disease may not be as constant as supposed). The impression that "everyone knows what happens to people with this disease" or "this never happens without intervention" is only as reliable as the data upon which it is based.¹⁸

The harms that Senator Kefauver identified as resulting from advertising, however, existed in a marketplace that did not require adequate and well-controlled trials to support any claim. The system now has changed. Claims reviewed for support under this standard of evidence can be separated from post-marketing claims that have not. The conclusion that clinicians should not base prescribing decisions on drugs inadequately studied for the safety and effectiveness of any claim, and therefore should not be exposed to any information about such products, does not apply to circumstances where a therapeutic claim has been supported, and carefully balanced information is provided about other claims.

Once a product is approved and a first claim substantiated, many things are known about the product (*see* Appendix II). A spokesperson for the agency recently stated that "[f]irst, we know that the drug has a benefit in a defined population, and we know something about the size of the benefit. Second, major common risks and their frequency are known or well estimated."¹⁹

Consideration should be given to the effect of cautioned claims made after a chemical entity's safety profile has been established for one indication and the initially hypothetical mechanistic theory of action has been confirmed in another setting. The balanced

¹⁷ Pub. L. No. 78-871, § 102(c), 76 Stat. at 781-82 (codified at 21 U.S.C. § 355(d) (1988)).

¹⁸ FOOD AND DRUG ADMIN., DHHS, FINAL REPORT OF THE COMM. FOR CLINICAL REVIEW 11, 15 (Mar. 1993) (based on a review of selected medical device applications) (emphasis in original).

¹⁹ Janet Woodcock, M.D., Statement at Conference on Comparing Treatments: Safety, Effectiveness, and Cost-Effectiveness 12 (Mar. 23, 1995).

presentation of such claims will not result in widespread adoption of unproved therapies.

Indeed, the opposite may be true. The current proscription on off-label promotion may facilitate rather than limit such practices because of the nature of the underground information marketplace. A comparison must be made between the present system with underground information transfer, and a system with controlled off-label promotion. For example, is it true that clinicians cannot properly evaluate a change in dosing strategy for tPA based on clinical experience, approved labeling, and advertising with cautionary provisos that is based on peer-reviewed publications? Would the net effect of physician decisions made in an environment of controlled and balanced off-label advertising be worse than the current effect of decisions made where the same information is inconsistently disseminated by the academic community or through anonymous forms of communication that lack the accompanying level of skepticism about information with the potential for bias or self-interest?

Is it reasonable to conclude that clinicians familiar with side effects and actions of various ACE inhibitors in hypertension, who use experience, an understanding of the differing clinically proven mechanisms of action, and scientific publications accompanied by the aforementioned provisos, would be worse at evaluating the use of the same commodity for unloading the pressure confronted by a weakened heart if they got the same information without the provisos through a different marketplace for information? Nothing suggests that this proposition is true because manufacturers currently are proscribed from educating physicians about the appropriate use of newer data on ACE inhibitors, and must use the underground information network to suggest such uses. Unless the competitive interests of the marketplace can discuss both off-label uses and relative data quality together, underground information may be more misleading.

The better the quality and penetration of information, the more likely it is that there will be limits on the widespread adoption of unproved therapies. Separating labeling from advertising and requiring warnings on advertising may provide for better information transfer. The current policy uses both marketing approval based only on controlled clinical data and the proscription of any advertising with lesser substantiation to prevent clinically unsubstantiated pre-1962 drug claims. Limiting market access to substantiated claims effectively deals with the problem. The same justification then should not be used to proscribe other claims about approved products.

B. More Efficient Use of Government Oversight

The proscription of off-label information dissemination by manufacturers creates a limitless need for enforcement resources. There are not enough FDA investigators to ensure that company agents are not making off-label promotions. A shift from proscription to control, however, would permit the agency to craft a system that does not require additional FDA enforcement resources.

C. Advertising as an Educational Tool About Data Quality

The transfer of controlled, critically balanced off-label information empowers the clinical community to be cautious. The source of information is identified. Physicians receive both a balanced analysis of the data, and the benefits of the skepticism that attends economically-driven advertising. In contrast, a ban on information neither empowers the clinician nor imparts a responsibility to be critical. Furthermore, the more

inadequate the supporting scientific data is, the more damaging the accompanying critical analysis is, and the less likely it will be that a manufacturer will be interested in the dissemination of such information. Currently, the only disincentive to disseminate off-label information is discovery by the FDA and the eventual embarrassing public withdrawal of the information.

