FDA REGULATION OF COMMUNICATIONS ON PHARMACEUTICAL PRODUCTS†

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I. INTRODUCTION

Legal commentators have long been awed by the regulatory reach of the United States Food and Drug Administration (FDA) in the arena of communications on therapeutic products. With few exceptions, the FDA deems information on therapeutic products emanating from vendors and intended for the marketplace to be subject to scrutiny under the labeling and, for certain products, advertising provisions of the Federal Food, Drug, and Cosmetic Act (FDC Act or the Act).[1] The legal and philosophical basis for this regulatory posture, challenged over the years in various settings, remains both constant and controversial.[2]

This Article describes the FDA's complex and interesting relationship with the flow of information on therapeutic products by addressing the types of information the FDA views as having regulatory consequences, the regulatory mission that drives the agency's conduct in this arena, and the legal authority the agency relies on to regulate information. Although most of the principles and policies discussed herein apply generally to therapeutic products, the

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† This Article was delivered at the Symposium on The U.S. Pharmaceutical Industry in the 1990s: Facing Health Care Reform, Regulation, and Judicial Controls, on November 16, 1993, at the Seton Hall University School of Law.

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1 21 U.S.C. §§ 321-393 (1988 & Supp. IV 1993).

2 The agency's policies have been challenged in books, journals articles, and newspaper editorial papers. *See, e.g.*, BAD PRESCRIPTION FOR THE FIRST AMENDMENT: FDA CENSORSHIP OF DRUG ADVERTISING AND PROMOTION (Richard T. Kaplar ed., 1993); Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309 (1992); Richard M. Cooper, *Marketing "Violations,"* 47 FOOD & DRUG L.J. 155 (1992); Sandra J.P. Dennis, *Promotion of Devices: An Extension of FDA Drug Regulation or a New Frontier?*, 48 FOOD & DRUG L.J. 87 (1993); John E. Chalfee, *The FDA vs. the First Amendment*, WALL ST. J., Feb. 13, 1992, at A18. Moreover, the agency's policies have been challenged administratively by a legal advocacy group. *See* Washington Legal Foundation citizen petition filed with the Food and Drug Administration (Docket No. 92N-0434/CP1) (filed Oct. 22, 1993) (on file with FDA); Andrew Skolnick, *Pro-Free Enterprise Group Challenges FDA's Authority to Regulate Drug Companies' Speech*, 5 JAMA 271 (1994).

Article focuses primarily on the agency's regulation of communications on pharmaceutical products because this has been the arena of the most intense regulation of product information.

II. INFORMATION AT ISSUE

Although there have been a number of exceptions or policy refinements recognized by the agency over the years, the scope of information arousing the regulatory interest of the FDA has generally included communications that emanate directly or indirectly from vendors of therapeutic products within the agency's jurisdiction[3] when those communications are intended for the marketplace and have the potential to affect decisions related to the purchase or use of the product.[4] Given the wide array of therapeutic products subject to FDA jurisdiction, the myriad avenues of information on those products in the marketplace, and the breadth of the audience of potential purchasers, users, and intermediaries involved in purchase decisions on those products, it becomes clear that the agency has undertaken a heroic task.

The array of therapeutic products regulated by the FDA is itself extraordinary. Interpreting the FDC Act liberally, with the support of the courts, the agency has asserted jurisdiction over virtually all products intended for the treatment, cure, prevention, or diagnosis of disease or physiological condition. This includes not only the full array of pharmaceutical products, but also sophisticated medical technologies, dietary supplements,[5] and even one's own blood.

As the array and sophistication of regulated products have grown over the years, so too have avenues of information emanating from product vendors. The marketplace of communications on therapeutic products has grown not only in volume, but also in

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[3] Although the term "therapeutic" is distinguished from the term "diagnostic" for certain regulatory purposes, as used in this Article the term "therapeutic" includes the concept of diagnostic use. The various therapeutic products are subject to FDA jurisdiction. *See, e.g.*, 21 U.S.C. § 321(g) (1988 & Supp. IV 1993) (human and animal drugs); 21 U.S.C. § 321(h) (1988 & Supp. IV 1993) (devices); 42 U.S.C. § 262(a) (1988) (biological products). The agency also asserts a regulatory interest in information regarding the relationship between nutrition and disease for certain food products. *See* 21 C.F.R. § 101.14 (1993).

[4] *See* Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56,412 (proposed Nov. 27, 1992) [hereinafter Draft Policy Statement]; *see also* David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising and Promotion*, 264 JAMA 2409 (1990).

[5] *See* 21 C.F.R. § 101.14 (1993), as amended, 59 Fed. Reg. 395 (1994) (rulemaking on health claims for dietary supplements).

complexity. It includes not just traditional labeling and advertising formats, such as newspaper, medical journal, television, and radio advertisements, but also a complex and sophisticated network of agents and mechanisms that manufacturers and distributors support and influence.

The regulatory challenge facing the agency is further complicated by the growth in the breadth and complexity of the audience of potential purchasers, users, and intermediaries as new entities become involved in prescribing and purchase decisions, and vendors target consumers for information on both prescription and over-the-counter products.

The FDA has thus asserted a broad regulatory interest in information provided not only to product purchasers, but also to intermediaries involved in purchase decisions. This has included information provided to health-care professionals in scientific and educational meetings and symposia, as well as in books and articles disseminated in the context of product promotion. It has also included submissions to state and hospital formularies and managed care providers. Even the media has been viewed as an intermediary, with the FDA scrutinizing information provided to the media through press releases, press kits, and video news releases, as well as through spokespersons in media interview formats, such as press conferences and talk shows.

III. Regulatory Mission

The agency's assumption of this regulatory burden has often been questioned and sometimes challenged. Critics have suggested that the agency seeks to regulate these conduits of information because the agency is inherently biased against product promotion. Others have suggested a simpler etiology: regulation run amok; a powerful and unrestrained regulatory agency has failed to recognize reasonable bounds on its regulatory efforts.

Regardless of the merits of such criticisms, it is legitimate to ask whether the agency's aggressive approach to regulating product information is grounded in a reasonable policy concern that the agency can articulate. This is not only a requirement of the Constitution, but also of good government.

The agency clearly believes that it has a reasonable policy basis for its actions—a policy basis that flows directly from its regulatory mission. This mission, as stated by the agency, is to ensure that the therapeutic products within the agency's jurisdiction are safe and

effective.[6]

In this context, terms such as "safety" and "effectiveness" are relative. The safety and effectiveness of a therapeutic product cannot be assessed in an information vacuum. In the view of the FDA, the safety and effectiveness of the product must be assessed in relation to the product's intended use. The agency determines the intended use of the product largely by the vendor's characterization of its product in the marketplace.

As a consequence, the FDA examines the information provided by the vendor to induce product use or purchase. This includes, obviously, information provided by the vendor to explain how the product can be used to treat or diagnose a disease or medical condition. This concern over the vendor's characterization of its product in the marketplace naturally leads to the agency's examination of information beyond the label affixed to the product. The indication for use set forth in the label may, in some instances, bear no relation to the use for which the vendor actually markets its product. The agency thus considers the vendor's use of the broad array of information conduits mentioned above, including books, articles from scientific journals, scientific and educational symposia, and materials provided to the media, to determine whether the product is safe, effective, and properly labeled.

The second, related aspect of the agency's regulatory mission is equally important. It is the FDA's position that therapeutic products must be demonstrated safe and effective for *all* labeled indications based on scientific evidence, including adequate and well-controlled clinical investigations in the case of drugs. The FDA requires that such studies support either general recognition by qualified experts that the drug is safe and effective, or FDA approval of the product.

This, together with the agency policy that all intended uses must be set forth in the product labeling, results in a regulatory regime having a profound effect on the marketplace, not only with regard to the availability of therapies, but also with regard to the information provided on available therapies. Manufacturers and distributors are generally restrained from providing information on the safety and effectiveness of their products unless the information is not only consistent with product labeling but, in the case of an indication for use, actually within the product labeling. Moreover, in the case of drugs, suggested uses must be supported

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[6] FDA Mission Statement (1993) (on file with FDA).

by adequate and well-controlled clinical studies and, in most instances, must conform to labeling approved by the agency in a new drug application or to labeling standards set by regulation for a class of drugs.

Where is the authority for such an intense regulatory approach? The agency believes it is in the provisions of the FDC Act, a venerable document that the FDA has used as a constitution to develop a stringent and coherent regulatory scheme with, for the most part, the support of the courts.

IV. AUTHORITY

A. *Substantiation of Claims: On and Off Label*

By 1950, the FDA had established a legal principle of far-reaching consequences. Faced with attempts by product vendors to circumvent the FDC Act's labeling requirements by providing the information to consumers in communications falling outside the labeling definition, the FDA moved to extend its reach beyond labeling. Relying on the statute's charge that product labeling bear "adequate directions for use,"[7] the agency asserted that labeling must bear a description of all intended uses, including those communicated outside of labeling. In *Alberty Food Products Co. v. United States*,[8] the Ninth Circuit agreed, finding a product misbranded because its labeling failed to bear a description of therapeutic uses suggested in newspaper advertisements.[9]

Following *Alberty*, the agency promulgated its oft-cited regulation defining the concept of intended use for the purpose of determining the uses that must be addressed in labeling.[10] This regulation on intended use makes clear that the vendor's responsibility to provide labeling for all intended uses is broad and objective, reaching uses suggested in any form or format.[11]

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7 21 U.S.C. § 321(f)(1) (Supp. IV 1993).

8 185 F.2d 321 (9th Cir. 1950).

9 *Id.* at 325.

10 21 C.F.R. § 200.128 (1993). *See* Eugene M. Elson, *The Expanded Meaning of "Adequate Directions for Use,"* 7 FOOD DRUG COSM. L.J. 743 (1952).