D. Supplement Enhancement

The FDA contends that proscription of off-label advertising “provides an incentive for performing the necessary clinical studies to put additional claims on the label.”²⁰ Applications for supplemental indications, however, are filed when the expected growth in the product’s market would compensate the company for the expense of data collection, including clinical studies and filing costs. The expected growth may include an assessment of the ability to control the new market, based on either patent protection or the marketing exclusivity that is provided for new clinical trials.²¹ A quantification of the expected growth compares the increase in market from direct advertising to the gain from using alternative information transfer. The true comparison is between the effect of the two alternative forms of information transfer: advertising with provisos, or the use of the underground market without provisos or source identification. If the current underground system is better at market creation than future off-label direct marketing constrained by balancing information, then the incentive to perform clinical trials and file supplements would increase after a change in policy. Both probably are sufficient to establish a market when a new indication is limited to a few practitioners, academic centers, or a patient population served by a narrow medical community (such as exists for cancer chemotherapy). When the potential market is large, however, requiring the alternative information to contain warnings about data quality may impede market saturation in intermediate markets and increase incentives for filing a supplement.

Permission to engage in off-label promotion as balanced by critical information also liberates competitors to critique the data foundation used to promote the new use. A competitor’s ability to critique directly the quality of data supporting an extended indication also may discourage inappropriate drug prescribing and increase supplements filing.

Manufacturers seek supplemental indications based on anticipated market size and the best way to reach that market, rather than on whether the FDA has evaluated and audited the relevant underlying clinical data. The changing market shares of various thrombolytic agents over the years following the reports of multicenter clinical trials illustrates the ineffectiveness of current FDA controls.

E. Level Playing Fields

The agency also contends that controls on off-label promotion “provides a level playing field for competitors and establishes rules for the types of claims they are permitted to make about their product.”²² Proscription, however, provides less enforceable rules than the controlled dissemination of some off-label information and, therefore, less of a level playing field. Companies that use the underground market and escape

²⁰ *Id.* at 15.

²¹ 21 U.S.C. § 355(c)(3)(D)(v) (1988).

²² Woodcock, *supra* note 19, at 15.

detection, are not following the same rules as companies that do not use an underground market, thus necessitating a new set of reasonable and universally enforceable rules that will provide a better and more level playing field.

IX. DEPARTMENTAL INCONSISTENCY

Under the Medicare program, the Health Care Financing Administration provides reimbursement for certain drugs based on acceptance within the medical community as demonstrated through peer reviewed scientific publications.²³ A change in FDA policy on off-label promotion based on peer-reviewed data would thus harmonize departmental policy and provide guidance as to the substantive meaning of peer review.

X. CONCLUSION

The role of the FDA in drug advertising should be modified to accommodate marketplace changes: more sophisticated buyers and sellers; a growing underground market in information; and the distinction between approval of a new drug, and the use of that approval information and other clinical and scientific information to understand uses in other medical conditions. The FDA's role should remain the review of data for product approval and supplemental applications; oversight of advertising should be shifted to identifying when physicians are being appropriately educated via dissemination of off-label information about the differences between off-label and approved label scientific support. The FDA thus can use the medical and managed care communities to ensure the safe and effective use of pharmaceuticals and information that does not meet the efficacy standard.

APPENDIX I

Adequately controlled comparisons of these drugs [various steroids] are almost impossible to find. By adequately controlled comparisons I mean trials in which a group of patients has been randomly allocated without bias to one of two preparations and then again without bias insofar as this is possible in trying to achieve equal therapeutic effects and keeping track of the incidence of side effects. As I say, these kind of comparisons are almost impossible to find.

* * *

If one were to truly compare two steroids for side effects let us say, to make the question simple, one would have to take a group of patients, let us say with rheumatoid arthritis, and it would have to be a sizable group of patients. One would have to, by a flip of the coin, assign a patient either to one steroid or the other. One would have to administer that particular steroid to that particular patient for a period of time, and assuming that these particular doses that had been picked achieved equal therapeutic effects, one could then compare the side effects. Since this is almost never done in this field, it is very hard to say that adequate comparisons have actually been achieved. All one can do is look at what I would call

²³ 42 U.S.C. § 1395x(t)(2) (1988).

uncontrolled trials available in the literature, and try to come to some feeling for the incidence of side effects.