11 21 C.F.R. § 200.128 (1993) defines the term "intended uses" for purposes of a companion regulation and 21 C.F.R. § 201.5 (1993), which incorporates the statutory standard of adequate directions for use. The term "intended uses" refers

> to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.

After establishing that therapeutic products must be labeled for all intended uses, the agency moved to tighten its grip on unfounded claims by broadening the scientific substantiation requirements for claims of effectiveness. Although the misbranding provisions of the Act provide the agency with the authority to address misleading claims in labeling,[12] they do not provide a precise standard for substantiation. With its hand strengthened by Congress's passage of the 1962 drug amendments,[13] however, the agency moved to establish a rigorous and universal standard for drug product claim substantiation.

In the 1962 amendments, Congress added an important new requirement to the new drug provisions of the Act.[14] New drugs were required to be approved as both safe and effective and, to escape the requirement for new drug approval, drugs were required to be generally recognized by qualified experts as both safe and effective.[15] Moreover, Congress provided a specific standard of proof of effectiveness in the drug approval process: "substantial evidence."[16] This standard was defined to include adequate and well-controlled clinical investigations upon which experts could reasonably base a determination that the drug is effective.[17] As applied by the agency, this standard evolved into a rigorous test, requiring, essentially, *proof* of efficacy based on replicated, statistically significant findings.[18]

Although Congress failed to expressly provide a similar substantiation requirement for drugs that were not new drugs, the agency had convinced the Supreme Court by 1973 that the substan-

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21 C.F.R. § 200.128 (1993). *See also* United States v. Three Cartons, 132 F. Supp. 569, 574 (S.D. Cal. 1952).

12 21 U.S.C. § 352(a) (1988).

13 Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified at 21 U.S.C. § 356 (1988)).

14 The requirement of FDA approval of new drugs dates back to the 1938 Act. In response to the 1938 Elixir of Sulfanilamide tragedy, Congress provided a new regulatory requirement for all "new drugs." Congress required that such drugs be approved by the FDA as safe for their labeled indications. The class of "new drugs" was defined to allow, with certain qualifications, drugs "generally recognized" by qualified experts as safe to escape new drug status. Pub. L. No. 75-717, § 201(p), 52 Stat. 1041 (1938) (current version at 21 U.S.C. § 321(p) (1988)).

15 21 U.S.C. § 355(c) (1988). Congress had provided grandfather clauses for certain drugs on the market prior to the passage of the 1938 Act and prior to the passage of the 1962 amendments. These provisions have been narrowly interpreted by the agency and by the courts. *See, e.g.*, USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655 (1973); United States v. Allan Drug Corp., 357 F.2d 713 (10th Cir. 1966). They have not proved to be a useful mechanism for escaping new drug status.

16 21 U.S.C. § 355(d) (1988).

17 *Id.*

18 *See, e.g.*, Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3d Cir. 1986).

tial evidence standard was applicable not only to the agency's determination in the new drug approval process but also to the general recognition standard in the new drug definition by which drugs escape new drug status.[19] In *Weinberger v. Hynson, Westcott, & Dunning, Inc.*,[20] the Court held that a drug could not escape the new drug approval process and its requirement of substantial evidence unless the general recognition of the product as effective was also based on substantial evidence of effectiveness.[21]

The significance of this victory cannot be overstated. This requirement, that all drugs be approved or generally recognized based on substantial evidence, enabled the agency to fashion a uniform substantiation requirement for pharmaceutical labeling claims. The *Hynson* and *Alberty* cases, their progeny, and the agency's corollary regulations, formed a formidable legal basis for the agency's assertion of a seamless regulatory regime in which pharmaceutical products cannot be suggested for any use by a manufacturer or distributor in the absence of labeling for that use approved or officially sanctioned by the FDA.[22]

This is the primary legal framework supporting the FDA's assertion of regulatory control over information provided by drug vendors related to the use of their products. The requirement that all promoted uses be included in labeling and supported by substantial evidence is at the heart of the agency's perception of its regulatory mission. It is not, however, the sole basis for the FDA's assertion of regulatory control over product information emanating from vendors. Much of this information is transmitted in formats that the agency deems subject to regulation under the provisions governing content of labeling and advertisements.

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19 21 U.S.C. § 321(p) (1988).

20 412 U.S. 609 (1973).

21 *Id.* at 619. In a companion case, the Court also agreed with the agency that this data supporting general recognition be published in the scientific literature. Weinberger v. Bentex Pharmaceuticals, 412 U.S. 645 (1973).

22 In *United States v. Undetermined Quantities of an Article of Drug*, 709 F. Supp. 511 (D.N.J. 1987), *aff'd*, 857 F.2d 1466 (3d Cir. 1988), *cert. denied*, 488 U.S. 1040 (1989), the agency established that to escape new drug status, the substantial evidence supporting the product must consist of published studies, not just on the active ingredients in the product, but on the product itself—a requirement that precluded general recognition for most, if not all, drugs.