Testimony of Dr. Louis Lasagna, *Hearings Before the Subcomm. on Antitrust and Monopoly of the Comm. on Judiciary Pursuant to S. 57*, 86th Cong., 1st Sess. 8139, 8156 (1959) [hereinafter *1959-60 Hearings on Drug Marketing Practices*].

Meprobamate is most often prescribed for the treatment of anxiety or tension in the patient seen in the doctor's office, and there have been numerous reports of impressive results from such use of the drug. But according to the Johns Hopkins investigators, most of the studies were so poorly conducted that no valid conclusions can be drawn from their data. The few studies that were adequately controlled raise a question as to whether meprobamate in smaller doses has much more effect than a placebo in relieving anxiety and tension, though the larger doses used with institutionalized patients clearly did have an effect.

1 MEDICAL LETTER reprinted in *1959-60 Hearings on Drug Marketing Practices*, app. exhibit 122, at 9507. The 1994 edition of the *Physician's Desk Reference* also notes that the "effectiveness of 'Miltown' in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies." PHYSICIAN'S DESK REFERENCE 2478 (4th ed. 1994).

This is, I think, well recognized by most investigators. They try to back away as far as they can. They have got what they call the double blindfold method of testing, so that a blank pill and an action pill are given under certain circumstances when neither the physician nor the patient knows when he is getting an active substance or something that is not active. Then after the results are in, the doctor finds out which way the patient reacted. Did this drug in fact produce the effect or was the effect nearly as good as with inert material?

Testimony of Dr. William Bean, Chmn., Dep't Medicine, Iowa State Univ., *1959-60 Hearings on Drug Marketing Practices* at 10,341-42.

But let me turn to the practice which forms the backbone of all advertising and promotion of drugs. This is the use of the testimonial as scientific evidence of the efficacy of drugs. . . . Since the beginning of time men have stumbled over the meaning of the simple fact that when something is done for or to a person, especially if that something has magical or emotional significance, that person frequently feels better. . . . Since the dawn of time men have stumbled over the error of attributing to various agents the ability to ward off or to cure disease without taking into account what happens to those who do not get the benefit of the agent. This practice was not abandoned in the Middle Ages and one need examine only any current medical journal to find examples of it masquerading as science.

Since the committee has had adequate exposure to the controlled study, the double blind, and the placebo, I shall not take the time to expand on this. This incidentally, would require a statement at least as long as this.

Let me emphasize that no drug study is foolproof, but that the scientific validity of any study can be immeasurably increased by proper experimental design. A drug

trial which makes no allowance for placebo effect, and which fails to make accurate comparison with an untreated group is suspect, and the vast majority of reports on such studies are simply testimonials, not scientific evidence. . . . Yet the claims for the efficacy of an amazing number of modern drug products are based exclusively on this type of evidence.

Testimony of A. Dale Console, M.D., *1959-60 Hearings on Drug Marketing Practices* at 10,371-72.

At the moment, new drug applications need include only clinical evaluations of an inexpert sort rapidly performed.

* * *

In my opinion, none of the currently submitted files that I have seen would allow the kind of judgment as to efficacy that I think would be useful. I think it would require that the drug be studied longer and to a greater extent before it was submitted to the Food and Drug Administration.

Testimony of Frederick Meyers, M.D., *1959-60 Hearings on Drug Marketing Practices* at 10,402, 10,406.

From the comments made, it was quite obvious that there are few actual clinical indications for combined therapy based on controlled clinical observation. . . . It was also the feeling that evidence of synergism and delay of resistance in other infections is largely theoretical based on laboratory data not confirmed clinically. . . . This important distinction has been ignored in much of your promotional literature, and this undoubtedly motivated much of the criticism which came out of the meetings. We would like to know what you propose to do in the future to correct this situation.

Letter from Charles N. Lewis, M.D., Chief, Antibiotic Branch, FDA, to Howard Hedger, Chas. Pfizer & Co., *reprinted in 1959-60 Hearings on Drug Marketing Practices* at 12,011.

See also testimony of Haskell Weinstein, M.D., *1959-60 Hearings on Drug Marketing Practices* at 10,254 (“definitive efficacy studies” as a requirement for approval; “[a]dvertising standards must be clearly established and enforced”).

Throughout the course of the drug investigation medical authorities criticized the FDA for failure to require adequate clinical testing of new drugs prior to clearance for marketing; for failure to act when new evidence reveals significant undesirable effects of drugs previously cleared. . . . Senator Kefauver made a number of criticisms of the manner in which FDA was handling the “package inserts.” These represent the one document approved by that agency describing the uses, dosages, efficacy, and side effects of a new drug. . . . Another example of the general “tightening up” [as a result of hearings] is the increase in the amount of data required to accompany new applications [before enactment of any legislation]. The need for securing more complete information, particularly in the form of con-

trolled clinical studies, before a drug is approved for marketing was dramatized by the recent action of three more drug companies in sending to physicians warnings of newly discovered side effects of two important antibiotics [revealed by such studies].

S. REP. NO. 1304, 87th Cong., 2d Sess. 7-8 (1961).

The staff members . . . should be supported in their utmost to obtain submission of truly dependable scientific information on the efficacy and safety of the products.

Report of the Special Committee to Review FDA, *reprinted in Drug Industry Antitrust Act: Hearings on S. 1552 Before Subcomm. on Antitrust and Monopoly of the Senate Comm. on Judiciary*, 87th Cong., 1st Sess. 459-61 (1961) [hereinafter *Hearings on S. 1552*].

All of use who have seen the mass of laboratory and clinical information submitted to the FDA, even by the very best drug houses, in support of new drug applications are repeatedly dismayed by the welter of anecdotal case reports and uncontrolled clinical studies by physicians who are not equipped with the training and facilities for meaningful pharmacological and toxicological studies of new drugs in patients. All this is very expensive and very time consuming, adds to the cost of drugs, and doesn't provide the necessary information for the proper evaluation of a candidate drug.

Testimony of Dr. Louis Goodman, Univ. of Utah, *Hearings on S. 1552* at 215.

But without the controlled experiment, without the realization of biological variation among persons and with time, mazes in the still incompletely mapped terrain of the natural history of disease conspire to make the practicing physician's judgment of efficacy difficult and uncertain.

Testimony of Dr. William Bean, Iowa State Univ., *Hearings on S. 1552* at 270.

There are certain areas of disease . . . where the absence of such controlled trials leads to, in my opinion, chaos. In some other areas — acute leukemia, for example — an answer might be easily obtainable in a small number of patients without the use of double-blind controls. The emphasis should be on scientifically acceptable evidence, of whatever quantity and quality required to give a reliable answer to the questions posed concerning the drug's effects.

Testimony of Dr. Louis Lasagna, Johns Hopkins, *Hearings on S. 1552* at 283.

In current private practice, it is rarely possible for the physician to evaluate in a scientific fashion the effect of new and complicated drugs on one or a few patients. It is the total experience of controlled clinical testing and prolonged clinical use that determines the usefulness and toxicity of drugs.

The physician does not have time, and, as a rule, the competence to judge whether the claims for therapeutic effectiveness of a drug made by a manufacturer are

justified.

* * *

This bill would merely . . . provide for better validation of the efficacy and toxicity of drugs in such clinical trial before being marketed, and I think that is highly desirable.

It must be done by physicians who have the facilities to set up controlled, clinical testing, and so nothing in this bill, in my estimation, would inhibit proper research and proper introduction of new drugs.

Testimony of Allan Butler, M.D., Detroit Metro. Hosp., *Hearings on S. 1552* at 338, 355.

Only by this method [double-blinding] could the efficacy of such a drug be tested properly.

* * *

When the individual physician treats a patient with pneumonia with sulfadiazines, therefore, he must rely on the results of tests made on a large group of patients by competent investigators and reported in the medical journals to which he has access. The proposed bill would make sure that the proper tests had been done and that a summary of this information was available to him at the same time that the drug was placed on the market.

* * *

[T]he physician in practice . . . is not always sufficiently familiar with what he should be doing in testing new drugs. The Food and Drug Administration, if they were allowed to pass upon the efficacy of all drugs before they were marketed, would see that the proper procedures were carried out, and they would, by the very fact that they were studying this field all the time, and the methodology would be very familiar to them, they would know the procedures that should be carried out.

Testimony of Dr. Harry Dowling, Univ. of Illinois, *Hearings on S. 1552* at 411, 412, 414.

If he is honest, the individual physician will admit that he can only gather impressions concerning the effect of the remedy he uses in an individual patient, but he cannot even in that case determine the likelihood that the response was matter of chance or was due to any of the different methods of treatment that he employed, nor can he say what might have been the result were some other drug used. Only when adequate numbers of properly studied cases are gathered and the responses analyzed and compared with similar data from other well documented experiences can one gain some approximation of the true effectiveness of any remedy.