The only large class of drugs acknowledged by the agency to escape the requirement of approval under the new drug provisions of the Act are drugs in the OTC (Over-the-Counter) Review. These drugs escape new drug status through compliance with FDA-promulgated monographs that establish labeling claims acceptable to the agency as supported by substantial evidence. *See* 21 C.F.R. § 330.10(a)(4)(ii) (1993).

B. Jurisdiction Over Labeling

In addition to the requirement of scientific support for effectiveness for all indications for use, the FDC Act provides other labeling requirements that apply generally to therapeutic products, including the requirements that (1) labeling not be false or misleading in any particular,[23] (2) labeling contain all material facts[24] and adequate warnings,[25] and (3) the products be safe for the uses set forth in the labeling.[26] To apply these standards to the broadest array of promotional communications, the agency adopted an expansive interpretation of the Act's definition of labeling. The term "labeling" is defined in the Act as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[27]

Finding room for interpretation in the reference to materials "accompanying" a product, the agency adopted an interpretation that went far beyond physical accompaniment. The agency's liberal interpretation of the labeling definition was placed before the Supreme Court in 1948. In *Kordel v. United States*,[28] the Court agreed with the agency that the labeling definition was not limited to materials that physically accompany a product and could include materials that supplement or explain a product where the materials originate from the same source (the vendor) and are intended for the same audience (the purchaser or user).[29] The Court deemed the textual relationship between the materials and the products to be significant.

Since *Kordel*, the agency's interpretation has been tested in a number of cases, and has remained largely intact.[30] Emboldened by its victories in court, the agency has continued to take an aggressive posture toward product information in written, printed, or graphic form that emanates directly or indirectly from the vendor.

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23 21 U.S.C. § 352(a) (1988).

24 21 U.S.C. § 321(n) (1988).

25 21 U.S.C. § 352(f) (Supp. IV 1993).

26 21 U.S.C. § 352(j) (1988).

27 21 U.S.C. § 321(m) (1988).

28 335 U.S. 345 (1948). *See also* United States v. Urbuteit, 335 U.S. 355 (1948).

29 335 U.S. at 348.

30 *See, e.g.*, United States v. Articles of Drug, 344 F.2d 288 (6th Cir. 1965); United States v. Articles of Drug, 32 F.R.D. 32 (S.D. Ill. 1963); United States v. Eight Cartons, 103 F. Supp. 626, 627 (W.D.N.Y. 1951). *But see* United States v. 24 Bottles, 338 F.2d 157, 159 (2d Cir. 1964) (finding that books sold in a health food store that mentioned a product marketed in the store were not part of a joint promotional effort related to the product).

As the agency stated in testimony before Congress in 1976, "[l]abeling has been defined quite broadly in the [FDC Act] and by the Courts and includes virtually all printed materials about drugs placed into interstate commerce and supported by a drug firm."[31]

The agency maintains a vigilant attitude toward the dissemination by vendors of books and articles on or related to their regulated products, even where the materials are peer-reviewed and produced independently from the vendor. The agency also continues to take a broad view of the concept of accompaniment, holding that information from a "common origin" with the product includes not only information prepared by the vendor but also information prepared with the financial support of the vendor where the vendor controls, or is in a position to influence, the content of the information.[32]

C. *Jurisdiction Over Prescription Drug Advertisements*

In providing the FDA with direct regulatory authority over prescription drug advertisements in 1962,[33] Congress did not, as it had for labeling, provide a definition for the term. Indeed, there is only one reference to prescription drug advertisements in the Act. The provision which authorizes the FDA to promulgate regulations requiring a brief summary for such advertisements fails to define the term "advertisement," providing only that the term does not include materials that fall within the definition of labeling.[34]

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[31] *Hearings before the Subcomm. on Monopoly of the Senate Select Comm. on Small Business*, 94th Cong., 2d Sess. 14,096 (1976) [hereinafter *Hearings*] (statement of J. Richard Crout, M.D., Director, Bureau of Drugs, United States Food and Drug Administration).

The agency has provided by regulation that a broad array of written, printed, and graphic materials disseminated by or on behalf of a drug company are subject to regulation as labeling. 21 C.F.R. § 202.1(*l*)(2) (1993). However, the agency has steadfastly maintained that the list of materials in the regulation are examples of labeling, rather than an exclusive description of all the materials falling within the statutory definition of labeling.

[32] The agency has sought to regulate some sole-sponsored supplements to peer-reviewed journals as labeling regardless of whether the supplements were disseminated by the sponsoring company. The agency's regulatory posture is based, at least in part, on the sponsor's payment for the supplement and control or influence over content.

[33] In the Wheeler-Lea Amendments of 1962, Congress provided the FDA with jurisdiction over prescription drug advertisements, leaving exclusive jurisdiction over advertisements for over-the-counter (OTC) drugs with the FTC. Although the FTC retains jurisdiction over prescription drug advertisements under its authority to regulate unfair trade practices, a memorandum of understanding between the two agencies leaves the FDA with the primary role in regulating these forms of communications.

[34] 21 U.S.C. § 352(n) (1988). Congress also provided jurisdiction over the adver-

The agency has read this specific exclusion of labeling from the provisions on advertisements to support its view that Congress intended the term advertisement to have a meaning similar to that of labeling—information originating from the same origin as the product that is intended to supplement or explain the product. Under the FDA's interpretation of the FDC Act, the definitions of labeling and advertisements are distinguishable only by the form of the communication. Generally speaking, if the communication is in written, printed, or graphic form, it is subject to regulation as labeling; otherwise it is subject to regulation as an advertisement.[35]

Although some commentators have noted that the reference in the Act to "advertisements and other descriptive printed matter"[36] suggests that the term "advertisement" is meant to include only written advertisements,[37] the agency has traditionally interpreted the concept much more broadly to include information transmitted through the broadcast media, such as in television and radio advertisements, media appearances by vendor spokespersons, and information communicated in live oral sales presentations, including speeches and sales calls. In its regulation on prescription drug advertisements, the agency includes advertisements transmitted through the broadcast media as an example of an advertisement over which the agency has jurisdiction.[38]

The agency's interpretation of its jurisdiction over labeling and advertisements provides a seamless regime for regulating the substance of almost all prescription drug information emanating from a vendor. If the information is intended ultimately for the marketplace and supplements or explains the product, it will generally be deemed by the FDA to be subject to regulation either as labeling or as an advertisement.[39]

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tising of restricted devices and made misleading advertisements for such devices illegal. 21 U.S.C. § 352(q) (1988). No definition of the term advertisement is provided in this section of the Act.

35 Promotional information placed in newspapers, journals, and other written, printed, or graphic media is generally regulated as an advertisement rather than as labeling unless the material placed in medium is disseminated by the vendor.

36 21 U.S.C. § 352(n) (1988).

37 *See, e.g.*, Noah, *supra* note 2.

38 The regulations provide that "[a]dvertisements subject to section 502(n) of the Act include advertisements in published journals, magazines, and other periodicals, newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems." 21 C.F.R. § 202.1(*l*)(1) (1993).

39 *See* Daniel D. Adams & William E. Nelson, Note, *The Drug Amendments of 1962*, 38 N.Y.U. L. REV. 1082 (1963).

V. POLICY REFINEMENTS

Within these broad policy parameters and assertions of legal authority over product information, the agency has moved over the years to refine its policies and to recognize necessary exceptions. The agency has long recognized that health-care professionals utilize drugs for off-label indications in the practice of medicine[40] and find it important to keep abreast of the latest scientific information about FDA-regulated products.[41] This often involves information that cannot be provided in labeling or in advertisements, because the information relates to a product use that is not approved by the agency and may not be supported by adequate and well-controlled studies.[42] As the agency has acknowledged, "the constraints on advertising and labeling when applied to scientific and educational activities, can restrict the freedom of participants to discuss their data or express their views," including, "[i]n particular, discussions of unapproved uses."[43]

Because the regulated industry often plays an important role in developing this information and in supporting scientific and educational activities designed to provide such information to health-care professionals, the agency recognizes a number of legal and policy exceptions allowing for involvement by product vendors in the dissemination of information related to product uses outside of the labeled indications.

A. *Independent Scientific and Educational Activities*

One of the most controversial policy developments in recent years has been the agency's attempt to define a "safe harbor" for industry involvement in and support for scientific and educational activities, such as seminars and scientific symposia. Although the basic elements of agency policy in this arena had been in effect for years, the agency recognized as early as the 1970s the need to articulate a more refined and detailed regulatory structure for the regulated industry's involvement in ostensibly independent scientific and educational activities.[44] The agency's effort in this regard drew little attention until the circulation of a draft "Concept Pa-

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40 37 Fed. Reg. 16,503 (1972).

41 *See Hearings*, *supra* note 31, at 14,068 (statement of J. Richard Crout, M.D., Director, Bureau of Drugs, United States Food and Drug Administration).

42 *See, e.g.*, Draft Policy Statement, *supra* note 4.

43 *See* Draft Policy Statement, *supra* note 4, at 56,412 (footnote omitted).

44 *See Hearings*, *supra* note 31, at 14,102-03 (statement of J. Richard Crout, M.D., Director, Bureau of Drugs, United States Food and Drug Administration).

per" in 1991 by the FDA's Center for Drug Evaluation and Research.[45] Immediately controversial, the issuance of this document was followed by an intense and directed dialogue between the agency and representatives from the regulated industry, as well as from the health-care profession, including major accrediting bodies such as the Accreditation Council for Continuing Medical Education. This dialogue led, in late 1992, to the publication in the Federal Register of a draft agency policy statement covering all therapeutic products.[46] Although the agency invited comment on the draft policy statement and has not issued a final policy statement, agency personnel indicated shortly after publication of the document that the draft policy statement reflects current agency policy on this issue.[47]

The safe harbor described in the draft policy statement, in which the regulated industry can involve itself in providing product information outside the parameters of FDA regulation, is defined largely in terms of the relationship between the supporting company and the independent provider. Rather than attempt to distinguish education from promotion and allow industry to script "educational" programs, the agency's approach is to determine whether the activity is independent and is *designed* to be an educational program characterized by balance, objectivity, scientific rigor, and appropriate disclosure of financial support.