* * *

The essence of their [AMA's] argument is that the practicing physician is the only one who can determine efficacy and that he alone should have the opportunity to grope with the problem of determining for himself whether any new drug is good or bad for his patient. This is an invitation to all manufacturers to dump into the hands of practitioners any and all types of good and bad, useful or useless, drugs and devices and let them learn, at the expense and perils of their patients, whether they may be of help in each instance. He could go on doing this ad infinitum, much, of course, to the delight and profit of the manufacturer who is only delighted to preserve his privilege of supplying all kinds of new drugs to be used exactly in this manner.

Testimony of Maxwell Finland, M.D., Harvard Medical School, *Hearings on S. 1552* at 430, 434.

During the course of these hearings others will undoubtedly tackle the fallacy of assuming individual physicians, singly or collectively, can evaluate each drug's efficacy. A collection of impressions will not furnish the truth — this approach did not prevent doctors from having unbounded faith in the curative powers of leeches for hundreds of years before scientific evaluation become the preferred means of judging efficacy of therapy.

* * *

The magnitude of sales a drug after vigorous promotion is no recommendation of its usefulness or efficacy. if we are going to permit free promotion of drugs released to the market, let's at least empower the Food and Drug Administration to make certain only drugs of reasonably demonstrated efficacy are placed at the physician's disposal. The citizens have the right to this much protection before the doctors exercise their freedom.

* * *

I think the present concept of controlled methods of evaluation of drugs requires that the evidence accrued therefrom be evaluated by experts and that this be done for the physician before he is asked to accept the responsibility of using this drug and gathering his experience and contributing to the growing body of knowledge which may ultimately expand our concept of its usefulness or its uselessness, either one.

* * *

My basic reason is because of my conviction that in modern times the methods required for scientific evaluation of a drug require design of experiments, controlled experiments, beyond the facilities of each and every individual physician.

* * *

[O]ne can certainly anticipate a reasonable evaluation of the efficacy before allowing the drug to be made available to physicians.

* * *

One reason [that a doctor would prescribe a non-efficacious drug] would be that he did not know that to be true . . . He would be unlikely to find out very readily by his own efforts to try the drug in various patients. He would be more apt to find out by systematic, scientific evaluation according to the best modern procedures.

Testimony of Dr. Charles May, N.Y.U., *Hearings on S. 1552* at 195-96, 204, 207. *See also* Dr. Russell Cecil, *1959-60 Hearings on Drug Marketing Practices* at 7982-7983 (testimony on unproven therapies for arthritis such as bee venom, tonsillectomy, ineffective vaccines, immune milk, fever treatment, vitamins, and other extracts, including cod liver oil).

[The AMA's argument] that the new law restricts the freedom of the physician in his choice of drugs . . . is a most specious one.

The average practicing physician — and I have helped to train hundreds of them — just does not have the time, the facilities, the skill, nor the training to be an expert in the determination of drug efficacy. He is not capable of, or interested in, carrying out the elaborate and extensive controlled clinical and laboratory tests to determine drug efficacy.

Testimony of Dr. Louis Goodman, Univ. of Utah, *Hearings on S. 1552* at 216-17.

Everyone who has tried to test drugs knows how extremely difficult it is to determine whether a drug is or is not effective.

Testimony of Dr. David Barr, H.I.P. of N.Y., *Hearings on S. 1552* at 259.

[T]he position of the AMA presented by Dr. Hussey is that the judgment of efficacy should be left in the hands of the practicing physician who is dealing essentially with an individual case. Unhappily, this has been the source of much, if not most, of the error in our comprehension of disease and in our beliefs in the effectiveness of various long discarded and outmoded forms of therapy.

Testimony of Dr. William Bean, Iowa State Univ., *Hearings on S. 1552* at 269.

The history of medicine is, unhappily, replete with examples of useless drugs employed for years, decades, or centuries, by countless physicians before a few properly conducted experiments proved the drugs to be without value.

* * *

[I]t is difficult for physicians in all instances to quickly or even slowly come to the right conclusions about drugs.

* * *

[D]octors may prescribe agents that are inefficacious without so knowing. I would like to help them not [t]o prescribe ineffective agents.

* * *

What I am plunking for is a harder look at the evidence for efficacy whenever decisions are being made in regard to toxicity.