If the program is truly an independent scientific and educational program, product vendors can, within the parameters of the safe harbor described in the draft policy statement, provide financial, logistical, and technical support for the program without being held responsible for the program's content. Thus, the program can address off-label uses of the vendor's products that would otherwise have regulatory consequences for those products.[48]

The key test for the agency in determining whether the program is an independent scientific and educational program is the existence of a written agreement between the supporting company and the provider of the activity. To qualify for the safe harbor, the

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45 Food and Drug Administration, Drug Company Supported Activities in Scientific and Educational Contexts: Draft Concept Paper (Oct. 26, 1991).

46 *See* Draft Policy Statement, *supra* note 4. For a general discussion of the development and content of the draft policy statement, see David G. Adams, *FDA Policy on Industry-Supported Scientific and Educational Activities: Current Developments*, 47 FOOD & DRUG L.J. 629 (1992).

47 *See* Adams, *supra* note 46, at 633.

48 *See* Draft Policy Statement, *supra* note 4, at 56,412.

supporting company is advised to enter into a written agreement with the provider stating that the funded event is not to be a promotional event for the supporting company's products, but rather is to be an educational program, controlled on content and format by the provider. The agency provides in the draft policy statement that "[i]f the company abides by such a written agreement and does not otherwise circumvent its purpose, the agency does not intend to regulate the activity under the labeling and advertising provisions of the act."[49]

The draft policy statement provides that the written agreement should address independence, program design, and disclosure. With regard to independence, the draft policy statement makes clear that provider control over content means not only final editorial control, but also insulation from influence by the supporting company over the content.[50] Technical assistance by the supporting company is allowed as long as there is no attempt to script presentation content.[51] Independence also requires, in the agency's view, that the supporting company not be involved in the selection of presenters or moderators, other than in response to an unsolicited request for assistance in identifying possible presenters.[52]

The written agreement should also stipulate that the provider is to design a non-promotional, educational program.[53] This requires that the provider and supporting company agree to an educational program, characterized by objectivity, balance, and scientific rigor.[54] The agency suggests that the written agreement stipulate, among other things: (1) that the program provide for an objective and balanced discussion of the supporting company's product and of treatment alternatives; (2) that limitations on data be disclosed; (3) that unapproved uses be identified as such; and (4) that for live presentations there be opportunities for questioning or debate.[55] Ancillary promotional activities should not be a part of the program, although exhibits can be provided in a separate room and away from a necessary pathway to the program.[56]

The provider should also agree with the supporting company

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49 *Id.* at 56,413.
50 *Id.*
51 *Id.*
52 *Id.*
53 *Id.*
54 *Id.*
55 *Id.* at 56,413-14.
56 *Id.* at 56,413.

to disclose to the audience the source of funding for the activity, as well as any significant relationship between the supporting company and the provider or between the company and any presenter or moderator.[57]

B. Original Research Submitted to Peer-Reviewed Publications

A second important policy refinement, similar in concept to the policy on industry-supported scientific and educational activities, is the agency's policy on submission of original research to peer-reviewed publications. As in the case of educational activities such as symposia, the agency has recognized the need among health-care professionals for peer review and dissemination of the latest significant scientific data and information regarding therapeutic products. The agency has thus acknowledged an exception to the ordinary regulatory consequences that may flow from industry involvement in dissemination of information on off-label uses where original research is submitted to peer-reviewed journals. As in the case of scientific and educational symposia, the provider of the information must be independent from the vendor and exercise control over content.

This policy has continued over the years with little apparent misunderstanding or controversy. There has, however, been one consistent area of controversy related to journal supplements that are sponsored by companies marketing products discussed in the supplements. These publications, commonly referred to as "sole-sponsored supplements," are special issues of peer-reviewed journals that are different from regular issues in several respects that have drawn comment from the agency.[58]

The agency's concerns have generally revolved around four issues. First, these supplements are often paid for by companies marketing products discussed in the supplements, distinguishing the content of the supplement from articles published in regular journal issues without such payments. Second, these supplements are often composed of collections of articles and studies that are assembled by the supporting company, often relating only to the company's products. Third, these supplements are generally not subjected to the same quality of peer review as are articles pub-

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57 *Id.*

58 This issue was addressed publicly by the agency as early as 1976. *See Hearings*, *supra* note 31, at 14,079-80 (statement of J. Richard Crout, M.D., Director, Bureau of Drugs, United States Food and Drug Administration).

lished in regular issues. Finally, the tone and content of these supplements often appear to the agency to be promotional.

C. *Responses to Unsolicited Requests for Information*

Another important policy exception relates to industry responses to unsolicited requests for scientific information by health-care professionals. Scientific departments within companies generally maintain a large body of information on their products. Where health-care professionals contact companies requesting such information, companies can respond freely and fully without incurring a charge by the agency that they are suggesting off-label uses for their products. The agency may attach regulatory consequences to the information, however, if the company packages information in a manner that is not responsive to the request or provides information that is not requested. The agency may also seek to regulate the company's conduct if the request for the information was solicited by the company through the company's sales force or by some other means. Thus, although companies cannot offer or promote specific scientific materials to health-care professionals, they can provide virtually any information that a health-care professional requests.[59]

D. *Dissemination of Independently Prepared Textbooks*

Another less significant policy refinement relates to the dissemination of independently prepared educational materials. The agency's general assertion of regulatory authority over industry dissemination of books and similar materials containing product information is, as discussed above, well established in the case law. The agency recognized as early as the 1970s, however, that this strict application of the statute made little sense where companies were distributing established educational materials, such as medical textbooks, that were prepared independently and were recognized and used by health-care professionals. The agency thus acknowledged that industry could provide such materials to health-care professionals if the material: (1) was prepared solely for educational use; (2) was in the form of balanced educational material and not promotional in nature; (3) was independently prepared; (4) covered several different products; and (5) was not associated

[59] Although this exception also applies to requests for information by consumers, there are fewer such requests and there is greater potential for liability. This is because the agency believes consumers can be more easily misled than health-care professionals.

with a promotional campaign for a specific product.[60]

Under these criteria, the agency has allowed the dissemination of recognized medical textbooks by the regulated industry. The agency has not, however, allowed the dissemination of such books by sales personnel, nor has it allowed the dissemination of books that are prepared in accordance with the specifications of the supporting company.

VI. CONSTITUTIONAL ISSUES

The constitutionality of the agency's assertion of regulatory authority over communications on therapeutic products has been challenged on numerous occasions, generally unsuccessfully.[61] The issue has not gone away, however, and interest in the constitutionality of the agency's approach has intensified in recent years in the context of the agency's much-publicized Draft Policy Statement on Industry-Supported Scientific and Educational Activities.[62]

The central thesis of the current challenge is that much of the information regulated by the agency is pure non-commercial speech that cannot be restricted under the First Amendment or, at least, is commercial speech outside the sphere of regulation permitted by the First Amendment because it is truthful and nonmisleading.

Although the agency has yet to address these questions in any formal manner with regard to pharmaceutical products, the agency has addressed similar issues in the context of food labeling. In response to comments challenging its 1991 proposed rules on food labeling,[63] the agency stated that the restrictions on speech inher-

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60 *See Hearings*, *supra* note 31, at 14,097-99 (statement of J. Richard Crout, M.D., Director, Bureau of Drugs, United States Food and Drug Administration). These criteria are commonly known within the agency as the Sabshin criteria, because they were first announced in a letter to Melvin Sabshin. *See* Letter from J. Richard Crout, Director, Bureau of Drugs, United States Food and Drug Administration, to Melvin Sabshin, Medical Director, American Psychiatric Association (May 22, 1975) (on file with author).

61 *See, e.g.*, United States v. General Nutrition, Inc., 638 F. Supp. 556, 562 (W.D.N.Y. 1986) (because labeling is commercial speech, injunction against marketing of product based on statements in labeling that may be truthful does not necessarily violate First Amendment rights of product vendor); United States v. Articles of Drug, 32 F.R.D. 32, 35 (S.D. Ill. 1963) (seizure of books used by product vendor to promote product does not violate First Amendment rights of author); United States v. Eight Cartons, 103 F. Supp. 626, 628 (W.D.N.Y. 1951) (seizure of books used by product vendor to promote product does not violate First Amendment rights of publisher).

62 *See supra* note 2.

63 56 Fed. Reg. 60,537 (1991).

ent in regulation of labeling claims are incidental and related to regulation of the products themselves and that, in any event, the constitutional protections for commercial speech are not abridged by the proposed regulation.[64]

The agency's response is relevant to pharmaceutical products because, among other things, the food labeling claims at issue include health claims, some of which could be subject to regulation under the drug provisions of the Act if not specifically authorized by the FDA under its food labeling authority.[65] In its response to the comments, the agency dismissed the notion that the information regulated in labeling includes pure non-commercial speech. The agency argued not only that its regulatory approach is consistent with commercial speech jurisprudence, but also that its regulation of speech in food labeling may be entitled to even wider latitude because it is incidental and necessary to protect the public health and safety. This latter argument was the primary focus of the agency's response.

The agency advanced the argument that food labeling claims constitute a "distinct category of communications," similar to securities, labor, and antitrust regulation, in which the government's power to regulate may be broader than with respect to commercial speech.[66] The agency further suggested that a stronger case could be made for regulation of food labeling than for the other spheres of economic regulation because regulation of food labeling "protects consumer health and safety in an area where harm to the public can be direct and immediate."[67]

The agency also noted that, although its position does not depend on a finding that the regulated information is commercial speech, at least one court has categorized labeling as commercial speech. Viewing food labeling as commercial speech, the agency argued that its regulations are consistent with constitutional protections accorded such speech.[68] The agency stated at the outset

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64 58 Fed. Reg. 2478, 2524 (1993).