* * *

[M]odern therapeutics is too difficult and too dangerous for today's doctor to go it alone. He needs help, and from many sources, including the Government.

Testimony of Dr. Louis Lasagna, Johns Hopkins, *Hearings on S. 1552* at 283, 285, 287, 290, 291.

See also J. Starr, *The Testing of New Drugs and Other Therapeutic Agents*, JAMA (July 8, 1961), reprinted in *Hearings on S. 1552* at 827; M.C. Sheps, *The Clinical Value of Drugs: Sources of Evidence*, 51 AM. J. PUBL. HEALTH, reprinted in *Hearings on S. 1552* at 886-93. *See* Testimony of Dr. Moulton, former medical officer, FDA, *1959-60 Hearings on Drug Marketing Practices* at 12,041 ("Testimony before this committee has shown that even the inclusion of these words in the law [potency as requirement for antibiotic approval] was no deterrent to the marketing of products of exceedingly questionable efficacy").

Contra, *1959-60 Hearings on Drug Marketing Practices* at 9405-07 (Senator Kefauver himself suggested that extensive clinical testing was unnecessary on new medications derived from herbal products in comments on the utility of extracts of *Rauwolfia Serpentina* from which reserpine is derived, noting that the bark of the root had been in use for 900 years in India for medicinal purposes and that "the great Indian leader, Mahatma Gandhi, used to chew on this bark," despite comments by T.F. Davies Haines, President of Ciba Pharmaceuticals, that further testing was required to identify active ingredients, dosages and appropriate indications.).

APPENDIX II

Thrombolysis

In September, 1993, a clinical trial on the use of thrombolytics in acute myocardial infarction (AMI), GUSTO, reported significant patient benefit using a tPA dosing strategy different from that recommended in the package insert. GUSTO Investigators, *An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction*, 329 NEW ENG. J. MED. 673 (1993). As a result, in April, 1995, the FDA approved changes in the package insert to reflect the new dosing strategy. During the eighteen month interim, the manufacturer was in the anomalous position of promoting a product with a dosing interval that members of the academic community had abandoned. A new physician could be contacted by the drug company and in-

formed about dosing for AMI that actually could not be used because the cardiac care committee of the medical center had adopted the newer protocol.

ACE Inhibition and CHF

ACE inhibitors first were labeled for use in the management of hypertension. R.J. Cody, *Hemodynamic Responses to Specific Renin Angiotensin Inhibitors in Hypertension and Heart Failure: A Review*, 28 *DRUGS* 144-169 (1984). Later studies have suggested that some ACE inhibitors are useful in the long-term management of congestive heart failure (CHF). M.A. Pfeffer, et al., *Effect of Captopril on Mortality and Morbidity in Patients with Left Ventricular Dysfunction after Myocardial Infarction: Results of the Survival and Ventricular Enlargement Trial*, 327 *NEW ENG. J. MED.* 669-77 (1992). SOLVD Investigators, *Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fraction*, 327 *NEW ENG. J. MED.* 685-91 (1992). These differences in data have been reflected in differences in labeled indications. Cf. *PHYSICIANS' DESK REFERENCE* (4th ed. 1994) (CHF indications limited to captopril, enalapril, and lisinopril).

The issue of transfer of appropriate accurate and balanced information transfer is complicated by the fact that there are differences in pricing among the ACE inhibitors. To that end, captopril is approved for the management of CHF but also is among the most expensive inhibitors. Pricing differences may stimulate requests from managed care formulary committees for preliminary data on use in CHF for other ACE inhibitors when the few products shown to be effective in CHF are also the most expensive. In this circumstance, pricing differences may motivate selection of a formulary product based on less than reliable information. Information transfer based on poor quality of data cannot be prohibited, however, in the setting of an oral presentation to formulary committees based on information requested by the committee.

ACE Inhibitors, Beta Blockers, and Post-MI Prophylaxis

More recently, ACE inhibitors have been suggested for use in patients recovering from acute myocardial infarction to reduce mortality. ISIS Collaborative Group, *ISIS-4: Randomized Study of Oral Captopril in Over 50,000 Patients with Suspected Acute Myocardial Infarction*, 88 *CIRCULATION* I-394 (1993). As of the 1994 *Physicians' Desk Reference*, however, no approved ACE inhibitors are indicated in approved labeling for prophylaxis following AMI. While differences among ACE inhibitors in therapeutic effectiveness in CHF may be clearer, the early clinical data on post-AMI therapy is more confusing because two agents have been studied in three trials. Not infrequently, early data serve a hypothesis generation function in contrast to prospective and well controlled studies which may be designed to confirm such hypotheses. As noted by the FDA in its testimony, suggestions derived from data not designed to address the specific question may simply turn out to be wrong.