65 These health claims, if approved by FDA, are regulated under the food labeling provisions of the Act, 21 U.S.C. § 434(r), and are exempt from possible regulation under the drug definition, 21 U.S.C. § 321(g)(1).

66 58 Fed. Reg. at 2525 (quoting SEC v. Wall St. Publishing Inst., 851 F.2d 365, 372-73 (D.C. Cir. 1988), *cert. denied*, 489 U.S. 1066 (1989); citing NAACP v. Claiborne Hardware Co., 458 U.S. 886, 912 (1982); Dun & Bradstreet, Inc. v. Greenmoss Builders, 472 U.S. 749, 785 n.5 (1985); Ohralik v. Ohio State Bar Ass'n, 436 U.S. 447, 456 (1978); S.E.C. v. Suter, 732 F.2d 1294, 1299 (7th Cir. 1984)).

67 *Id.*

68 *Id.* (citing United States v. General Nutrition, Inc., 638 F. Supp. 556 (W.D.N.Y. 1986)).

that the unsubstantiated health claims that are precluded under the agency's regulations are inherently misleading and are not entitled to protection.[69] The agency further argued that, even if such speech were deemed only potentially misleading, its regulations are consistent with protections offered by the First Amendment.

The agency acknowledged that, under *Central Hudson Gas & Electric Corp. v. Public Service Commission*, the restrictions on potentially misleading commercial speech must directly advance a substantial governmental interest and be no more extensive than necessary to serve that interest.[70] The agency posited that the Supreme Court has recognized "the health, safety, and welfare of . . . citizens" as a substantial government interest,[71] and concluded that the regulations directly advance that interest and are no more extensive than necessary because they "reasonably and effectively ensure that health claims on food labels will be scientifically valid, informative, and not misleading."[72]

In arguing that its restrictions are consistent with constitutional protection for commercial speech, the agency dismissed arguments that the regulated speech is pure non-commercial speech that cannot be regulated. The agency found support in Supreme Court jurisprudence for the proposition that labels are not immune from regulation as commercial speech merely because they contain discussions of issues of broad public interest,[73] contain information that discuss products generically rather than by specific name,[74] or contain information that is protected in other contexts.[75]

This discussion suggests that the agency believes it has a constitutional footing for its approach to the regulation of information provided by vendors on therapeutic products, not only in the context of labeling but also in advertisements, which the agency views as involving similar issues and regulates similarly to labeling.

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69 *Id.* at 2526.

70 *Id.* (citing *Central Hudson*, 447 U.S. 557, 566 (1980)).

71 *Id.* (quoting Posadas de Puerto Rico Assocs. v. Tourism Co., 478 U.S. 328, 341 (1986)).

72 *Id.* at 2527 (citing Board of Trustees v. Fox, 109 S. Ct. 3028, 3032-35 (1989)). The agency cited *Board of Trustees* for the proposition that narrow tailoring requires a "reasonable fit" between regulatory means and ends; "not necessarily the single best disposition but one whose scope is 'in proportion to the interest served.'" *Id.* (citing *Board of Trustees*, 109 S. Ct. at 3035).

73 *Id.* (citing *Board of Trustees*, 109 S. Ct. at 3032; Bolger v. Youngs Drug Prods., 463 U.S. 60, 63 (1983); *Central Hudson*, 447 U.S. at 562 n.5).

74 *Id.* (citing *Bolger*, 463 U.S. at 66 n.13).

75 *Id.* (citing Zauderer v. Officer of Disciplinary Counsel, 471 U.S. 626, 637 n.7 (1985)).

VII. CONCLUSION

Notwithstanding the aforementioned policy refinements, the FDA has staked out a heroic claim of authority over information on therapeutic products provided by product vendors. Information provided directly or indirectly by therapeutic product vendors, in any format, for any individual involved in purchase decisions for the product, may have regulatory consequences under the agency's interpretation of the FDC Act. Through its authority over labeling of therapeutic products, advertising of prescription drugs, and approval of new drugs, the agency has created a seamless regulatory regime in which virtually all product claims of effectiveness emanating directly or indirectly from a drug vendor must be supported by scientific proof, including adequate and well-controlled clinical investigations. This facilitates the agency's pursuit of its regulatory mission to ensure that pharmaceutical products are safe and effective for any use for which they are directly or indirectly promoted by the product vendor.

The agency acknowledges the rights of individual experts to express their views about therapeutic products. However, the agency reserves the right to regulate and, in fact, has regulated, products based on such expressions where the presentation was supported by, and subject to the influence of, the product vendor. The agency has recognized exceptions for the dissemination of information by independent educational providers, for the publication of original research in peer-reviewed publications, for the dissemination of textbooks, and for responses to unsolicited requests for information. The agency's general resolve, however, to regulate therapeutic products based on the vendor's characterization of the product in the marketplace, tested time and again, remains firm, even in the face of constitutional challenge.