To that end, some of the differences may just represent the drug that was chosen for the study. ISIS-4 used captopril. *Id.* GISSI-3 used lisinopril. GISSI Collaborative Group, *GISSI-3: Effects of Lisinopril and Transdermal Glyceryl Trinitrate Singly and Together on 6-Week Mortality and Ventricular Function after Acute Myocardial Infarction*, 343 *LANCET* 115-22 (1994). These studies suggest modest mortality benefit from judicious use of ACE inhibition in the first 24 hours after infarction. In CONSENSUS-2, however, enalapril was not shown to have such a beneficial effect. K. Swedberg et al.,

Effects of the Early Administration of Enalapril on Mortality in Patients with Acute Myocardial Infarction: Results of the Cooperative New Scandinavian Enalapril Survival Study II, 327 *NEW ENG. J. MED.* 678-84 (1992). Data may not have reached the level of certainty, especially with regard to dosage and blood pressure titration, necessary for clinical decision-making. Furthermore, there are obvious and serious potential negative consequences that can arise from data presentation or extrapolation without appropriate control, even to a sophisticated audience.

Some beta blockers, in contrast, have been shown definitively to reduce the incidence of re-infarction after AMI. Propranolol and timolol have been widely studied. BBHAT Research Group, *A Randomized Trial of Propranolol in Patients with Acute Myocardial Infarction*, 247 *JAMA* 1701-14 (1982); Norwegian Multicenter Study Group, *Timolol-Induced Reduction in Mortality and Reinfarction in Patients Surviving Acute Myocardial Infarction*, 304 *NEW ENG. J. MED.* 801-7 (1981). Approved labeling for these products includes this information. Others in this class, however, such as pindolol, do not have this benefit. Australian & Swedish Pindolol Study Group, *The Effect of Pindolol on the Two Years Mortality after Complicated Myocardial Infarction*, 4 *EUR. HEART J.* 367 (1983). Calcium channel blockers, which have some overlapping indications with beta blockers (such as the treatment of hypertension or certain arrhythmias), do not have this effect. Israeli SPRINT Study Group, *Secondary Prevention Reinfarction Israeli Nifedipine Trial: A Randomized Intervention Trial of Nifedipine in Patients with Acute Myocardial Infarction*, 9 *EUR. HEART J.* 354-364 (1988); R.S. Gibson, et al., *Diltiazem and Reinfarction in Patients with Non Q-Wave Myocardial Infarction: Results of a Double-Blind Randomized, Multicenter Trial*, 315 *NEW ENG. J. MED.* 423-429 (1986).

What are clinicians actually doing in the post-AMI patient? A recent retrospective analysis of the GUSTO data showed that there are significant differences in the use of ACE inhibitors, beta blockers and calcium channel blockers in the post-AMI environment between the United States and Canada. D.B. Marks, et al., *Use of Medical Resources and Quality of Life After Acute Myocardial Infarction in Canada and the United States*, 331 *NEW ENG. J. MED.* 1130 (1994). Canadian physicians were more likely to use beta blockers and ACE inhibitors while U.S. physicians used calcium channel blockers and nitrates. Other data also demonstrates that beta blockers, although of proven efficacy, are less frequently used post-infarction than calcium channel blockers, where efficacy is questionable. NRMI Investigators, *Limited Use of Adjunctive Therapy in Females Post-Myocardial Infarction*, 90 *CIRCULATION* I-527 (1994); NRMI Investigators, *Is the Treatment of Myocardial Infarction in the United States Consistent with Recommendations of Recent Clinical Trials?* 90 *CIRCULATION* 2109-20. Furthermore, the FDA recently took enforcement actions against alleged marketing of calcium channel blockers for post-myocardial infarction management.

At a minimum, information transfer about the post-AMI use of ACE inhibitors, calcium channel blockers, and beta blockers has not only taken place but is inconsistent in penetration. The FDA action and the lack of penetration are signs of the inefficient underground market that exists under current regulatory control, which includes prescription of all off-label information if disseminated by drug sponsors.